Year: September 2017 Volume: 4 Issue: 4

ISSN: 2147-9445
E-ISSN: 2587-2478

The Journal of Pediatric Research

Official Journal of Ege University Children's Hospital

Ceylin Özbay, 9 yaş

galenos yayınevi

The Journal of Pediatric Research Year: 2017 Volume: 4 Issue: 3 Page: 90 - 170

JPR
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The Journal of Pediatric Research, Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı'nın bir yayın organıdır.

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Basım Yeri/Printing at: Creative Basım Ltd. Şti.
Litros Yolu Cad. 2. Matbaacılar Sitesi
ZD1 Topkapı-İstanbul Tel: 0212 709 75 25
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Basım Tarihi/Printing Date: Aralık 2017/December 2017
ISSN: 2147-9445 **E-ISSN:** 2587-2478

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

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Dergi Hakkında

The Journal of Pediatric Research, Ege Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı ve Ege Çocuk Vakfı'nın bir yayın organıdır. Dergi üç ayda bir, Mart, Haziran, Eylül, Aralık aylarında İngilizce dilinde yayınlanır.

The Journal of Pediatric Research hakemli, online erişilebilir bir dergidir ve pediatri alanında araştırma makaleleri, davetli derlemeler, klinik çalışmalar ve olgu sunumları yayınlar.

Derginin amacı araştırmacılara ve sağlık alanında çalışanlara çocuk sağlığı ve hastalıklarının tanısı, izlemi, tedavisi, yeni araştırma alanlarının yaratılması ve klinik yaklaşım gibi konularda rehberlik yapmak ve yeni araştırma alanlarının yaratılmasına aracılık etmektir. Derginin web sayfasına http://www.jpedres.org/ yoluyla ulaşabilirsiniz.

Yayın politikası, "ICMJE Recommendations" (2016, http://www.icmje.org/) kuralları temel alınarak belirlenmiştir.

Araştırma bulgularının denetlenmesi istatistik editörü tarafından yapılır.

Dergi içeriği pediatri ile ilgili öncelikle genel pediatri konuları olmakla birlikte, pediatri yan dallarını (Acil Tıp, Allerji ve İmmünoloji, Endokrinoloji, Gastroenteroloji, Beslenme ve Hepatoloji, Genetik, Kardiyoloji, Hematoloji-Onkoloji, Enfeksiyon Hastalıkları, Metabolizma, Nefroloji, Nöroloji, Romatoloji, Solunum Yolları, Sosyal Pediatri, Yenidoğan, Yoğun Bakım, Etik ve Sağlık Servisleri), Çocuk Psikiyatrisi, Çocuk Cerrahisi, Çocukluk Yaş Grubunun Ağız ve Diş Sağlığı ve Çocuk Sağlığı ve Hastalıkları Hemşireliği ile ilgili genel konuları kapsamaktadır.

The Journal of Pediatric Research'e gönderilen çalışmalarınızın ortalama değerlendirme süresi 6 haftadır.

Makalenin kabulünü takiben bütün yazarların makalenin son halini görmesi ve içeriğini onaylaması beklenmektedir. Başka bir yayın organında basılmış ya da değerlendirme aşamasında olan makaleler kesinlikle değerlendirme sürecine giremezler. Araştırma makalelerinde etik onay belgesi (etik onay numarası ile birlikte), olgu sunumlarında bilgilendirilmiş onam formu istenir.

The Journal of Pediatric Research, **Web of Science-Emerging Sources Citation Index (ESCI), Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, ProQuest, Index Copernicus, Tübitak/Ulakbim TR Dizini, TurkMedline ve Türkiye Atıf Dizini'nde** 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.

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Yazarlara bilgi dergi sayfasında ve www.jpedres.org web sayfasında yayınlanmaktadır.

Materyal Sorumluluk Reddi

The Journal of Pediatric Research, 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.

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The Journal of Pediatric Research abonelik işlemleri için Galenos Yayınevi ile iletişime geçmeleri gerekmektedir. Ait olduğu dönemler içinde dergi eline ulaşmamış aboneler, Galenos Yayınevi'ne müracaat etmelidirler. Derginin tüm sayılarına ücretsiz olarak www.jpedres.org adresinden tam metin olarak ulaşılabilinir.

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Yazarlar dergimizde yayınlanmak üzere çocuk temalı ve düşündürücü özelliği olan fotoğraflar gönderebilirler. Uygun görülen fotoğraflar ilgili sayıda yayınlanacaktır. Fotoğraflarınızı ozgur.cogulu@ege.edu.tr adresine göndermenizi rica ederiz.

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About Journal

The Journal of Pediatric Research is the official publication of Ege University Faculty of Medicine, Department of Pediatrics and Ege Children's Foundation. It is a peer-reviewed journal published quarterly in March, June, September and December in English language.

The Journal of Pediatric Research is a peer-reviewed, open access journal, which publishes original research articles, invited review articles, clinical reports and case reports in all areas of pediatric research.

The journal publishes original research and review articles, which summarize recent developments about a particular subject based on standards of excellence and expert review and case reports. Target audience includes specialists in general pediatrics and pediatric subspecialties (Emergency Medicine, Allegy and Immunology, Endocrinology, Gastroenterology, Hepatology and Nutrition, Genetics, Cardiology, Hematology-Oncology, Infectious Diseases, Metabolism, Nephrology, Neurology, Rheumatology, Pulmonology, Social Pediatrics, Newborn, Critical Care Medicine, Ethics and Health Service Research), as well as relevant specialties such as Pediatric Surgery, Child and Adolescent Psychiatry, Pedodontics, Pediatric Nursing and Family Physicians. The web page of The Journal of Pediatric Research is http://www.jpedres.org/.

The journal's editorial policies are based on "ICMJE Recommendations" (2016, http://www.icmje.org/) rules.

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The Journal of Pediatric Research, Ege Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı ve Ege Çocuk Vakfı'nın yayın organı olup, çocuk sağlığı ve hastalıkları ile doğrudan ya da dolaylı olarak ilgili konularda özgün klinik ve laboratuvar araştırmaları, olgu sunumları, derleme yazıları yayınlar. Derginin yayın dili İngilizce'dir.

The Journal of Pediatric Research Dergisi makale başvuru ücreti veya makale işlem ücreti uygulamamaktadır.

The Journal of Pediatric Research'nin kısaltması JPR'dir, ancak kaynaklarda kullanılırken J Pediatr Res şeklinde belirtilmelidir. Uluslararası indekslerde ve veritabanında, derginin adı The Journal of Pediatric Research, İngilizce kısaltması J Pediatr Res olarak kaydedilmiştir.

Dergiye kabul edilen eserlerin özgün ve daha önceden başka ortamlarda yayınlanmamış olması esas alınır. Yayın için dergiye yollanan her yazı hakem değerlendirmesine gönderilir. Yazarlar 6 hafta içinde süreçle ilgili haberdar edilir. Değerlendirme sonucunda basılması kabul edilen yazılar dergide basılır ve dergi web sayfası olan http://www.jpedres.org adresinde yayınlanır.

Yazıların bilimsel ve etik sorumlulukları yazarlara, telif hakkı ise JPR'ye aittir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur. Yazarlar, yayın haklarının devredildiğini belirten onay belgesini (Yayın Hakları Devir Formu) yazıları ile birlikte göndermelidirler. Bu belgenin tüm yazarlar tarafından imzalanarak dergiye gönderilmesi ile birlikte yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermiş, bilimsel katkı ve sorumluluklarını beyan etmiş sayılırlar.

Dergiye yayımlanmak üzere gönderilen tüm yazılar 'iThenticate' programı ile taranarak intihal kontrolünden geçmektedir. İntihal taraması sonucuna göre yazılar red ya da iade edilebilir.

The Journal of Pediatric Research'te yayınlanmak amacıyla gönderilen ve etik kurul onayı alınması zorunluluğu olan deneysel, klinik ve ilaç araştırmaları için uluslararası anlaşmalara ve 2013'te gözden geçirilmiş Helsinki Bildirisi'ne uygun etik kurul onay raporu gereklidir (http://www.wma.net/en/30publications/10policies/b3/). Etik kurul onayı ve "bilgilendirilmiş gönüllü onam formu" alındığı araştırmanın "Gereç ve Yöntem" bölümünde belirtilmelidir. Deneysel hayvan çalışmalarında ise yazarlar, "Guide for the care and use of laboratory animals" (http://oacu.od.nih.gov/regs/guide/guide.pdf) doğrultusunda hayvan haklarını koruduklarını belirtmeli ve kurumlarından etik kurul onay raporu almalıdır.

Yayın, direkt ya da indirekt ticari bağlantı içeriyorsa veya çalışmaya materyal desteği veren bir kuruluş varsa, yazarlar kullanılan ticari ürün, ilaç, firma vs. ile ticari hiçbir ilişkisinin olmadığını ya da var ise nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar), editöre sunum sayfasında belirtmek zorundadır.

Araştırmalara yapılan her türlü yardım ve diğer desteklerin alındığı kişi ve kuruluşlar beyan edilmeli ve çıkar çatışmasıyla ilgili durumları açıklamak amacıyla Çıkar Çatışmaları Bildirim Formu doldurulmalıdır.

Tüm yazılar, editör ve editör yardımcıları ile danışman hakemler tarafından incelenir.

The Journal of Pediatric Research bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan süreli bir yayın organıdır. Hakemler, yazının konusuyla ilgili uluslararası literatürde yayınları ve atıfları olan bağımsız uzmanlar arasından seçilmektedir. Makale baş editöre ulaşınca değerlendirmeye alınır ve bölüm editörüne gönderilir. Bölüm editörü ilk değerlendirmeyi takiben makaleyi hakemlere gönderir. Hakemler 21 gün içinde kararlarını bildirmelidirler. Bölüm editörü hakem kararlarına kendi değerlendirme ve önerisini ekleyerek baş editöre gönderir ve son kararı hakemlerin görüşleri doğrultusunda bölüm editörü verir. Hakemlerin kararları birbirleriyle çelişkili ise dergi editörü gerektiğinde yeni hakem atayabilir.

Dergide yayınlanacak yazıları değerlendiren hakemler dergide belirtilen danışmanlar ve gerekirse yurt içi/dışı konu ile ilgili uzmanlar arasından seçilir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör, editör yardımcıları, biyoistatistik uzmanı ve İngilizce dil uzmanının düzeltme yapmalarını kabul etmiş sayılır.

İncelemeye sunulan araştırmada olası bir bilimsel hata, etik ihlal şüphesi veya iddiasıyla karşılaşılırsa, bu dergi verilen yazıyı destek kuruluşların veya diğer yetkililerin soruşturmasına sunma hakkını saklı tutar. Bu dergi sorunun düzgün biçimde takip edilmesi sorumluluğunu kabul eder ancak gerçek soruşturmayı veya hatalar hakkında karar verme yetkisini üstlenmez.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2016, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır:

Araştırma makalelerinin hazırlığında sistematik derlemeler ve meta analizler için aşağıdaki tasarım klavuzları:Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097) (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting "Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12).

GENEL KURALLAR

Yazılar sadece çevrim-içi olarak kabul edilmektedir. Yazarların makale gönderebilmesi için Journal Agent web sayfasına (http://www.journalagent.com/jpr/) kayıt olup, şifre almaları gerekmektedir. Bu sistem çevrim-içi yazı gönderilmesine ve değerlendirilmesine olanak tanımaktadır. Bu sistem ile toplanan makaleler Web of Science-Emerging Sources Citation Index (ESCI), Directory of Open Access Journals (DOAJ), EBSCO,

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Sayfa düzeni: Özgün Araştırmalar, klinik araştırma, klinik gözlem, yeni teknikler, deneysel ve laboratuvar çalışmalarını kapsar. Özgün araştırmalar, başlık, özet, yazının ana konusu ile ilgili anahtar kelimeler, giriş, gereç ve yöntem, bulgular, tartışma, teşekkür, kaynaklar, tablolar, resimler bölümlerini içermelidir. Özet bölümü, "Öz" başlığı ile yazılmalıdır. Metin "Times New Roman" yazı stili, 12 punto, 1,5 satır aralığı ile yazılmalıdır. Metnin tümü 2500 kelimeyi geçmemelidir. Olgu Sunumları, nadir görülen ya da tanı ve tedavide farklılık gösteren, mevcut bilgilerimize katkıda bulunan, eğitici olguyu/olguları içermeli, giriş, olgu sunumu, tartışma bölümlerini kapsamalıdır. Metnin tümü 1500 kelimeyi geçmemelidir. Derlemeler güncel bir konuyu, bağımsız, literatür bilgisini de içerecek şekilde derinlemesine inceleyen yazılardır. Metnin tümü 18 adet A4 sayfasını geçmemelidir. Editöre Mektuplar yayınlanmış makaleler hakkında ya da güncel pediatrideki gelişmeleri içeren 1000 kelimeyi geçmeyen ve kaynak belirten yazılar olmalıdır. Özet bölümü içermez. Kaynak sayısı 5 ile sınırlıdır.

Kısaltmalar: Kelimenin ilk geçtiği yerde parantez içinde ve tüm metin boyunca kullanılır. Uluslararası kullanılan kısaltmalar için "Bilimsel Yazım Kuralları" kaynağına başvurulabilir.

Editöre sunum sayfası: Gönderilen makalenin kategorisi, daha önce başka bir dergiye gönderilmemiş olduğu, var ise çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu kuruluşların yazarlarla ilişkileri, makale İngilizce ise; İngilizce yönünden kontrolünün ve araştırma makalesi ise biyoistatistiksel kontrolünün yapıldığı belirtilmelidir.

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Kaynakların gerçekliğinden yazarlar sorumludur.

Metin içinde: Kullanılan kaynaklar, ilgili cümlenin içinde veya sonunda parantez içinde belirtilmelidir. Eğer, kullanılan kaynağın yazar/yazarları cümle başında belirtiliyorsa, kaynak isimden hemen sonra gelecek şekilde parantez içi olarak yazılmalıdır. Tüm yazılarda Türk yazarlarca yapılmış yerli veya yabancı yayınların kullanılmasına özellikle dikkat edilmeli ve Türkçe dil kurallarına uyulmasına özen gösterilmelidir.

Kongrelerde sunulan bildiriler, basılmamış yayınlar, tezler, internet kaynaklı adresler, kişisel görüşme ya da deneyimler kaynak olarak belirtilmemelidir. Adı geçen kaynaklardan bahsedilmek isteniyorsa, yazıda geçtiği cümlenin sonunda kaynak numarası belirtilmeden, açık yazı ile parantez içine alınarak kaynağın niteliği belirtilmelidir.

Kaynaklar bölümünde: Kaynaklar metin içerisinde geçiş sırasına göre Arap rakamları ile numaralandırılmalıdır. Kaynaklarda tüm yazarlar belirtilmelidir. Ancak yazar sayısı 6'dan fazla olan çalışmalarda ilk 3 yazarın adı yazılmalı, daha sonra Türkçe makalede (ve ark.), İngilizce makalede (et al.) eki yapılmalıdır. Dergilerin isimleri Index Medicus'ta kullanılan stillere göre kısaltılmalıdır.

Kaynak yazılımı için örnekler:

Dergi: Yazar(lar)ın soy isim(ler)i ve yazar isim(ler)inin ilk harfi, makale başlığı, dergi adı (dergide belirtilen orijinal kısaltması), yıl, cilt ve sayfa numaraları.

Örnek: Koening JQ. Air pollution and asthma. J Allergy Clin Immunol 1999;104:717-22.

Kitap: Yazar(lar)ın soy isim(ler)i ve yazar isim(ler)inin ilk harfi, bölüm başlığı, editörün(lerin) ismi, kitap ismi, kaçıncı baskı olduğu, basıldığı şehir, basım yeri, yayınevi, basım yılı ve sayfa numaraları.

Örnek: Fletcher CDM, Unni KK, Mertens F. Genetics of Tumours of Soft Tissue and Bone. Lyon, France, IARC Press, 2002. p. 225-419.

Kitap bölümü: Yazar(lar)ın soy isim(ler)i ve yazar isim(ler)inin ilk harfi, bölüm ve kısım, editörün(lerin) ismi, kitap adı, basım yeri, yayınevi adı, basım yılı, sayfa numaraları.

Örnek: Whitsett JA, Pryhuber GS, Rice WR. Acute respiratory disorders. In: Avery GB, Mac- Donald MG (eds). Neonatology: Pathophysiology and Management of the Newborn, 5th ed. Philadelphia, Lippincott Williams&Wilkins, 1999;505-15.

RESİM, TABLO, GRAFİK VE ŞEKİLLER

Tüm görsel materyaller metnin sonunda ayrı birer sayfa olarak hazırlanmalıdır. Şekil, resim, tablo ve grafiklerin açıklamaları makale sonuna eklenmelidir. Orijinal filmler, EKG kayıtları gibi belgeler kesinlikle yollanmamalıdır. Renkli resimlerin masrafları yazarlar tarafından bizzat karşılanacaktır.

Resimler: Resimlere metindeki geçiş sırasına göre numara verilmeli ve kısa birer başlık yazılmalıdır. Başka bir yayından alıntı yapılıyorsa yazılı baskı izni birlikte yollanmalıdır. Fotoğrafların ayrıntıları seçilmeli, JPEG formatında ve en az 300 dpi (çözünürlük) olarak kaydedilmelidir.

Tablolar, Grafikler, Şekiller: Tüm tablolara, grafiklere ve şekillere metinde geçiş sırasına göre numara verilmeli ve kısa birer başlık yazılmalıdır. Tablolar yazıda geçiş sıralamasına göre Romen rakamlarıyla (I, II) sıralandırılmalı ve başlık taşımalıdır. Şekiller geçiş sıralamasına göre Arap harfleri (1,2) ile sıralanmalıdır. Kullanılan kısaltmalar alt kısımda mutlaka açıklanmalıdır. Özellikle tablolar metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır. Olgu sunumlarında en çok 2 şekil veya resim kullanılmalıdır.

BİYOİSTATİSTİK

Araştırma bulgularının denetlenebilirliğini sağlamak için, araştırma düzeni, örneklem, yöntem, bilimsel yaklaşımlar ve uygulamalar tanımlanarak kaynakları sunulmalıdır.

Anlamlılık sınırı olarak seçilen "p" değeri ile birlikte uygun hata ve belirsizlik payları (güven aralıkları, vs) belirtilmelidir. Kullanılan istatistiksel terimler, kısaltmalar ve semboller tanımlanmalı, kullanılan yazılım (software) belirtilmelidir. İstatistik terminolojisi (random, signifikant, korelasyon, vs.) istatistik dışı anlamlarda kullanılmamalıdır.

Verilerin ve analizin tüm sonuçları tablo, şekil veya grafik olarak "Bulgular" bölümünde, kullanılan biyoistatistiksel yöntemler ve uygulama ayrıntıları yazının "Gereç ve Yöntem" bölümünde veya ayrı bir başlık altında sunulmalıdır.

YAZI ÇEŞİTLERİ

Özgün Araştırmalar

Klinik araştırma, klinik gözlem, yeni teknikler, deneysel ve laboratuvar çalışmalarını kapsar. Özgün araştırmalar; başlık, özet, yazının ana konusu

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Yazarlara Bilgi

ile ilgili anahtar kelimeler, giriş, gereç ve yöntem, bulgular, tartışma, çalışmanın kısıtlılıkları, sonuç, teşekkür, kaynaklar, tablolar, grafikler, resimler bölümlerini içermelidir. Başlık, özet ve anahtar kelimeler Türkçe ve İngilizce olarak yazılmalıdır. Makale yukarıda belirtilen yazım kuralları ile yazılı 16 A4 sayfasını aşmamalıdır.

Başlık sayfası: Makalenin başlığı, kısa başlık, yazar isimleri ve yazar bilgilerini kapsayan sayfadır. Sırasıyla şu tanımlar yapılmalıdır;

1. Makalenin başlığı (Türkçe ve İngilizce) mümkün olduğunca kısa ve açıklayıcı olmalı, boşluklar dahil 135 karakteri geçmemeli, kısaltma içermemelidir.

2. Kısa başlık (Türkçe ve İngilizce), en fazla 60 karakterden oluşmalıdır.

3. Yazar isimleri (yazarların isimleri tam olarak kısaltılmadan yazılmalıdır, yazarın akademik görevi yazılmamalıdır) ve bağlı bulunduğu kurumlar.

4. İletişim kurulacak yazarın ismi, adresi, telefon ve faks numarası ile e-posta bilgileri.

5. Bilimsel toplantılarda sunulan ve özeti kongre kitabında yer almış eserlerin toplantı yeri ve tarihi.

Öz: Yazının ana hatlarını içeren, en fazla 200 kelimeden oluşan öz Türkçe ve İngilizce olarak hazırlanmalıdır. Öz bölümünde kaynak gösterilmemeli, kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.

Araştırma makalelerinde öz 5 alt başlık olarak hazırlanmalıdır:

Amaç: Çalışmanın amacı açıkça belirtilmelidir.

Gereç ve Yöntemler: Çalışma tanımlanmalı, standart kriterleri, randomize olup olmadığı, retrospektif veya prospektif olduğu ve varsa istatistiksel yöntem belirtilmelidir.

Bulgular: Çalışmanın detaylı sonucu verilmeli, istatistik anlamlılık derecesi belirtilmelidir.

Sonuç: Çalışmanın sonuçlarını yansıtmalı, klinik uygulanabilirliği tanımlamalı, olumlu ve olumsuz yönleri gösterilmelidir.

Anahtar Kelimeler: En az 3, en çok 5 anahtar kelime özetin sonunda yer almalıdır. İngilizce anahtar kelimeler "Medical Subject Headings'e (MESH) uygun olarak verilmelidir (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler ise MESH terimlerinin aynen çevirisi olmalıdır. Anahtar kelimeler uygun nitelikte ve standart terminolojide yazılmalıdır. Türkçe anahtar kelimeler "Türkiye Bilim Terimleri" arasından seçilmelidir. Yazarlar bilgilendirme için http://www.bilimterimleri.com adresini kullanabilir.

Araştırma makalelerinde ana metin aşağıdaki başlıkları içermelidir;

Giriş: Konu hakkında kısa ve öz bilgi verilmeli, çalışmanın amacı belirtilmeli, bunlar literatür bilgisi ile desteklenmelidir.

Gereç ve Yöntem: Çalışma planı verilmeli, randomize olup olmadığı, retrospektif veya prospektif olduğu, denek sayısı, özellikleri, çalışmaya dahil edilme ve dışlanma kriterleri, kullanılan istatistiksel yöntem belirtilmelidir.

Bulgular: Elde edilen sonuçlar belirtilmeli, tablo ve resimler numara sırasıyla verilmeli, sonuçlar uygulanan istatistiki analiz yöntemine göre değerlendirilmelidir. Görsel materyallerin yazım kuralları hakkında gerekli bilgi "Genel Kurallar" başlığı altında bulunan "Resim, Tablo, Grafik ve Şekiller" bölümünde bulunmaktadır.

Tartışma: Elde edilen değerler olumlu ve olumsuz yönleriyle tartışılmalı, literatür ile karşılaştırılmalı, çalışmadan elde edilen sonuç vurgulanmalıdır.

Sonuç: Çalışmadan elde edilen sonuç vurgulanmalıdır.

Teşekkür: Her türlü çıkar çatışması, finansal destek, bağış ve diğer editöryal (istatistik analiz, İngilizce/Türkçe değerlendirme) ve/veya teknik yardım var ise metnin sonunda sunulmalıdır.

Kaynaklar: Kaynakların gerçekliğinden yazarlar sorumludur. Kaynakların yazım kuralları hakkında gerekli bilgi "Genel Kurallar" başlığı altında bulunan "Kaynaklar" bölümünde bulunmaktadır.

Olgu Sunumları

Nadir görülen, tanı ve tedavide farklılık gösteren, mevcut bilgilerimize yenilerini ekleyip, katkı sağlayan olguları içermelidir. Türkçe ve İngilizce başlık, 50 kelimeyi aşmayan, yapılandırılmamış özet ve anahtar kelimeler ilk sayfada yer almalıdır. Sunum metni, giriş, olgu sunumu, tartışma ve kaynaklardan oluşmalıdır. Metnin tümü yukarıda bahsedilen yazım kuralları çerçevesinde 1500 kelimeyi geçmemelidir. Olgu sunumları için en fazla 10 kaynak kullanılmalıdır.

Derlemeler

Bir bilgi ya da konunun klinikte kullanılması için vardığı son düzeyi anlatan, tartışan, değerlendiren ve gelecekte yapılacak olan çalışmalara yön veren bir formatta hazırlanmalıdır. **Dergi yalnızca davetli derleme kabul eder ve yayınlar.** Derleme başvurusu yapılmadan önce konunun editör ile görüşülmesi önerilir.

Güncel bir konuyu, bağımsız, hiçbir farklı görüşü öne çıkarmadan derinlemesine inceleyen yazılardır. Yazının ilk bölümünde Türkçe ve İngilizce başlık, özet, anahtar kelimeler bulunmalıdır. Özet bölümü yapılandırılmamalıdır. Konuda geçen her alıntının kaynağı mutlak gösterilmelidir. Tümü 18 A4 sayfayı geçmemelidir.

Editöre Mektuplar

Yayınlanmış makaleler hakkında ya da güncel pediatrideki, bilimsel ve sosyal yönden irdeleyen veya özellikle The Journal of Pediatric Research Dergisi'nde yayınlanan yazılarla ilgili soru veya katkı içerikli 1000 kelimeyi geçmeyen ve kaynak belirten yazılar olmalıdır. Başlık ve özet bölümleri içermez. Kaynak sayısı 5 ile sınırlıdır.

REKLAMLAR

Reklamlar için Editör ile görüşülmelidir. Derginin dış ve iç kapakları ile iç sayfalarında renkli reklam yayınlanması mümkündür.

YAYIN HAKKI

Derginin her türlü yayın hakkı söz konusu kurumlara aittir.

The Journal of Pediatric Research, Ege Çocuk Vakfı (EÇV) tarafından desteklenen, Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı'nın yayın organıdır.

YAZIŞMA

Prof. Dr. Özgür Çoğulu

The Journal of Pediatric Research

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Intructions to Authors

The Journal of Pediatric Research is an official peer-reviewed publication of Ege University Faculty of Medicine, Department of Pediatrics and Ege Children's Foundation. This publication organ is responsible for the issue of unique clinical and laboratory research papers, case reports, reviews directly or indirectly related to children's health and diseases. The publication language of the journal is English.

The Journal of Pediatric Research does not charge any article submission or processing charges.

The abbreviation of The Journal of Pediatric Research is JPR, however, it should be denoted as J Pediatr Res when referenced. In the international index and database, the name of the journal has been registered as The Journal of Pediatric Research and abbreviated as J Pediatr Res.

A manuscript will be considered only with the understanding that it is an original contribution that has not been published elsewhere. All manuscripts submitted to the journal for publication are peer-reviewed. Authors shall be informed within a period of 6 weeks about the process. Upon review, those manuscripts, which are accepted, shall be published in the journal and issued on the http://www.jpedres.org official internet address.

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All manuscripts submitted to the The Journal of Pediatric Research are screened for plagiarism using the 'iThenticate' software. Results indicating plagiarism may result in manuscripts being returned or rejected.

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Authors must provide disclosure/acknowledgment of financial or material support, if any was received, for the current study.

If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the cover letter that they have no relationship with the commercial product, drug, pharmaceutical company, etc. concerned; or specify the type of relationship (consultant, other agreements), if any.

Authors must provide a statement on the absence of conflicts of interest among the authors and provide authorship contributions.

The Journal of Pediatric Research is an independent international journal based on double-blind peer-review principles. The manuscript is assigned to the Editor-in-Chief, who reviews the manuscript and makes an initial decision based on manuscript quality and editorial priorities. Manuscripts that pass initial evaluation are sent for external peer review, and the Editor-in-Chief assigns an Associate Editor. The Associate Editor sends the manuscript to reviewers (internal and/or external reviewers). The reviewers must review the manuscript within 21 days. The Associate Editor recommends a decision based on the reviewers' recommendations and returns the manuscript to the Editor-in-Chief. The Editor-in-Chief makes a final decision based on editorial priorities, manuscript quality, and reviewer recommendations. If there are any conflicting recommendations from reviewers, the Editor-in-Chief can assign a new reviewer.

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, selected from national and international authorities. The Editor-in-Chief, Associate Editors, biostatistics expert and English language consultant may make minor corrections to accepted manuscripts that do not change the main text of the paper.

In case of any suspicion or claim regarding scientific shortcomings or ethical infringement, the Journal reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. The Journal accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

GENERAL GUIDELINES

Manuscripts can only be submitted electronically through the Journal Agent website (http://journalagent.com/tjo/) after creating an account. This system allows online submission and review.

The manuscripts are archived according to Web of Science-Emerging Sources Citation Index (ESCI), Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, ProQuest, Index Copernicus, Tübitak/Ulakbim TR Index, TurkMedline and Turkiye Citation Index.

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The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be created at http://orcid.org.

Format: Unique research papers cover clinical research, observational studies, novel techniques, and experimental and laboratory studies. Unique research papers shall consist of a heading, abstract, keywords related to the main topic of the paper, introduction, materials and methods, results, discussion, acknowledgements, bibliography, tables and figures. Manuscripts should be prepared using 12 pt "Times New Roman" and 1.5 line spacing. The text shall not exceed 2500 words. Case reports must contain rare cases or those that are unique in diagnosis and treatment, those which contribute to current knowledge and provide educational information, along with the introduction, case reporting and discussion sections. The whole text must not exceed 1500 words. Reviews are texts in which a current subject is examined independently, with reference to scientific literature. The whole text must not exceed 18 A4 paper sheets. Letters to the Editor must be manuscripts, which do not exceed 1000 words, with reference to scientific literature, and those written in response to issued literature or those, which include development in the field of pediatrics. These manuscripts do not contain an abstract. The number of references is limited to 5.

Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

Cover letter: The cover letter should include statements about manuscript type, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipment (if applicable), approval of language for articles in English and approval of statistical analysis for original research articles.

REFERENCES

Authors are solely responsible for the accuracy of all references.

In-text citations: References shall be listed as the below formats on a separate page according to their sequence within the text and referred to within the text in parentheses.

Presentations presented in congresses, unpublished manuscripts, theses, Internet addresses, and personal interviews or experiences should not be indicated as references. If such references are used, they should be indicated in parentheses at the end of the relevant sentence in the text, without reference number and written in full, in order to clarify their nature. In all manuscripts, care must be given to the inclusion of references related to domestic and international studies performed by Turkish authors and compliance to Turkish written language rules.

References section: All author names shall be stated within all references. References shall be listed as the below formats on a separate page according to their sequence within the text and referred to within the text in parentheses. However, in studies where author numbers exceed 6, names of the first 3 authors shall be stated; "ve ark." and "et al." additions shall be made to the list of authors in Turkish and English references, respectively. The titles of journals should be abbreviated according to the style used in the Index Medicus.

Reference Format

Journal: Last name(s) of the author(s) and initials, article title, publication title and its original abbreviation, publication date, volume, the inclusive page numbers.

Example: Koening JQ. Airpollutionandasthma. J Allergy Clin Immunol 1999; 104:717-22.

Book: Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the extract cited.

Example: Fletcher CDM, Unni KK, Mertens F. Genetics of Tumours of Soft Tissue and Bone. Lyon, France, IARC Press, 2002. p. 225-419.

Book Chapter: Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the cited piece.

Example: Whitsett JA, Pryhuber GS, Rice WR. Acuteres piratory disorders. In: Avery GB, Mac- Donald MG (eds). Neonatology: Pathophysiology and Management of the Newborn, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 1999;505-15.

TABLES, GRAPHICS, FIGURES, AND IMAGES

All visual materials together with their legends should be located on separate pages that follow the main text. Original documents such as films, ECG records must not be delivered. All cost related to colored printouts shall be covered by the authors' own expenses.

Images: Images (pictures) should be numbered and include a brief title. Permission to reproduce pictures that were published elsewhere must be included. All pictures should be of the highest quality possible, in JPEG format, and at a minimum resolution of 300 dpi.

Tables, Graphics, Figures: All tables, graphics or figures should be enumerated according to their sequence within the text and a brief descriptive caption should be written. Tables shall be numbered by Roman numerals (I, II) according to their sequence, and shall include a heading. Figures shall be numbered by Arabic numerals (1,2) according to their sequence. Any abbreviations used should be defined in the accompanying legend. Tables in particular should be explanatory and facilitate readers' understanding of the manuscript, and should not repeat data presented in the main text. A maximum of 2 figures or photographs shall be added to case reports.

BIOSTATISTICS

To ensure controllability of the research findings, the study design, study sample, and the methodological approaches and applications should be explained and their sources should be presented.

The "p" value defined as the limit of significance along with appropriate indicators of measurement error and uncertainty (confidence interval, etc.) should be specified. Statistical terms, abbreviations and symbols used in the article should be described and the software used should be defined. Statistical terminology (random, significant, correlation, etc.) should not be used in non-statistical contexts.

All results of data and analysis should be presented in the Results section as tables, figures and graphics; biostatistical methods used and application details should be presented in the Materials and Methods section or under a separate title.

MANUSCRIPT TYPES

Original Articles

Unique research papers cover clinical research, observational studies, novel techniques, and experimental and laboratory studies. Unique research papers shall consist of a heading, abstract, keywords related to the main topic of the paper, introduction, materials and methods, results, discussion, acknowledgements, bibliography, tables and figures. The text shall not exceed 2500 words. Case reports must contain rare cases or those that are unique in diagnosis and treatment, those which contribute to current knowledge and

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provide educational information, along with the introduction, case reporting and discussion sections. The whole text must not exceed 1500 words. Reviews are texts in which a current subject is examined independently, with reference to scientific literature. The whole text must not exceed 18 A4 paper sheets. Letters to the Editor must be manuscripts, which do not exceed 1000 words, with reference to scientific literature, and those written in response to issued literature or those, which include development in the field of pediatrics. These manuscripts do not contain an abstract. The number of references is limited to 5.

Title Page: This page should include the title of the manuscript, short title, name(s) of the authors and author information. The following descriptions should be stated in the given order:

1. Title of the manuscript (Turkish and English), as concise and explanatory as possible, including no abbreviations, up to 135 characters

2. Short title (Turkish and English), up to 60 characters

3. Name(s) and surname(s) of the author(s) (without abbreviations and academic titles) and affiliations

4. Name, address, e-mail, phone and fax number of the corresponding author

5. The place and date of scientific meeting in which the manuscript was presented and its abstract published in the abstract book, if applicable

Abstract: A summary of the manuscript should be written in both Turkish and English. References should not be cited in the abstract. Use of abbreviations should be avoided as much as possible; if any abbreviations are used, they must be taken into consideration independently of the abbreviations used in the text.

For original articles, the structured abstract should include the following sub-headings:

Aim: The aim of the study should be clearly stated.

Materials and Methods: The study and standard criteria used should be defined; it should also be indicated whether the study is randomized or not, whether it is retrospective or prospective, and the statistical methods applied should be indicated, if applicable.

Results: The detailed results of the study should be given and the statistical significance level should be indicated.

Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

Keywords: A list of minimum 3, but no more than 5 key words must follow the abstract. Key words in English should be consistent with "Medical Subject Headings (MESH)" (www.nlm.nih.gov/mesh/MBrowser.html). Turkish key words should be direct translations of the terms in MESH.

Original research articles should have the following sections:

Introduction: Should consist of a brief explanation of the topic and indicate the objective of the study, supported by information from the literature.

Materials and Methods: The study plan should be clearly described, indicating whether the study is randomized or not, whether it is retrospective or prospective, the number of trials, the characteristics, and the statistical methods used.

Results: The results of the study should be stated, with tables/figures given in numerical order; the results should be evaluated according to the statistical analysis methods applied. See General Guidelines for details about the preparation of visual material.

Discussion: The study results should be discussed in terms of their favorable and unfavorable aspects and they should be compared with the literature. The conclusion of the study should be highlighted.

Study Limitations: Limitations of the study should be discussed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article.

References: Authors are responsible for the accuracy of the references. See General Guidelines for details about the usage and formatting required.

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Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in Turkish and English, an unstructured summary not exceeding 50 words, and key words. The main text should consist of introduction, case report, discussion and references. The entire text should not exceed 1500 words (A4, formatted as specified above). A maximum of 10 references shall be used in case reports.

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JPR
The Journal of Pediatric Research
Official Journal of Ege University Children's Hospital

Contents / İçindekiler

The
Journal of Pediatric Research

Official Journal of Ege University Children's Hospital

Editorial / Editörden

Değerli Okurlar,

Elinizde tuttuğunuz sayı dergimizin 2017 yılına ait son karma (Türkçe ve İngilizce) sayısıdır. Bu sayı ile dergimizin geçiş dönemi tamamlanmış olacaktır. Devamında, 2018 için Science Citation Index-Expanded ve 2019 için PubMed gibi indekslerce taranmayı hedefliyoruz. Bu doruklara, hep birlikte siz okurlar, yazarlar, hakemlerimiz ile birlikte emek ve azimle ulaşacağımıza inanıyoruz. The Journal of Pediatric Research (JPR) ailesini ayakta tutan ve yükselten "takım ruhudur"; bu takım ruhu ki size hastaların tanısını koyduran; ekip çalışması yaptıran ve devamında bizlerle paylaşmayı sağlayandır.

Sizlere bu sayıda dört farklı konuda derleme sunuyoruz: Turner sendomu; ilaç dışı zehirlenmeler; yenidoğan taramaları ve süperior mezenterik arter sendromu. Gurur duyarak ülkemizin değişik yerlerinde yapılmış 8 adet araştırmayı beğeninize takdim ediyoruz. Hep birlikte çocukluk çağı alt solunum yolu enfeksiyonlarında idrarda amino-terminal pro-brain natriüretik peptid ölçümünün klinik şiddetinin bir göstergesi olup/olmadığını; günübirlik laparoskopik kolesistektomiyi etkileyen faktörler nelerdir; talasemik çocuklar hangi endokrin problemler ile karşılaşır ve çocuklarda nöbet öz-yeterlik ölçeğinin doğrulayıcı ve açıklayıcı faktörleri nelerdir sorularının yanıtını aramaya davet ediyoruz.

Sevgili okurlar, bildiğiniz gibi 1-30 Kasım arası prematüre bebek farkındalık ayı olarak ilan edilmesi nedeni ile biz de dergimizde bu konuyu irdeleyen üç güzel araştırmayı sizinle paylaşmak istedik: "Prematürite ve sorunları konusunda farkındalık düzeyinin değerlendirilmesi"; "Kritik hasta yenidoğanların annelerinde ardışık ve eş zamanlı süt sağmanın etkinlik ve konforu" ve "Pediatrik Periferal İntravenöz Ölçeği'nin Türkçe güvenirliği ve yenidoğana uyarlanması". Ayrıca, iki yenidoğan-prematür olgu örneği (iboprofen sonrası gelişen spontan intestinal perforasyon ve subgrup uyuşmazlığı olan olgu) ile de bu konuyu vurgulamak istedik.

Son olarak iki eğitici olgu ile "gastrik by-pass cerrahisi sonrası gelişen polinöropati" ve "diazoksit yanıtsız hiperinsülinemik hipoglisemili" ile sayımızı tamamladık.

Keyifli okumalar sevgili okurlar…

Bir başka JPR sayısında siz sevgili yazarlarımız, değerli hakemlerimiz, çalışkan editörlerimiz ve özverili Galenos yayınevi çalışanları ile yeniden buluşmak dileğiyle;

Sevgi ve JPR dergisi ile kalın!

Prof. Dr. Sema Kalkan Uçar

Editör

J Pediatr Res 2017;4(4):171-5
DOI: 10.4274/jpr.35744

Review / Derleme

Turner Syndrome and Its Variants

Turner Sendromu ve Varyantları

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ABSTRACT

Turner syndrome (TS) is a genetic disorder which is characterized by the complete or partial absence of the X chromosome. The incidence is 1/2500 female live births. The main clinical findings are short stature, primary amenorrhea and infertility, and phenotypical features include webbed neck, a low posterior hairline, cubitus valgus and shortening of the fourth metacarpal. While 1% of all still births have 45,X monosomy, this rate has been reported to be approximately 10% in spontaneous abortions. The karyotype is determined as 45,X in about half of the patients. Therefore, most of the TS fetuses are considered to end in spontaneous abortion and only mosaic cases survive to term. Isochromosome Xq is the most common structural rearrangement of the X chromosome. Furthermore, ring X chromosome, deletions and Y chromosome abnormalities can be detected in patients with TS.

Keywords: Turner syndrome, mosaicism, isochromosome, ring chromosome, short stature

ÖZ

Turner sendromu (TS), X kromozomunun tamamen ya da parsiyel olarak yokluğu sonucu oluşan genetik bir bozukluktur. Canlı doğan kız çocuklarındaki sıklık 1/2500 olarak bildirilmektedir. Kısa boy, primer amenore ve infertilite gibi klinik bulgularla birlikte hastalarda boyunda yelelenme, düşük ense saç çizgisi, kubitus valgus, kısa 4. metakarpal kemik gibi fenotipik özellikler görülebilir. Ölü doğumların %1'inde 45,X monozomisi saptanırken, bu oran spontan düşüklerde yaklaşık olarak %10 olarak bildirilmektedir. Hastaların %50'sinde karyotip 45,X monozomisi şeklindedir. Ancak bu karyotipe sahip TS'li olguların çoğu fetal dönemde spontan düşükle sonlanmakta olup hayatta kalanların ise mozaik oldukları düşünülmektedir. En sık görülen yapısal X kromozomu anomalisi ise izokromozom Xq'dur. Ayrıca halka kromozom, delesyonlar gibi X kromozomunun yapısal anomalileri ile birlikte hastalarda Y kromozomuna ait patolojiler de saptanabilir.

Anahtar Kelimeler: Turner sendromu, mozaiklik, izokromozom, halka kromozom, kısa boy

Introduction

Turner syndrome (TS) is a genetic disorder that was first described by Turner (1) in 1938, and is the result of the complete or partial absence of the X chromosome.

TS is one of the most common chromosomal abnormalities among female live births with an estimated frequency of 1/2500 (2). Clinical findings include short stature, primary amenorrhea, infertility and characteristic stigmatas. The phenotypic features are low nuchal hair line, low-set ears, small mandibula, cubitus valgus, nail hypoplasia, high palate, swelling of the hands and feet in the neonatal period, short 4th metacarpal bone, discrete nipples and wide thoracic cage. Cardiac and renal anomalies, hypothyroidism, hearing and vision disorders, gastrointestinal and dermatological problems and neoplasms may also been seen in TS (3). Although some of the patients may be diagnosed at birth due to the presence of dysmorphic findings, diagnosis is delayed until childhood, adolescence or later. Intelligence is generally not affected. However, learning difficulties that affect nonverbal, perceptual, motor and visuo-spatial skills can be seen in 70% of the patients (4). In a recent study the authors compared TS patients with healthy individuals and suggested that verbal and nonverbal cognitive impairment may be due to anomalies in gray matter development (5).

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Received/Geliş tarihi: *21.11.2015* **Accepted/Kabul tarihi:** *21.12.2015*

Approximately 50% of TS patients have 45,X karyotype and the most common structural X chromosome abnormality is isochromosome Xq. The retained X chromosome is maternally derived in two thirds of the patients. The patients with 46,XY cell line mosaicism or structural rearrangement of the Y chromosome mostly have masculinized external genitalia and are at increased risk of developing gonadoblastoma and other gonadal tumors, whereas patients with mosaic 46,XX karyotype or isochromosome Xq have a milder phenotype (6).

TS with 45,X karyotype has been observed in 1-2% of human conceptions, 10% of first trimester pregnancy losses and 1% of stillbirths. More than 99% of 45,X fetuses end with abortion, typically by the 28th week of gestation, which suggests that living 45,X individuals must have mosaicism for another cell line (7,8). The etiology includes pre and post-conceptional errors, as well as meiotic non-disjunction and anafase lag.

The pseudoautosomal regions (PAR) of X and Y chromosomes are both necessary for normal development. It has been reported that haplo-insufficiency in the *CSF2RA* gene located in the PAR1 region, which plays a role in normal placental development, is responsible for high mortality in 45,X karyotype embryos (9,10). Recently, it has been suggested that all living patients in whom TS with 45,X karyotype has been diagnosed, are cryptic mosaics. Loss of X chromosome in these embryos frequently result in mitotic error, but it has been reported that this loss may occur at various stages of postfertilization (11).

The diagnosis is made by karyotype analysis of peripheral blood which shows the numerical and/or structural abnormalities of the X chromosome. However, mosaicism can be better defined in approximately 30% of non-mosaic patients by increasing the number of cells examined in the karyotype analysis, evaluating additional tissue samples or using fluorescence in situ hybridization method (12). In this review, we aimed to evaluate the phenotypical characteristics, clinical variability and the responsible genes of TS and its variants, and provide a general approach to patients with suspected TS.

Turner Syndrome with Structural Abnormalities of the X Chromosome

Isochromosome X [46,X,i(X)]

Isochromosome is a structural chromosomal aberration consisting of two short arms or two long arms, which are derived by centromere division. The most common structural abnormality of X chromosome is 46,X,i(Xq). The frequency of isochromosome was reported to be 15-18% in TS cases with or without mosaicism (13). Short stature, which is one of the most frequently observed clinical features, can be explained by *SHOX* haplo-insufficiency (14). Therefore, while short stature is more frequently present in patients with 46,X,i(Xq) karyotype, gonadal dysfunction is more likely to be seen in patients with 46,X,i(Xp) karyotype, which is a very rare entity.

The incidence of autoimmune thyroid disease in TS increases with advanced age. Recently, a twofold increase in the prevalence of autoimmune thyroid disease has been observed from the first to the third decade of life in patients with the isochromosome karyotype (15). In addition, patients with 45,X or 46,X,i(Xq) karyotype carry a higher risk of developing hearing loss when compared to patients with mosaic karyotypes. A linear relationship was also found between age and hearing loss (16).

Ring Chromosome [46,X,r(X)]

Ring chromosomes usually result from two terminal breaks in both chromosome arms, followed by the fusion of the broken ends. The ascentric part often disappeares and partial monosomy occurs. Ring chromosomes cause complex mitotic events. The phenotype is highly variable according to the size of ring chromosome and the deletions of short and long arms. A ring X chromosome is found in approximately 6% of the patients with TS, generally with mosaicism for a 45,X cell line (4).

Females with 46,X,r(X) karyotype may have typical TS findings such as short stature, peripheral edema, characteristic facial features, low neck hairline, ovarian dysgenesis, and endocrine disorders. On the other hand, mental retardation, learning disability, autism spectrum disorders, and structural brain abnormalities are more frequently observed in TS with ring chromosome than TS with 45,X karyotype. Some patients may have more severe phenotypical features and this is thought to be related to whether the X inactivation center is functional or not (17).

In normal females one of the two X chromosomes becomes inactive in the early stages of life and the expression of the X-linked genes is equalized for both sexes. The inactivation of an X chromosome is random, which is maintained in a clonal manner throughout subsequent cell divisions. As a result, females become mosaic in terms of gene expression associated with the X chromosome (18).

X inactivation center, which plays an important role in the expression of the X-inactive specific transcript *(XIST)* gene, is localized on the X chromosome at position q13. Also, *XIST* gene appears to be a key master regulatory locus for X inactivation. In patients with structural abnormalities of the X chromosome, the abnormal X chromosome (such as deletions, duplications, isochromosomes) is always the one inactivated. Smaller ring chromosomes may lack the *XIST* locus, rendering them functionally disomic for the genes present on the ring. Females with mosaic ring X chromosome without *XIST* expression can also have extremity anomalies, abnormal pigmentation and facial features of Kabuki make-up syndrome in addition to mental retardation (18,19). Hyperinsulinemic hypoglycemia is an atypical feature which can be seen especially in patients with mosaic karyotype (20).

Deletion (Xp or Xq)

The frequency of Xp deletion in patients with TS is approximately 2% (4). Short stature, gonadal dysgenesis

and characteristic TS stigmatas are especially observed in patients who show deletion of the entire short arm. Furthermore, the phenotype is variable in partial deletions.

The region Xp22.33-Xp22.12 contains the *SHOX* gene, which is located in the terminal region. The gene escapes from X inactivation, and its function is dosage dependent. Therefore, haplo-insufficiency of *SHOX* gene causes growth retardation (21). The *SHOX* gene is expressed in the pharyngeal arch, limbs, osteogenic cells, bone marrow, and fibroblasts. As well as short stature, skeletal abnormalities including short metacarpals, high palate, cubitus valgus, Madelung deformity, and mesomelic dysplasia may also be seen in the haplo-insufficiency of the gene. (22). Mutations involving the *SHOX* gene or its regulatory regions can be detected in approximately 17% of the patients with idiopathic short stature, and in 50-90% of the patients with Leri-Weill syndrome (23).

The genes located on Xp and Yp are necessary for normal development of the cardiovascular system. Congenital heart diseases have an important role in prenatal and postnatal mortality in patients with TS. The most common cardiovascular defects are bicuspid aortic valve (30%) and aortic coarctation (12%). Additionally, hypoplastic left heart syndrome, usually lethal, is seen in about 10% of the patients (24,25). In particular, left ventricular outflow tract defects are associated with the terminal region of Xp.

The cytogenetic studies have shown that the region between Xq13 and Xq28 is important for normal ovarian function. The Xq13-q21 region is defined as the critical region (CR) 1, and the proximal deletions of this region are usually compatible with normal menstruation and fertility. The terminal and interstitial deletions of the CR2 at Xq23-q28 are mostly responsible for premature ovarian failure (26). The *FMR1* gene, which is important in the ovarian function, is localized in the Xq27.3 locus, and expansions in the exon 1 triplet repeat of the gene are associated with an increased risk of early menopause (27).

Turner Syndrome with Mosaicism

Although classic TS karyotype is 45,X, 30-40% of the remaining have a mosaic pattern with a second cell line (45,X/46,XX, 45,X/47,XXX, 45,X/46,XY, 45,X/47,XYY and 46,X,delXq) (4,28).

45,X/46,XX

The most common form of mosaicism is 45,X/46,XX (15%) which includes both the cell line with the normal karyotype and the pathological cytogenetic structure (29). These patients may have a normal phenotype rather than typical TS features. However, spontaneous menstruation occurs in about 3% of the 45,X females, and up to 20% of mosaic females. While the mean adult length is higher in mosaic females, the probability of the presence of a somatic anomaly is lower.

Psychiatric disorders can also be seen. Especially, the majority of TS patients with schizophrenia had a mosaic 45,X/46,XX karyotype. It has been suggested that the potential of gene dose-effect might be associated with the abnormal expression of an X chromosome gene product which has a susceptibility for schizophrenia in TS (30). Recently, it has been suggested that the *HOPA* gene which is located on Xq13, might be involved in the development of schizophrenia as well as being associated with mental retardation and thyroid dysfunction (31).

45,X/46,XY

TS with 46,XY cell line can be seen in 5-10% of the patients (32). Its clinical features are quite variable. The patients may have typical TS phenotype, normal male appearance, moderate masculinization, male pseudohermaphroditism, and mixed gonadal dysgenesis which can be transformed into a malignant form (33). However, the presence of Y cell line can not be predicted from the phenotype. Patients with a normal female phenotype without evidence of masculinization may also have a 46,XY cell line. Therefore, the patients should be closely followed-up due to the risk of any germ cell tumor, especially gonadoblastoma. In current literature, the frequency of developing germ cell tumor is reported to be about 15% in patients with 45,X/46,XY karyotype (32).

45,X/47,XXX

Triple X syndrome occurs at a frequency of 1/1000 in live-born females. Clinical features include long stature with large hands/feet and microcephalic appearance, hypotonia, seizures, genitourinary abnormalities, and premature ovarian failure. Onset of puberty, sexual development, and fertility are usually normal. Speech and motor retardation, learning disability, attention deficit and behavioral disorders may be seen also in patients with 47,XXX karyotype (34).

The 45,X/47,XXX karyotype, which is extremely rare, constitutes 3-4% of the patients with TS and the etiology can be attributed to post-zygotic non-dysjunction that occurs in the normal disomic cell lines. The patients usually have a milder phenotype and the characteristic stigmatas of TS may not be seen. Ovarian failure may be observed however, and spontaneous menarche and fertility are more common in patients with 45,X/47,XXX karyotype than those with monosomy (35). Previous studies reported the frequency of spontaneous menarche and fertility as 84% and 69% respectively in patients with 45,X/47,XXX karyotype (36). Morever, there was no significant difference between the patients with 45,X karyotype and those with 45,X/47,XXX and 45,X/46,XX/47,XXX karyotype with regard to the development of mental retardation. However, cell counts that provide a ratio of 45,X to 47,XXX cells should not be considered to have predictive value, because they vary in different tissues (36,37).

In conclusion, TS is a complex, reproductive and developmental disorder. Because the clinical features are

quite variable, the phenotype-genotype correlation may not always be achieved. For this reason, karyotype analysis should be done in patients with a clinical suspicion of TS, even in the absence of the phenotypic stigmatas, and the probability of a mosaic karyotype should be kept in mind. Early diagnosis will improve the life quality of these patients and could prevent future problems that may arise during adulthood.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., D.E., Concept: D.E., Design: D.E., Data Collection or Processing: S.G., Analysis or Interpretation: S.G., D.E., Literature Search: S.G., Writing: S.G., D.E.

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

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

References

1. Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology 1938;23:566-74.
2. Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991;87:81-3.
3. Homer L, Le Martelot MT, Morel F, et al. 45,X/46,XX mosaicism below 30% of aneuploidy: clinical implications in adult women from a reproductive medicine unit. Eur J Endocrinol 2010;162:617-23.
4. Sybert VP, Mccauley E. Turner's syndrome. N Engl J Med 2004;351:1227-38.
5. Zhao Q, Zhang Z, Xie S, et al. Cognitive impairment and gray/white matter volume abnormalities in pediatric patients with Turner syndrome presenting with various karyotypes. J Pediatr Endocrinol Metab 2013;26:1111-21.
6. Al Alwan I, M K, Amir, et al. Turner Syndrome Genotype and phenotype and their effect on presenting features and timing of Diagnosis. Int J Health Sci (Qassim) 2014;8:195-202.
7. Hook EB, Warburton D. The distribution of chromosomal genotypes associated withTurner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. Hum Genet 1983;64:24-7.
8. Held KR, Kerber S, Kaminsky E, et al. Mosaicism in 45,X Turner syndrome: does survival in early pregnancy depend on the presence of two sex chromosomes? Hum Genet 1992;88:288-94.
9. Urbach A, Benevisty N. Studying early lethality of 45, XO (Turner's syndrome) embryos using human embryonic stem cells. PLoS One 2009;4:e4175.
10. Migeon BR. Females are mosaics: X-inactivation and sex differences in disease. Oxford University Press: Oxford, 2014.
11. Hook EB, Warburton D. Turner syndrome revisited: review of new data supports the hypothesis that all viable 45,X cases are cryptic mosaics with a rescue cell line, implying an origin by mitotic loss. Hum Genet 2014;133:417-24.
12. Freriks K, Timmers HJ, Netea-Maier RT, et al. Buccal cell FISH and blood PCR-Y detect high rates of X chromosomal mosaicism and Y chromosomal derivatives in patients with Turner syndrome. Eur J Med Genet 2013;56:497-501.
13. Wolff DJ, Van Dyke DL, Powell CM; Working Group of the ACMG Laboratory Quality Assurance Committee. Laboratory guideline for Turner syndrome. Genet Med 2010;12:52-5.
14. Cuesta Hernández M, Rueda Valencia ME, Pérez Rodríguez O, López de Lara D. [X isochromosomes: delayed diagnosis of Turner's syndrome]. An Pediatr (Barc) 2015;82:131-4.
15. De Kerdanet M, Lucas J, Lemee F, Lecornu M. Turner's syndrome with X-isochromosome and Hashimoto's thyroiditis. Clin Endocrinol (Oxf) 1994;41:673-6.
16. Oliveira CS, Ribeiro FM, Lago R, Alves C. Audiological abnormalities in patients with Turner syndrome. Am J Audiol 2013;22:226-32.
17. Lepping KA, Sybert VP, Ross JL, et al. Phenotype and X inactivation in 45,X/46,X,r(X) cases. Am J Med Genet 2004;3:276-84.
18. Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine. 7th ed. Philadelphia, Saunders, 2007.
19. Tomkins DJ, McDonald HL, Farrell SA, Brown CJ. Lack of expression of XIST from a small ring X chromosome containing the XIST locus in a girl with short stature, facial dysmorphism and developmental delay. Eur J Hum Genet 2002;10:44-51.
20. Cappella M, Graziani V, Pragliola A, et al. Hyperinsulinemic Hypoglycaemia in a Turner Syndrome with Ring (X). Case Rep Pediatr 2015;2015:561974.
21. ChoSY, Ki CS, Jang JH, et al. Familial Xp22.33-Xp22.12 deletion delineated by chromosomal microarray analysis causes proportionate short stature. Am J Med Genet A 2012;158:1462-6.
22. Seo GH, Kang E, Cho JH, et al. Turner syndrome presented with tall stature due to over dosage of the SHOX gene. Ann Pediatr Endocrinol Metab 2015;20:110-3.
23. Child CJ, Kalifa G, Jones C, et al. Radiological Features in Patients with Short Stature Homeobox-Containing (SHOX) Gene Deficiency and Turner Syndrome before and after 2 Years of GH Treatment. Horm Res Paediatr 2015;84:14-25.
24. Ho VB, Bakalov VK, Cooley M, et al. Major vascular anomalies in Turner syndrome: prevalence and magnetic resonance angiographic features. Circulation 2004;110:1694-700.
25. Sachdev V, Matura L, Sidenko S, et al. Aortic valve disease in Turner syndrome. J Am Coll Cardiol 2008;51:1904-9.
26. Mercer CL, Lachlan K, Karcanias A, et al. Detailed clinical and molecular study of 20 females with Xq deletions with special reference to menstruation and fertility. Eur J Med Genet 2013;56:1-6.
27. Murray A. Premature ovarian failure and the FMR1 gene. Semin Reprod Med 2000;18:59-66.
28. Ranke MB, Saenger P. Turner's syndrome. Lancet 2001;358:309-14.

29. Rapaport R. Hypofunction of theOvaries. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, (eds). Nelson Textbook of Pediatrics. 18th ed. Philadephia, Saunders, 2008;2316-40.
30. Prior TI, Chue PS, Tibbo P. Investigation of Turner syndrome in schizophrenia. Am J Med Genet 2000;96:373-8.
31. Jung SY, Park JW, Kim DH, Jun YH, Lee JS, Lee JE. Mosaic Turner syndrome associated with schizophrenia. Ann Pediatr Endocrinol Metab 2014;19:42-4.
32. Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW, Looijenga LH. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev 2006;27:468-84.
33. Hennekam RCM, Krantz ID, Allanson JE. "Turner syndrome", in Gorlin's syndromes of the head and neck. Oxford, Oxford University Press, 2010.
34. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L.A review of trisomy X (47,XXX). Orphanet J Rare Dis 2010;5:8.
35. Maciejewska-Jeske M, Czyzyk A, Meczekalski B. The Turner syndrome in patient with 45X/47XXX mosaic karyotype -- case report. Gynecol Endocrinol 2015;31:526-8.
36. Sybert VP. Phenotypic effects of mosaicism for a 47,XXX cell line in Turner syndrome. J Med Genet 2002;39:217-20.
37. Everest E, Tsilianidis LA, Haider A, Rogers DG, Raissouni N, Schweiger B. 45,X/47,XXX Mosaicism and Short Stature. Case Rep Pediatr 2015;2015:263253.

J Pediatr Res 2017;4(4):176-85
DOI: 10.4274/jpr.84803

Review / Derleme

Evaluation of Common Non-pharmacological Chemical Substance Poisonings in Childhood

Çocuklarda Sık Gözlenen İlaç Dışı Kimyasal Madde Zehirlenmelerinin Değerlendirilmesi

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ABSTRACT

Acute intoxications in adolescents and adults are mostly associated with intentional or accidental ingestions. Intoxications are commonly seen in children aged between 1 and 5 years and most of the cases are associated with accidental intake. In most of the children, no clinical symptoms related to intoxication are observed or only mild effects can develop. The main route of drug elimination is through kidneys. Absolute clearance in children is often lower than in adults but weight-adjusted clearance is higher. Depending on more rapid elimination in children the plasma half-life of the drug might be shorter in children than in adults. A shorter elimination half-life means that plasma steady-state is achieved with repeated doses. It is important to prevent childhood intoxications, and the use of child-resistant packaging and adequate supervision together with the secure storage of household substances are the basis of prevention of accidental childhood intoxications. Intoxications represent one of the most common medical emergencies in children, and epidemiological characteristics vary in different countries. Therefore, special epidemiological surveillance is necessary for each country to determine the problem according to which preventive measures should be taken. Early awareness and taking appropriate therapeutic measures seems to be effective in the reduction of mortality rate. The major and most common non-pharmacological chemical intoxications in childhood have been reviewed here with the intent of helping health-care professionals, particularly pediatricians to recognize and reduce the risk of harmful childhood intoxications.

Keywords: Childhood, intoxication, child health, antidote

ÖZ

Ergen ve yetişkinlerdeki akut zehirlenmeler çoğunlukla kasıtlı veya kazara alımlar ile ilişkilidir. Bir ve beş yaş arasındaki çocuklarda zehirlenmeler yaygın görülmektedir ve olguların çoğu kazara alımlara bağlıdır. Çocukların çoğunda zehirlenmeye bağlı hiçbir klinik belirti gözlenmez veya sadece hafif etkiler gelişebilir. İlaç eliminasyonu esas olarak böbrekler aracılığı ile olur. Çocuklarda mutlak klerens yetişkinlere göre genellikle daha düşüktür, fakat vücut ağırlığına göre hesaplanan klerens daha yüksektir. Çocuklarda daha hızlı eliminasyona bağlı olarak, ilacın plazma yarı ömrü yetişkinlere kıyasla daha kısa olabilir. Eliminasyon yarı-ömrünün daha kısa olması, plazma kararlı durumuna tekrarlanan dozlarda ulaşıldığı anlamına gelir. Çocukluk çağı zehirlenmelerinin önlenmesi önemlidir, çocuk emniyeti olan ambalaj kullanılması ve evsel ürünlerin kontrollü olarak güvenli muhafaza edilmeleri, kazara oluşan çocukluk çağı zehirlenmelerinin önlenmesinin esasını oluşturur. Zehirlenmeler, çocukluk çağında en sık görülen acil tıbbi durumlardan biridir ve epidemiyolojik özellikleri ülkeden ülkeye farklılık göstermektedir. Bu nedenle, sorunu belirlemek için hangi önleyici tedbirlerin alınabileceği konusunda her ülke için özel epidemiyolojik takip gereklidir. Zehirlenmelerde erken farkındalık ve uygun terapötik önlemlerin alınması ölüm oranının düşmesinde etkili görünmektedir. Çocukluk çağındaki ciddi zehirlenmeler konusunda riski tanımak ve azaltmak için başta pediatristler olmak üzere sağlık çalışanlarına yardımcı olacağı düşüncesiyle, çocukluk çağında en önemli ve en sık görülen ilaç dışı kimyasallarla olan zehirlenmeler derlendi.

Anahtar Kelimeler: Çocukluk çağı, zehirlenme, çocuk sağlığı, antidot

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Received/Geliş tarihi: *26.01.2016* **Accepted/Kabul tarihi:** *21.03.2016*

Introduction

Besides toxicokinetic properties of the intoxicating agent, the response to it in children is different than in adults, and this fact should be taken into consideration when dealing with children. It should be kept in mind that intoxication symptoms in children can be similar to those of some diseases. Therefore, medical history, physical examination, and clinical symptoms of the patient should be evaluated, and the treatment of the patient with suspicion of intoxication should be performed as soon as possible.

In the present review, some common non-pharmacological intoxicating agents, and epidemiological and clinical features of intoxications and treatment approaches have been discussed.

1. Yellow Phosphorus

Yellow phosphorus is a waxy, yellow-colored inorganic material which has a transparent appearance (1). It is used in industry, mainly in making matches, pesticide, firework, watches, and explosive material. It is also present in the composition of ammunition, and agricultural fertilizers (1,2), and is used as rodenticide in agriculture. As the rodenticides containing 2-5% yellow phosphorus are often prepared as paste, intoxications due to accidental oral intake being mistaken for toothpaste by children is frequently observed (2,3). The strong garlic odor of yellow phosphorus can be definitive in the diagnosis of the patients with suspicion of intoxication (1,2).

Skin, epithelial, and mucous membranes of respiratory and gastrointestinal systems are among the contamination routes. After oral intake, it distributes to all tissues, mainly liver and reaches maximum blood concentration within 2-3 hours (2,4). The lethal dose of yellow phosphorus is 1 mg/kg. The main exposure in children is via oral route, and it is rapidly absorbed through intestines following oral intake and leads to many complications, hepatotoxicity being in the first place. It causes severe damage in various organs such as the heart, kidneys, spleen, and brain in addition to liver. Apart from oral intake, intoxications can be seen as a result of the inhalation of industrial particles, or dermal exposures (1,4,5).

When a firework-like substance containing yellow phosphorus (10%), silica, potassium chlorate, ferrous oxide, and magnesium carbonate, and known as "cracker" in Turkey is eaten by children, intoxication is frequently observed (1,5,6). The mortality rate is high (23%), and upper abdominal pain, vomiting, lethargy, respiratory distress, hepatotoxicity, and coagulation dysfunction are observed. Severe intoxications cause arrhythmia, coma, hypotension, and lead to death (5). The clinical signs of acute intoxications occur in mainly three stages. The first stage is gastrointestinal symptoms characterized with vomiting, nausea, diarrhea, and abdominal pain, which develop within 24 hours following oral intake. Although laboratory tests seem to be normal at this stage, sudden death can occur. It is thought that this situation is due to the consequence of cardiovascular arrhythmia, and collapse developing within the first 24 hours. Cardiac collapse can also develop as a result of fluid and electrolyte loss caused by vomiting or diarrhea. The second stage (1-4 days) is a latent period without any symptoms. However, hepatic enzyme and bilirubin levels increase and hepatotoxicity begins to progress at this stage. The third stage (4-7 days) is characterized by acute hepatic failure and acute renal failure together with metabolic disturbance, encephalopathy, coagulopathy, arrhythmia, cardiogenic shock, abnormal liver function tests, acute tubular necrosis, changes in mental status such as confusion, psychosis, hallucination; coma, hypotension, cardiac toxicity, and multiple organ failure (1,2). It is suggested that yellow phosphorus leads to transient proliferation in erythrocytes although it often causes no change in hematological parameters. Bone marrow pathology should be examined in critical patients (4).

There is a limited number of studies on its metabolism and the enzymatic destruction pathways are not known in details. It has been reported that yellow phosphorus, which is a protoplasmic toxin, disturbs glycogenesis, leads to lipid peroxidation, and disturbs the synthesis of plasma proteins regulating prothrombin time and coagulation (1,2).

There is no specific method for the diagnosis of intoxication, and the measurement of blood phosphorus levels is not found to be practical in clinics. The diagnosis is mostly provided with the medical history taken from the children or the parents. If the history is not clear, the garlic odor in breath or luminescence in stool/vomit can be beneficial in the diagnosis. The odor of the stool is named as "smoking stool syndrome". There is no specific antidote or treatment approach in yellow phosphorus intoxications. Unfortunately this makes the selection of correct treatment difficult. Laboratory findings can be helpful in determining the stage of the clinical picture. In biochemical tests, metabolic acidosis, hypoglycemia, hyperbilirubinemia, increased levels of aspartate aminotransferase and alanine aminotransferase are observed. Abnormal partial thromboplastin time and leukopenia are among the hematological abnormalities. Electrocardiography (ECG) findings show changes in T (ventricular repolarization) and QRS (ventricular depolarization) waves, arrhythmia and atrial fibrillation. All of these findings can be easily observed particularly in the third stage (1,6). The time interval between the ingestion of the intoxicating agent and the emerging of symptoms can vary. In addition to the cases in which the symptoms appear within a few minutes, there are also cases where symptoms appear after 24 hours. Gastric lavage and decontamination within 2-5 hours following the ingestion of the poison can be beneficial. The first treatment method is the prevention of the absorption of oxidized phosphorus. At the beginning of the treatment, isotonic serum physiological solution, vitamin K, and ranitidine are given, and oxygen support is supplied with face mask. Plasma transfusion is performed. While the mortality rate is 23% in patients with the symptoms of vomiting and abdominal pain, and who have been diagnosed

in the early period; the mortality rate is 73% in intoxications with the symptoms of anxiety, nervousness, somnolence or coma. For supportive treatment, the monitoring of electrolyte balance, acid-base status, liver and renal functions, and the determination of coagulation parameters is important (3,5). In the treatment of acute intoxications, gastric lavage is performed, or the oxidation of the toxin to less toxic phosphoric acid and phosphates is provided by using potassium permanganate (1:5000). Alternatively, the transformation of phosphorus to non-toxic copper phosphite can be done by gastric lavage with copper sulfate solution (0.2%). Use of fatty substances that increase the absorption of phosphorus or consumption of fatty nutrients should be avoided. However, the efficacy of all these treatment methods is not definite. Furthermore, it is suggested that the use of intravenous (i.v.) steroids and N-acetylcysteine for treatment is not practical. Hypotension, hypoglycemia, hypocalcemia, convulsions, coagulopathy, and arrhythmias should be corrected with supportive treatment. It has been reported that supportive treatment is partially effective in the first and second stages, but the only treatment method in the first stage is liver transplantation. In a study which has evaluated the survival rates in patients who had acute liver failure and living donor transplantation due to yellow phosphorus intoxication in Turkey, it has been reported that one out of 4 children who had medical treatment and three out of 6 children who had liver transplantation have survived (1).

Due to the development of resistance against rodenticides containing warfarin in rodents, the use of rodenticides with yellow phosphorus has become popular. As the commercial forms of rodenticides containing yellow phosphorus are produced as paste to be consumed by the rodents, their consumption by children has also become easy (2).

2. Ethylene Glycol

Apart from being used as anti-freeze in automobiles, ethylene glycol is also used in carpet washing shampoos in industry, as cooler in air conditioners, in the composition of cloth and metal cleaners, and pesticides, in fire extinguishers, and wood sheathing. Ethylene glycol is an odorless, colorless, sweetish liquid which has syrup consistency (7,8). Both accidental and suicidal intake of ethylene glycol is frequently observed owing to the sweet taste and easy access (9). Its intestinal absorption and tissue distribution is rapid as its water solubility is good. Its serum concentration reaches the maximum level within 30-60 minutes following oral intake. Before it is metabolized, it is relatively non-toxic. The main metabolites responsible for toxicity are glycolaldehyde, glycolic acid, glyoxylic acid, and oxalic acid (8). These metabolites cause accumulation of calcium oxalate crystals in the tissues leading to tissue damage, metabolic disorders, metabolic acidosis with anion gap, lactic acidosis, and hypoglycemia. Ethylene glycol intoxication occurs mainly in three stages. The symptoms in the first stage (first 12 hours) is due to ethylene glycol (8,9). Its depressant effect on the central nervous system (CNS) is observed (8-10). Metabolic acidosis, which is seen between the first and second stages, can usually be misleading for the determination of the stage of the intoxication. In the second stage (12-24 hours), in addition to severe metabolic acidosis, multiple organ failure due to the metabolites of ethylene glycol can be observed. It has been reported that the most mortality is seen in this stage. The third stage (24-48 hours) is characterized by acute tubular necrosis and renal failure. Oliguria, anuria, hematuria, proteinuria, and crystalluria are also observed. Oliguric or anuric renal failure can sometimes develop even 45 days later (8,9). The history in ethylene glycol intoxications is very important for diagnosis, as in other intoxications. As drunkenness often attracts attention, it can be confused with ethanol induced drunkenness, so it can be misleading for diagnosis. However, the absence of ethanol odor can be beneficial for differential diagnosis (9,10).

Ethylene glycol toxicity is observed when exposure is above 1 g/kg or when serum level >20 mg/dL (9). In recent years, it has been reported that ethylene glycol intoxications are more common than methanol intoxication, which is one of the frequently seen intoxications (11). As formation of calcium oxalate crystals is observed in both of them, often ethylene glycol intoxications can be confused with methanol intoxications. General supportive treatment including respiratory and circulatory support is primarily performed (9). Gastric decontamination is not effective. In asymptomatic children, serum calcium levels, electrolytes and renal functions should be evaluated for the estimation of plasma ethylene glycol levels (7). It is rapidly absorbed, so gastric lavage and/or ipeca syrup is not beneficial in decontamination; and as high amounts of activated charcoal is required for small amounts of ethylene glycol, the use of activated charcoal in clinical settings is not practical (9). It is suggested that the main source of severe acidosis due to ethylene glycol is the circulating glycolic acid (11). The formation of calcium oxalate crystals also induces an acidic environment. Sodium bicarbonate should be given for the correction of acidosis (8). It is necessary to act quickly for the administration of sodium bicarbonate, particularly when pH is below 7.3 (10,11). Continuous infusion of bicarbonate can be performed together with i.v. thiamin (100 mg) and pyridoxine (vitamin B6, 100 mg) for urine alkalinization. Dialysis can be necessary for the inhibition of toxic metabolite formation and for removal of the main product and its metabolites. Hemodialysis should be performed, particularly when severe acidosis is observed, when renal function is diminished or when damage is observed in other organs. Serum magnesium levels should also be followed up. Together with thiamin, magnesium also functions as a co-factor in the alternative degradation pathway of ethylene glycol (9). Although there is limited data supporting the efficacy of pyridoxin in treatment, it is thought to be beneficial in diminishing the toxicity of glycolic acid (11). Calcium support is also recommended to prevent tetanus (9). Ethanol infusion

prevents toxic metabolite formation. In acute ethylene glycol intoxications, empiric treatment begins with 10% i.v. ethanol (7,9). Ethanol (40%) is given at a dose of 2 mL/kg for 30 minute as oral loading dose. Fomepizole (4 methyl pirazole), which is another antidote as an alternative to ethanol, is a competitive antagonist of alcohol dehydrogenase. I.v. fomepizole (15 mg/kg within 30 minutes) should be given to symptomatic children or to the children with plasma ethylene glycol levels above 200 mg/L (3.2 mmol/L). Fomepizole should be repeated every 12 hours (4 doses 10 mg/g, then 15 mg/kg) until plasma ethylene glycol level diminishes below 200 mg/L (7,10). It has been reported that the effectiveness of fomepizole is highest when it is given before the formation of toxic metabolites. When the fomepizole dose is arranged during treatment, it is recommended to arrange the dose according to the concentration of toxic metabolites instead of serum ethylene glycol concentration. In developed countries, fomepizole is preferred instead of ethanol. Fomepizole has been reported to have no side effects except rare allergic reactions. It has also been reported that it is not necessary to arrange the dose in patients with renal or hepatic diseases, and that it does not interact with other drugs (11). On the other hand, there are investigations which report that it has disadvantages such as CNS depression and hypoglycemia (7). Nevertheless, fomepizole is said to be effective in ethylene glycol intoxications in newborns (12,13). Hemodialysis can be necessary for patients with renal failure or resistant metabolic acidosis (7). Fomepizole administration and hemodialysis have been performed in a pediatric case at the age of 8 months to correct acidosis and oxalate crystaluria that developed due to the ingestion of more than 120 mL ethylene glycol. Following fomepizole and hemodialysis, acidosis was corrected by preventing the conversion of ethylene glycol to toxic metabolites, and the patient has been reported to have improved within 48 hours (12). However, there are reports that show that fomepizole administered at a dose of 10 mg/kg every 12 hours following a loading dose of 15 mg/kg was also successful without any need for hemodialysis in newborns (13).

3. Lead

Infants, pregnant women, and occupational groups that are in close contact with lead are more sensitive to its toxic effects. Lead exposure in children develops due to a high incidence of pica (earth eating), more exposure to street and home dusts, less clearance of lead from the body, and increased absorption in the presence of iron deficiency anemia. In children asymptomatic lead intoxication is observed most frequently. Chronic exposure to low dose lead can cause persistent mental dysfunction which can only be understood by screening methods (14).

Lead passes to placenta during pregnancy and causes premature birth and low birth weight in the fetus or death (15). 40-50% of lead exposure in children is due to the use of domestic dyes with lead content (16,17). Exposure to dye powders through respiratory tract during grinding is also mentioned. Other sources of exposure are drinking the water contacting lead pipes, food in tin or ceramic containers, alternative treatment methods such as ayurveda (16).

Lead inactivates enzymes by binding sulfhydryl, phosphate and carboxyl groups on proteins. Furthermore, it interacts with calcium, zinc and iron, disturbs nerve conduction by affecting cell membrane, influences redox events, and causes multiple organ dysfunction by disturbing nucleotide metabolism (15).

When the lead level is above 400-600 µg/L, classical effects of lead intoxication such as colic, abdominal pain, lack of appetite, vomiting, and constipation are observed; and if blood lead concentration is >450 µg/L, microcytic anemia is seen. The neurological effects depend on the chronicity and severity of intoxication. If the lead level is above 750-1000 µg/L, encephalopathy, delirium, ataxia, coma, and convulsions occur. Chronic exposure to low doses of lead in children causes reduction in IQ levels of about 1-2 points. If lead intoxication is suspected in children, complete blood count and abdominal X-ray should be requested. I.v. ethylene diamine tetra acetic acid (EDTA) and oral dimercapto succinic acid (DMSA) (2,3) are used for chelation in treatment (16). At the present time, previous agents such as British anti-lewiste and penicillamine are rarely used (16). Although the efficacy of DMSA is similar to EDTA, due to the inadequacy of clinical experiences its use is approved only in children with blood lead levels between 45-69 µg/dL (18). It is necessary to be careful during chelation therapy in children. If there is encephalopathy in the child and if the blood lead level is above 750 µg/L, referral of the child to the intensive care unit might be needed. The bad odor and taste of DMSA makes its oral use in children difficult. Thus, it is recommended to give it by mixing with nutrients such as jam and jelly. In recent studies it is suggested that chelation treatment is not beneficial in children with blood lead level above 450 µg/L (16). The use of penicillamine in lead intoxication has not been approved by Food and Drug Administration. Also because the benefit of chelation treatment in patients with lead level below 25 µg/dL has not been approved, this level is a criteria for the discontinuation of the treatment. Centers for Disease Control and Prevention has decreased the limit for toxic blood level of lead in children from 40 µg/dL to 30 µg/dL in 1975, to 25 µg/dL in 1985, and to 10 µg/dL in 1991 (19). In Turkey, several studies evaluating lead levels in children have been conducted. In the study of Vural and Güvendik (20) which was conducted in 1987 with children living in Ankara, mean blood level of lead was found as 19.35 µg/dL; in the study of Bostancı et al. (21) which was conducted in 1995 to determine the lead level in umbilical cord samples of the newborns living in the center and villages of Ankara, it was found as 9.4-15.5 µg/dL. The study of Göker (22) conducted in İstanbul in 1995, found the lead level as 5.55 µg/dL, and the study of Can et al. (23) which was conducted in Tekirdağ in 1997 found it as 29.6 µg/dL. The lead level was found as 23.4 µg/dL in the study of Yapıcı et al. (24) conducted in Silivri in 1999.

Lead exposure at low doses can cause severe motor and cognitive dysfunction. These effects of lead exposure particularly in children younger than 6 years of age should not be ignored. As the prenatal and neonatal periods are durations of rapid growth, absorption of heavy metals in nutrients is higher compared to the adults. As a result, this group is at more severe risk. Although toys containing lead in their composition have been banned in many countries, lead intoxications due to toys contaminated with lead are still being reported all over the world (25).

Illegal employment in Turkey is common and most of these workers are children, and this makes lead exposure and lead toxicity unavoidable in children. Toxic levels of lead have been identified in blood samples in 8% of the lead workers aged below 18 years (18).

Controlling the children at risk at certain time intervals, regular monitoring of blood lead levels in occupational groups that are in close contact with lead, monitoring blood lead levels with more extended screening, and also developing protection and prevention strategies against lead exposure by conducting environmental analyses (soil, plant, water etc.) are necessary particularly for the protection of children from the toxic effects of lead (14).

4. Methanol

Methanol is found in the composition of several products which are used in daily life such as stain removers, cologne, and spirit, solvents such as anti-freeze, washing solutions and brake fluids (7,16). In children the ingestion of even a small amount of methanol can cause severe intoxication, similar to that of ethylene glycol (16). Methanol is metabolized to toxic metabolites by alcohol dehydrogenase. Severe abdominal pain, retina toxicity, acidosis, convulsions, and coma are among its toxic effects (7,26). Exposure to high doses of methanol leads to severe clinical effects such as metabolic acidosis, CNS depression, hypotension, acute renal failure, and methanol blindness (16,26). Although there are some differences in methanol intoxications, the treatment approach is similar to the one applied in ethylene glycol intoxication. The half-life of methanol is 43 hours and severe symptoms develop hours later (7). As hypoglycemia and hypothermia can develop due to ethanol particularly in young children, its use in treatment is not preferred. Fomepizole does not cause hypoglycemia and sedative side effects, and its tolerability is also more than ethanol. However, its higher cost compared to ethanol restricts its use in clinics (16,26-28).

In a study conducted in Turkey, it has been reported that 3.3% of the intoxication cases which were notified to the National Poisoning Research Center between 1993 and 2002 were alcohol intoxications, and 11.3% of the alcohol intoxications were due to methanol. The rate of methanol intoxication in children aged between 0 and 12 years was found as 55.7% (29). In a study conducted by Türkmen et al. (30) it was reported that when the medical history of a 4-year-old girl with complaints of nausea, vomiting, and abdominal pain was taken, she had drunk washing solution 2 days before. Toxicological studies performed following autopsy have shown that blood level of methanol is 79 mg/dL. It has been stated that although the lethal dose of methanol is reported to be 1-2 mg/kg, exposure to even small doses such as 0.1 mg/kg can lead to blindness or death. According to the reports most of the methanol intoxication cases were children under 6 years of age (30).

5. Essential Oils

Although essential oils are used in perfumery, aromatherapy or massage, they are compounds with high toxicity potential (31,32). When they are topically applied, they demonstrate analgesic and anti-pyretic effects. Furthermore, they are also widely used in the treatment of common cold and coughing (33). Although the chemical structure and toxic effects of most of the essential oils are not exactly known, they are a mixture of esters, alcohols, aldehydes, and ketones (32,34). Resulting from the increased use of essential oils, the number of admissions to emergency departments due to intoxications with these substances has increased in recent years. In a study evaluating the toxic agents in intoxication cases admitted to the emergency services, poisonings due to essential oils was found to be at the 9th range among 35 agents. Most of the time there is no child safety latch in packagings, and this forms a basis for the intoxication events in children (34).

The initial signs of intoxication with essential oils are mucosal irritation, vomiting, epigastric pain, and diarrhea. Convulsions, CNS depression, hepatic and renal failure are the other signs. Asymptomatic children should be monitored for at least 6 hours after providing fluid support. Hospitalization can be necessary in symptomatic children. Presence of respiratory distress should remind us of the aspiration of essential oils. Supportive treatment is recommended, and blood glucose levels should also be monitored (31,32).

At the present time, turpentine oil is more commonly used than other essential oils due to its relatively low toxicity. Symptoms develop 24 hours after ingestion. In addition to chemical pneumonia, gastrointestinal system irritation, burning due to oral ingestion, metabolic acidosis, hepatic failure, and renal damage, mental changes can also be observed. Gastric decontamination is contraindicated in treatment. In all patients, oxygen saturation should be measured and presence of respiratory distress should be determined. Most of the patients with intoxications due to turpentine oil are asymptomatic. When hospitalization is not found to be necessary, the parents should be informed that they should again refer to a hospital when coughing, noisy or rapid respiration are observed (31). Camphor oil is a volatile oil which causes gastrointestinal irritation and CNS depression, and symptoms often develop within 5-10 minutes following ingestion. The lethal dose of camphor oil in children is 5 mL. Convulsions are observed 20-30 minutes after ingestion. The symptoms of intoxication due to eucalyptus oil are epigastric

pain, vomiting, burning sensation in mouth and throat, convulsions, respiratory difficulty, and CNS depression. While CNS symptoms can develop within 30 minutes, they can also develop 4 hours later. Oral ingestion of 3-5 mL of pure eucalyptus oil causes transient coma and convulsions. Mainly supportive treatment is recommended in the treatment of intoxications due to camphor oil and eucalyptus oil. However, as it may lead to sudden convulsions, the use of ipeca syrup is not recommended, and the efficacy of activated charcoal and hemoperfusion has not been approved yet (33).

6. Organophosphates

Organophosphates are irreversible inhibitors of acetylcholinesterases and they cause accumulation of acetylcholine in the cholinergic receptors. Exposure is mainly through oral route, skin, mucous membranes, conjunctiva or respiratory tract (35). The symptoms can be observed even 24 hours later in organophosphate intoxications. As a result of the excessive stimulation of the parasympathetic system, salivary and lacrimal gland secretions, bronchial and gastrointestinal secretions increase, peristaltic activity increases, bronchoconstriction, bradycardia, reduction in visual acuity, hypotension, headache, somnolence, convulsions, and miosis develop. Urine and fecal incontinence, loss of sphincter control are among the secondary findings. Paralysis is observed when taken at high doses. Hyperglycemia and glycosuria without ketonuria can also be observed. Symptoms related to the dermal absorption of organophosphates are rarely seen. The highest risk for acute toxicity is through oral ingestion. Asymptomatic children should be monitored for 24 hours, and symptomatic children need more careful monitoring (7,35,36). One of the antidotes used in specific treatment is atropine, which has anti-muscarinic effects, and the other antidote is pralidoxime, which is an enzyme reactivator. Atropine antagonizes the competitive effects of acetylcholine on muscarinic receptors. In general, its short-term and intermittent use is recommended. Data related to its long-term use as i.v. infusion is limited. Mild symptoms can be corrected with supportive treatment. The patients who gave no response to treatment with atropine should be treated with pralidoxime. Administration of pralidoxime within 24 hours following ingestion increases the effectiveness of treatment. Two children who had been admitted to the emergency department after eating peach with remnants of pesticide containing organophosphate, were elethargic, their pupils were miotic, they responded to stimulation with agitation, and had increased secretions, bradycardia, tachypnea, and dyspnea. Both of them were intubated and mechanically ventilated as they had excessive secretions in the respiratory tract alongside respiratory distress. I.v. atropine and pralidoxime were administered. But as the bronchial secretions increased and bronchospasms became more severe, i.v. infusion of atropine (0.02-0.08 mg/kg/hour) was started. Following this, a significant reduction in the secretions and bronchospasms was observed. In organophosphate intoxications which give no response to short-term and intermittent atropine, long-term i.v. atropine is recommended (35). In another patient who had been admitted to hospital after exposure to pesticide containing organophosphate, acetylcholine esterase level was found to be low, and the initial treatment with activated charcoal and fluid administration which was begun in another center was continued. In intermediate syndrome which develops within 1-4 days following acute organophosphate intoxication, paralysis is observed in the flexor muscles of the neck, muscles innervated by cranial nerves, muscles of proximal extremities, and respiratory muscles; and the paralysis of the respiratory muscles can necessitate respiratory support. The symptoms and findings of cholinergic over-stimulation are not often observed in these patients. electromyography can be helpful in diagnosis. Early treatment with antidote, and supportive treatment can prevent the development of this syndrome or decrease its severity. The symptoms usually disappear within 5-18 days (37). Antidote administration for treatment is performed according to the degree of toxicity. In exposures through skin, washing the skin and clothes with water and soap is necessary to prevent further absorption of the substance. Gastric lavage and activated charcoal is necessary in oral exposures. The dose of atropine in children is 0.05 mg/kg in moderate intoxications. If no effect is observed, this dose should be repeated every 5-10 minutes until muscarinic symptoms disappear (35).

According to the 2008 data of National Poison Data System, 8% of the intoxications are due to pesticides (38). Intoxications usually happen accidentally at home or in people working in agriculture, industry (during the production and transport of these agents), and in insect control areas. As these compounds can be easily reached, accidental or suicidal intoxications are frequently observed particularly in developing countries. Early diagnosis and treatment is important in these severe and life-threatening intoxication cases. When the expected respiratory system complications emerge, mortality rates can be decreased by starting appropriate treatment without delay and by providing respiratory support when required. In severe intoxication cases, it should not be forgotten that long-term use of i.v. atropine in addition to short-term and intermittent atropine administration has vital importance (35).

7. Carbon Monoxide

Carbon monoxide (CO) is an important intoxicating agent which is lethal particularly in winter in Turkey. In normal conditions, it is found at a concentration of 0.001% in the atmosphere. It is formed at very low amounts (0-5%) endogenously from the breakdown of hemoglobin molecule. CO has been detected at a concentration of 3-7% in newborns. Its concentration is 5-10% in patients with hemolytic anemia and in smokers (39). Intoxications are most commonly encountered in winter and windy weathers as the carbon compounds in the structure of charcoal don't

burn completely and CO develops during burning. Another source of exposure is the exhaust fumes of cars (39,40). In a study consisting of 250 children diagnosed with acute CO intoxication, it has been reported that intoxications develop most commonly due to exhaust fumes and incompletely burned charcoal (41). CO intoxications have been reported as the most common cause (31%) of lethal intoxications in Turkey (42). The incidence of CO intoxications in children is quite high. It disturbs cellular metabolism by reacting with other heme-proteins just as the mitochondrial cytochromes. A level of 20% carboxyhemoglobin (COHb) causes headache and nausea, 20-40% causes convulsions, and above 40% it causes ataxia, collapse, and coma. Cardiac arrhythmia, cerebral edema, and acidosis can also be observed. Cherry-red color in lips and purplish color in nail folds are among the signs. Metabolic acidosis, cardiovascular and neurological signs are frequent symptoms (7). In intoxications, the risk of toxic effects is higher in tissues sensitive to hypoxia, mainly brain and heart. Although neurological symptoms are well-known, the knowledge related to cardiovascular system findings in children is limited. It has been reported that myocardial damage can develop without the development of clinical findings. CO intoxications often develop acutely in childhood and can occur with different and non-specific signs and symptoms (42). As non-specific findings such as headache, dizziness, nausea-vomiting are observed in mild CO intoxications, these patients may be easily misdiagnosed with non-specific viral infections that are particularly observed in winter, food intoxication, gastroenteritis, and even colic in infants (39). Therefore, particularly in winter, CO intoxication should be suspected in the presence of nausea, vomiting and headache with unknown etiology, and blood COHb level should be measured in these patients (42). If the exposure continues, tachycardia, tachypnea, exercise intolerance, findings related to myocardial ischemia, life threatening arrhythmias and cardiac arrest might develop. Difficulty in thinking, blurred vision, weakness, ataxia, syncope, convulsions, retinal hemorrhage, renal failure, non-cardiogenic pulmonary edema, and coma are observed. It is necessary to remove the patient from the environment with CO and to give oxygen support for treatment. After opening the airway, 100% inhalation of oxygen should be provided. While the half-life of CO is approximately 5 hours, this period can decrease to 1 hour (30-150 minutes) when 100% oxygen is administered. Hyperbaric oxygen therapy (HBOT) is another method which has been used in CO intoxications since 1962. HBOT can be performed in certain centers in various parts of the world, but the transfer of the patients to these centers may pose a problem. However, it is a preferred method as it decreases the mortality rates and has beneficial effects in the long term. In Turkey, HBOT is performed in 7 centers that are present in Ankara, İstanbul, Eskişehir, and Bodrum (39).

8. Cyanide

The pip and seed of some fruits such as apples, apricots, and peaches contain significant amounts of cyanide. The toxicity potential of the apricot pip is higher due to its cyanogen and hydrogen cyanide content (43). Cyanide and CO intoxication are often observed in combination. In a previous study it was found that 4% of the patients who had died in a house fire had lethal levels of cyanide. Cyanide mainly causes cellular hypoxia, anoxia, lactic acidosis, and metabolic acidosis. Metabolic acidosis is observed in 67% of acute intoxications. The clinical findings are observed immediately after ingestion. Headache, agitation, confusion, loss of consciousness, convulsions, and cardiac rhythm disturbances are among the symptoms. Following oral intake of cyanide, deep and rapid respiration, shortness of breath, acute dyspnea are observed. Exposure to high concentrations of cyanide leads to symptoms such as epileptic convulsions, apnea, cardiac arrest. The main cause of cyanide-induced death is the depression of the respiratory center (43). It is important to start the treatment early in cyanide intoxications (7). Oxygen support should be provided initially. Cyanide antidote kits containing amyl nitrite and sodium nitrite are used. They produce methemoglobin by interacting with the cyanide that is present in cyanomethemoglobin. The sodium thiosulfate in the content of the antidote kits transforms cyanomethemoglobin to thiocyanate which is a less toxic molecule. Another antidote that is used in treatment is hydroxycobalamin. It forms cyanocobalamin by reacting with cyanide. The use of activated charcoal is also suggested to be effective in cyanide intoxication (43).

9. Addictive Drugs

According to the results of the previous studies, although substance abuse among the students of primary and secondary education in Turkey is found to be lower than the other countries, tobacco use is found to be quite common. It has been reported that the most commonly used substances in developing countries are tobacco products, alcohol, marijuana, and volatile substances. This is also true for Turkey (44).

Ecstasy (3,4) methylenedioxymethamphetamine, is a derivative of amphetamine and it leads to locomotor stimulation, euphoria, excitement, and stereotypic behaviors. Ecstasy also has psychotomimetic effects which change perception and mood. Although the action mechanism of ecstasy is not exactly known, it is suggested that it increases free 5-hydroxytryptamine (5-HT) levels by decreasing re-uptake of 5-HT from nerve terminals. The addiction potential is low, but tolerance develops rapidly to its positive effects, and its negative effects become intensified in long-term exposure to high doses. Coma, convulsions, arrhythmia, malignant hyperthermia, rhabdomyolysis, hypertension, and multiple organ failure can be observed after intake. Activated charcoal shows its effect within 1 hour in asymptomatic

children. Monitoring blood pressure, body temperature and ECG are recommended. Blood levels should be measured to determine the degree of exposure. When the symptoms disappear, after a 24-hour follow-up, the children can be discharged under the control of their parents. The children in whom the symptoms are observed should be kept under observation for at least 48 hours. Hospitalization to intensive care may be necessary in patients with cardiac and CNS symptoms. Careful monitoring of hematological and biochemical parameters is recommended. Hyperthermia can be corrected with simple precautions. However, if it is not successful, i.v. dantrolene 1 mg/kg can be administered for approximately 10-15 minutes. In unresponsive patients, the dose can be repeated in 15-minute intervals without exceeding a total dose of 10 mg/kg within 24 hours. Hypertension can be corrected with labetolol. Convulsions and agitation should be treated with benzodiazepines. Chlorpromazine and haloperidol are among the initially preferred drugs to lower the seizure threshold (7).

Lysergic acid diethylamide (LSD), which has a strong hallucinogenic effect, is a 5-HT agonist. It is absorbed rapidly and its duration of action is very short. Dermal absorption of LSD is weak. In intoxications, hypertension, hyperthermia, and psychosis are observed. It is necessary to be careful particularly in symptomatic children. Gastric decontamination is not recommended. Sedation with phenothiazines should be avoided. In some situations, LSD may be associated with malignant hyperthermia (7,45).

Cocaine demonstrates its effect by inhibiting the re-uptake of dopamine, noradrenalin, and 5-HT. Agitation, hallucination, convulsions, hypertension, myocardial ischemia, and cranial infarction can be seen depending on its intake. In asymptomatic children, administration of activated charcoal within 1 hour following intake is beneficial. Blood pressure and ECG should be monitored. It is necessary to monitor symptomatic children more carefully. Agitation, hallucination, and convulsions can be controlled with benzodiazepines. It is necessary to correct acidosis as soon as possible as acidosis can intensify cardiac toxicity. Hypertension, arrhythmia, and angina can be treated with diazepam, nitrates, and calcium antagonists. Combined use of β-blockers and phenothiazines should be avoided due to the unpredictable interaction between these drugs. Coagulation and thrombosis should be kept in mind in terms of the probability of myocardial infarction development (7).

10. Nicotine

Nicotine is a toxic alkaloid which is found in the structure of many plants, mainly the tobacco. It demonstrates its effect by stimulating nicotinic acetylcholine receptors (7). When it is taken orally, nausea, vomiting, abdominal pain, increased salivation, confusion, agitation, clouding of consciousness, convulsions, coma, hypertension, tachycardia, and tachypnea are observed (15). In severe intoxications, arrhythmias and parasympathetic stimulation also accompany the symptoms. Nicotine intoxication in children is often observed as a result of eating cigarette derivatives such as cigarette or cigar. Vomiting is frequently seen after eating cigarette, which is a good thing as it contributes to the reduction of the gastric absorption of nicotine (7). One cigarette contains approximately 13-30 mg nicotine. While it's lethal dose in adults is 40-60 mg, in children 1 mg (0.2 mg/kg) is lethal. Severe intoxications develop when nicotine is taken at a dose of 1.4-1.9 mg/kg (15). In intoxications due to oral intake of one or two cigarette ends, asymptomatic children should be kept under observation for 2 hours. No specific treatment is needed. However, activated charcoal and gastric lavage are recommended in exposure to large amounts in children (7). For convulsions, diazepam (i.v. 0.1-0.2 mg/kg, not exceeding 5 mg/kg) or midazolam (i.v. 0.05 mg/kg within 20-30 seconds, or intramuscular 0.1-0.2 mg/kg) are administered (15).

11. Isopropanol

Isopropanol is an alcohol derivative which is found in the composition of nail polish, hairspray, anti-freeze, and screen washers. It is rapidly absorbed by the stomach and causes gastric irritation, CNS depression, and hypotension. Isopropanol transforms into acetone via alcohol dehydrogenase enzyme and the acetone is excreted primarily through lungs and kidneys. Asymptomatic children should be kept under observation for at least 2 hours. Activated charcoal is not effective in the reduction of isopropanol absorption, and it is contraindicated in the presence of CNS depression. Gastric lavage and vomiting are effective only when performed within the first hour. Intensive supportive therapy is necessary in symptomatic patients. Treatment with i.v. fluid and inotropic agents might be needed in the case of hypotension and peripheral vasodilatation. Hemodialysis is recommended in patients with blood isopropanol concentration of 4 g/L. Peritoneal dialysis has also been reported to be effective in isopropanol intoxications. However, this method can be ineffective in some patients, as it may cause refractory hypotension (7).

Conclusion

In conclusion, due to the rapidly developing technological advancements, people are exposed to various natural and/or synthetic chemical agents in routine daily life, either consciously or unconsciously. In addition to drugs, exposure to natural toxins of herbal and animal origin, industrial pollutants, food additives and contaminants, environmental agents, and domestic products has become unavoidable. Incorrect preservation of domestic chemicals, parents not acting responsibly enough, and putting objects into mouth, which is a common behavior particularly in toddlers, are among the causes of intoxications in children. It is important to increase awareness of intoxications related to toxic agents, and unwanted effects among all individuals in the society, mainly the children, to take necessary precautions

and to follow appropriate treatment approaches. Although some drug packages have child safety latch, such packages are not used in many products on sale. The responsible attitude of the producing companies towards this subject can be effective in reducing intoxications in children. In addition to acute mild findings observed in intoxications in children, severe and irreversible damage and death are also observed. Therefore, it is necessary to inform foremost the parents, healthcare personnel, manufacturers, and children about intoxications. As early treatment is important making arrangements to reach National Poisoning Research Centers, and increasing the number of similar organizations would contribute to reducing the number of intoxication cases.

Ethics

Peer-review: Externally peer-reviewed.

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

References

1. Ates M, Dirican A, Ozgor D, et al. Living donor liver transplantation for acute liver failure in pediatric patients caused by the ingestion of fireworks containing yellow phosphorus. Liver Transpl 2011;17:1286-91.
2. Mauskar A, Mehta K, Nagotkar L, Shanbag P. Acute hepatic failure due to yellow phosphorus ingestion. Indian J Pharmacol 2011;43:355-6.
3. McCarron MM, Gaddis GP, Trotter AT. Acute yellow phosphorus poisoning from pesticide pastes. Clin Toxicol 1981;18:693-711.
4. Tafur AJ, Zapatier JA, Idrovo LA, Oliveros JW, Garces JC. Bone marrow toxicity after yellow phosphorus ingestion. Emerg Med J 2004;21:259-60.
5. Taskesen M, Adıguzel S. A rare cause of poisoning in childhood: yellow phosphorus. J Emerg Med 2012;43:270-2.
6. Akman SA, Cakır M, Baran M, et al. Liver transplantation for acute liver failure due to toxic agent ingestion in children. Pediatr Transplant 2009;13:1034-40.
7. Riordan M, Rylance G, Berry K. Poisoning in children 5: Rare and dangerous poisons. Arch Dis Child 2002;87:407-10.
8. Patocka J, Hon Z. Ethylene glycol, hazardous substance in the household. Acta. Medica (Hradec Kralove) 2010;53:19-23.
9. Davis DP, Bramwell KJ, Hamilton RS, Williams SR. Ethylene glycol poisoning: case report of a record-high level and a review. J Emerg Med 1997;15:653-67.
10. Zakhari N. Ethylene glycol poisoning: Resolution of cranial nerve deficit. The Journal for Nurse Practitioners 2014;10:616-9.
11. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med 2009;360:2216-23.
12. Baum CR, Langman CB, Oker EE, Goldstein CA, Aviles SR, Makar JK. Fomepizole treatment of ethylene glycol poisoning in an infant. Pediatrics 2000;106:1489-91.
13. Detaille T, Wallemacq P, Clement de Clety S, Vanbinst R, Dembour G, Hantson P. Fomepizole alone for severe infant ethylene glycol poisoning. Pediatr Crit Care Med 2004;5:490-1.
14. Hızel S, Şanlı C. Çocuklarda beslenme ve kurşun etkileşimi. Çocuk Sağlığı ve Hastalıkları Dergisi 2006;49:333-8.
15. http://www.zipasilaclama.com/zehirlenmelersahauygulamasi.pdf. Erişim tarihi: Aralık 2015.
16. Jones AL, Dargan PI. What's new in toxicology? Current Paediatrics 2001;11:409-13.
17. Kennedy C, Lordo R, Sucosky MS, Boehm R, Brown MJ. Evaluating the effectiveness of state specific lead-based paint hazard risk reduction laws in preventing recurring incidences of lead poisoning in children. Int J Hyg Environ Health 2016;219:110-7.
18. Yapıcı G, Can G, Şahin Ü. Asymptomatic lead poisoning in children. Cerrahpaşa J Med 2002;33:197-204.
19. Hayes EB, McElvaine MD, Orbach HG, Fernandez AM, Lyne S, Matte TD. Long-term trends in blood lead levels among children in Chicago: Relationship to air lead levels. Pediatrics 1994;93:195-200.
20. Vural N, Güvendik G. Ankara'da yaşayan çocuklarda kurşun absorbsiyonunun çevre kirliliği ile ilgisinin araştırılması, Ulusal Çevre Sempozyumu, Adana, Kasım 1994.
21. Bostancı İ, Beyazova U, Kılıç Z. Kord kanı kurşun düzeyi ve prenatal kurşunla etkilenmenin erken çocuklukta zihinsel fonksiyonlara etkisi. XXXI. Türk Pediatri Kongresi, İstanbul, Ekim 1995.
22. Göker Ş. İstanbul çocuklarında kan kurşun taraması. İ.Ü.Cerrahpaşa Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları. Uzmanlık tezi. 1996.
23. Can G, Yapıcı G, Şahin Ü. Tekirdağ ili merkezinde yaşayan 1-6 yaş grubu çocuklarda kan kurşun düzeylerinin değerlendirilmesi, I.Ulusal Çevre Hekimliği Kongresi, Ankara, 1997.
24. Yapıcı G, Can G, Kızıler AR, et al. Prevalence of asymptomatic lead poisoning among 6 months-6 years old children in Silivri. Uluslar arası Halk Sağlığı Kongresi, İstanbul, Ekim 2000.
25. Karrari P, Mehrpour O, Abdollahi M. A systematic review on status of lead pollution and toxicity in Iran; Guidance for preventive measures. DARU 2012;20:2.
26. Chen TH, Kuo CH, Huang CT, Wang WL. Use of fomepizole in pediatric methanol exposure: The first case report in Taiwan and a literature review. Pediatr Neonatol 2016;57:351-4.
27. Brown MJ, Shannon MW, Woolf A, Boyer EW. Childhood methanol ingestion treated with fomepizole and hemodialysis. Pediatrics 2001;10877.
28. White ML, Liebelt EL. Update on antidotes for pediatric poisoning. Pediatr Emerg Care 2006;22:740-6.
29. Kalkan S, Çevik AA, Çavdar C, et al. Acute methanol poisonings reported to the Drug and Poison Information Center in İzmir, Turkey. Vet Hum Toxicol 2003;45:334-7.
30. Türkmen N, Eren B, Cetin G. Fatal methanol ıngestion in a child: case report. Acta Medica 2009;52:125-7.
31. Jepsen P, Ryan M. Poisoning in children. Current Paediatrics 2005;15:563-8.
32. Riordan M, Rylance G, Berry K. Poisoning in children 4: household products, plants, and mushrooms. Arch Dis Child 2002;87:403-6.
33. Flaman Z, Pellechia-Clarke S, Bailey B, McGuigan M. Unintentional exposure of young children to camphor and eucalyptus oils. Paediatr Child Health 2001;6:80-3.
34. Hockey R. Childhood poisoning and ingestion. Injury Bulletin 2000;60:1-6.

35. Taşkesen M, Pirinççioğlu AG, Üzel H, İyi O. Organofosfat zehirlenmesinde uzun süreli intravenöz atropin kullanımı: İki vaka takdimi. Çocuk Sağlığı ve Hastalıkları Dergisi 2011;54:216-9.
36. Jones K, Everard M, Harding AH. Investigation of gastrointestinal effects of organophosphate and carbamate pesticide residues on young children. Int J Hyg Environ Health 2014;217:392-8.
37. Gözkeser E, Yüksel S, Atalay H. Geç dönem Pralidoksim uygulamasına yanıt veren organofosfat zehirlenmesi olgusu. Pam Tıp Derg 2013;6:26-9.
38. Özcan N, İkincioğulları D. Ulusal Zehir Danışma Merkezi 2008 yılı çalışma raporu özeti. Türk Hij Den Biyol Derg 2009;66(Özel Sayı 3):29-58.
39. Kırel B, Akın A, Sezgin ME, Şenses EY, Ünal Y. Karbon monoksit zehirlenmesi ve hiperbarik oksijen tedavisi: Üç vaka takdimi. Çocuk Sağlığı ve Hastalıkları Dergisi 2005;48:164-7.
40. Karapirli M, Kandemir E, Akyol S, Kantarci MN, Kaya M, Akyol O. Forensic and clinical carbon monoxide (CO) poisonings in Turkey: A detailed analysis. J Forensic Leg Med 2013;20:95-101.
41. Mendoza JA, Hampson NB. Epidemiology of severe carbon monoxide poisoning in children. Undersea Hyperb Med 2006;33:439-46.
42. Besli GE, Ergüven M, Karadoğan M, Yılmaz Ö. Çocuklarda karbon monoksit zehirlenmesi. Akademik Acil Tıp Dergisi 2010;9:26-30.
43. Kaya A, Okur M, Üstyol L, Temel H, Çaksen H. Kayısı çekirdeği yeme sonrası akut siyanür zehirlenme olgusu. Türk Ped Arş 2012;47:141-2.
44. Ögel K, Çorapçıoğlu A, Sır A, ve ark. Dokuz ilde ilk ve ortaöğretim öğrencilerinde tütün, alkol ve madde kullanım yaygınlığı, Türk Psikiyatri Dergisi 2004;15:112-8.
45. Akkan G. Akut zehirlenmelerde farmakolojik yaklaşım, İ.Ü. Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri, Acil Hekimlik Sempozyumu, İstanbul, 1997;145-66.

J Pediatr Res 2017;4(4):186-90
DOI: 10.4274/jpr.22932

Derleme / Review

Topuk Kanı Örneği ile Yapılan Ulusal Yenidoğan Tarama Testleri ve Önemi

National Newborn Screening Tests Carried Out with Heel Lance and Their Importance

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ÖZ

Ülkemizde akraba evlilikleri çok görülmektedir. Bu da çeşitli doğumsal metabolik hastalıkları beraberinde getirmektedir. Doğumsal metabolik hastalıkların erken dönemde yakalanması için yenidoğanda birçok tarama testleri yapılmaktadır. Türkiye'de yenidoğan tarama programı kapsamında yer alan metabolik hastalıklar fenilketonüri, konjenital hipotiroidi, biyotinidaz eksikliği ve kistik fibrozistir. Bebeğin topuk kanından alınan kan örneği ile tarama testi yapılmaktadır. Tarama testlerinin yapılmasında amaç; hastalıklı bebekleri saptamak ve telafisi olmayan zararları engellemek için en yakın zamanda tedavilerine başlamaktır.

Anahtar Kelimeler: Doğumsal metabolik hastalık, tarama testleri, yenidoğan

ABSTRACT

Inbreeding is very common in our country, and this brings along various congenital metabolic diseases. In order to detect the congenital metabolic diseases at an early stage, lots of screening tests are carried out on the newborn. In Turkey, the metabolic diseases which are in the scope of newborn screening program are phenylketonuria, congenital hypothyroidis, biotinidase deficiency, and cystic fibrosis. The screening test is carried out with the blood sample obtained by heel lance. The aim of the screening tests is to identify the babies with diseases, and start treatment as soon as possible in order to prevent irrevocable damage.

Keywords: Congenital metabolic disease, screening tests, newborn

Giriş

Doğumsal metabolik hastalıklar, nadir görülen, çoğu otozomal resesif geçişli hastalıklardır. Ülkemiz gibi akraba evliliğinin sık görüldüğü ülkelerde, kalıtsal metabolik hastalıkların sıklığındaki artış ciddi toplumsal sağlık problemlerine yol açmaktadır (1). Hastalıkları erken veya presemptomatik dönemde yakalamak düşüncesi çok çeşitli tarama testlerinin gelişimi için ilham kaynağı olmuştur. Birçok testler yetersiz olmuş, bu nedenle etik ve verimli tarama programlarının geliştirilmesi hedeflenmiştir (2).

Ülke düzeyinde yenidoğan bebeklerin yaşama daha sağlıklı başlamalarını sağlayabilmek için tarama programları yürütülmektedir. Bu tarama programları ülkelerin kendi koşullarına göre, toplumda sık görülen hastalıklara karşı yapılmaktadır. Yenidoğan tarama programlarının ilk hedefi doğumsal metabolik hastalıkların görülme oranları yüksek olanlara karşı yapılıp, hastalığın erken dönemde tanılanması ve müdahale edilmesidir. Türkiye'de yenidoğan tarama programı kapsamında yer alan metabolik hastalıklar fenilketonüri (FKÜ), konjenital hipotiroidi, biyotinidaz eksikliği ve kistik fibrozistir (KF). Bu hastalıkların taranması için sağlık personeli bebekten doğum

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Geliş tarihi/Received: *16.02.2016* **Kabul tarihi/Accepted:** *25.04.2016*

sonrası, bebek proteinli besinler almaya başladıktan sonra ve genelde taburcu olmadan önce, ilk 24-72 saat içerisinde topuk kanı almaktadır (3,4). Uygulama, tarama testi için bebeğin ayak topuğundan alınan birkaç damla kanın özel olarak hazırlanmış bir filtre kağıdı (Gutrie) üzerine damlatılarak yapılmasıdır (4).

Topuk Kanı Örneği ile Yapılan Yenidoğan Tarama Testinin Ülkemizdeki Tarihçesi

Türkiye Bilimsel ve Teknolojik Araştırma Kurumu aracılığıyla yapılan projede, Türkiye'deki yenidoğanlarda FKÜ görülme sıklığı beklenenden daha yüksek bulunmuştur. Bunu takiben, T.C. Sağlık Bakanlığı tarafından 1986 yılında yenidoğan tarama programına başlanmış ve daha sonra bu tarama programı genişletilmiştir. Programın ilk yıllarında taramalar bazı pilot merkezleri kapsamıştır. İstanbul ve İzmir illeri de bu program kapsamında yer almıştır. 1994 yılında program, "Ulusal Fenilketonüri Tarama Programı"na dönüştürülmüş ve tüm ülkeyi kapsamıştır. Konjenital hipotiroidinin 25 Aralık 2006 tarihinde FKÜ tarama programına eklenmesiyle programın ismi "Ulusal Yenidoğan Tarama Programı" olarak değiştirilmiştir (5). Programa, Ekim 2008 itibarıyla biyotinidaz eksikliği, 1 Ocak 2015 tarihi itibarıyla da KF eklenmiştir (3,5).

Fenilketonüri Taraması

Yenidoğanda FKÜ hastalığının taranması amacıyla yapılmaktadır (6). Klasik FKÜ, genellikle fenilalanin hidroksilaz (PAH) olarak bilinen bir karaciğer enziminin eksikliği sonucu nadir görülen doğumsal metabolik bir hastalıktır (1,7-9). PAH enzimi kan fenilalanini, tetrahidrobiopterine (BH4) yardımcı faktör olarak gerektiren tirozine hidroksile eder (10). Bu enzim eksikliği, kan ve diğer dokularda amino asit fenilalaninin yüksek seviyede olmasına neden olur (7). PAH ya da BH4'ün üretimi ya da geri dönüşümünde defekt olması tedavi edilmediği takdirde zeka geriliği yapabilen hiperfenilalaninemiye neden olur (10).

Türkiye, FKÜ hastalığının en sık görüldüğü ülkelerden biridir. Görülme sıklığı 3000-4000 yenidoğanda birdir. Akraba evliliklerinin sıklıkla yapılması anne ve babanın taşıyıcı olduğu bu gibi hastalıkların görülme sıklığını arttırmaktadır. Türkiye'de her 100 kişiden 4'ünün bu hastalık açısından taşıyıcı olması, akraba olmayan bireylerin de çocuklarının hastalıklı doğmasına sebep olabilir (7,8). Ayrıca, hastalığın yeterince bilinmemesi, zihinsel gelişim bozukluğu olan çocukların bu hastalık yönünden incelenmemesi hastalığın yayılımına neden olmaktadır (11).

Fenilketonüri Belirtileri

FKÜ olan bebekler hayatlarının ilk birkaç ayında sağlıklı bebeklerden ayırt edilmezler. Bebek beslenmeye başladıktan sonra vücutta fenilalanin birikimi nörolojik gelişimini etkilemeye başlar. FKÜ'lü çocuklarda 5-6. aylardan sonra gelişme geriliği belirginleşmeye başlar. Akranları gibi oturma, yürüme ve konuşma gibi becerileri kazanamazlar. Beyin gelişimi yeterince olmadığından mikrosefali gelişir. Çocuk etrafla ilgisiz, hiperkinetik hatta otistik davranışlar gösterebilir. Olguların %60'ında açık renk saç, göz ve deri rengi görülür. Vücut sıvıları ve idrarlarında küf kokusu dikkati çeker (1,8).

Bebek taburcu olmadan hemen önce ve özellikle proteinli besinler almaya başladıktan sonraki 24-72 saatler arasında kan örneği alınır. Bu sürenin 7 günü aşmamasına dikkat edilmelidir. Kan örneği ilk 24 saat içerisinde alınmış ise, bebek 1-2 haftalık olunca örnek alımının tekrarlanması gerekir (4). Kan fenilalanin düzeylerinin 0-12 yaş arasında 2-6 mg/dL olması normal seviyede olduğunu göstermektedir (7,8).

Tedavi ve İzlem

Yakın zamana kadar fenilalanini azaltılmış bir diyet, mevcut olan tek tedavi yöntemiydi (9). FKÜ diyeti, doğal proteinlerden ve ek olarak vitaminler, mineraller ve fenilalanin dışında tüm temel amino asitleri içeren özel tıbbi formüllerden oluşmaktadır (10,11). Ancak uzun vadede yeni tedavi yaklaşımları ortaya çıkmıştır. Bunlar;

- Büyük nötr amino asit, fenilalanin emilimini ve beyne girişini azaltmak için mide-barsak ve kan-beyin bariyerinden fenilalanin taşıyıcısı ile mücadele edebildiğinden alternatif olarak kullanılabileceğinin,
- Fenilalaninden düşük, mükemmel bir protein kaynağı olan ve doğal olarak oluşan glikomakropeptit proteinin,
- Üretimi ya da geri dönüşümünde defekt olması hiperfenilalaninemiye neden olan BH4 testi yapılmasının,
- Enzim tedavisinin de yararlı olabileceği belirtilmektedir (10).

Fenilalanin kan düzeyleri özellikle yaşamın ilk yıllarında sık sık, yaş ilerledikçe daha az sıklıkla izlenmelidir (6). Böylelikle bu bebeklerin tamamen sağlıklı gelişmesi mümkün olabilecektir.

Konjenital Hipotiroidi

Konjenital hipotiroidi, doğumda tiroid hormon eksikliği olarak tanımlanır. Konjenital hipotiroidi 4000 canlı doğumda 1'i etkileyen en yaygın doğum kusurlarından biridir (12-14). Tiroid hormonu (tiroksin veya T4) bebeklerde normal büyüme ve nörolojik gelişim için kesinlikle gereklidir. Tedavi edilmezse, tiroid hormonu eksikliği erken yaşamda ciddi nörolojik bozukluk, kalıcı mental retardasyon ve gelişme geriliği ile sonuçlanmaktadır. Erken tanı ve tedavi yenidoğanın normal büyümesi ve entelektüel gelişimi ile sonuçlanabilmektedir (13).

Topuktan filtre kağıdına alınan kandan tiroid stimülan hormon (TSH) ölçüm esasına dayalı olarak uygulanmaktadır (12).

Konjenital Hipotiroidi Belirtileri

Konjenital hipotiroidi olan bebeklerin çoğu doğumda belirti vermezler. Klinik belirti ve bulgular non-spesifik ya da anlaşılması güç olabilir. Konjenital hipotiroidi olan bebeklerin

%5'inden az doğumda fizik muayene ile tespit edilebilir (13).

Görülebilecek başlıca klinik belirtiler; açık arka fontanel, kaba sesle ağlama, kuru deri, hipotermi, beslenme güçlüğü, kabızlık (konstipasyon), çıkık karın, büyük dil, geniş düz burun, umblikal herni, uzamış yenidoğan sarılığı, letarji, hipotoni, guatr (nadir) olmaktadır (13).

Tedavi ve İzlem

Günde tek doz 10-15 mcg/kg/gün L-tiroksin (Synthroid) ile replasman tedavisi derhal başlanmalıdır. Merkezi sinir sistemi sekellerini önlemek için tedavi geciktirilmemelidir. Güvenilmez doz olamayacağı için tedavide hiçbir sıvı solüsyon onaylanmamış, sadece tablet kullanılmaktadır. Tablet ezilir ve anne sütü ya da formül mama içine karıştırılarak verilir (15,16).

Tedavide, en yakın zamanda TSH seviyesini normal düzeye getirmek, TSH'nin 5 mU/L'den az olmasını sağlamak, serum T_4 ya da serbest T_4'ü normal aralığın üst yarısında tutmak, yaşamın ilk senesinde serum T_4'ün 10-16 mcg/dL ve serbest T_4'ün 1,4-2,3 ng/dL aralığında olması hedeflenmektedir.

Klinik değerlendirme yaşamın ilk 3 yılında birkaç ayda bir yapılmalıdır. Laboratuvar değerlendirmesi ise optimal dozu ayarlayabilmek için;

- Tedavi başladıktan sonra 2 ve 4. haftalarda,
- Yaşamın ilk yılında her 1-2 ayda bir,
- Bir ve üç yaşları arasında her 2-3 ayda bir,
- Büyüme tamamlanana kadar her 3-12 ayda bir,
- Dozda herhangi bir değişiklikten 2 hafta sonra yapılmalıdır (12,17).

Biyotinidaz Eksikliği

Biyotin, B grubu vitaminlerinden biridir. Uygun büyüme, gelişme ve enerji sağlanması için birçok yiyecekte bulunan, suda çözünen gerekli vitamindir (18). Normalde vücudumuzda bulunan biyotinidaz enzimi, biyotin vitamininin geri dönüşümü için gerekli olan bir enzimdir (19).

Biyotinidaz, biyotinin görevini yerine getirebilmesi için bağlı olduğu proteinden biyotini ayırır. Biyotin proteinden ayrıldığında "serbest biyotin" adını alır (20).

Vücudun karbonhidrat, protein ve yağ kullanımı ve bunların yok edilmesi için biyotine ihtiyacı vardır. Gıdalar tarafından alınan biyotin proteine bağlı bulunur ve vücut tarafından kullanılamaz. Yeterli biyotinidaz aktivitesi olmadığı zaman, biyotini proteinden ayırmak mümkün değildir. Bu da zararlı ürünlerin vücutta toplanması ile sonuçlanır. Yeterli biyotinidaz enzim aktivitesi olmadan, vücut normal diyetten aldığından çok daha fazla serbest biyotine ihtiyaç duyar (20). Mevcut değilse, genellikle nörolojik, dermatolojik, immünolojik ve görme ile ilgili sağlık sorunları ortaya çıkar (21).

Dünyada görülme sıklığı yaklaşık olarak 1/60,000'dir. (2,21). Akraba evliliklerinden dolayı dünya ülkeleri içinde biyotinidaz eksikliğinin en sık görüldüğü ülkelerin Türkiye ve Suudi Arabistan olduğu bildirilmiştir (22,23).

Biyotinidaz Eksikliği Belirtileri

Biyotinidaz eksikliği tedavi edilmediği takdirde, doğum sonrası birkaç hafta ya da ay içerisinde, yaklaşık 3-6 ay arasında belirtiler ortaya çıkmaya başlar (19,20).

Başlıca görülebilecek belirtiler; gelişimsel gerilik, hipotoni, nöbetler, deri döküntüsü ve saç dökülmesidir. Ayrıca ataksi, uyuşukluk, işitme kaybı, göz problemleri ve solunum problemleri de mevcut olabilir. Etkilenen çocuklarda yaşamı tehdit edici biyokimyasal değişimler (örneğin; hiperamonyemi, asidoz ve organik asidüri) de olabilir.

Biyotinidaz eksikliği semptomları beyin, deri, iç kulak ve gözler gibi önemli organlara zarar verebilir. Bazı tedavi edilmeyen yenidoğan ve çocuklar bu nedenle ölmektedirler (18-20).

Tedavi ve İzlem

Tedavisi olan, ancak, tedavisi hayat boyu devam eden bir hastalıktır (18). Biyotinidaz eksikliği olan çocukların ekstra biyotin almaları gerekmektedir. Önerilen doz miktarı 5-20 mg arasında değişmektedir (20). Biyotin takviyesi hap ve sıvı formlarda olabilir. Bebeklerin ayrıca uzman doktor ve diyetisyen ile düzenli kontrolleri olmalıdır. Düzenli ve dikkatli bir takip ve tedavi ile normal büyüme ve gelişmeleri sağlıklı bir şekilde sağlanabilir (18).

Kistik Fibrozis

KF, ekzokrin salgı bezlerinde fonksiyon bozukluğu ile karakterize, birçok sistemi tutan otozomal resesif geçişli bir hastalıktır. Ekzokrin bezler üzerinde etkili olduğu için gastrointestinal, solunum ve üreme siteminde fiziksel değişikliklere yol açar (24). Ülkemizde KF görülme sıklığı 3000 canlı doğumda 1'dir (25).

KF'de, 7. kromozomun bacağı üzerindeki gen mutasyona uğramıştır. *KF* geni, kistik fibroz transmembran regülatör proteininin sentezini kodlamaktadır. Bu proteinin mutasyonu, klor iyonunun transportunu bozmaktadır. Solunum yolu epitelinde bu patolojinin olması sodyum emiliminin artmasına yol açar ve sekresyonların yoğunluğu artar. Su miktarı normalden daha az olan sekresyonlar koyu kıvamlı ve yapışkan bir hale gelerek solunum yollarını tıkar. Buna benzer olaylar aynı zamanda pankreas ve safra kanallarında da meydana gelir. Ter bezlerinde ise suyun emilimi bozulmuş olduğundan tuz kaybı artmıştır (24).

Topuk kanından alınan örneklerde immün reaktif tripsinojen (IRT) ölçümü yapılıp değerlendirilmektedir. IRT değeri belirlenen düzeyin üzerinde bulunan bebeklerin topuk kanından ölçümü tekrarlanır. Tekrarlanan ölçümün de belirlenen düzeyin üzerinde çıkması durumunda, bebekler ter testi yapılan merkezlere yönlendirilmelidir (3).

Ter testi, klor düzeyini belirlemek için yapılır. Bebeklere ter testi birkaç günlük olunca yapılabilir, ancak bebekler 4 haftalık olmadan önce yeterli düzeyde ter toplanamayabilir. Bebeklerde klor düzeyinin 40 mEq/L'den fazla olması KF düşündürmektedir (24).

Terin toplanma işlemi: Pilokarpin, bacak ya da kol üzerinde küçük bir alana uygulanır. Bölgeye ter yapımının uyarımı için düşük elektrik akımlı bir elektrot yerleştirilir. Uygulanacak bölge temizlenir ve bölgenin üzerine filtre kağıdı yerleştirilerek, bacak ya da kol kapatılır. Otuz dakika sonra filtre kağıdı çıkartılır (24).

Kistik Fibrozis Belirtileri

Amerikan Kistik Fibrozis Kurumu tarafından 1998 yılında bir konsensüs raporu hazırlanmış ve KF tanısının; bir ya da birden fazla tipik KF bulguları veya KF'li kardeş öyküsünün varlığı veya yenidoğan tarama testinde pozitiflik varlığında terde artmış klor konsantrasyonu veya kistik fibroz transmembran iletim düzenleyicisi *(KFTR)* geninde mutasyon veya anormal nazal epitelyum iyon transportu ile KFTR anomalisinin laboratuvar şartlarında gösterilmesi ile konulabileceği belirtilmiştir (26).

KF gebelikte başlamaktadır, ancak semptomlar ilk başta fark edilememektedir. Semptomları fark etmek uzun yıllar alabileceğinden tanıyı koymakta geç kalınabilir. Tipik belirtiler şunlardır; deride tuzlu bir tat olması (ebeveynler bebeklerini öptüklerinden genellikle bunu fark eder), hırıltı veya nefes darlığı, inatçı öksürük ve aşırı mukus, zatürre ve bronşit gibi sık akciğer enfeksiyonları, sık sinüs enfeksiyonları (sinüzit), burunda büyümeler (nazal polipler), düşük tartı alımı ve büyümede gerilik, kötü kokulu ve yağlı dışkı, karında gaz ve şişlik, el ve ayak parmaklarının genişlemesidir (27).

Tedavi ve İzlem

Erken yaşta gen terapisi, KF genetik bir hastalık olduğundan beri hastalığı önlemek ve tedavi etmek için tek yoldur denilebilir. Gen terapisi, kusurlu geni tamir edebilir veya yerine geçebilir. Tedavide bir başka seçenek KF'li bir kişiye az ya da eksik olan protein ürününün aktif formunu vermektir. Hastalığı çok ilerlemiş olan hastalarda, akciğer transplantasyonu bir seçenek olabilir.

Son 20 yılda geliştirilen daha iyi tedavi yöntemleri KF'li hastaların ömrünü yaklaşık olarak 30 sene arttırabilmektir. Bunlar;

- Akciğer sorunlarının yönetimi: Fizik tedavi, egzersiz ve ilaç (bronkodilatatörler, mukolitikler ve dekonjestanlar), akciğer hava yollarının mukus ile tıkanmasını azaltmak için kullanılır.

- Sindirim problemlerinin yönetimi: Dengeli, yüksek kalorili diyet, yağ oranı düşük ve protein açısından zengin ve pankreas enzimleri (sindirime yardımcı olan) sık reçete edilir. İyi bir beslenmenin sağlanması için A, D, E ve K vitaminleri takviyesi yapılabilir. Lavman ve mukolitik ajanlar barsak tıkanıklıkları tedavisinde kullanılabilir (28).

Yenidoğan Tarama Testlerinde Ebe ve Hemşirelerin Görevi

Yenidoğan tarama testleri topuktan kan alınmasıyla yapılan rutin bir uygulamadır (2). Bu uygulama, çoğunlukla ebe ve hemşireler tarafından yapılmaktadır. Topuktan kan alma basit bir işlem olmakla birlikte yanlış sonuçların olmaması için doğru alınmasına çok dikkat etmek gerekir. Bu amaçla işlem esnasında aşağıdaki basamaklar izlenmelidir;

- Bebeğin ayağı kanın alınacağı alana kan akımının arttırılması için ılık bir havlu ile 3 dakika boyunca ısıtılır. Havlunun ısısının 42 °C'yi geçmemesine dikkat edilmelidir.
- Venöz basıncın artması için bebek ayağının kalp seviyesinin altında tutulması daha uygundur.
- Bebeğin topuğu %70'lik izopropil alkol ile temizlenir ve deride kalan alkolün örneği seyreltmemesi için topuk kuru steril gazlı bir bez ile kurulanır.
- Bebeğin topuğu derinliği 2,5 mm'den daha derin olmayacak şekilde steril bir lanset ile topuğun planlar yüzünün mediyal ve lateral dış kenarlarından delinir.
- İlk kan damlası örneği seyrelten doku sıvısı içerebildiğinden, steril gazlı bez ile silinir.
- Bölge çok hafif sıkılarak sonraki damlanın kendiliğinden serbest kan akımı ile oluşması beklenir.
- Oluşan kan damlası filtre kağıdındaki halkanın ortasına değdirilerek kağıdın uygun miktarda kan damlasını emmesi sağlanır. Kan damlasının kağıdın arka tarafına da eşit miktarda geçtiğinden emin olunmalıdır.
- Halkanın tümü doldurulmadan kan akımı durursa, bu kısım yeniden doldurulmaya çalışılmamalı, işlem kağıdın başka bir kısmında tekrarlanmalıdır.
- Kan örneği alımı tamamlandıktan sonra bebeğin ayağı vücudun üzerine doğru kaldırılır ve iğne bölgesi steril gazlı bir bez ile silinir.
- Alınan kan örneğin ıslak bir şekilde zarfın içine konulmamasına dikkat edilmelidir. Bunun için yapılması gereken örneğin en az 3 saat oda sıcaklığında, yatay pozisyonda kurumasını beklemektir.
- Başka bebeklerden alınan kan örneği ile temas etmemesine dikkat edilmelidir.
- Zarfların plastik torba içine konulmamasına dikkat edilmelidir.
- Özel filtre kağıdına bebek ile ilgili gerekli bilgilerin tam ve doğru olarak doldurulmasına özen gösterilmelidir.
- Kuruyan kan örneklerinin mümkün olduğunca hızlı bir şekilde ilgili merkezlere gönderilmesi sağlanmalıdır (1).

Bu uygulama, yenidoğanlarda ağrılı bir uygulama olduğu için annelerde büyük anksiyete sebebi olabilmektedir. Annelerde ortaya çıkan anksiyetenin en büyük sebebi ise bilinmeyen korkusudur. Yapılan araştırmalar sonucunda ebeveynlerin yenidoğana yapılan girişimler konusunda yeterince bilgilendirilmedikleri ve işlemler ile ilgili eğitime ihtiyaç duydukları görülmüştür (29,30). Ebe ve hemşireler annelerin yenidoğana yönelik gereksinimlerini değerlendirip annelere gerekli bilgilendirmeyi yaptıklarında ve onları desteklediklerinde, annelik rolüne uyumları kolaylaşır ve yenidoğanın sağlığıyla daha çok ilgilenmeye başlar (29,31).

Yenidoğana yapılacak her tür tedavi, girişim ve tarama

testleri ile ilgili ebeveynler mutlaka bilgilendirilmelidir. Sağlık ekibi içerisinde ebe ve hemşireler bu bilgilendirmeyi yapması gereken ilk akla gelen meslek gruplarıdır (29). Annenin anksiyetesinin giderilebilmesi ve rahatlaması için ebe ve hemşirenin hem doğum öncesi hem de doğum sonrası dönemde anneye gerekli bilgilendirmeleri yapmayı görev edinmelidir (29,32). Ailelere uygun eğitim ortamı sağlanmalı ve öğrenmek istedikleri doğrultuda eğitim verilmelidir. Çünkü yapılan çalışmalarda ailelerin daha çok bu testlerin ne zaman yapılması gerektiği, sonuçlarını nasıl öğreneceğini ve çıkan sonuçları nasıl yorumlayabilecekleri hakkında bilgi sahibi olmak istedikleri belirlenmiştir (29,30).

Sonuç

Ülkemizde akraba evlilikleri oranının fazla olması, doğumsal metabolik hastalıkların görülme sıklığında ciddi artışlara neden olmaktadır. Yenidoğan tarama testleri, bazı metabolik hastalıkları erken veya presemptomatik dönemde yakalamak açısından önemlidir. Bebeğin topuk kanından alınan kan örneği ile tarama testi yapılmaktadır. Topuktan kan alma basit bir işlem olmasına rağmen, oldukça dikkat gerektiren bir işlemdir. Ebeler ve hemşireler tarafından doğum sonrası uygun zamanda ve uygun tekniklerle kan alınması yenidoğanda doğumsal metabolik hastalıkların erken tanılanıp, tedaviye erken başlanmasına yardımcı olur. Bu durum, gelecekte bireyin nitelikli yaşam hakkının korunması açısından önemlidir.

Etik

Hakem Değerlendirmesi: Editörler kurulu ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Konsept: S.İ., R.E.G., Dizayn: S.İ., R.E.G., Literatür Arama: S.İ., R.E.G., Yazan: S.İ., R.E.G.

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. Zeybek ÇA. Fenilketonüri tarama programı. Sağlam Çocuk İzlemi Sempozyum Dizisi 2003;35:65-71.
2. Tanyalçın T. Yenidoğanlarda biyokimyasal tarama testleri. Türk Biyokimya Dergisi 2002;27:69-78.
3. Ersu R, Çakır E. Kistik fibrozis yenidoğan tarama testi ile tanı alan hastaları izleme rehberi. T.C Sağlık Bakanlığı Türkiye Halk Sağlığı Kurumu, 2015.
4. Yıldız S, Balcı S, Görak G. Guthrie tarama testi için örnek alma uygulamalarının ve test sonuçlarının değerlendirilmesi. Atatürk Üniv. Hemşirelik Yüksekokulu Dergisi 2006;9:17-28.
5. Tezel B, Dilli D, Bolat H, et al. The development and organization of newborn screening programs in Turkey. J Clin Lab Anal 2014;28:63-9.
6. National Institute of Health Consensus Statement. Phenylketonuria (PKU): screening and management. 2000;17:3:16-8.
7. Sönmez G. Fenilketonüri nedir? TEB Haberler 2008;3:32-3.
8. Müslümanoğlu MH, Çine N, Özdemir M ve ark. Fenilketonüri hastalığında prenatal-postnatal tanıda VNTR bağlantısı ve direkt mutasyon analizleri birlikteliğinin avantajları. Kocatepe Tıp Dergisi 2004;5:19-23.
9. Strisciuglio P, Concolino D. New Strategies for the treatment of phenylketonuria (PKU). Metabolites 2014;4:1007-17.
10. Yazgan, U. Fenilketonüri: 1-7 Haziran Fenilketonüri haftası. Eczacı. 2003;4:23.
11. Sağlık Ansiklopedisi: Fenilketonüri PKU. http://www.medicinehospital.com.tr/ansiklopedi/terim/1493/fenilketonuri-pku.html adresinden 20/05/2015 adresinde erişilmiştir.
12. Ataş A, Çakmak A, Karazeybek H. Konjenital hipotiroidizm. J Curr Pediatr 2007;5:70-6.
13. Murray MA. Primary TSH screen for congenital hypothyroidism. UTAH Department Of Health-Newborn Screening Program 2009;1:1-6.
14. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010;5:17.
15. Morning Report. Congenital hypothyroidism. 2006, April. http://pediatrics.uchicago.edu/chiefs/documents/congenitalhypothyroidism.pdf adresinden 31/05/2015 tarihinde erişilmiştir.
16. Australasian Paediatric Endocrine Group. Guidelines for Management of Congenital Hypothyroidism.http://www.apeg.org.au/Portals/0/documents/guidelines%20for%20management%20of%20congenital%20hypothyroidism.pdf adresinden 31/05/2015 tarihinde erişilmiştir.
17. American Academy of Pediatrics, Rose SR; Section on Endocrinology and Committee on Genetics, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290-303.
18. Tanyalçın Tıp Laboratuvarı. Biyotinidaz eksikliği. 2008. http://www.tanyalcin.com/Data/Bilgilendirme/AileBiotinidaz.pdf adresinden 31/05/2015 tarihinde erişilmiştir.
19. Ontario. Biotinidase deficiency. Newborn Screening Program. 2006, January. http://www.newbornscreening.on.ca/data/1/rec_docs/525_fs_biot.pdf adresinden 31/05/2015 tarihinde erişilmiştir.
20. The Patient Education Institute. Biotinidase deficiency. http://www.kaahe.org/health/en/ArabicSampleModules/modules/peditrcs/pd0401a1/pd040102/pd040102.pdf adresinden 31/05/2015 tarihinde erişilmiştir.
21. Thapar R, Venkatnarayan K. A case of biotinidase deficiency presenting as quadriparesis. Indian Journal of Clinical Practice 2013;24:680-3.
22. İşcan A, Altıntaş İ, Tatlı MM, Karazeybek AH. Biotidinaz eksikliği: Olgu sunumu. Harran Üniversitesi Tıp Fakültesi Dergisi 2004;1:45-7.
23. Afroze B, Wasay M. Biotinidase deficiency in Pakistani children; what needs to be known and done. J Pak Med Assoc 2012;62:312-3.
24. Törüner EK, Büyükgönenç L. Solunum sistemi sorunu olan çocuk: kistik fibrozis. Göktuğ Yayıncılık 2012:627-36.
25. Uslu HS, Zübarioğlu AU, Bülbül A. Neonatoloji perspektifinden selektif metabolik tarama testleri. JAREM 2015;5:39-46.
26. Uyan, ZS. Kistik fibrozis. Kocaeli Üniversitesi Tıp Fakültesi Çocuk Göğüs Hastalıkları Bilim Dalı. http://file.lookus.net/TGHYK/tghyk.32.pdf adresinden 07/05/2015 tarihinde erişilmiştir.
27. Cystic Fibrosis Canada. The facts about cystic fibrosis. 2014.
28. National Institutes of Health National Heart, Lung, and Blood Institute. Cystic Fibrosis. NIH Publication 1995:95-3650.
29. Büyük ET. Annelerin bebeklerine yapılan topuk kanı alma işlemi hakkındaki bilgileri. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi 2014;3:883-91.
30. Tluczek A, Orland KM, Nick SW, Brown RL. Newborn screening: an appeal for improved parent education. J Perinat Neonatal Nurs 2009;23:326-34.
31. Beydağ KD. Doğum sonu dönemde anneliğe uyum ve hemşirenin rolü. TSK Koruyucu Hekimlik Bülteni 2007;6:479-84.
32. Gürel SA, Gürel H, Balcan E. Doğum öncesi bakım esnasında gebelik, doğum ve doğum sonu döneme ilişkin bilgi edinme durumu. Perinatoloji Dergisi 2006:14.

J Pediatr Res 2017;4(4):191-4
DOI: 10.4274/jpr.49368

Derleme / Review

Çocuk Yoğun Bakım Ünitesinde Süperior Mezenterik Arter Sendromu

Superior Mesenteric Artery Syndrome at Pediatric Intensive Care Unit

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ÖZ

Süperior mezenterik arter sendromu oral beslenme intoleransı olan hastalarda nadir olarak gözlenen bir durumdur. Duodenumun etrafındaki yağ dokusunun hızlı kaybına bağlı süperior mezenterik arter ile duodenum arasındaki açının derecesi azalmaktadır. Yeterli peristaltizmi olsa da duodenum geçilememektedir. Birçok nedeni vardır. Tedavi yaklaşımlarının temelinde erken nütrisyonel destek yatmaktadır. Bu yayını sendromun farkındalığının artırılması ve immobilize hastaların nütrisyonel desteklerinin erken başlanmasını hatırlatmak için paylaştık.

Anahtar Kelimeler: Malnütrisyon, süperior mezenterik arter, duodenum, yağ dokusu

ABSTRACT

Superior mesenteric artery syndrome is a rare condition in patients who have oral feeding intolerance. Due to decreased fat tissue around the duodenum, the angle between the superior mesenteric artery and duodenum also decrease. Despite normal peristaltic bowel activity, nutrients cannot pass the duodenum. There are various causes for this. The basic treatment modality is early nutritional support. We share this article to increase awareness of this condition and recommend early nutritional support for immobilised patients.

Keywords: Malnutrition, superior mesenteric artery, duodenum, fat tissue

Giriş

Süperior mezenterik arter (SMA) sendromu, barsak obstrüksiyonlarının nadir görülen nedenlerinden biridir. Bu sendrom duodenumun üçüncü parçasının aorta ve mezenterik arterin arasında basıya uğramasıyla karakterizedir (1,2). Bu basının nedeni duodenum etrafındaki yağ dokusunun azalmasıdır. Cast sendromu, Wilkie sendromu gibi başka isimlerle de anılır (3,4). SMA sendromu bir dışlama tanısıdır. Klinik her zaman radyografik bulgularla uyuşmayabilir ve tedavi sonrası semptomlarda gerileme olmayabilir (5,6). Bu nedenle proksimal intestinal obstrüksiyon yapabilecek diğer tanılar da göz ardı edilmemelidir.

SMA sendromunda duodenumun üçüncü parçası, aort ve mezenter arterin arasında kalmaktadır (Şekil 1, 2). SMA L1 seviyesinde aortadan ayrılır. Aralarında duodenumun üçüncü parçasını sarar şekilde lenfatik ve yağ dokusu bulunur. SMA ve aorta arasındaki açının normal insanlarda 38-65 derece (7), aralarındaki mesafenin de 10-28 mm (1) kadar olması beklenmektedir. Ancak çalışmalar SMA sendromu tanısı alan hastalarda bu açının 6 dereceye kadar azaldığı, aradaki mesafenin 2 mm'ye kadar kısaldığı gösterilmiştir

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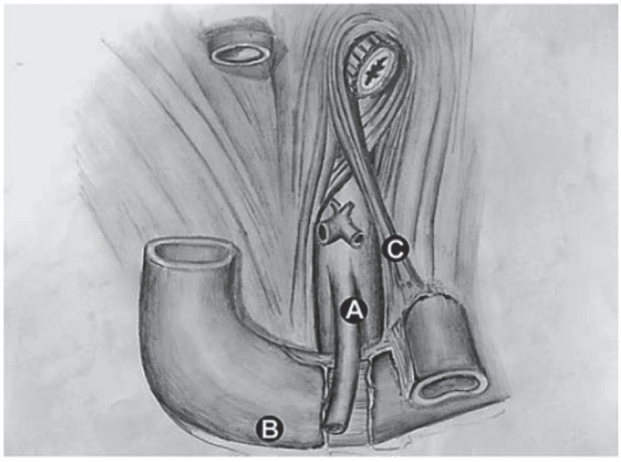
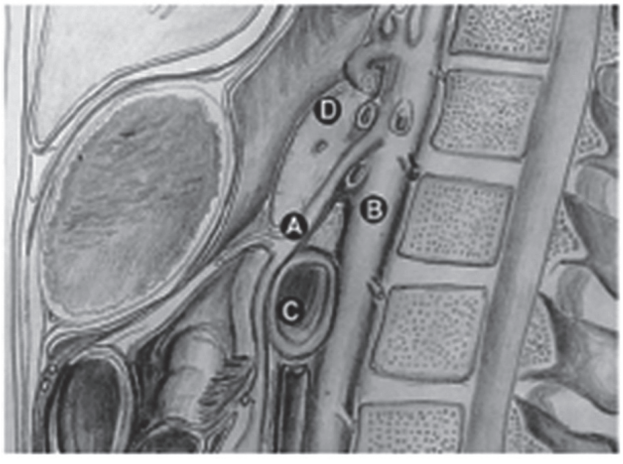
Geliş tarihi/Received: *12.12.2016* **Kabul tarihi/Accepted:** *28.01.2017*

(8,9). Bu açının vücut kitle indeksi (VKİ) ile orantılı olduğu da düşünülmektedir (10).

SMA sendromu için pek çok risk faktörü bulunmaktadır (2). Maligniteler (9,11), yanıklar (12), travmalar (13), anoreksiya nevroza (14) gibi beslenmenin hızlıca bozulduğu hastalıklar veya malabsorbsiyon sendromları (9), HIV (15) gibi beslenmenin kronik olarak azlığı ile giden hastalıklar SMA sendromu için başlıca risk faktörleridir. Ayrıca immobilite oluşturarak hızlı kilo kaybına yol açan spinal kord anomalileri (1), parapleji, özellikle skolyoz olmak üzere ortopedik cerrahi geçirme (16-18) veya uzamış yatak istirahati gerektiren hastalıklarda da risk artar. Bunlar dışında bazı kişilerde de mezenter arterin başlangıç noktasının daha aşağı yerleşimli (11) ya da Treitz ligamentinin başlangıç noktasının daha proksimalde olmasının (19) SMA sendromuna neden olduğu gösterilmiştir.



Şekil 1. A) Süperior mezenterik arter, B) Duodenumun 3. parçası, C) Treitz ligamenti; aorta da L1 seviyesinde ayrılan süperior mezenterik arter, duodenumun 3. parçasının üzerinden geçmektedir



Şekil 2. A) Süperior mezenterik arter, B) Aort, C) Duodenumun 3. parçası, D) Pankreas; duodenumun 3. parçası aorta ve süperior mezenter arter arasında kalmaktadır, süperior mezenter arter sendromunda, çevre yağ dokunun azalması nedeni ile duodenum basıya uğramaktadır (2)

Klinik

Hastalar hızlı ilerleyici bir klinik gösterebileceği gibi, yavaş seyirli olarak da karşımıza çıkabilir (5). Genel olarak ikisi de intestinal obstrüksiyon bulguları taşımaktadır. Yemek sonrası hafif mide ağrısından elektrolit dengesini bozabilecek, ciddi kilo kaybına yol açabilecek kusmalarla giden geniş bir semptom yelpazesi bulunmaktadır. En sık görülen semptomu epigastrik ağrı olmakla birlikte bulantı, kusma, safralı kusma, reflü bulguları, batın distansiyonu görülen semptomlardan birkaçıdır (6,20,21). Epigastrik ağrının karakteristik özelliği, prone pozisyonunda, sol lateral dekübit ve diz-göğüs pozisyonlarında azalmasıdır. Bu durum duodenuma yapılan basının bu pozisyonlarda azalması ile açıklanmaktadır (9). Laboratuvar bulguları da benzer şekilde duodenal obstrüksiyon ve kusmaya sekonder gelişmektedir. Ancak bunların hiçbiri tanı koydurabilecek spesifik bulgular değildir.

Tanı

SMA sendromunda semptomların non-spesifik olması nedeni ile tanı koyabilmek için öncelikle bu tanının akla getirilmesi gerekir. SMA sendromu nadir görülen bir dışlama tanısıdır. Tanı konmadan önce intestinal obstrüksiyon yapan ve daha sıklıkla görülen hastalıklar dışlanmalıdır.

Direkt batın grafisi ilk yapılabilecek tetkiklerdendir. Mide ve proksimal duodenal dilatasyon tanıyı destekler niteliktedir. Yine oral kontrastla çekilen mide-duodenum grafilerinde de opak maddenin mide ve proksimal duodenumda birikimi diğer obstrüktif hastalıklarda olabileceği gibi destekleyici bulgulardandır (22). Obstrüksiyon bulgularının lateral dekübit ve prone pozisyonunda düzelmesi ise SMA tanısını destekler niteliktedir (9).

Daha spesifik tanısı batın ultrasonografisi (USG) ve kontrastlı batın bilgisayarlı tomografisi (BT) ile yapılan ölçümlerle konabilmektedir. Türkiye'de yapılan bir çalışmada (20), USG ile ölçülen aorta ve SMA arasındaki mesafe; SMA sendromlu hastalarda 3,8 mm iken, kontrol grubunda 9 mm saptanmıştır. Yine aynı çalışmada, SMA ve aorta arasındaki açı SMA sendromlu hastalarda 7 derece iken, kontrol grubunda 32 derece saptanmıştır. Benzer ölçümler BT ile de yapılmış olup SMA sendromlu hastalarda mesafe 3,8 mm iken, kontrol grubunda 11 mm ölçülmüştür. SMA tanısına yönelik bu ölçümler yine batın manyetik rezonans (MR) anjiyografi ile de alınabilmektedir. Kontrastlı batın BT ve MR anjiyografi arasında ölçümleri saptama açısından anlamlı bir fark bulunmamıştır (11).

SMA sendromu tanı kriterleri yapılan çalışmalar doğrultusunda belirlenmiştir. Aktif peristaltizm olmasına rağmen, duodenumun üçüncü kısmında obstrüksiyon bulgularının olması ve yapılan tetkiklerde anlamlı ölçümlerin elde edilmesi tanı koydurucudur. Ölçümler için SMA ve aorta arasındaki açının 25 derecenin altında olması ve aralarındaki mesafenin 8 mm altında olması anlamlı kabul edilmektedir (20,23). Yine yüksek yerleşimli Treitz ligamanı ve anormal

distal başlangıçlı SMA, tanı aşamasında düşünülmesi gereken diğer durumlardır.

Tedavi

Tedavide öncelikle destek tedavi yer almalıdır (24). Gastrik ve duodenal dilatasyonu olan olguya nazogastrik tüp ile dekompresyon uygulanmalıdır (22). Ancak buradan kaybedilen sıvı miktarına da dikkat edilmesi gerekmektedir.

SMA sendromlu hastalarda ciddi kusma ve safra kayıpları nedeni ile elektrolit dengesizliği görülebilmektedir. Hipovolemi, hipokalemi, metabolik alkaloz görülebilmektedir ve bu konuda dikkatli olunarak replasman tedavilerinin verilmesi gerekmektedir (22,25). SMA sendromlu hastalarda beslenme diğer dikkat edilmesi gereken önemli konulardandır. Yağ doku kaybı ile belirginleşen klinik tablo, beslenme düzenlenmediği müddetçe önüne geçilemeyen bir durum olmaktadır. Beslenme girişimsel olarak gastrojejunal sonda yerleşimi ile enteral olarak ya da tedavi sürecinde total parenteral nütrisyon şeklinde olabilir. Yüksek kalorili beslenmenin sağlanmasının, bu klinik duruma neden olan hastalıklardan bağımsız olarak, tedavi sürecinde önemli bir rol oynadığı gösterilmiştir (11).

SMA sendromu için diğer bir tedavi yöntemi de cerrahi yaklaşımdır. Strong prosedürü, Treitz ligamanını keserek duodenumu serbestleştirmek esasına dayanmaktadır (26,27). %25 olguda pankreatikoduodenal arter nedeni ile serbestleştirme yapılamamaktadır (28). Gastrojejunostomi ve duodenojejunostomi de diğer tedavi yöntemleridir. Gastrojejunostomi gastrik dekompresyon sağlamakla birlikte duodenum basısı devam ettiği için ikinci bir girişim gerektirebilmektedir. Duodenojejunostomide de bası öncesi bölüm jejunum ile ağızlaştırılır. Bu yöntemde kör barsak sendromu riski daha az görülmektedir ve %90 başarı şansı mevcuttur (29). 1986 yılında yapılan 146 olgu içeren bir çalışmada, ciddi olgularda duodenojejunostominin diğer iki yönteme göre daha efektif olduğu gösterilmiştir (28).

Son yıllarda aynı cerrahi yöntemler, laparoskopik olarak da yapılabilmektedir. İlk olarak 1995 yılında Massoud (30) tarafından 3 hastaya Strong operasyonu, 1998 yılında da Gersin ve Heniford (31) tarafından 1 hastaya duodenojejunostomi operasyonu laparoskopik olarak yapılmıştır. Yapılan çalışmalar, laparoskopik girişim ile operasyon sonrası ağrıların daha az yaşandığını, hastanede kalış süresinin kısaldığını ve normal aktiviteye dönüşün hızlandığını göstermektedir (32). Bu nedenlerle minimal invaziv girişim gerektiren laparoskopik yöntemler günümüzde daha çok tercih edilmektedir.

SMA sendromu ilk olarak 1842 yılında Rokitansky (33) tarafından arteriyomezenterik oklüzyon olarak tanımlanmıştır. Yetmiş beş hasta içeren en geniş seri Wilkie (34) tarafından, 1927 yılında yayınlanmıştır. Sonrasında pek çok merkez tarafından çoklu olgu bildirimleri yapılmıştır. Günümüzde SMA ile ilgili 330'dan fazla olgu sunumu ve derleme mevcuttur. Ancak yine de özellikle yoğun bakımda yatan ve izleminde intestinal obstrüksiyon gözlenen hastalarda, akla geç gelen bir tanıdır (2,35).

Bu klinik durum erişkinlerde yapılan çalışmalara göre kadınlarda ve genç erişkinlerde (10-39 yaşları arasında) daha sık görülmektedir (6,34,36). Bizim olgularımız da adölesan çağındaki hastalardı. Genç erişkin dönemde daha sıklıkla görülen bu klinik tablonun sıklıkla predispozan bir faktörü olduğu ve VKİ düşüklüğünün hastalığa yatkınlık yarattığı da bilinmektedir (10). Bizim hastalarımızın da travmaya bağlı immobilize olmaları, ince uzun yapıda olmaları, düşük VKİ'ye sahip olmaları, kilo kaybının eşlik etmesi kliniği kolaylaştıran risk faktörleriydi. Kliniğimizin takip ettiği ve SMA sendromu tanısı konulan iki hasta olurken ikisi de astenik vücut yapısına sahip gençlerdi. VKİ'leri 16,5 ve 16,3 olarak ölçüldü.

Ani kilo kaybına yol açan nedenler bu kliniğe neden olmaktadır. Özellikle yoğun bakım kliniklerinde yatmakta olan ciddi enfeksiyona sahip hastalar, travma hastaları, yanık hastaları, malignitesi olan hastalar risk altındadır. Bu nedenle, bizim olgularımızda olduğu gibi yoğun bakım ünitesinde izlenmekte olan olgularda beslenme sorunları, ani kilo kayıpları gözlendiğinde SMA sendromu akla gelmesi gereken bir klinik durumdur. Risk faktörü olan hastalarda ciddi kilo kayıplarının gözlenmesi de SMA sendromu riskini arttırmaktadır (35). Kilo kaybını önlemek amacıyla yoğun bakım ünitelerinde tedavisi sürmekte olan olguların beslenmesine de gereken önemin verilmesi bu durumun önlenmesi açısından önemli bir yere sahiptir. Cerrahi girişim düşünülen olgularda da preoperatif beslenme, postoperatif komplikasyon riskini azaltmaktadır (35).

Sonuç olarak, yoğun bakım ünitelerinde izlenmekte olan hastalarda, klinik durumun uygun olduğu en erken dönemde beslenmeye başlanmalıdır. Beslenmesi mümkün olmayan olguların da total parenteral nütrisyon desteği ile yeterli kalori almaları sağlanmalı ve kilo kayıpları önlenmelidir. Ancak yine de alınan önlemlere rağmen kilo kayıpları durdurulamayan, ciddi beslenme sorunu ve intestinal obstrüksiyon bulguları olan olgularda SMA sendromu akla gelmesi gereken bir tanıdır.

Etik

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: M.A.K., Konsept: M.A.K., Dizayn: M.A.K., E.B.Y., Veri Toplama veya İşleme: E.B.Y., Analiz veya Yorumlama: B.K., Literatür Arama: M.A.K., Yazan: M.A.K., E.B.Y.

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. Sapkas G, O'Brien JP. Vascular compression of the duodenum (cast syndrome) associated with the treatment of spinal deformities. A report of six cases. Arch Orthop Trauma Surg 1981;98:7-11.

2. Welsch T, Büchler MW, Kienle P. Recalling superior mesenteric artery syndrome. Dig Surg 2007;24:149-56.
3. Dorph MH. The Cast Syndrome; Review of the literature and report of a case. N Engl J Med 1950;243:440-2.
4. Wilkie DP. Chronic Duodenal Ileus. Br J Surg 1921;9:204.
5. Cohen LB, Field SP, Sachar DB. The superior mesenteric artery syndrome. The disease that isn't, or is it? J Clin Gastroenterol 1985;7:113-6.
6. Ylinen P, Kinnunen J, Höckerstedt K. Superior mesenteric artery syndrome. A follow-up study of 16 operated patients. J Clin Gastroenterol 1989;11:386-91.
7. Derrick JR, Fadhli HA. Surgical anatomy of the superior mesenteric artery. Am J Surg 1965;31:545-7.
8. Wayne ER, Burrington JD. Duodenal obstruction by the superior mesenteric artery in children. Surgery 1972;72:762-8.
9. Hines JR, Gore RM, Ballantyne GH. Superior mesenteric artery syndrome. Diagnostic criteria and therapeutic approaches. Am J Surg 1984;148:630-2.
10. Ozkurt H, Cenker MM, Bas N, Erturk SM, Basak M. Measurement of the distance and angle between the aorta and superior mesenteric artery: normal values in different BMI categories. Surg Radiol Anat 2007;595-9.
11. Lippl F, Hannig C, Weiss W, Allescher HD, Classen M, Kurjak M. Superior mesenteric artery syndrome: diagnosis and treatment from the gastroenterologist's view. J Gastroenterol 2002;37:640-3.
12. Reckler JM, Bruck HM, Munster AM, Curreri PW, Pruitt BA Jr. Superior mesenteric artery syndrome as a consequence of burn injury. J Trauma 1972;12:979-85.
13. Smith BM, Zyromski NJ, Purtill MA. Superiorm mesenteric artery syndrome: an underrecognized entity in the trauma population. J Trauma 2008;64:827-30.
14. Elbadaway MH. Chronic superior mesenteric artery syndrome in anorexia nervosa. Br J Psychiatry 1992;160:552-4.
15. Agarwal T, Rockall TA, Wright AR, Gould SW. Superior mesenteric artery syndrome in a patient with HIV. J R Soc Med 2003;96:350-1.
16. Keskin M, Akgül T, Bayraktar A, Dikici F, Balık E. Superior mesenteric artery syndrome: an infrequent complication of scoliosis surgery. Case Rep Surg 2014;2014:263431.
17. Schwartz A. Scoliosis, superior mesenteric artery syndrome, and adolescents. Orthop Nurs 2007;26:19-24.
18. Crowther MA, Webb PJ, Eyre-Brook IA. Superior mesenteric artery syndrome following surgery for scoliosis. Spine (Phila Pa 1976) 2002;27:528-33.
19. Moskovich R, Cheong-Leen P. Vascular compression of the duodenum. J R Soc Med 1986;79:465-7.
20. Unal B, Aktaş A, Kemal G, et al. Superior mesenteric artery syndrome: CT and ultrasonography findings. Diagn Interv Radiol 2005;11:90-5.
21. Yakan S, Calıskan C, Kaplan H, Deneclı AG, Coker A. Superior mesenteric artery syndrome: a rare cause of intestinal obstruction. Diagnosis and surgical management. Indian J Surg 2013;75:106-10.
22. Dietz UA, Debus ES, Heuko-Valiati L, et al. Aorto-mesenteric artery compression syndrome. Chirurg 2000;71:1345-51.
23. Neri S, Signorelli SS, Mondati E, et al. Ultrasound imaging in diagnosis of superior mesenteric artery syndrome. J Intern Med 2005;257:346-51.
24. Attard AR. The superior mesenteric artery syndrome. Maltese Med J 1994;6:41-3.
25. Barnes JB, Lee M. Superior mesenteric artery syndrome in an intravenous drug abuser after rapid weight loss. South Med J 1996;89:331-4.
26. Wilson-Storey D, MacKinlay GA. The superior mesenteric artery syndrome. J R Coll Surg Edinb 1986;31:175-8.
27. Strong EK. Mechanics of arteriomesenteric duodenal obstruction and direct surgical attack upon etiology. Ann Surg 1958;148:725-30.
28. Lee CS, Mangla JC. Superior mesenteric artery compression syndrome. Am J Gastroenterol 1978;70:141-50.
29. Fromm S, Cash JM. Superior mesenteric artery syndrome: an approach to the diagnosis and management of upper gastrointestinal obstruction of unclear etiology. S D J Med 1990;43:5-10.
30. Massoud WZ. Laparoscopic management of superior mesenteric artery syndrome. Int Surg 1995;80:322-7.
31. Gersin KS, Heniford BT. Laparoscopic duodenojejunostomy for treatment of superior mesenteric artery syndrome. JSLS 1998;2:281-4.
32. Makam R, Chamany T, Potluri VK, Varadaraju PJ, Murthy R. Laparoscopic management of superior mesentric artery syndrome: A case report and review of literature. J Minim Access Surg 2008;4:80-2.
33. Rokitansky C. Handbuch der pathologischen Anatomie, in Handbuch der pathologischen Anatomie, 1st ed. 1842:187.
34. Wilkie DP. Chronic duodenal ileus. Am J Med Sci 1927;173:643-9.
35. Merrett ND, Wilson RB, Cosman P, Biankin AV. Superior mesenteric artery syndrome: diagnosis and treatment strategies. J Gastrointest Surg 2009;13:287-92.
36. Biank V, Werlin S. Superior mesenteric artery syndrome in children: a 20-year experience. J Pediatr Gastroenterol Nutr 2006;42:522-5.

J Pediatr Res 2017;4(4):195-9
DOI: 10.4274/jpr.36449

Original Article / Orijinal Araştırma

Prevalence of Proteinuria in School-Aged Turkish Children, and Its Association with Obesity and Hypertension

Okul Çağı Türk Çocuklarında Proteinüri Sıklığı ve Obezite ve Hipertansiyonla İlişkisi

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ABSTRACT

Aim: In kidney diseases, renal damage may be mild and initially asymptomatic. Proteinuria, a marker of kidney injury, directly contributes to chronic tubulointerstitial damage. We investigated the prevalence of proteinuria (POP) in school-aged children in Turkey.

Materials and Methods: The cluster sampling method was used to calculate the required size of the study group for this cross-sectional study. Urine samples were randomly obtained to determine urinary protein/creatinine ratio (Upr/Ucr) from 1374 children aged 6 to 18 years. POP was also specifically assessed in hypertensive and obese children.

Results: The mean age of the subjects was 11.68±3.43 years. The children were from rural (23.9%) and urban (76.1%) regions of Tokat, Turkey. Upr/Ucr ≥0.20 was detected in 92 children, corresponding to a POP rate of 6.7%, without any statistically significant difference between girls and boys. Among 141 obese children, 16 (11.3%) and 76 of 1233 non-obese children (6.2%) had proteinuria ($p<0.05$). Children with hypertension had a POP of 7.5% compared to the 6.7% of those without hypertension ($p>0.05$).

Conclusion: Among school-aged Turkish children POP was 6.7%. POP was higher in obese than in non-obese children. But there was no association between POP and hypertension. While screening programs allow the early detection of renal disease, further cohort studies are required to be able to suggest urinary screening programs.

Keywords: Proteinuria, children, obesity, protein creatinine ratio, hypertension

ÖZ

Amaç: Böbrek hastalıklarında renal hasar başlangıçta asemptomatik ve hafif olabilir. Böbrek hasarının bir belirteci olan proteinüri, kronik tübülointerstisyel hasara doğrudan katkıda bulunur. Okul çağındaki çocuklarda proteinüri prevalansını (PP) araştırdık.

Gereç ve Yöntemler: Bu kesitsel çalışma için çalışma grubunun gerekli boyutunu hesaplamak için küme örnekleme yöntemi kullanıldı. Altı-on sekiz yaş arasındaki 1374 çocuğun idrar protein/kreatinin oranını (Upr/Ucr) belirlemek için idrar numuneleri rastgele elde edildi. PP hipertansif ve obez çocuklarda ayrıca hesaplandı.

Bulgular: Olguların yaş ortalaması 11,68±3,43 yıl idi. Olguların %23,9'u kırsal alanlardan ve %76,1'i kentsel bölgeden alındı. Kız ile erkek çocuklar arasında istatistiksel olarak anlamlı farklılık olmaksızın, 92 çocukta Upr/Ucr ≥0,20 saptandı, PP %6,7'ye karşılık geldi. Yüz kırk bir obez çocuktan 16'sında (%11,3) proteinüri vardı; obez olmayan 1233 çocuğun 76'sında (%6,2) proteinüri vardı ($p<0,05$). Hipertansiyonlu çocuklarda proteinüri %7,5 iken hipertansif olmayanlardaki prevalans oranı %6,7 idi ($p>0,05$).

Sonuç: Okul çağındaki Türk çocuklarında PP %6,7 idi. PP, obezlerde obez olmayan çocuklardan daha yüksekti. Ancak, PP ve hipertansiyon arasında herhangi bir ilişki mevcut değildi. Tarama programları, böbrek hastalığını erken tespitte yardımcı olsa da üriner tarama programlarının önerilmesi için daha fazla kohort araştırmaları gereklidir.

Anahtar Kelimeler: Proteinüri, çocuklar, obezite, protein kreatinin oranı, hipertansiyon

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Received/Geliş tarihi: *10.07.2017* **Accepted/Kabul tarihi:** *05.09.2017*

Introduction

Chronic kidney disease (CKD), characterized by the irreversible deterioration of kidney function, leads to end-stage renal disease (ESRD), which is a major and growing public health problem (1,2). The early detection of kidney disease based on the determination of proteinuria and the identification of its cause are important for early treatment to prevent CKD, and therefore, ESRD development (1). Almost all of the proteins filtered by the kidney glomeruli are reabsorbed in the proximal tubule by endocytosis at the luminal membrane. Significant proteinuria occurs when this energy-requiring mechanism is saturated and it can thus be measured by determining the amounts of protein (mg) and creatinine (mg) in a random urinary sample, expressed as the urinary protein/creatinine ratio (Upr/Ucr) (3). In children <2 years of age the normal upper limit of the Upr/Ucr is 0.50; in children >2 years of age, it is 0.20 (4,5). The Upr/Ucr correlates well with 24 h urine protein excretion (3).

In kidney diseases, renal damage may be mild and initially asymptomatic. If proteinuria is detected before nephrotic involvement, the progression of renal injury to ESRD can be prevented or delayed. A failure to promptly refer patients with early kidney disease to a nephrologist may result in the need for renal replacement therapy (6). Because proteinuria is a significant symptom of renal injury, it is also a stronger marker of CKD progression; if the loss of function is minimal there will be little or no proteinuria (7). Moreover, while proteinuria was previously considered a marker of the severity of the underlying disease, it is now clear that proteins filtered through the glomerular capillaries have an intrinsic renal toxicity that contributes to disease progression (8). This finding has highlighted the importance of the early detection of proteinuria to prevent CKD, and its progression to ESRD (9). The worldwide prevalence of childhood obesity has increased greatly over the past three decades (10). This led to an increase in CKD prevalence in the last decade of the century. It has been recently emphasized that obesity is an independent risk factor for CKD (11). The initial body mass index (BMI) is recommended as an independent predictor of the progression of CKD (12).

We investigated the prevalence of proteinuria (POP) as a benign symptom or a sign of CKD in the province of Tokat in northern Turkey by measuring protein levels in random urine samples collected from a pediatric population. Also in this study, we aimed to determine the effect of obesity and hypertension on POP in school aged-children.

Materials and Methods

The number of students to be surveyed and the number of clusters to be surveyed from each school were determined by multi-layered proportional cluster sampling method considering the number of students in primary, secondary and high schools in the province center and districts according to the 2013-2014 academic year records of the provincial national education directorate sex and age groups. The potential study population consisted of 108.514 school children between the ages of 6 and 18 years. The cluster sampling method was used to calculate the number of participants needed to power the study according to an expected (p) POP of 50% and a deviation (d) of 0.05 based on the 97% confidence interval. Thus, in this cross-sectional study the required size of the study group was 1584 children. However, 210 children were excluded from the study due to inadequate or inappropriate sampling. The remaining 1374 children were enrolled. Although first morning and two urine samples were suggested including the first urine in the morning, we used only one randomized urine sample in the day time in favor of usability. Urinary samples were randomly obtained from the children in the schools between April 2014 and June 2014.

Total protein and creatinine levels were measured using a Cobas 6000 auto analyzer and commercial kits (Roche Diagnostics, USA). The urine samples were denatured with benzethonium chloride before measuring the amount of protein using the turbidimetric method, and the amount of creatinine using the Jaffe colorimetric method. The results were expressed as mg/dL. The Upr/Ucr (mg/mg) was also calculated from the samples. The cut-off value for proteinuria to determine POP was 0.20.

Age, sex, weight, height, BMI, body temperature, and systolic and diastolic blood pressure (BP) were recorded, as was a history of drug use or chronic disease of any kind. Since five children to be enrolled to the study had been diagnosed with epilepsy, five with Familial Mediterranean Fever, one child with atypical autism, and one with celiac disease, a total of twelve children from the substitute list were recruited in their place. Weights were measured using a digital scale (Seca Corp., Chino, California, USA). The measurements were taken while the patients were barefoot and wearing light clothing. Height was measured using a portable stadiometer (Seca) together with weight. BMI was calculated as weight in kg divided by the square meter of the height (kg/m^2). The subjects were diagnosed as obese according to BMI >95 percentile, considering the sex-and age-specific growth curves and cut-off levels for Turkish children. BPs were measured by using a digital sphygmomanometer (Omron 705IT, Omron Healthcare Co., Kyoto, Japan), and if the measured BP was high according to age, sex and height, the mean of the two measurements were noted. Hypertension has been defined as BP ≥95th percentile according to age and sex, and height (13). The relationships between obesity and proteinuria and between hypertension and proteinuria were investigated by determining the POP value in subgroups of the participants. In addition, for POP and Upr/Ucr determinations, the children were divided into three age-based groups: 6-9 years, 10-13 years, and 14-18 years.

The study protocol was in accordance with the Helsinki Declaration of the World Medical Association, and ethical standards. Gaziosmanpaşa University Ethics Committee

approval was received for this study (approval number: 14-KAEK-035). Informed consent was obtained from, and the questionnaires used to gather information about the children were answered by the parents and families.

Statistical Analysis

Quantitative data are expressed as the arithmetic mean and standard deviation. An independent sample t test or one-way analysis of variance was used to compare continuous normal data between the groups. A χ^2 test or the Yates correction χ^2 test was used to compare categorical data. Categorical variables were expressed as counts and percentages. A multivariate logistic regression model was implemented to determine the relation between selected variables and proteinuria. A p value <0.05 was considered to indicate statistical significance. The statistical analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., and Somers, New York).

Results

Urine samples were collected from 1374 children, 683 (49.7%) females and 691 (50.3%) males. Their mean age was 11.68±3.43 years (6-18 years). The mean ages of girls and boys (11.70±3.46 years and 11.66±3.41 years respectively) were similar. The children resided in rural (n=329, 23.9%) and urban (n=1045; 76.1%) regions. The characteristics of the study group are provided in Table I.

A Upr/Ucr ≥0.20 was determined in 92 children, corresponding to a POP of 6.7%. POP was 5.8% in the girls and 7.6% in the boys; the difference was not statistically significant (p>0.05).

Among 141 obese children, 16 (11.3%) had proteinuria, whereas in 1233 non-obese children proteinuria was measured in 76 (6.2%); the difference was statistically significant (p<0.05). Children with hypertension had a POP of 7.5% compared to the 6.7% of those without hypertension but the difference was not statistically significant (p>0.05). POP in children living in urban areas was 7.6%, and those in rural areas had a POP of 4%; the difference was statistically significant (p<0.05).

POP was 0.5%, 3.0%, and 16.7% in the age groups 6-9 years, 10-13 years, and 14-18 years respectively. A statistically significant difference was observed when age increased (p<0.001, Table I).

An association between the risk of proteinuria and obesity, age group and settlement was estimated using multivariate logistic regression. In multivariate analysis, proteinuria as the dependent variable was entered into a multiple logistic regression model with adjustment variables, age group, obesity and settlement as independent predictor variables. Both the 10-13 years and 14-18 years groups, obese, and urbans showed a significantly increased risk for proteinuria. Table II shows the results of the logistic regression model for proteinuria.

Discussion

Among school-aged children in Tokat province, located in northern Turkey, POP was 6.7%. Asymptomatic POP in school-aged children in other regions of Turkey has been reported to be 1.81% in Trabzon (14), 2.7% in Ankara (15), 8.7% in Isparta (16), and 4.06% in Kayseri (17). A POP of 0.12% in primary school children has been reported in Malaysia (18) and a 2.7% POP has been reported in children of ages 2 to 5 years in Nigeria (14). In those studies, however, the urine dipstick method was used, which is not as sensitive a method as Upr/Ucr determination because of the high false-negative rate (19). Nonetheless, while the Upr/Ucr is recommended for the determination of proteinuria in a single random urine sample or a limited number of samples, the dipstick method is more practical for mass screening programs (9,20,21). In fact, there are few studies in which the Upr/Ucr was used to identify POP (22,23).

Like other childhood diseases, kidney disease can be

Table I. Demographic and clinical characters of the subjects

Variables		Total n=1374	Proteinuria		p
			No 1282 (93.3)	Yes 92 (6.7)	
Gender	Female	683 (49.7)	631 (92.4)	52 (7.6)	0.176
	Male	691 (50.3)	651 (94.2)	40 (5.8)	
Obesity	Obese	141 (10.3)	125 (88.7)	16 (11.3)	0.020
	Nonobese	1233 (89.7)	1157 (93.8)	76 (6.2)	
Age group	6-9 ages[a]	417 (30.3)	415 (99.5)	2 (0.5)	<0.001
	10-13 ages[b]	508 (36.9)	493 (97.0)	15 (3.0)	
	14-18 ages[c]	449 (32.7)	374 (83.3)	75 (16.7)	
Settlement	Urban	1045 (76.1)	966 (92.4)	79 (7.6)	0.022
	Rural	329 (23.9)	316 (96.0)	13 (4.0)	
Hypertension	Yes	67 (4.9)	62 (92.5)	5 (7.5)	0.797
	No	1307 (95.1)	1220 (93.3)	87 (6.7)	

[a,b,c]Different superscripts indicate statistical significant difference
Data are shown as n (%)

Table II. Odds ratios for the combined (multivariate, including age group, obesity, and settlement) effects of variables on proteinuria risk

Variables	β	p	OR	95% CI
10-13 years group	1.837	0.015	6.277	1.425-27.648
14-18 years group	3.780	<0.001	43.826	10.661-180.157
Obese	0.874	0.006	2.397	1.289-4.456
Urban	0.654	0.039	1.923	1.034-3.578

Reference categories are non-obese for obese variable, 6-9 years group for age group variable, rural for settlement variable
OR: Odds ratio, CI: Confidence interval

initially asymptomatic, which has led to the assessment of screening programs and prevalence research (14,20,24). Mass urinalysis screening in children has been implemented since 1973 in Japan (20) and since 1998 in Korea (25).

A comparison of Japan with its mandatory urinary screening program in school children, and the USA, which lacks a similar program, showed that when adjusted for the population, the rate of ESRD based on new cases annually is about 4-fold higher in America than in Japan (20,26). Dipstick-based screening programs were previously carried out in the USA, and in 2000 the American Academy of Pediatrics suggested urine screening in preschool children and in adolescents. However, subsequent studies have confirmed that dipstick-based urinary screening is not suitable because it is not cost effective (21,27). Similarly, there are no mass screening programs in Europe.

We found that POP was higher in obese than in non-obese children. Csernus et al. (28) reported a positive association between proteinuria and adult obesity, consistent with the identification of obesity as an independent risk factor for proteinuria. However, in other studies, either proteinuria was not related to obesity (29) or obese children had higher albuminuria than the control group (28).

In our study population, there was no association between proteinuria and hypertension. While this finding is in agreement with some studies (24,28), it conflicts with another, which found a positive correlation (30).

Our age-based analysis showed that the POP increased with age. In Korea, the POP in elementary and junior high school children is 0.34% and 0.48% (25) respectively; in Japan, the corresponding rates are 0.06% and 0.32% (20). However, it has also been proposed that the increased physical activity of older children results in transient proteinuria, due to orthostatic or exercise-induced proteinuria, resulting in a higher rate of POP to be recorded. So, the higher POP in the older age group may be a reflection of orthostatic proteinuria.

Finally, we found that POP was also higher in urban than in rural areas. While we were unable to find similar studies in the literature, we can suggest that in densely populated areas such as cities and towns, infections and therefore fever are more common. Because fever causes transient proteinuria, this scenario may explain the higher rate of POP in urban children. However, this hypothesis remains to be confirmed in further studies.

Study Limitations

Since this is a prevalence study, investigation of individuals in whom renal disease was detected requires a cohort study. So, it is beyond the scope of this study. The first morning and two urine samples have been suggested, but we used only one randomized urine sample in the day. These were the limitations of our study.

Conclusion

Proteinuria in children may be the first indicator of CKD. However, the early diagnosis of renal disease in asymptomatic individuals can prevent or slow its eventual progression to CKD, and thus the development of ESRD. Among school-aged Turkish children POP was 6.7%. POP was higher in obese than in non-obese children, but there was no association between POP and hypertension. Although screening programs allow the early detection of renal disease, further cohort studies are required to suggest urinary screening programs.

Ethics

Ethics Committee Approval: The study was approved by the Gaziosmanpaşa University Local Ethics Committee (approval number: 14-KAEK-035).

Informed Consent: Inscriptive informed consent was obtained from parents who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.G., S.Ö., R.Y., N.Ö.K., Ş.Ü., E.S., Concept: A.G., S.Ö., R.Y., Design: R.Y., S.Ö., E.S. Data Collection or Processing: Ş.T., Y.Ö., R.Ç., İ.B., Analysis or Interpretation: A.G., S.Ö., Ş.T., Literature Search: A.G., R.Y., Ş.T., T.K., Writing: A.G., R.Y., S.Ö., T.K.

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

Financial Disclosure: This study was supported financially by Commission of Scientific Researches in Gaziosmanpaşa University.

References

1. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int 2003;63:1468-74.
2. Soylemezoglu O, Duzova A, Yalçınkaya F, Arinsoy T, Süleymanlar G. Chronic renal disease in children aged 5-18 years: a population-based survey in Turkey, the CREDIT-C study. Nephrol Dial Transplant 2012;27(Suppl 3):146-51.
3. Guignard JP, Santos F. Laboratory investigations. In: Avner ED, Harmon WE, Niaudet P, (eds). Pediatric nephrology. 5th ed. Lippincott Williams & Wilkins, 2004;399-424.
4. Wong CS, Pierce CB, Cole SR, et al. Association of proteinuria with race, cause of chronic kidney disease, and glomerular filtration rate in the chronic kidney disease in children study. Clin J Am Soc Nephrol 2009;4:812-9.
5. Pais P, Avner ED. Introduction to the Child with Proteinuria. In: Kliegman RM, Stanton B, Geme JS, Schor NF, Behrman RE, (eds). Nelson textbook of pediatrics. 20th ed. Elsevier Health Sciences, 2015:2517-8.
6. Jungers P, Massy ZA, Nguyen-Khoa T, et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. Nephrol Dial Transplant 2001;16:2357-64.

7. Neild GH. What do we know about chronic renal failure in young adults? II. Adult outcome of pediatric renal disease. Pediatr Nephrol 2009;24:1921-8.
8. Hebert LA, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman NS Jr, Rovin BH. Renoprotection: one or many therapies? Kidney Int 2001;59:1211-26.
9. Yap H, Quek C, Shen Q, Joshi V, Chia KS. Role of urinary screening programmes in children in the prevention of chronic kidney disease. Ann Acad Med Singapore 2005;34:3-7.
10. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet 2010;375:1737-48.
11. Ross WR, McGill JB. Epidemiology of obesity and chronic kidney disease. Adv Chronic Kidney Dis 2006;13:325-35.
12. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney Int 2008;73:19-33.
13. Tümer N, Yalçinkaya F, Ince E, et al. Blood pressure nomograms for children and adolescents in Turkey. Pediatr Nephrol 1999;13:438-43.
14. Mocan H, Ökten A, Gedik Y, Erduran E, Akyazıcı P. Trabzon il merkezi ilkokul çocuklarında preteinüri hematüri ve hipertansiyon prevalansı. Türk Nefroloji Dializ ve Transplantasyon Dergisi 1992;1:15-8.
15. Piyal B, Selma A, ARISOY M, Yaman LS. Ankara'nın dört merkez ilköğretim okulu'nun ikinci ve altıncı sınıf öğrencilerinde glukozüri ve proteinürü görülme sıklığı. Ankara Üniversitesi Tıp Fakültesi Mecmuası 1998;51:191-5.
16. Tunç B, Akdoğan M, Serel TA, Aydemir M, Yorgancıgil B, Tahan V. İlkokul Çocuklarında Asemptomatik Piyüri, Bakteriüri ve Proteinüri Prevalansı. SDÜ Tıp Fakültesi Dergisi 1995;2:21-4.
17. Düşünsel R, Hasanoğlu E. Kayseri il merkezi ilkokul çocuklarında proteinüri-hematüri prevalansı. Çocuk Sağlığı ve Hastalıkları Dergisi 1988;31:117-24.
18. Zainal D, Baba A, Mustaffa BE. Screening proteinuria and hematuria in Malaysian children. Southeast Asian J Trop Med Public Health 1995;26:785-8.
19. Rumley A. Urine dipstick testing: comparison of results obtained by visual reading and with the Bayer CLINITEK 50. Ann Clin Biochem 2000;37:220-1.
20. Murakami M, Hayakawa M, Yanagihara T, Hukunaga Y. Proteinuria screening for children. Kidney Int Suppl 2005:23-7.
21. Sekhar DL, Wang L, Hollenbeak CS, Widome MD, Paul IM. A cost-effectiveness analysis of screening urine dipsticks in well-child care. Pediatrics 2010;125:660-3.
22. Ferris M, Hogan SL, Chin H, et al. Obesity, albuminuria, and urinalysis findings in US young adults from the Add Health Wave III study. Clin J Am Soc Nephrol 2007;2:1207-14.
23. Chavers BM, Rheault MN, Foley RN. Kidney function reference values in US adolescents: national health and nutrition examination survey 1999-2008. Clin J Am Soc Nephrol 2011;6:1956-62.
24. Odetunde OI, Odetunde OA, Neboh EE, Okafor HU, Njeze NR, Azubuike JC. Urinary screening for asymptomatic renal disorders in pre-school children in Enugu metropolis, South-east Nigeria: Useful or useless. Saudi J Kidney Dis Transpl 2015;26:1241-5.
25. Park YH, Choi JY, Chung HS, et al. Hematuria and proteinuria in a mass school urine screening test. Pediatr Nephrol 2005;20:1126-30.
26. Hattori S, Yosioka K, Honda M, Ito H; Japanese Society for Pediatric Nephrology. The 1998 report of the Japanese National Registry data on pediatric end-stage renal disease patients. Pediatr Nephrol 2002;17:456-61.
27. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 2003;290:3101-14.
28. Csernus K, Lanyi E, Erhardt E, Molnar D. Effect of childhood obesity and obesity-related cardiovascular risk factors on glomerular and tubular protein excretion. Eur J Pediatr 2005;164:44-9.
29. Cındık N, Baskın E, Ağras PI, ve ark. Sağlıklı şişman okul çocuklarında böbrek fonksiyonları ve enflamasyon belirteçleri. Çocuk Sağlığı ve Hastalıkları Dergisi 2006;49:24-9.
30. Boulatov VA, Stenehjem A, Os I. Association between albumin: creatinine ratio and 24-hour ambulatory blood pressure in essential hypertension. Am J Hypertens 2001;14:338-44.

J Pediatr Res 2017;4(4):200-5
DOI: 10.4274/jpr.82905

Original Article / Orijinal Araştırma

Measurement of Urinary Amino-Terminal Pro-Brain Natriuretic Peptide in Childhood Lower Respiratory Tract Infections: An Indicator of Clinical Severity?

Çocukluk Çağı Alt Solunum Yolu Enfeksiyonlarında İdrarda Amino-Terminal Pro-Brain Natriüretik Peptid Ölçümü: Klinik Şiddetin Bir Göstergesi Olabilir mi?

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ABSTRACT

Aim: Prompt diagnosis and determination of the clinical severity and intervention of lower respiratory tract infections (LRTI) is essential for the prevention and management of life-threatening complications. Laboratory tests do not serve as accurate indicators of clinical severity. Our aim was to evaluate the contribution of urinary amino-terminal pro-brain natriuretic peptide (NT-ProBNP) concentrations in children with LRTI to clinical assessment in terms of determining clinical severity and the necessity of hospitalization.

Materials and Methods: This prospective non-randomised study included a total of 160 patients, aged 0-6 years, diagnosed with LRTI [(group 1=outpatient group (n=108), and (group 2=hospitalized patients (n=52)]. The control group (group 3) was comprised of 46 healthy children. Urinary NT-ProBNP level of each participant was measured by ELISA method.

Results: Although not significant, the mean urinary NT-ProBNP level of all patients was higher than that of the control group (p=0.322). When we compared the three groups separately, the highest levels belonged to

ÖZ

Amaç: Alt solunum yolu enfeksiyonlarında (ASYE) erken tanı ve klinik ciddiyetin belirlenmesi yaşamı tehdit eden komplikasyonların önlenmesi ve tedavisi için şarttır. Laboratuvar bulguları her zaman hastalığın klinik ciddiyeti hakkında fikir vermemektedir. Çalışmamızın amacı çocukluk çağı ASYE'lerinin ciddiyeti ve hastane yatışı gerektirip gerektirmediğinin belirlenmesinde idrarda amino-terminal pro-brain natriüretik peptid (NT-ProBNP) düzeyi ölçümünün klinik değerlendirmeye katkısının değerlendirilmesidir.

Gereç ve Yöntemler: Bu prospektif non-randomize çalışmaya 0-6 yaş aralığında ASYE tanısı alan toplam 160 hasta dahil edildi. [(Grup 1: Ayakta tedavi edilen hastalar (n=108) ve grup 2: Hospitalize edilerek tedavi edilen hastalar (n=52)]. Kontrol grubuna benzer yaş grubunda sağlıklı 46 hasta dahil edildi (grup 3). Hastaların idrar NT-ProBNP düzeyi ELİSA metodu ile ölçüldü.

Bulgular: İstatistiksel olarak anlamlı olmasa da hastaların idrar NT-ProBNP düzeyi kontrol grubuna göre daha yüksekti (p=0,322). Üç grup ayrı ayrı karşılaştırıldığında; en yüksek değerlerin ayakta tedavi edilen hastalara ait olduğu ve hospitalize edilen hastaların idrar peptid düzeylerinin kontrol

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Received/Geliş tarihi: *25.03.2017* **Accepted/Kabul tarihi:** *05.05.2017*

outpatients whereas hospitalized patients showed slightly lower levels than the control group without any statistical significance (p=0.128). As for newborns (n=16), patients showed higher levels than the controls (p=0.041). P value <0.05 was considered significant.

Conclusion: Although urinary NT-ProBNP level tends to increase to some extent in childhood LRTI, this alteration does not seem to be valuable in the prediction of the severity of the disease. We believe that the establishment of further studies including larger series of patients, especially neonates, is warranted.

Keywords: Child, lower respiratory tract infection, amino-terminal pro-brain natriuretic peptide, urine

grubundan hafif olarak düşük olduğu, gruplar arası istatistiksel olarak anlamlı fark olmadığı görüldü (p=0,128). Hasta yenidoğanların bebeklerin kontrol grubundan daha yüksek değerler gösterdiği belirlendi (p=0,041). P<0,05 istatistiksel olarak anlamlı kabul edildi.

Sonuç: Çocukluk çağı ASYE'lerinde idrar NT-ProBNP değerleri yükselse de sonuçlarımız bu değişikliğin hastalığın klinik şiddetinin tayininde değerli bir belirteç olarak görülmediğine işaret etmektedir. Gelecekte bu konuda özellikle yenidoğanların dahil edildiği daha fazla hasta sayısı ile yapılacak çalışmalara ihtiyaç olduğunu düşünüyoruz.

Anahtar Kelimeler: Çocuk, alt solunum yolu enfeksiyonu, amino-terminal pro-brain natriüretik peptid, idrar

Introduction

Childhood lower respiratory tract infections (LRTI) are encountered as widespread and common infectious diseases. Pneumonia is the leading cause of mortality (17%) in children aged <5 years (1). Estimatedly 1 million children younger than five years of age died from pneumonia in 2014 according to the most recent "Child Mortality Report" of UNICEF (2). Bronchiolitis is the most common cause of hospitalization in the first year of life. Prompt diagnosis, the determination of clinical severity, and intervention of LRTI is essential for the prevention and management of life-threatening complications. This can only be achieved by proper clinical assessment. Laboratory tests and chest radiographs do not always serve as accurate indicators of clinical severity (3).

Brain natriuretic peptide (BNP) is a peptide hormone mainly released from cardiac atrial myocytes but it is also secreted by the ventricular myocardium in response to pressure and volume overload. Enzymatic cleavage of pro-BNP results in the production of BNP and amino-terminal pro-BNP (NT-ProBNP) (4). Serum levels of NT-ProBNP can be tested easily, quickly and economically. Thus, measuring plasma concentrations of NT-ProBNP has emerged as a useful estimator of cardiac dysfunction and has been incorporated into major adult guidelines for the detection and management of heart failure as a diagnostic test (5).

The first studies evaluating plasma NT-ProBNP levels in children focused on cardiac dysfunction and its predictivity in differentiating between congestive heart failure (CHF) and lung disease among infants with acute respiratory distress (6,7). Research assessing plasma peptide levels in arrytmia, febrile convulsion, epilepsy, syncope, sepsis, and more have further been conducted (8-10). NT-ProBNP is also found in the urine as small peptides undergo renal filtration (11). Studies measuring urinary NT-ProBNP levels in children are generally limited to the prediction and follow-up of hemodynamically significant patent ductus arteriosus (hs-PDA) in preterm infants (12,13).

It has been proposed that plasma NT-ProBNP levels may elevate to some extent in LRTI based on cardiac overload even in the absence of cardiac failure. Studies using plasma NT-ProBNP levels in children with LRTI have reported a significant increase accompanying heart failure only in children most of whom also had an underlying congestive heart disease (CHD) (14,15). On the other hand, no published report estimating the "clinical severity" of LRTI in the absence of heart failure by detection of plasma or urine NT-ProBNP levels exists hitherto in pediatric practice.

In this study, we planned to measure urinary NT-ProBNP concentrations in children with LRTI. Our aim was to evaluate the contribution of this easily applicable and non-invasive diagnostic test in childhood LRTI to clinical assessment for the determination of clinical severity and the necessity of hospitalization.

Materials and Methods

Patients and Study Design

This prospective non-randomised study was conducted in the Pediatric Outpatient Clinic, Emergency and Infectious Diseases Departments, Neonatal and Pediatric Intensive Care Units of Ankara University Faculty of Medicine between November 2014-May 2015. The study protocol was approved by the Clinical Research Ethical Commitee of Ankara University (approval number: 17-735-14; October 2014). Written informed consent was given by each parent.

We enrolled a total of 160 children, aged between 0-72 months, who were diagnosed with LRTI (acute pneumonia or bronchiolitis). Since current knowledge indicates that plasma NT-ProBNP value is high in the umbilical cord with a further increase in the first two days of life, followed by a rapid decrease in the first week (3-8 days), we included neonates beyond the first week of life (16). Exclusion criteria were outlined as previously diagnosed CHD, chronic lung disease, respiratory tract abnormality, immune deficiency, neuromuscular disease, major congenital malformation, and inability to obtain written informed consent. Routine echocardiographic evaluation was not performed unless a suspicion of CHD or CHF was raised.

Clinical Evaluation of Patients

Each patient was clinically evaluated by a pediatrician. Vital signs (heart rate, respiratory rate and oxygen saturation)

were recorded at arrival. Tachycardia and tachypnea were defined as pulse and respiratory rates at rest exceeding upper limits of normal according to age (17,18).

Modified Wood's Clinical Asthma Score (M-WAS) was applied to patients diagnosed with bronchiolitis to assess clinical severity (19). This clinical scoring scale focuses on five signs; oxygen saturation, inspiratory breath sounds, expiratory wheezing, use of accessory muscles, and mental status. Patients were regarded as "mildly, moderately or severely ill" based on this assessment.

Clinical severity in pneumonia was categorized as "mild" or "severe" based on body temperature, signs of respiratory distress, skin color, mental status, oxygen saturation, feeding problems, signs of dehydration, heart rate, and capillary refill time (3,20).

Patients were divided into two subgroups according to clinical evaluation; group 1 (outpatient group, n=108) included "mildly" or "moderately" ill patients who were evaluated and discharged either from the outpatient clinic or emergency department. Group 2 (n=52) consisted of hospitalized patients, either in the infectious diseases department or intensive care units, who were considered as "severe" patients. Control group (Group 3) consisted of 46 healthy children of similar age without signs of recent infection.

Urine Amino-Terminal Pro-Brain Natriuretic Peptide Measurement

Urine was collected for the measurement of NT-ProBNP within the first 2 h of admission for outpatients, and within 6 h for hospitalized patients. Samples (2 mL) were further centrifuged at 4000 rpm for 5 minutes, and cell-free urine was stored at -80 °C until assessment. Urine NT-ProBNP quantification was handled in Ankara University Faculty of Medicine, Immunology Laboratory with the enzyme immunoassay for the quantitative measurement of BNP fragment in biological fluids as per instructions (YH Biosearch Laboratory, Shangai, China). The NT-ProBNP measuring range in urine reported by the manifacturer is 5 to 2000 pg/mL. Results above this range were rediluted and assessed again.

Statistical Analysis

Differences amongst the three groups for the ordinal or non-normally distributed continuous variables were evaluated by Kruskal-Wallis variance analysis. Mann-Whitney U test was used to test ordinal or non-normally distributed continuous variables. Categorical variables were assessed by chi-square test or Fisher's exact test, where applicable. Degree of association between variables was evaluated by Spearman's correlation coefficient. P value less than 0.05 was considered significant.

Results

Patient Characteristics

Although the mean age of the control and patient groups was similar (p=0.669), hospitalized patients were younger than out-patients [median (minimum-maximum) 16.1 (0.5-65) versus 19 (2-71) months)].

Baseline clinical characeristics of the patients are summarized in Table I. Mean admission time since symptoms first appeared was similar between the two groups. Heart and respiratory rates were higher in hospitalized patients. Nevertheless, these findings were not totally regarded as of clinical importance as hospitalized patients were younger. The only statistically significant clinical difference between the two groups was higher M-WAS, and pneumonia scores on admission in hospitalized patients. Echocardiography was performed in 11 outpatients (10.2%) and 13 hospitalized patients (25%). All results were revealed as normal.

No Difference in Urinary Amino-Terminal Pro-Brain Natriuretic Peptide Levels Amongst Groups

Table II shows urinary NT-ProBNP levels of our study group. We observed higher urinary NT-ProBNP levels in the patients in comparison with the control group, not reflecting statistical significance (p=0.322). When we compared the three groups separately, the highest levels belonged to outpatients whereas hospitalized patients had slightly lower levels than the control group. The difference between levels of urinary NT-ProBNP of the three groups did not represent any statistical significance (p=0.128). When we examined urinary NT-ProBNP levels of the newborns (n=16) in our study group, the patients (mean ± standard deviation: 696.9±147.1 pg/mL) had higher levels than controls (509.7±326.2 pg/mL) (p=0.041).

Table I. Baseline clinical characteristics of the outpatient group and hospitalized patients

	Outpatient group	Hospitalized patients	p
Admission time since signs first appeared (day) [mean ± SD; median (min-max)]	4.5±4.0 3.00 (1-20)	4.9±3.90 4.00 (1-20)	0.075
Respiratory rate (/min) [mean ± SD; median (min-max)]	40.1±10.70; 40.0 (15-70)	46.5±12.2 46.0 (16-80)	0.001
Tachypnea (%) (WHO criteria)	27.8	34.6	0.377
Low oxygen saturation (≤%92) (%)	16.7	25	0.212
Heart rate (/min) [mean ± SD; median (min-max)]	123.4±21.1; 120 (88-170)	142.0±19.2 146 (90-170)	0.001
Tachycardia (%) (based on age)	22.2	34.6	0.095
M-WAS score (for bronchiolitis) (% of "moderately/severely ill" patients)	5.7	42.1	<0.001
Pneumonia score (% of severe cases)	0	20.9	<0.001

Max: Maximum, Min: Minimum, /Min: /Minute, SD: Standard deviation, WHO: World Health Organization, M-WAS Score: Modified Wood's Clinical Asthma Score

Correlation of Amino-Terminal Pro-Brain Natriuretic Peptide and Clinical Characteristics

We investigated the correlation between urinary NT-ProBNP values and the patients' clinical characteristics. Inverse weak correlation was observed between urinary NT-ProBNP values and both heart rate and mean admission time. NT-ProBNP levels were higher in patients without tachycardia [(median (minimum-maximum) 541.2 (65.5-1073.8) pg/mL)] in contrast to patients who had tachycardia [363.3 (107-1028.9) pg/mL] (p=0.001). We observed no relationship between other clinical characteristics and urinary NT-ProBNP levels (Table III).

Discussion

We measured higher urinary NT-ProBNP levels in LRTI patients compared to the control group. However, this finding did not reach statistical significance and was consistent with the previously published data reporting plasma NT-ProBNP levels in children diagnosed with LRTI (6,7,14,15). On the other hand, our main goal was to evaluate the diagnostic acccurracy of urinary peptide levels in determining "severe" cases. We observed no differerence between clinically severe cases who required hospitalization, and outpatients who presented a milder clinical course. In the case of neonates, the patients showed significantly greater values than controls but this subgroup was relatively small in size. Furthermore, since all neonates with LRTI should be hospitalized, and clinical severity was similar with no existing severe cases in our subgroup, we did not consider this finding of clinical importance.

We proposed that one of the issues related to lower values in hospitalized patients than in outpatients was the later collection of urine (6 hr versus 2 hr). Delayed testing might have resulted in lower values because of the altered clinical course. We also believe that accompanying tachycardia in our patients may present as an additional factor leading to lower results as the correlation between tachycardia and urinary NT-ProBNP was found to be strongly negative. Although we did a thorough search, we could not reach any statement in the literature indicating the effect of tachycardia on plasma/urine NT-ProBNP levels. However, we assume that tachycardia may cause reduced urinary protein levels as a result of less emphasized volume and pressure overload.

Previous work concerning children concluded that plasma NT-ProBNP levels are significantly high in children with CHF regardless of the etiology, and significant reduction is observed after an appropppriate intervention (6,7,14,15). These studies indicated a statistically insignificant increase of plasma NT-ProBNP values in children diagnosed with LRTI but who did not have CHF, and concluded that plasma NT-ProBNP might serve as a useful index for the differentiation of dyspnea due to cardiac failure from a respiratory illness.

The cardiovascular and respiratory systems may be regarded to be functioning as a single unit, as changes in one reflect the other (21,22). Even little alterations in intrathoracic pressure may cause substantial changes on the afterload of small children (14). Nonetheless, an increase in plasma NT-ProBNP level as a result of instant afterload changes without clinically evident CHF may also be observed in patients with LRTI. Aydemir et al. (23) reported increased plasma NT-ProBNP levels in "severe" cases of transient tacyhpnea of the newborn (TTN). This study documented that echocardiographic evaluation revealed preserved systolic functions in all infants although "near to normal limit" was detected in severe cases (23). Authors linked this rise to the contribution of natriuretic peptides in the regulation of extracellular fluid volume. Whilst we think that events occuring in the first days of life happen to be much more complex representing "early transition" and should be discussed separately, we believe this data pointing to increased NT-ProBNP levels in infants with TTN with normal cardiac functions is of value. Moreover, few studies provided evidence that the secretion of natriuretic peptides is induced by cytokines and inflammatory mediators (24,25).

Table II. Comparison of urinary amino-terminal pro-brain natriuretic peptide levels (pg/mL) between groups

Groups	Urine NT-ProBNP (pg/mL)				
	n	Mean ± SD	Median	Minimum	Maximum
Control	46	476.6±324.8	423.2	37.4	1189.9
Outpatients	108	527.4±244.2	543.4	98.1	1028.9
Hospitalized patients	52	459.5±254	475.0	65.5	1073.8
All patients (hospitalized and outpatients)	160	505.4±248.8	527.3	65.5	1073.8

n: Number, SD: Standard deviation, NT-ProBNP: Amino-terminal pro-brain natriuretic peptide

Table III. Correlation between urinary amino-terminal pro-brain natriuretic peptide values (pg/mL) and clinical characteristics

Parameters	Urine NT-ProBNP (pg/mL)	
	Correlation coefficient (r)	p
Mean admission time (days)	-0.164	0.038
Age (month)	-0.065	0.357
Breath rate (/min)	-0.048	0.549
Heart rate (/min)	-0.228	0.004
Oxygen saturation (%)	0.130	0.102
Bronchiolitis score	0.024	0.773
Pneumonia score	0.097	0.339

Min: Minute, NT-ProBNP: Amino-terminal pro-brain natriuretic peptide

This information might be regarded as an additional factor resulting in increased plasma peptide levels in LRTI.

Adult studies reported that plasma NT-ProBNP levels serve as a strong predictor of severe pneumonia (26,27). These studies found higher NT-ProBNP levels in patients requiring intensive unit care and non-survivors, and linked this increase to comorbidities (e.g. heart failure, renal failure) and inflammatory mediators (26). We found only one study reporting the predictive potential of plasma NT-ProBNP as independent of comorbidities in adults with pneumonia (27).

Studies have assessed the diagnostic and prognostic value of NT-ProBNP in urine as a simple and non-invasive test (11,28). Although slightly lower values than plasma are detected, urine NT-ProBNP was shown to have a diagnostic accuracy to that of plasma NT-ProBNP for the diagnosis of heart failure in adults (29). As far as we searched, we found few studies evaluating urinary NT-ProBNP values in children. Tosse et al. (12) designed the first study in children assessing urinary peptide levels and clinical characteristics and concluded that the measurement of urinary NT-ProBNP is a powerful and non-invasive method to diagnose hs-PDA in preterm infants. Subsequently, Celik et al. (13) noted similar results and notified that urinary NT-ProBNP levels may help clinicians to determine the effects of hs-PDA on the clinical status of preterm infants. Czernik et al. (30) published higher urinary NT-ProBNP levels in preterm neonates who further developed retinopathy of prematurity. Although we aimed to elucidate the predictive potential of urinary NT-ProBNP in the determination of "severity" in childhood LRTI, we could not demonstrate any relation.

Study Limitations

There are several limitations of this study. Firstly, echocardiography was not performed on the whole study group. Instead, it was carried out on patients whose clinical evaluation was unclear to minimize redundant investigation in patients showing typical signs of LRTI. The inability to analyze fresh urine could be considered as another limitation. A recent research reported slightly better predictive results with fresh rather than frozen samples of NT-ProBNP for the diagnosis of CHF in adults (31). A further point of discussion is the invalid reference values of urinary NT-ProBNP in childen. We gathered data of a limited number of patients from certain published studies. We believe further research is mandatory for the establishment of these values. Nevertheless, we assume that this factor may not have influenced the interpretation of our results since we "compared" the values of two different groups.

Conclusion

We investigated for the first time the contribution of NT-ProBNP in childhood LRTI to clinical assessment in the determination of "clinical severity". Although urinary NT-ProBNP levels tend to increase to some extent in childhood LRTI, this alteration does not seem to be valuable in the prediction of the severity of the disease. We believe that the establishment of further studies including larger series of patients, especially neonates, is warranted to clarify this issue of concern.

Ethics

Ethics Committee Approval: This study was approved by Clinical Research Ethical Commitee of Ankara University (approval number: 17-735-14; October 2014).

Informed Consent: Written informed consent was recruited from each participant.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.E.Ç.İ., F.G., Concept: N.E.Ç.İ., Ö.E., E.Ç., T.K., S.A., Design: N.E.Ç.İ., Ö.E., D.T., H.Ö., Data Collection or Processing: N.E.Ç.İ., F.G., Analysis or Interpretation: A.H.E., H.T., N.E.Ç.İ., Literature Search: N.E.Ç.İ., Ö.E., F.G., Writing: N.E.Ç.İ.

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

Financial Disclosure: This study was funded by research aid from Scientific Research Projects Coordination Unit, Ankara University, Ankara, Turkey (project number: 15H0230003).

References

1. Nair H, Simoes EA, Rudan I, et al. Global and regional burden of hospital admissions for severe acute respiratory infections in young children in 2010: a systematic analysis. Lancet 2010;381:1380-90.
2. Levels and trends in child mortality. Estimates developed by the UN Inter-agency Group for Child Mortality Estimation. UNİCEF; Report 2015 [Internet]. Available from http://www.childmortality.org [Accessed at February 15, 2016].
3. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:25-76.
4. Hall C. Essential biochemistry and physiology of (NT-pro) BNP. Eur J Heart Fail 2004;6:257-60.
5. Roberts E, Ludman AJ, Dworzynski K, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: a systematic review and diagnostic meta-analysis in the acute care setting. BMJ 2015;350:910.
6. Cohen S, Springer C, Avital A, et al. Amino-terminal pro-brain-type natriuretic peptide: heart or lung disease in pediatric respiratory distress? Pediatrics 2005;115:1347-50.
7. Koulouri S, Acherman RJ, Wong PC, Chan LS, Lewis AB. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. Pediatr Cardiol 2004;25:341-6.
8. Rauchenzauner M, Haberlandt E, Rösslhuber C, et al. Cerebrospinal fluid and serum NT-proBNP concentrations in children with epilepsy. Epilepsy Res 2009;86:131-7.
9. Wójtowicz J, Szczepański W, Bogdan A, Baran M, Szczurak J, Bossowski A. Natriuretic peptides in the evaluation of

syncope in children and adolescents. Scand J Clin Lab Invest 2014;74:301-5.

10. Samransamruajkit R, Uppala R, Pongsanon K, Deelodejanawong J, Sritippayawan S, Prapphal N. Clinical outcomes after utilizing surviving sepsis campaign in children with septic shock and prognostic value of initial plasma NT-proBNP. Indian J Crit Care Med 2014;18:70-6.
11. Palmer SC, Endre ZH, Richards AM, Yandle TG. Characterization of NT-proBNP in human urine. Clin Chem 2009;55:1126-34.
12. Tosse V, Pillekamp F, Verde P, et al. Urinary NT-proBNP, NGAL, and H-FABP may predict hemodynamic relevance of patent ductus arteriosus in very low birth weight infants. Neonatology 2012;101:260-6.
13. Celik IH, Erdeve O, Demırel G, Canpolat FE, Dilmen U. Elevated urinary NT-proBNP after pharmacological closure of patent ductus arteriosus in very low birth weight infants. Early Hum Dev 2013;89:187-9.
14. Sezgin Evim M, Ucar B, Kilic Z, Colak A. The value of serum N-terminal pro-brain natriuretic peptide levels in the differential diagnosis and follow-up of congestive cardiac failure and respiratory distress due to pulmonary aetiologies in infants and children. Cardiol Young 2010;20:495-504.
15. Zhou FJ, Zhou CY, Tian YJ, et al. Diagnostic value of analysis of H-FABP, NT-proBNP, and cTnI in heart function in children with congenital heart disease and pneumonia. Eur Rev Med Pharmacol Sci 2014;18:1513-6.
16. Nir A, Lindinger A, Rauh M, et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol 2009;30:3-8.
17. Hartman ME, Cheifetz IM. Pediatric Emergencies and Resuscitation. In: Kliegman RM, Stanton BF, St Geme JW, eds. Nelson Texbook of Pediatrics- 19th ed. 2011;280.
18. Shann F. WHO definition of tachypnoea in children. Lancet 1992;339:176-7.
19. Duarte-Dorado DM, Madero-Orostegui DS, Rodriguez-Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. J Asthma 2013;50:1056-61.
20. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax 2011;66(Suppl 2):ii1-23.
21. Meliones JN, Cheifetz IM. Pulmonary physiology and heart-lung interactions. In: Garson A, Bricker JT, Fisher DJ, Neish SR, eds. The Science and Practice of Pediatric Cardiology. 2nd ed. Williams and Wilkins, Baltimore, 1998;279-312.
22. Ilten F, Senocak F, Zorlu P, Teziç T. Cardiovascular changes in children with pneumonia. Turk J Pediatr 2003;45:306-10.
23. Aydemir O, Aydemir C, Sarikabadayi YU, et al. The role of plasma N-terminal pro-B-type natriuretic peptide in predicting the severity of transient tachypnea of the newborn. Early Hum Dev 2012;88:315-9.
24. Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol 2004;36:505-13.
25. Tanaka T, Kanda T, Takahashi T, Saegusa S, Moriya J, Kurabayashi M. Interleukin-6 induced reciprocal expression of SERCA and natriuretic peptides mRNA in cultured rat ventricular myocytes. J Int Med Res 2004;32:57-61.
26. Nowak A, Breidthardt T, Christ-Crain M, et al. Direct comparison of three natriuretic peptides for prediction of short- and long-term mortality in patients with community-acquired pneumonia. Chest 2012;141:974-82.
27. Lin SC, Tsai YJ, Huang CT, et al. Prognostic value of plasma N-terminal pro B-type natriuretic peptide levels in pneumonia patients requiring intensive care unit admission. Respirology 2013;18:933-41.
28. Michielsen EC, Bakker JA, van Kimmenade RR, Pinto YM, Dieijen-Visser MP. The diagnostic value of serum and urinary NT-proBNP in heart failure. Ann Clin Biochem 2008;45:389-94.
29. Hahn RG, Jaarsma T, Waldréus N, Linssen GC. Urine measurement indicates the plasma brain natriuretic peptide concentration during optimization of heart failure treatment. Scan J Clin Lab Invest 2016;76:112-7.
30. Czernik C, Metze B, Müller C, Müller B, Bührer C. Urinary N-Terminal B-Type Natriuretic Peptide Predicts Severe Retinopathy of Prematurity. Pediatrics 2011;128:545-9.
31. Toufan M, Namdar H, Abbasnezhad M, et al. Diagnostic values of plasma, fresh and frozen urine NT-proBNP in heart failure patients. J Cardiovasc Thorac Res 2014;6:111-5.

J Pediatr Res 2017;4(4):206-10
DOI: 10.4274/jpr.36844

Original Article / Orijinal Araştırma

Factors Affecting Same-Day Discharge Following Laparoscopic Cholecystectomy in Children

Çocuklarda Laparoskopik Kolesistektominin Günübirlik Uygulanmasını Etkileyen Faktörler

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ABSTRACT

Aim: Laparoscopic cholecystectomy (LC) as day surgery is widely performed on adults; however, experience in pediatric LC in an out-patient setting is limited. We aimed to review our experience and investigate related factors.

Materials and Methods: Medical records of patients who underwent elective LC from June 2005 to July 2016 were retrospectively reviewed. Patients were grouped according to the duration of hospital stay, and patient characteristics and outcome were compared. T-test and chi-square were used for statistical analysis.

Results: A hundred and sixty-seven patients with a mean age of 10.4 years were enrolled. There was no conversion to open surgery, with only one postoperative complication in a patient with consumption coagulopathy. Same-day discharge (SDD), overnight stay (ONS) and prolonged stay (PS) groups were constituted of 50, 92, 25 patients respectively. All groups had similar preoperative characteristics and median postoperative pain scores. Previous history of cholecystitis and underlying hematological diseases were more common in the PS group ($p<0.05$). Duration of anesthesia was shortest in SDD, longest in PS groups ($p<0.006$). Perioperative minor complications were more common in the PS group than the SDD group ($p=0.03$). Mean time for oral feeding was 3.2, 5.4 and 14.8 hours for SDD, ONS and PS groups respectively ($p<0.009$). There was no readmission.

Conclusion: LC may safely be performed as day surgery in children without comorbidities. Shorter duration of anesthesia and early oral feeding seem to play a key role in SDD in these cases.

Keywords: Laparoscopic cholecystectomy, day surgery, child

ÖZ

Amaç: Erişkinlerde günübirlik laparoskopik kolesistektomi (LK) yaygın olarak kullanılmaktadır. Çocuklarda ise bu konuyla ilgili deneyim sınırlıdır. Bu çalışmada çocuklarda günübirlik LK uygulamasını etkileyen faktörlerin ortaya konması amaçlanmıştır.

Gereç ve Yöntemler: Haziran 2005-Temmuz 2016 tarihleri arasında kliniğimizde semptomatik veya asemptomatik kolelitiyazis nedeniyle elektif LK uygulanmış hastaların kayıtları geriye dönük olarak incelendi. Hastalar yatış sürelerine göre gruplandırıldı. Gruplar; demografik veriler, eşlik eden hastalık, öykü, anestezi ve ameliyat özellikleri, postoperatif tedavi ve beslenme durumlarına göre karşılaştırıldı. Analiz için t-test ve ki-kare kullanıldı.

Bulgular: Ortalama yaşı 10,4 olan 167 olgu çalışmaya dahil edildi. Hiçbir olguda açığa dönüş gerekmezken tüketim koagülopatisi gelişen bir olgu dışında komplikasyon gelişmedi. Günübirlik (GB), tek gecelik yatış (TGY) ve uzamış yatış (UY) gruplarını sırasıyla 50, 92 ve 25 olgu oluşturdu. Gruplar preoperatif özellik ve postoperatif ağrı düzeyi açılarından benzerdi. Geçirilmiş kolesistit öyküsü UY grubunda daha sıktı ($p<0,05$). Anestezi süresi GB grubunda en az, UY grubunda en fazlaydı ($p<0,006$). UY grubunda perioperatif minör komplikasyonlar GB grubuna göre daha sıktı ($p=0,03$). Oral beslenmeye geçiş süreleri GB, TGY ve UY gruplarında sırasıyla 3,2, 5,4 ve 14,8 saatti ($p<0,009$). Hiçbir olguda yeniden yatış gerekmedi.

Sonuç: GB LK eşlik eden hastalığı olmayan çocuklarda güvenle uygulanabilir. Anestezi süresi ve oral beslenmenin geciktirilmeden başlanması en önemli faktörlerdir.

Anahtar Kelimeler: Laparoskopik kolesistektomi, günübirlik, çocuk

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Received/Geliş tarihi: *06.02.2017* **Accepted/Kabul tarihi:** *11.05.2017*

Introduction

The concept of day surgery has developed almost at the same time as the establishment of surgical facilities such as dispensaries or out-patient clinics since the early 1900's (1). Circumcisions, abscess drainages, excisions of glands along with amputations, hernias, and cleft palates were being carried out on an out-patient basis at that time. Decades later in the 1990's, with technical improvements and the development of minimal invasive surgery, laparoscopic cholecystectomy (LC) also became one of the day surgery procedures in adults. What is more, special units such as ambulatory surgery centers and post surgery recovery centers were established to minimize the cost and risk of patients (2). There are very few studies with a low number of patients on out-patient LC in the pediatric population. In this study we aimed to evaluate our experience in LC in terms of day surgery.

Materials and Methods

After Ege University Local Ethics Committee approved the study (approval number: 17-5.2/6), we reviewed the medical charts of patients with cholelithiasis who had undergone elective LC in our institution through June 2005 to July 2016. All participants' parents had signed consent form. Demographics, pre-operative imaging results, underlying hematological pathologies, and pre-surgical, surgical and post-surgical data were evaluated. Patients with additional procedures and urgent interventions were excluded. Groups were constituted according to the duration of in-hospital stay time (IHST); patients who were discharged on the same-day discharge (SDD) group, patients who stayed overnight stay (ONS) group and patients who had to stay more than 24 hours prolonged stay (PS) group. The groups were compared by means of data that could affect IHST.

Statistical Analysis

For statistical analysis, nominal values were evaluated with the chi-square test, and numeric values with two-tailed Student's t-test. $P<0.05$ was considered statistically significant.

Results

A total of 167 children (78 girls, 89 boys) were enrolled in the study. Mean operation age was 10.4 (1-18) years. Twenty-eight of the cases (16.8%) had underlying hemolytic diseases (hereditary spherocytosis in 11, thalassemia in 8, sickle cell disease in 7, and glucose-6-phosphate dehydrogenase deficiency in 2). The majority of the patients (n=102, 61.1%) had history of non-specific abdominal pain at admission, and 18 patients (10.8%) who had history of cholecystitis had been symptom-free for at least 3 months. Cholelithiasis was confirmed by preoperative ultrasonography in all patients. Seven children (4.2%) had co-existing stones in distal of the gallbladder. These patients had undergone prior endoscopic sphincterotomies and cystic channels were cleared with saline flushing in all during surgery.

All cholecystectomies were performed by either board certified surgeons or surgical residents under the supervision of board certified surgeons. Majority of the procedures (126, 75.4%) ended before 12:00 pm. Postoperative feeding regimes differed from early oral intake (minimum postoperative 3 hours) to oral feeding on the next day of surgery according to the surgeon's preference.

All patients received preoperative sedation with midazolam hydrochloride and were ventilated via an endotracheal tube with air, oxygen, and isoflurane. Intraoperative analgesia comprised intravenous fentanyl. In addition, all patients received intraoperative diclofenac or paracetamol where appropriate for age. All patients had infiltration of 0.25% levobupivacaine hydrochloride at port sites. Nasogastric drainage tube was used for all LC patients intraoperatively and prophylactic anti-emesis was provided by dexamethasone.

Minor perioperative complications including adhesions, gallbladder perforation, and bleeding were noted in 22 patients (13.2%), and conversion was necessary for none. Mean operation time was 101.1 (45-240) minutes. None of the patients required additional analgesia other than the routinely administered perioperative and postoperative acetaminophen (10 mg/kg per oral q6hr) and metamizole sodium [25 mg/kg intravenous (i.v.)]. The postoperative feeding regime differed from unrestricted to a light diet depending on the surgeon's choice. The pain was assessed at least twice (at the time of postoperative ward reception and before discharge) by the nurses and was scored using the wong and baker faces pain rating scale (3). All patients were seen at the end of the afternoon by the surgical and nursing team, and decision regarding discharge was left to the patients' families when it was appropriate. Discharge criteria were; the ability to be fed normally, being pain-free, and willing to leave. None of the patients were discharged after 22:00 pm. Postoperative period was uneventful for all the patients but one, a girl with a giant arteriovenous malformation, who developed consumption coagulopathy and required further hematological evaluation and treatment.

SDD, ONS, and PS groups consisted of 50, 92 and 25 patients respectively, and the difference of mean IHST for each group was statistically significant (p=0.000). The difference between mean age and gender distribution among groups was insignificant. History of cholecystitis and underlying hematological diseases were significantly higher in the PS group than the SDD and ONS groups (p=0.03 and 0.007). Mean operation times were 84.5, 103.9 and 117.7 minutes for SDD, ONS, and PS group respectively, and the difference between the SDD group with the ONS and PS group was significant (p=0.005 and 0.004). Minor perioperative complications including difficult dissection due to adhesions, gallbladder perforation, and minor bleeding were significantly higher in the PS group than the SDD group (p=0.03).

Mean postoperative time for oral feeding (PTOF) was significantly different between the SDD (3.2 hours), ONS (5.4 hours) and PS (14.8 hours) groups (p=0.001, 0.002 and 0.008). The difference between mean pain scores before discharge was insignificant for all groups and none of the patients required readmission. The comparison of preoperative, perioperative, and postoperative data of the three groups is depicted in Table I.

Table I. The comparison of pre/peri/postoperative characteristics of study groups. Group names and statistically significant values are highlighted

	SDD group (n=50)	ONS group (n=92)	PS group (n=25)	p
Mean age (years)	10.7 (0.5-18)	10.6 (1-18)	9.2 (1.5-17)	>0.05
Gender (boys/girls)	22/15	43/39	12/11	>0.05
History of cholecystitis	3 (8.1%)	6 (7.3%)	6 (26.1%)	**0.03**
Underlying hematological disease	8 (21.6%)	9 (11%)	9 (39.1%)	**0.007**
Mean operation time (minutes)	84.5 (45-174)	103.9 (46-188)	117.7 (60-240)	**0.005** **0.004**
Perioperative complication	3 (8.1%)	9 (11%)	7 (30.4%)	**0.03**
PTOF (hours)	3.2 (1.5-6)	5.4 (1-18)	14.8 (1-72)	**0.001** **0.002** **0.008**
Median postoperative pain score	2 (0-4)	3 (0-4)	3 (0-5)	>0.05
IHST (hours)	10.1 (5-12)	20.8 (16-36)	58.9 (36-124)	**0.000**

SDD: Same-day discharge, ONS: Overnight stay, PS: Prolonged stay, PTOF: Postoperative time for oral feeding, IHST: In-hospital stay time

Discussion

Today LC as a well-established option is the gold standard treatment in symptomatic cholelithiasis. According to adult series, LC may be performed on ambulatory setting safely and there seems to be no significant difference in terms of pain scores, readmission rates, quality of life and patient anxiety between outpatient procedures and procedures with an ONS (2,4-8). There are few studies related to LC as day surgery in children. In 2007 Méndez et al. (9) stated that LC may safely be performed on children as an out-patient procedure, but patients with co-morbidities benefit from an ONS. Despite a limited number of patients, their statement seems to be in parallel with our study. Agarwal and Bagdi (10) also showed the success of SDD in 11 patients. In 2013 Jawaheer et al. (11) proposed a clinical pathway for a day-case LC in 18 children. Dalton et al. (12) emphasized the importance of an SDD protocol to change conservative clinical habits to an out-patient approach. Readmission rate and related operations following LC as SDD were not different between in-hospital and out-patient LC cases in a recent study (13).

As also indicated by previous studies, out-patient surgery is widely performed for many different types of pathologies in pediatric surgery centers but there seems to be a legitimate skepticism for the day-case approach in gastrointestinal surgery although reports of laparoscopic fundoplication and laparoscopic appendectomy on children in an out-patient setting were recently published (14,15). Doubtlessly, patient safety can not be jeopardized against all hospital costs, parental issues and surgeons' will, but we believe there is sufficient data in the literature showing that SDD for LC is safe and feasible for children as it is for adults with appropriate patient selection bias and management. Age, preoperative and operative morbidities such as previous history of cholecystitis and underlying hematological diseases, the length of anesthesia, may be considered as factors that may have an influence on the decision of the surgeon for early discharge, and these are yet to be discussed in this article.

Age: As seen in our study population, age does not seem to affect the decision for SDD. The youngest patient was a 6-month-old girl in the SDD group, and there was no significant difference between the mean ages of the groups. This is also noted in other previous studies in the literature.

Previous history of cholecystitis: Fibrosis due to previous inflammation may be considered as a challenging factor against dissection. Indeed, previous history of cholecystitis was more common in the PS group than the ONS group in our study. On the other hand, it is not listed in patient selection criteria in previous adult and pediatric studies. Holcomb et al. (16) mentioned a large percentage (22%) of children who required hospitalization due to the complications of cholelithiasis, but the term "complication of cholelithiasis" may also have referred to obstructive incidents as well as cholecystitis.

Underlying hematological diseases: Concomitant pathologies such as hemoglobinopathies may prompt prolonged IHST following LC due to postoperative close follow-up or possible blood transfusions in both adults and children (17,18). In our series, all the patients with hematological problems were assessed and prepared by a pediatric hematologist prior to anesthesia. In our study group, all sickle cell disease patients were monitored for at least one night. There was a significant difference between the ONS and PS groups in terms of concomitant underlying hematological diseases but we had solely one patient who required blood transfusion postoperatively due to the consumption coagulopathy as a major complication. Hence, the higher rate of patients with hematological diseases in the PS group probably relates to the surgeon's preference and the need for monitoring rather than a complication.

Perioperative complications-duration of anesthesia: Hepatobiliary surgery necessitates surgical skill and expertise because vascular or biliary abnormalities may be encountered. Esposito et al. (19) have mentioned 3% of anatomic anomalies involving biliary duct and cystic artery. Due to the retrospective nature of our study, we refrained from commenting on anatomic variations as there may have been lacking information about anatomy in operative notes. Previous history of cholecystitis may also contribute to the

duration of anesthesia due to fibrosis-related difficulty in dissection.

Oral feeding, postoperative nausea: Although overnight nasogastric drainage was previously favored, we find it unnecessary to keep drainage catheters postoperatively in cases without comorbidities (10,19). In a study of short-term postoperative evaluation of complaints in adults, authors detected a severe postoperative nausea and vomiting (PONV) at a rate of 2% (20). Méndez et al. (9) discharged SDD patients after ingestion of clear liquids with no readmission and vomiting but Jawaheer et al. (11) reported a high PONV rate of 58% which dropped down to 0% after they changed the type of anesthesia (gaseous to intravenous), and the type of postoperative feeding regime from unrestricted to a light diet for 72 hours. In our practice, we don't use a strict feeding regime. Instead, feeding is started with water and clear liquids for a couple of hours, and if well-tolerated, we let patients switch to a moderately unrestricted diet. As mentioned before, there was no readmission for PONV in any of the groups under that approach.

Pain and anxiety: Pain management should certainly have an effect to some degree on IHST. Preoperative sedation with midazolam hydrochloride and the routine analgesic regimen (intraoperative diclofenac and acetaminophen with metamizole in the early postoperative period) used in our institution was equivalent and sufficient for all the patients in each group where we did not detect any significant difference between postoperative pain scores. The use of perioperative intravenous narcotics was favored in two recent pediatric series for better compliance but opioids were reported to have serious adverse effects (11,12,20,21). Agarwal and Bagdi (10) used a bilateral subcostal transversus abdominis plane block under ultrasound guidance with similar pain scores to those of our study group.

In this study, the most significant factors to play a role on IHST were found to be the length of anesthesia and PTOF. Hence, this study is the only one to indicate the importance of "minimal invasiveness" and early oral feeding for shorter IHST in the pediatric population. As in an adult series, an ONS was recommended in the presence of intra-operative difficulties which may also seem to be rational for pediatric patients while the surgeon's choice may be different. Patients with underlying hematological diseases, previous history of cholecystitis, and prolonged duration of anesthesia due to perioperative complications are likely to be monitored longer before discharge.

Study Limitations

Due to the retrospective nature of this study, there may be some limitations. Records of pain scores and feeding times on nurse charts were filled out by a heterogenic group of nurses. Also clerical errors may have affected the discharge hours.

Conclusion

LC as day surgery may safely be performed in the pediatric population. Shorter duration of anesthesia and well-tolerated early oral feeding are the key factors for decision-making for these patients without co-morbidities. LC in the out-patient setting is thought to gain popularity as the number of experienced centers increase. Prospective and multicenter studies are necessary to define its precise psychological (both parents and children) and economical advantages.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Local Ethics Committee (approval number: 17-5.2/6).

Informed Consent: Consent form was filled out by the parents of all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.D., E.D., G.Ö., A.Ç., O.E., Concept: Z.D., Design: Z.D., Data Collection or Processing: E.D., S.T., Analysis or Interpretation: Z.D., G.Ö., A.Ç., O.E., Literature Search: Z.D., Writing: Z.D.

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. Carachi R, Young DG, Buyukunal C. A history of surgical paediatrics. Singapore, World Scientific Publishing Co Ltd, 2009.
2. Llorente J. Laparoscopic cholecystectomy in the ambulatory surgery setting. J Laparoendosc Surg 1992;2:23-6.
3. Stinson JN, Kavanagh T, Yamada J, Gill N, Stevens B. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. Pain 2006;125:143-7.
4. Smith M 2nd, Wheeler W, Ulmer MB. Comparison of outpatient laparoscopic cholecystectomy in a private nonteaching hospital versus a private teaching community hospital. JSLS 1997;1:51-3.
5. Campanelli G, Cavagnoli R, Cioffi U, De Simone M, Fabbiani M, Pietri P. Can laparoscopic cholecystectomy be a day surgery procedure? Hepatogastroenterology 1998;45:1422-9.
6. Lillemoe KD, Lin JW, Talamini MA, Yeo CJ, Snyder DS, Parker SD. Laparoscopic cholecystectomy as a "true" outpatient procedure: initial experience in 130 consecutive patients. J Gastrointest Surg 1999;3:44-9.
7. Vaughan J, Gurusamy KS, Davidson BR. Day-surgery versus overnight stay surgery for laparoscopic cholecystectomy. Cochrane Database Syst Rev 2013;31:CD006798.
8. Gurusamy K, Junarkar S, Farouk M, Davidson BR. Meta-analysis of randomized controlled trials on the safety and

effectiveness of day-case laparoscopic cholecystectomy. Br J Surg 2008;95:161-8.

9. Méndez K, Sabater R, Chinea E, Lugo-Vicente H. Is there a safe advantage in performing outpatient laparoscopic cholecystectomy in children? J Pediatr Surg 2007;42:1333-6.
10. Agarwal P, Bagdi RK. Day case laparoscopic cholecystectomy in children: a review of 11 cases. J Indian Assoc Pediatr Surg 2014;19:61-4.
11. Jawaheer G, Evans K, Marcus R. Day-case laparoscopic cholecystectomy in childhood: outcomes from a clinical care pathway. Eur J Pediatr Surg 2013;23:57-62.
12. Dalton BG, Gonzales KW, Knott EM, St Peter SD, Aguayo P. Same day discharge after laparoscopic cholecystectomy in children. J Surg Res 2015;195:418-21.
13. Sacco Casamassima MG, Gause C, Yang J, Goldstein SD, Swarup A, Abdullah F. Safety of outpatient laparoscopic cholecystectomy in children: analysis of 2050 elective ACS NSQIP-pediatric cases. Pediatr Surg Int 2016;32:541-51.
14. Banieghbal B, Beale P. Day-case laparoscopic Nissen fundoplication in children. J Laparoendosc Adv Surg Tech A 2007;17:350-2.
15. Aguayo P, Alemayehu H, Desai AA, Fraser JD, St Peter SD. Initial experience with same day discharge after laparoscopic appendectomy for nonperforated appendicitis. J Surg Res 2014;190:93-7.
16. Holcomb GW, Morgan WM, Neblet WW, Pietsch JB, O'Neill JA Jr, Shyr Y. Laparoscopic cholecystectomy in children: Lessons learned from the first 100 patients. J Ped Surg 1999;34:1236-40.
17. Al-Mulhim AS, Alshehri MH. Laparoscopic cholecystectomy in adult patients with sickle cell disease. Surg Laparosc Endosc Percutan Tech 2012;22:454-8.
18. Al-Salem AH, Issa H. Laparoscopic cholecystectomy in children with sickle cell anemia and the role of ERCP. Surg Laparosc Endosc Percutan Tech 2012;22:139-42.
19. Esposito C, Alicchio F, Giurin I, Perricone F, Ascione G, Settimi A. Lessons learned from the first 109 laparoscopic cholecystectomies performed in a single pediatric surgery center. World J Surg 2009;33:1842-5.
20. Jensen K, Kehlet H, Lund CM. Post-operative recovery profile after laparoscopic cholecystectomy: a prospective, observational study of a multimodal anaesthetic regime. Acta Anaesthesiol Scand 2007;51:464-71.
21. Gurusamy K, Vaughan J, Toon CD, Davidson BR. Pharmacological interventions for prevention or treatment of postoperative pain in people undergoing laparoscopic cholecystectomy. Cochrane Database Syst Rev 2014;28:CD008261.

J Pediatr Res 2017;4(4):211-5
DOI: 10.4274/jpr.74436

Original Article / Orijinal Araştırma

Efficacy and Maternal Comfort of Sequential versus Simultaneous Breast Expression by Mothers of Critically Ill Newborns

Kritik Hasta Yenidoğanların Annelerinde Ardışık ve Eş Zamanlı Süt Sağmanın Etkinlik ve Konforu

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ABSTRACT

Aim: Expressed breast milk is beneficial for infants in neonatal intensive care unit (NICU) when direct breastfeeding is not possible. Breast expression with manual or electric breast pumps is promoted for the initiation and maintenance of lactation in this critical period. In this study, we aimed to compare the efficacy and maternal comfort of sequential versus simultaneous breast expression in newly delivered mothers whose infants were admitted to NICU.

Materials and Methods: Thirty five mothers were followed prospectively for milk expression either sequentially (n=21, group 1) or simultaneously (n=14, group 2) with breast pumps for 10 days. The total amount of milk expressed per day and per each period was recorded together with the duration of breast expression. The mothers' impressions about the easiness and comfort of the procedure, and their satisfaction with the amount of milk were evaluated with a questionnaire at the end of the study.

Results: The amounts of expressed milk per day and per each expression period were similar in both groups. However, time spent for each expression period was significantly lower in the simultaneous breast expression group. Mothers in this group gave higher scores with regard to ease of use when compared to mothers in the sequential expression group (4.36±0.50 vs. 4.00±0.44, p=0.046). The mothers graded both methods with similar scores in all other parameters.

Conclusion: Simultaneous breast expression is time saving while both simultaneous and sequential breast expression are similarly efficient for milk production, and both methods are helpful and tolerable in promoting breastfeeding for NICU mothers.

Keywords: Breastfeeding, breast pump, sequential, simultaneous, neonatal intensive care unit

ÖZ

Amaç: Yenidoğan yoğun bakım ünitesinde (YYBÜ) yatan bebeklerde direkt emzirme mümkün olmasa da sağılmış anne sütü çok faydalıdır. Bu kritik dönemde laktasyonun başlatılması ve sürdürülmesi için elle ya da elektrikli süt pompaları kullanılarak süt sağılması önerilir. Bu çalışmada bebekleri YYBÜ'ye yatırılan yeni doğum yapmış annelerde ardışık ve eş zamanlı süt sağmanın etkinlik ve konforunu karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya alınan 35 anne, elektrikli pompa kullanarak her iki memeden ardışık (n=21) ya da eş zamanlı (n=14) süt sağdıkları 10 gün içerisinde prospektif olarak izlendi. Süt sağma süresine ek olarak sağılan süt miktarı günlük ve her sağma için ayrı ayrı kaydedildi. Bu uygulamaların kolaylığı ve konforu konusunda annelerin görüşleri ve tatminkarlıkları çalışmanın sonunda bir anket ile değerlendirildi.

Bulgular: Günlük ve her sağma girişiminde elde edilen süt miktarları gruplar arasında benzer bulundu. Her iki memeden eş zamanlı süt sağan annelerin süt sağma süreleri anlamlı olarak daha kısa bulundu. Eş zamanlı olarak her iki memeden süt sağan anneler diğerleri ile karşılaştırıldıklarında; kullanım kolaylığı yönünden daha yüksek skorlar verdiler (4,36±0,50'ye karşı 4,00±0,44, p=0,046). Anketin diğer alanlarında her iki süt sağma tekniği de benzer bulundu.

Sonuç: Süt sağmak için her iki memenin eş zamanlı sağılması zaman kazandırıcı bir yöntemdir. Bununla beraber hem eş zamanlı hem de ardışık süt sağma yöntemleri; bebekleri YYBÜ'de yatan annelerde laktasyonun sağlanmasında etkin ve iyi tolere edilen yöntemlerdir.

Anahtar Kelimeler: Süt sağma, süt pompası, ardışık, eş zamanlı, yenidoğan yoğun bakım ünitesi

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Received/Geliş tarihi: *21.05.2017* **Accepted/Kabul tarihi:** *30.05.2017*

Introduction

American Academy of Pediatrics recommends the baby's own mother's milk as the primary nutrient for both term and preterm neonates (1). Mother's milk is beneficial for healthy newborns and is even lifesaving for sick preterm and term infants hospitalized in neonatal intensive care units (NICUs). The main benefits are listed as better tolerance of enteral feeds, prevention of necrotizing enterocolitis and systemic infections, and improvement in cognitive functions in these vulnerable infants (1-3). However, in NICUs, mothers are separated from their sick infants. Since they can not directly breastfeed during the serious illness period, this situation may negatively influence the initiation and maintenance of lactation (4). Early initiated and frequently applied emptying of the breasts by breast pumps along with the emotional support given to mothers may help to maintain and promote breastfeeding (5,6). Frequent breast expression improves milk production and breastfeeding success in mothers of premature infants (7). Educating the mothers on the benefits of human milk and the methods for breast expression is necessary to achieve optimal milk production (8). Milk expression with breast pumps also enhances prolactin release and has a positive effect on the quantity of milk (9). Zinaman et al. (10) showed that prolactin and oxytocin hormone releases were similar in directly breastfeeding mothers compared to mothers who delivered prematurely and used electrically powered pumps for collecting milk.

Several types of manual or electrically powered breast pumps are now in use for breast milk expression. Some breast pumps have double pumps making simultaneous expression of both breasts possible. Other breast pumps with only one pump are used by mothers to express breast milk sequentially. Simultaneous or sequential use of breast pumps may affect the duration and comfort of the procedure. The aim of this study was to compare the efficiency and maternal comfort of sequential versus simultaneous breast expression in newly delivered mothers whose infants were admitted to NICU.

Materials and Methods

The mothers of infants who were hospitalized in Ege University Children's Hospital NICU were included in this study. These infants were not breastfed due to their illnesses and their mothers were encouraged to use breast pumps to collect their milk. Mothers who had any illness or taking any medication which is contraindicated or may influence breastfeeding were excluded from the study. All study group mothers were divided into two groups according to their preference of sequential or simultaneous breast expression by electric breast pumps (Lactaline; Ameda, Lincolnshire, IL, USA). Each mother was provided with a breast pump for her use at home. The mothers were motivated to empty their breasts as often as they could, and the duration of pumping, the amount of milk collected until the mother felt that her breasts were emptied were noted at each period for 10 days in a diary provided by the researchers. At the end of the study, the mothers were questioned on the easiness and comfort of the procedure with a questionnaire applied by face to face interviews. The questionnaire was designed to evaluate their impressions (easiness to use, comfort, presence of pain, general opinions) and their satisfaction with the milk amounts with a 5-point scale from 1 (very bad) to 5 (very good). Total scores were calculated by the summation of points given for each category. This study was approved by Ege University Faculty of Medicine Ethical Committee (approval number: 12-4/11). All participating mothers gave a written informed consent.

Statistical Analysis

Statistical analysis was carried out using SPSS 17.0. Chi-square and Mann-Whitney U tests were used for statistical analysis. $P<0.05$ was considered as statistically significant.

Results

Thirty five mothers were enrolled in the study. Maternal ages varied between 19 and 42 years (30.8±5.7). Gestational ages of the infants varied between 25 to 38 weeks (31.9±3.8) and their birth weights were within 760 and 3200 grams (1554.8±663.6). Twenty one mothers preferred sequential milk expression using a single pump and fourteen mothers preferred simultaneous milk expression with double breast pumps. Since 5 mothers did not need to use breast pumps after the first two days, the study period for each mother varied between 2 and 10 days (mean ± standard deviation: 7.55±2.7).

The mothers used the pumps 4-6 times a day. The type of the breast pump did not change the dropout rate of the study (p=0.435). The daily frequency of using the pump was 5.42±0.67 times in the sequential expression group, and 5.57±0.51 times in the simultaneous expression group (p=0.507).

The total amounts of milk obtained with sequential versus simultaneous breast expression are shown in Figure 1 and detailed data regarding milk expression over a 10-day

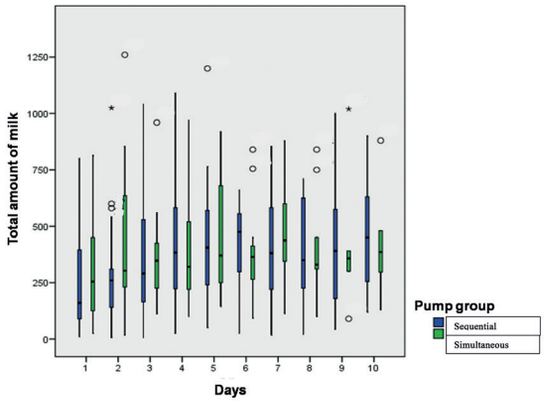

Figure 1. Total milk amounts obtained in one day with sequential versus simultaneous breast expression

study given in Table I. Although there was a tendency to obtain higher amounts of milk per day with simultaneous breast expression, no statistical difference was observed on any day between the two study groups. However, mothers in the simultaneous expression group achieved similar amounts of milk in shorter time periods.

Mothers in the simultaneous expression group gave higher scores regarding the ease of use than the mothers in the sequential expression group (4.36±0.50 vs. 4.00±0.44, p=0.046). The mothers' scores for other parameters (comfort of the procedure, their general impressions, and their

Table I. Characteristics of sequential and simultaneous breast expression for 10 days (data given as "mean (standard deviation)"

	Sequential	**Simultaneous**	**Sequential**	**Simultaneous**
	Day 1 (n=35)		Day 6 (n=21)	
Total amount of expressed milk, mL	251.38 (217.33)	325.79 (272.11)	416.25 (201.22)	388.36 (228.43)
Milk collected at each use, mL	51.83 (38.71)	70.71 (55.66)	73.33 (35.6)	77.00 (37.40)
Total time spent daily, min	90.05 (31.17)	56.21 (31.98)*	107.50 (23.78)	72.27 (24.22)*
Time spent for each use, min	18.90 (2.86)	11.57 (3.45)†	19.17 (2.88)	15.00 (5.00)*
Daily milk expression frequency	4.76 (1.44)	4.79 (1.76)	5.58 (0.79)	5.00 (1.18)
	Day 2 (n=33)		Day 7 (n=20)	
Total amount of expressed milk, mL	298.81 (432.86)	432 (344)	408.09 (250.01)	465.80 (215.16)
Milk collected at each use, mL	58.48 (40.67)	76.14 (56.96)	72.27 (46.6)	82.50 (34.39)
Total time spent daily, min	101.00 (28.91)	76.43 (26.48)*	121.82 (16.6)	79.5 (26.08)†
Time spent for each use, min	19.19 (2.60)	13.57 (4.56)†	20.00 (0.20)	14.50 (4.37)†
Daily milk expression frequency	5.29 (1.27)	5.71 (0.82)	5.91 (1.04)	5.50 (0.85)
	Day 3 (n=30)		Day 8 (n=15)	
Total amount of expressed milk, mL	376.16 (291.26)	367.86 (291.26)	391.00 (240.48)	409.44 (239.82)
Milk collected at each use, mL	71.21 (57.85)	66,36 (40,61)	69,64 (41,80)	78.00 (41.93)
Total time spent daily, min	98.42 (30.95)	85.3 (30.95)	112.73 (10.09)	74.44 (31.66)†
Time spent for each use, min	18.16 (3.80)	14.79 (4.87)*	20.00 (0.00)	13.33 (5.00)†
Daily milk expression frequency	5.10 (1.58)	5.79 (0.69)	5.64 (0.50)	5.56 (1.13)
	Day 4 (n=27)		Day 9 (n=15)	
Total amount of expressed milk, mL	419.94 (283.69)	383.36 (231.41)	419.27 (293.56)	419.17 (313.69)
Milk collected at each use, mL	83.81 (64.51)	77.50 (45.32)	71.82 (48,53)	74,00 (50,66)
Total time spent daily, min	100.00 (29.2)	73.50 (37.83)*	110.91 (18.68)	81.67 (28.57)*
Time spent for each use, min	17.31 (5.37)	14.50 (4.84)	19.55 (1.50)	15.00 (5.47)*
Daily milk expression frequency	5.38 (1.02)	5.29 (1.38)	5.82 (0.40)	5.50 (0.54)
	Day 5 (n=24)		Day 10 (n=15)	
Total amount of expressed milk, mL	426.14 (307.13)	456.85 (273.77)	485.00 (252.69)	426.00 (253.73)
Milk collected at each use, mL	75.79 (52.38)	86.08 (41.18)	88.22 (47.63)	72.67 (41.58)
Total time spent daily, min	103.57 (24.05)	81.77 (32.89)	111.11 (10.54)	83.33 (26.58)*
Time spent for each use, min	18.57 (3.63)	15.62 (5.39)	20.00 (0.00)	15.00 (5.47)*
Daily milk expression frequency	5.64 (0.74)	5.23 (1.16)	5.56 (0.52)	5.83 (0.40)

*p<0.005, †p<0.001
Min: Minimum

satisfaction with the milk amounts) did not differ between the two groups. Total scores calculated by the summation of the points given for easiness, comfort, satisfaction with the amounts of milk, and maternal general impression were slightly higher for simultaneous breast expression compared to sequential breast expression, with mean standard deviation values of 16.00 (1.88) versus 15.29 (2.07). However, this difference was not at a statistically significant level (p=0.370).

Discussion

The amounts of milk collected per day and per each period were similar in the simultaneous and sequential breast expression groups in our study. However, a similar amount of milk was obtained in a shorter time with simultaneous pumping being statistically significant on almost all study days. Mothers in the simultaneous expression group found breast expression procedure easier compared to the mothers in the sequential expression group. There was no difference between the total scores and scores for other parameters.

In an earlier study, we showed that electric pumps were easier to use and more efficient than manual pumps, and infants of mothers who used electric pumps even only during the NICU hospitalization period, reached birth weight earlier and had longer exclusive breast feeding and total breast feeding duration in the long term (11). Fewtrell et al. (12) have also found that electrically powered pumps are more efficient than manual pumps.

Simultaneous use of electrically powered breast pumps is more effective and plays a significant role in the continuity of lactation, and increases the amount of milk (13,14). Recently, Prime et al. (15) have shown that simultaneous breast expression is more efficient than sequential breast expression in the total amount of milk collected, lipid and therefore the energy content of the milk. As simultaneous expression yields more milk, the percentage of milk removed was 75% with simultaneous versus 66% with sequential pumping. Since healthy breastfed infants remove 67% of their mothers' milk, simultaneous breast expression increases breast drainage and stimulates milk synthesis. In Prime et al.'s (15) study mothers used the pumps for 15 minutes. However, in our study, mothers used both pumps until they felt that their breasts were totally emptied. The amount of milk obtained via both methods was similar between the two groups. The benefit of the simultaneous method was only the shorter period of breast expression for the mother.

Study Limitations

In this study, mothers were performing breast expression at home according to instructions and were keeping a diary provided by the researchers. Data was collected for 10 days. Factors that may have effected amount of expressed breast milk were not controlled.

Conclusion

This study shows that simultaneous breast expression with electrically powered breast pumps helps to achieve similar amounts of milk in a shorter time compared to sequential pumping in newly delivered mothers. Both methods are tolerable and effective. Working mothers may also find this time saving effect very helpful to express milk at work.

Acknowledgements

We acknowledge Assoc. Prof. Timur Köse from the Ege University Faculty of Medicine, Department of Biostatistics, for his assistance with the statistical analysis.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Faculty of Medicine Ethical Committee (approval number: 12-4/11).

Informed Consent: All participating mothers gave a written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A.K., N.C., B.Y.A., S.T., M.Y., M.A., N.K., Concept: M.A., N.K., Design: Ö.A.K., M.Y., Data Collection or Processing: Ö.A.K., N.C., B.Y.A., S.T., Analysis or Interpretation: Ö.A.K, B.Y.A., Literature Search: Ö.A.K, Writing: Ö.A.K, N.K.

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. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2012;129:827-41.
2. Schurr P, Perkins EM. The relationship between feeding and necrotizing enterocolitis in very low birth weight infants. Neonatal Netw 2008;27:397-407.
3. Pineda R. Direct breast-feeding in the neonatal intensive care unit: is it important? J Perinatol 2011;31:540-5.
4. Hurst N, Engebretson J, Mahoney JS. Providing Mother's Own Milk in the Context of the NICU: A Paradoxical Experience. J Hum Lact 2013;29:366-73.
5. Flaherman VJ, Lee HC. "Breastfeeding" by feeding expressed mother's milk. Pediatr Clin North Am 2013;60:227-46.
6. Friend D, Chertok IR. Evaluation of an educational intervention to promote breast pump use among women with infants in a special care nursery in Kenya. Public Health Nurs 2009;26:339-45.
7. Hill PD, Aldag JC, Chatterton RT. Effects of pumping style on milk production in mothers of non-nursing preterm infants. J Hum Lact 1999;15:209-16.
8. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ. Lactation counseling for mothers of very low birth weight infants:

effect on maternal anxiety and infant intake of human milk. Pediatrics 2006;117:67-75.

9. Hopkinson J, Heird W. Maternal response to two electric breast pumps. Breastfeed Med 2009;4:17-23.
10. Zinaman MJ, Hughes V, Queenan JT, Labbok MH, Albertson B. Acute prolactin and oxytocin responses and milk yield to infant suckling and artificial methods of expression in lactating women. Pediatrics 1992;89:437-40.
11. Genc B, Sen A, Akisu M, Bekler C, Kultursay N. Supporting breast milk intake in premature infants. Bulletin of Ege Pediatrics 1999;6:13-5.
12. Fewtrell M, Lucas P, Collier S, Lucas A. Randomized study comparing the efficacy of a novel manual breast pump with a mini-electric breast pump in mothers of term infants. J Hum Lact 2001;17:126-31.
13. Groh-Wargo S, Toth A, Mahoney K, Simonian S, Wasser T, Rose S. The utility of a bilateral breast pumping system for mothers of premature infants. Neonatal Netw 1995;14:31-6.
14. Hill PD, Aldag JC, Chatterton RT. The effect of sequential and simultaneous breast pumping on milk volume and prolactin levels: a pilot study. J Hum Lact 1996;12:193-9.
15. Prime DK, Garbin CP, Hartmann PE, Kent JC. Simultaneous breast expression in breastfeeding women is more efficacious than sequential breast expression. Breastfeed Med 2012;7:442-7.

J Pediatr Res 2017;4(4):216-9
DOI: 10.4274/jpr.45467

Original Article / Orijinal Araştırma

Endocrinopathies in Turkish Children with Thalassemia Major

Talasemi Majör Tanılı Çocuklarda Endokrin Problemler

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ABSTRACT

Aim: Endocrinopathies are common in patients with thalassemia major (TM) and affect their life quality. Our aim was to identify the frequency of growth retardation and endocrine complications in these patients.

Materials and Methods: Sixty-two patients aged 3-18 years with TM were evaluated retrospectively for height, weight, body mass index (BMI), and pubertal stage. Blood tests for endocrine function, and oral glucose tolerance test (OGTT) results were recorded.

Results: The mean age of 62 subjects (33 females/29 males) was 10.4±3.9 years. The frequency of ≤-2 standard deviation scores was 37.1% for height, 33.9% for weight and 11.3% for BMI. Short stature, being underweight, and low BMI were significantly more prevalent in children over 7 years old (p<0.001). Delayed puberty/hypogonadism was present in 37% of 19 adolescents. Thirteen percent of the subjects had vitamin D deficiency (<10 ng/mL), hyperparathyroidism was observed in 29% of the subjects, while subclinical hypothyroidism (thyroid-stimulating hormone 5-10 IU/mL) was determined in 3 (5.5%) of the 55 subjects. In OGTT, impaired fasting glucose was seen in 7 subjects (14.5%), impaired glucose tolerance in 3 (6.3%), diabetes mellitus in 1 (2.1%), and hypoglycemia at 120-min was observed in 5 subjects (10.4%). Overall, 67.7% of the 62 subjects had height standard deviation score ≤-2 and/or at least one endocrinopathy.

Conclusion: Growth retardation and endocrine problems are still a serious problem in TM patients, and develop particularly in those older than 7 years. Additionally, attention must be paid to hypoglycemia in these patients as well as diabetes.

Keywords: Thalassemia major, growth retardation, endocrinopathies, hypoglycemia

ÖZ

Amaç: Talasemi majörlü (TM) çocuklarda endokrinopatiler halen yaygın bir sorun olup hayat kalitesini önemli bir ölçüde etkilemektedir. Bu çalışmada TM'li çocuklarda büyüme geriliği ve endokrin komplikasyon sıklığının belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Yaşları 3-18 arasında olan 62 TM hastası boy, kilo, vücut kitle indeksi (VKİ) ve puberte açısından retrospektif olarak değerlendirildi. Hastaların yapılan endokrin testleri ve oral glukoz tolerans testi (OGTT) sonuçları kaydedildi.

Bulgular: Altmış iki (33 kız/29 erkek) hastanın ortalama yaşı 10,4±3,9 yıl idi. Hastaların %37,1'inin boyu, %33,9'unun kilosu ve %11,3'ünün VKİ'si ≤-2 standart sapma puanı idi. Kısa boy, düşük kilo ve düşük VKİ anlamlı olarak 7 yaş sonrasında görülmekteydi (p<0,001). Gecikmiş puberte/hipogonadizm ise 19 adölesanın %37'sinde saptandı. Hastaların %13'ünde vitamin D eksikliği (<10 ng/mL), %29'unda ise hiperparatiroidi görüldü. Subklinik hipotiroidi (tiroid stimüle edici hormon 5-10 IU/mL) ise 55 hastanın 3'ünde (%5,5) mevcuttu. OGTT sonuçlarına göre, bozulmuş açlık glukozu 7 (%14,5), bozulmuş glukoz toleransı 3 (%6,3), diabetes mellitus 1 (%2,1) ve 2. saatte hipoglisemi 5 (%10,4) hastada saptandı. Toplamda 62 hastanın %67,7'sinde boy kısalığı ve/veya en az bir endokrinopati mevcuttu.

Sonuç: Büyüme geriliği ve endokrin problemler halen ciddi bir sorun olup özellikle 7 yaş sonrasında ortaya çıkmaktadır. Ayrıca TM'li hastalarda diyabet kadar hipoglisemi açısından da dikkatli olunmalıdır.

Anahtar Kelimeler: Talasemi majör, büyüme geriliği, endokrinopati, hipoglisemi

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Received/Geliş tarihi: *28.03.2017* **Accepted/Kabul tarihi:** *02.06.2017*

Introduction

Thalassemia is the most common genetic blood disease, and patients with thalassemia major (TM) require regular blood transfusions. Iron chelation therapy is also essential for these patients in order to prevent morbidity and mortality. Although the main cause of death in TM is cardiac failure, endocrine complications are the most important problems affecting the quality of life in these patients.

Chelation therapy in order to reduce iron overload is provided with deferasirox, desferrioxamine or deferiprone (1). Few studies have compared each chelator with their combinations in terms of reducing iron overload and endocrine complications (2). So, there are no recommendations concerning the superiority of one over the other in the prevention of endocrine complications.

Although patients with TM take regular chelation therapy, the prevalence of endocrine problems is reported as high as 60% in some studies (3). Limited data are available concerning oral chelation therapy in preventing or improving endocrine disorders (4-6).

This study was planned to evaluate the growth and development status in children diagnosed with TM, and to investigate the prevalence of endocrine problems.

Materials and Methods

The 62 patients aged 3-18 years with TM that were followed-up at the Diyarbakır Child Health Hospital, Pediatric Hematology Unit, Diyarbakır, Turkey, between January and December 2015 were evaluated retrospectively.

During hematological follow-up, patients received blood transfusions every 3-4 weeks to maintain a pre-transfusion hemoglobin level of >9 g/dL. Iron chelation therapy, (deferasirox 20-40 mg/kg/d, desferrioxamine 25-60 mg/kg/d or deferiprone 50-75 mg/kg/d) was administered when ferritin level was >1000 ng/mL.

The patients' height, weight, body mass index [BMI weight (kg)/height (m^2)], pubertal stage and chelation therapy status were recorded. Basal cortisol (8:30-10:00 a.m.), adrenocorticotropic hormone (ACTH), Ca, P, alkaline phosphatase, parathyroid hormone (PTH), 25 hydroxyvitamin (OH) D_3, thyroid-stimulating hormone (TSH), sT4, HbA1c levels, and oral glucose tolerance test (OGTT, 1.75 gr/kg glucose-max 75 gr, and 0-120/min glucose and insulin) results were also evaluated. OGTT results were classified according to the criteria (7) of the International Society for Pediatric and Adolescent Diabetes.

Bone mineral density (BMD) was measured using a dual energy X-ray absorptiometer (DEXA). The L2-4 Z-scores and BMD values of the patients who had undergone DEXA measurement were recorded, and age and sex-adjusted data were calculated.

The study was approved by the Gazi Yaşargil Training and Research Hospital Local Ethics Committee and the patients or their parents provided informed consent for the study.

Statistical Analysis

SPSS v.18 software was used for statistical analysis. Data were analyzed as mean ± standard deviation or percentages. Chi-square and t-tests were used to compare mean values.

Results

The mean age of the 62 subjects (33 females/29 males) included in the study was 10.4±3.9 years. All the subjects received blood transfusion and took chelation therapy consisting of deferasirox (92%), desferrioxamine (3.2%), deferiprone (3.2%), and deferasirox and desferrioxamine (1.6%). Forty-two patients (67.7%) had height standard deviation scores (SDS) ≤-2 and/or at least one endocrinopathy.

The mean height, weight and BMI, SDS were -1.63±1.26, -1.44±1.31 and -0.70±1.07 respectively. The frequency of ≤-2 SDS was 37% for height, 34% for weight, and 11% for BMI. Short stature, being underweight, and low BMI were significantly more prevalent in children older than 7 years of age (p<0.001) (Table I). Delayed puberty/hypogonadism was present in 7 (37%) of the 19 adolescents aged ≥13 years old, and all of these patients also had short stature (≤-2 SDS). The growth hormone (GH) stimulation test was performed on 6 of the 23 patients of short stature, and one patient (peak GH: 3.4 and 4.7 µg/L) was administered GH therapy. The mean ferritin level was 1963±2185 mg/dL, however 12 patients had levels >2000 mg/dL. Ferritin levels were not significantly correlated with short stature, being underweight or low BMI (p=0.35, p=0.40, and p=0.32, respectively).

The mean basal cortisol level was 10.6±4.5 µg/dL (n=50), while 10 (20%) patients had <7 µg/dL. Peak cortisol levels in the low dose ACTH test were higher than 18 µg/dL in 4 patients who had cortisol levels <5 µg/dL. Also, 25(OH) vitamin D_3 insufficiency (10-20 ng/mL) was determined in 21 (46%), and deficiency (<10 ng/L) in 6 (13%) patients. Hyperparathyroidism (PTH >65 ng/L) was observed in 16 (29%) patients, but accompanying low vitamin D_3 was detected in only 8 of them. BMD Z-scores were below -2 SDS in 12 (48%) of the 25 patients in whom DEXA was able to be measured. BMD Z-score was calculated according to

Table I. The mean age, height, weight, body mass index and ferritin levels of the subjects

	All subjects	<7 years	≥7 years	p*
n	62	15	47	
Age	10.37±3.93	4.75±1.28	12.16±2.52	
Height SDS	-1.63±1.26	-0.76±0.93	-1.91±1.23	<0.001
Weight SDS	-1.43±1.31	-0.21±0.96	-1.82±1.16	<0.001
BMI SDS	-0.70±1.07	0.31±0.82	-1.03±0.93	<0.001
Ferritin (mg/dL)	1963±2185	1362±703	2274±2609	0.10

*Subjects between <7 and ≥7 years old
BMI: Body mass index, SDS: Standard deviation scores

their sex and bone age, and 4 patients were evaluated as osteopenic (Z-score -1>-<-2), and 1 as osteoporotic (Z-score -2.19). Subclinical hypothyroidism (TSH 5-10 IU/mL) was determined in 3 (5.5%) of the 55 patients, and low sT4 was not observed in any (Table II).

Table II. The frequency of endocrinopathies in the subjects with thalassemia

	Number of the subjects	%
Growth retardation	23/62	37
Adrenal insufficiency	0/50	0
Hypothyroidism		
Overt	0/55	0
Subclinical	3/55	5.5
Vitamin D insufficiency	21/46	46
Vitamin D deficiency	6/46	13
Hyperparathyroidism	16/55	29
Osteoporosis	1/25	4
OGTT		
IFG	7/48	14.5
IGT	3/48	6.3
DM	1/48	2.1
Hypoglycemia	5/48	10.4

OGTT: Oral glucose tolerance test, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus

When the OGTT results were analyzed, impaired fasting glucose was determined in 7 patients (14.5%), impaired glucose tolerance (IGT) in 3 (6.3%), diabetes mellitus in 1 (2.1%) patient. Hypoglycemia values were <60 mg/dL at 120-min in 5 patients (10.4%). The mean fasting glucose and insulin levels were 90±9.9 mg/dL and 4.8±2.8 mUI/mL respectively. The glucose and insulin levels at 120-min in OGTT were 100.3±33 mg/dL and 13±11.9 mIU/mL respectively. 4/5 subjects with hypoglycemia had higher than 2 mIU/mL insulin levels at 120-min in OGTT. The subjects' mean HbA1c values were 6.7±0.6%, and this value was even more elevated when individuals with abnormal OGTT were excluded.

Discussion

In this retrospective study, quite a high number (67.7%) of transfusion-dependent thalassemia subjects were of short stature and/or had endocrinopathy. These results are comparable to other studies. Also, growth retardation was seen especially in subjects over 7 years old.

Growth retardation in patients with TM may develop due to various causes. The factors affecting growth include chronic anemia and hypoxia, chronic malnutrition, micronutrient deficiencies such as zinc, hypersplenism, hepatic involvement, delayed puberty, and GH deficiency (8). Approximately 37-40% of the adolescents with thalassemia are of short stature, and this problem is around 64-70% in developing countries. In Turkey, the prevalence of short stature has been reported as 25-40% (3,9), and we had 37.1% in this study. Several studies have shown low insulin-like growth factor 1 (IGF1) levels in patients with thalassemia and short stature, but GH deficiency has been determined in only 20-50% of these patients (3,10). Low IGF1 levels without GH deficiency suggest a possible association with chronic anemia, malnutrition or GH neurosecretory dysfunction (11). The GH stimulation test could only be performed in 6 cases in our study, and GH deficiency was determined in 1 (16.6%) of these subjects.

Approximately 50-60% of TM patients had at least one endocrine dysfunction, and the prevalence increased with age (1,3,9). The frequency was 67.7% in the present study, and growth retardation was seen especially in the older than 7-year-old subjects. However, no relation was determined between these findings and ferritin levels. In several previous studies there was no statistically significant relationship between ferritin levels and endocrinopathies (3,12). From this we can derive that serum ferritin levels may also increase with infection, inflammation and hepatic function disorders, and are also an indirect measure of iron overload. Calculation of iron overload with hepatic and cardiac T2- magnetic resonance imaging reflects iron deposition (13) more accurately.

Delayed adolescence and hypogonadism are one of the most common endocrine problems in adolescents with TM. The prevalence ranges between 40% and 50% (3,14). They may be caused by chronic malnutrition and iron deposition-related pituitary dysfunction. Incomparable with previous findings, delayed adolescence/hypogonadism was determined as 37% in our study.

The prevalence of hypothyroidism in these patients was 6-16%, the majority of the cases being subclinical. Overt hypothyroidism is quite rare (3,14). Similar to the literature, the prevalence of hypothyroidism was 5.5%, and no overt hypothyroidism was observed in this study. Hypoparathyroidism can develop in up to 10% of the patients with TM (15). Although it was not observed in our patients, we detected a secondary hyperparathyroidism associated with vitamin D deficiency. Whereas the prevalence of vitamin D deficiency in Turkey is decreasing, it still presents a significant problem in patients with thalassemia. Isik et al. (9) reported vitamin D deficiency or insufficiency in 78% of their patients, the comparable level in our study being 59%. However, it was not the cause of osteoporosis or osteopenia in any patient.

Abnormalities in glucose metabolism in patients with thalassemia generally appear in the second decade. The cause is insulin resistance, followed by insulin deficiency

associated with iron overload in the pancreas. The prevalence of diabetes and IGT in these patients ranges between 8% and 11% (3,14). Our study showed a similar frequency to that observed in these studies (8.4%). In addition, thalassemic patients tend to have more hypoglycemia when compared to Type I and Type II diabetes. In a recent study, severe hypoglycemia was common (56%) in thalassemic patients with diabetes who were treated with insulin (16). In our study, hypoglycemia in OGTT unexpectedly came up in 10.4% of the patients who had no diabetes. This present study suggested that hypoglycemia is not only seen in thalassemic patients with diabetes, but also in normoglycemic thalassemic patients. Hemosiderosis impairing glucagon secretion, and low liver glycogen storage due to hepatic fibrosis are possible mechanisms (16). Insulin resistance and delayed insulin secretion due to hemosiderosis could be other possible mechanisms of hypoglycemia, as seen in patients with cystic fibrosis (17).

Study Limitations

The higher number of the patients could give the frequencies of rare endocrine problems in patients with thalassemia.

Conclusion

This study emphasizes that growth retardation and endocrine problems are still a serious problem in patients with thalassemia, and become apparent particularly after age 7. So, close endocrinological monitoring is required from the time of diagnosis. In addition, hypoglycemia should be taken into consideration alongside diabetes in these patients.

Ethics

Ethics Committee Approval: The study was approved by the Gazi Yaşargil Training and Research Hospital Local Ethics Committee.

Informed Consent: The patients or their parents provided informed consent for the study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

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

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. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and disease complications in thalassemia major. Ann N Y Acad Sci 1998;850:227-31.
2. Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo controlled, double-blind trial of the effect of combined therapy with Deferoxamine and Deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation 2007;115:1876-84.
3. Aydinok Y, Darcan S, Polat A, et al. Endocrine complications in patients with beta-thalassemia major. J Trop Pediatr 2002;48:50-4.
4. Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassemia major. Br J Haematol 2010;148:466-75.
5. Farmaki K, Tzoumari I, Pappa C. Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications. Blood Cells Molec Dis 2011;47:33-40.
6. Platis O, Anagnostopoulos G, Farmaki K, Posantzis M, Gotsis E, Tolis G. Glucose metabolism disorders improvement in patients with thalassemia major after 24-36 months of intensive chelation therapy. Pediatr Endocrinol Rev 2004;2(Suppl 2):279-81.
7. Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2015;16:392.
8. Chatterjee R, Bajoria R. Critical appraisal of growth retardation and pubertal disturbances in thalassemia. Ann N Y Acad Sci 2010;1202:100-14.
9. Isik P, Yarali N, Tavil B, et al. Endocrinopathies in Turkish children with Beta thalassemia major: results from a single center study. Pediatr Hematol Oncol 2014;31:607-15.
10. Theodoridis C, Ladis V, Papatheodorou A, et al. Growth and management of short stature in thalassemia major. J Pediatr Endocrinol Metab 1998;11(Suppl 3):835-44.
11. Roth C, Pekrun A, Bartz M, et al. Short stature and failure of pubertal development in thalassemia major: evidence for hypothalamic neurosecretory dysfunction of growth hormone secretion and defective pituitary gonadotropin secretion. Eur J Pediatr 1997;156:777-83.
12. Gulati R, Bhatia V, Agarwal SS. Early onset of endocrine abnormalities in beta- thalassemia major in a developing country. J Pediatr Endocrinol Metab 2000;13:651-6.
13. Wood JC, Noetzl L, Hyderi A, Joukar M, Coates T, Mittelman S. Predicting pituitary iron and endocrine dysfunction. Ann N Y Acad Sci 2010;1202:123-8.
14. No authors listed. Multicentre study on prevalence of endocrine complications in thalassaemia major. Italian Working Group on Endocrine Complications in Non-endocrine Diseases. Clin Endocrinol (Oxf) 1995;42:581-6.
15. Chern JP, Lin KH. Hypoparathyroidism in transfusion- dependent patients with beta-thalassemia. J Pediatr Hematol Oncol 2002;24:291-3.
16. Warncke K, Konrad K, Kohne E, et al. Diabetes in patients with B-thalassemia or other hemoglobinopathies-Analysis from the DPV database. Klin Padiatr 2016;228:307-12.
17. Haliloglu B, Gokdemir Y, Atay Z, et al. Hypoglycemia is common in children with cystic fibrosis and seen predominantly in females. Pediatr Diabetes 2016;187:607-13.

J Pediatr Res 2017;4(4):220-6
DOI: 10.4274/jpr.60490

Original Article / Orijinal Araştırma

Seizure Self-Efficacy Scale for Children with Epilepsy: Confirmatory and Exploratory Factor Analysis

Çocuklarda Nöbet Öz-Yeterlik Ölçeği: Doğrulayıcı ve Açıklayıcı Faktör Analizi

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ABSTRACT

Aim: In the past few years, the concept of self-efficacy in children with epilepsy has become increasingly important. This study aimed to analyze the psychometric aspects of the Turkish version of the Seizure Self-Efficacy Scale for Children.

Materials and Methods: This is a cross-sectional survey. The study data were collected using the Seizure Self-Efficacy Scale for Children and Child Introduction Form. The study sample included 166 children who were between 9 and 17 years of age. The authors assessed the reliability and construct validity of the study data using exploratory and confirmatory factor analyses (CFA).

Results: The original model was not confirmed by the CFA. The analysis tool included 15 items in two factors. Reliability analysis showed that the two factors were acceptable and valid. The tool was valid and reliable for measuring the self-efficacy of epileptic children. The factor structure was derived from and confirmed by the original tool. It was found that the Turkish version of the modified Seizure Self-Efficacy Scale for Children had excellent satisfactory psychometric aspects for a Turkish population.

Conclusion: Health professionals can present a more effective drug process and nursing care by identifying and assessing seizure self-efficacy levels in children with epilepsy, and they can make a positive contribution to disease management and the way the child deals with the disease.

Keywords: Epilepsy, self-efficacy, confirmatory factor analysis, exploratory factor analysis

ÖZ

Amaç: Son yıllarda epilepsi hastalığı olan bireylerde öz yeterlik kavramı gittikçe önem kazanmaktadır. Bu çalışmanın amacı, epilepsi hastalığı olan çocuklarda Nöbet Öz-Yeterlik Ölçeği'nin Türkçe versiyonunun psikometrik yönlerini analiz etmektir.

Gereç ve Yöntemler: Bu çalışma kesitsel desendedir. Araştırmanın verileri Çocuklarda Nöbet Öz-Yeterlik Ölçeği ve Çocuk Tanıtım Formu kullanılarak toplanmıştır. Araştırmanın örneklemini 9-17 yaş arası 166 çocuk oluşturmuştur. Verilerin geçerliği ve güvenirliğinin incelenmesinde açıklayıcı ve doğrulayıcı faktör analizleri (DFA) kullanılmıştır.

Bulgular: DFA sonucunda ölçeğin geliştirildiği örneklem grubundaki faktör yapısının doğrulanmadığı belirlendi. Analiz edilen 15 maddelik ölçekte, iki faktörlü yapı belirlendi. Bu iki faktörlü yapının geçerliği ve güvenirliği yapılan analizlerle doğrulandı. Ölçeğin yeni faktör yapısı ise ölçeğin orijinalinden elde edilerek doğrulandı. Bununla birlikte Nöbet Öz-Yeterlik Ölçeği'nin iki faktörlü yapısının psikometrik analizlerinin Türk çocuklarında kabul edilebilir düzeyde olduğu ve epilepsi hastalığı olan çocuklarda öz-yeterliği ölçmede geçerli güvenilir bir araç olduğu belirlendi.

Sonuç: Sağlık profesyonelleri, epilepsi hastalığı olan çocuklarda nöbet öz-yeterlik düzeyini belirleyerek ve değerlendirerek daha etkili bir tedavi süreci ve hemşirelik bakımı sunabilirler, bunun sonucunda çocuğun hastalıkla baş etmesine ve hastalığın yönetim sürecine olumlu katkı sağlayabilirler.

Anahtar Kelimeler: Epilepsi, öz-yeterlik, doğrulayıcı faktör analizi, açıklayıcı faktör analizi

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Received/Geliş tarihi: *01.06.2017* **Accepted/Kabul tarihi:** *04.09.2017*

Introduction

Epilepsy is one of the most common chronic illnesses of childhood and adolescence (1). It influences roughly 0.5 to 1% of all children up to the age of 16 years. The incidence of epilepsy in developing countries is almost twice as much as in developed countries (2). There are few studies conducted in Turkey aiming to ascertain the incidence and prevalence of epilepsy. Topbaş et al. (3) reported that the prevalence of childhood epilepsy in this country is between 0.8 and 1.7%.

Epilepsy has an important effect on the maintenance of the individual's physical, psychological, and social well-being (4). In contrast to other chronic illnesses, epileptic seizures are unpredictable, which reduces the child's perception of controlling his/her own life remarkably (5). Therefore, there are social restrictions in the daily activities of epileptic children (6). Individuals with epilepsy may have feelings of inadequacy, fear, stigmatization, anger, and desperation, and they may show passive behaviors. These factors reduce the individual's psycho-social functions, self-efficacy, and quality of life, which may lead to self-destruction. Medical treatment and its side effects may also influence self-efficacy, ability to adjust to treatment, and the relationship between the patient and the caretaker (7,8).

Self-efficacy is one of the most frequently used theories to anticipate health behavior, and it is an important equalizer in individuals with chronic illnesses (9). In coping with epilepsy, the patients' perception of self-efficacy is essential to their process of making decisions about their illness. In the management of epileptic seizures, self-efficacy is described as an individual's ability to cope with seizures in an effective way. Successful management of seizures is the principle goal in the course of the treatment of epilepsy (7,10,11).

Individuals with high self-efficacy adjust better to treatment, their quality of life increases, and the frequency of seizures is reduced (7,12). Moreover, high self-efficacy is correlated with a more positive attitude towards epilepsy, fewer depressive symptoms, less anxiety about having seizures, and less stigmatization. In these patients, a positive attitude towards and perception about the illness and self-care behavior facilitate the adjustment to the management and treatment of the illness.

It is necessary to develop certain tools to analyze and measure the levels of self-efficacy in children with epilepsy in order to achieve a better disease management. There are few studies conducted in Turkey on this. The objective of our study was to examine the psychometric aspects of the Turkish version of the Seizure Self-Efficacy Scale for Children (SSES-C).

Materials and Methods

Study Design

This is a methodological study. The authors performed the validity analysis of the SSES employing confirmatory and exploratory factor analyses (EFA). Confirmatory factor analysis (CFA) is frequently used in scale development in nursing studies. However, there has been little discussion of its use in scale testing in nursing science research. CFA is a special approach of Structural Equation Modeling (SEM). SEM combines factor analysis and regression analysis, allowing the study of the causal relationships between factors using regression analysis. CFA and EFA are included in the family of factor analyses. CFA is different than EFA since EFA is used to ascertain an exploratory factor model without making a prior assumption of the association between variables. EFA investigates the structure of correlation or covariance matrices (13).

Participants and Procedure

The study population included children between the ages of 9 and 17, who were diagnosed with epilepsy, and who visited University of Health Sciences Antalya Training and Research Hospital, Akdeniz University Hospital, and Bursa Dörtçelik Children's Hospital between June 2012 and March 2013. The children had been diagnosed with epilepsy at least six months previously and did not have any other chronic disease (e.g., diabetes or cerebral palsy), or mental retardation. Consent form was filled out by all participants. The study was approved by the Akdeniz University Local Ethics Committee (approval number: B.30.2.AKD.0.20.05.05/39). The authors suggest that five to twenty times of the number of variables in the scale be included to determine the sample size in the validity and reliability analysis (14). This study did not use any sample selection method. In the light of the literature, 166 children who met the inclusion criteria were recruited to the study.

Based on the suggestions of experts, the authors reviewed the whole content of the scale and conducted a pilot study. The authors held interviews with the children in a silent environment in the pediatric neurology polyclinic of the tertiary care hospital where the study was conducted. The information forms were filled out by the authors during the interviews with the children. The pilot study was conducted with 10 children whose data were excluded from the study.

Instruments

Data in this study were collected using the Child Introduction Form and the SSES-C.

Child Introduction Form: The authors created this form based on the relevant literature (12). It included 28 questions about the socio-economic status and the illness process of the children.

The Seizure Self-Efficacy Scale for Children: This is a 5-point Likert-type scale of 15 items. All items in the scale contained positive statements. The responses to the scale items were enumerated from 1 to 5. The scores for each item ranged between 1 and 5 and were created by dividing the total score on the instrument by the number of questions in the instrument. This instrument was created for the children between 9 and 14 years of age, had had epilepsy for at least

six months, and had no other chronic illnesses or intellectual disability. The Cronbach's alpha coefficient of the instrument was 0.93 which indicates that the scale was quite reliable (12).

The cross-cultural validation of the instruments allows researchers to avoid the early phases of the development of a new questionnaire. This is a big advantage since it is a very long procedure. Moreover, the translation and conversion of an instrument into different languages enables us to employ the questionnaires in comparative multi-national studies. The scale was translated and back-translated to ensure its validity and reliability, along with some other aspects, for the Turkish sample. The translation and cultural conversion of the study were performed at a very initial phase (8). Reliability and validity analysis of the questionnaire were done specifically for this study since the scale did not have a Turkish version. All 15 items in the instrument were translated into Turkish by four authors (S.G., H.T., D.B., and G.M.) and the items were resolved into a completely new translated version. Then, back-translation of the items into English was blindly done, and items were checked by a bilingual Turkish scientist and a native English speaker fluent both in spoken and written Turkish and with a great deal of experience as a medical paper reviewer. Authors and the other experts discussed and agreed on the translation of each item. Moreover, the authors conducted a pilot study with bilingual individuals to determine the linguistic accuracy of the translated scale. The authors also decided that the translation was acceptable and required no revision.

Statistical Analysis

The authors encoded and scored all the items in the scale, encoded and checked all the study data, and finally analyzed it using SPSS 11.0 and statistical analysis system 7.0 statistical programs. All of the required information was collected from the participants and all the forms were completed. To be able to describe the main variables, the authors made use of descriptive statistics including means, skewness and standard deviation.

Confirmatory Factor Analysis

Using CFA, researchers ascertain the goodness of fit indices (GFI) between a model that has previously been created by a different author and the sample data in question. In this study, the authors employed the maximum likelihood estimation method to do CFA in order to confirm the exploratory model which (12) was created. The authors followed the original one-factor model and used the same model specification in this analysis. The factor variances were fixed at 1, which provided the identification of the model.

The authors also calculated a variety of GFI to be able to measure the level of the fit. To many researchers, the standard GFI is 0.90 (15-18). The authors also used some other criteria for this calculation. Initially, the authors determined 0.90 for the GFI and 0.90 for the adjusted GFI. Then, they evaluated how well the new model fit the data using the root mean square error of approximation (RMSEA) with a 90% confidence interval. An RMSEA value of 0.06 or less indicates an accepted model fit (15). A moderate fit would be indicated by values around 0.08, and poor fit would be shown by values above 0.10 (19). After that the authors administered a GFI chi-square test, which included the best fit where the chi-square was statistically insignificant. Next, the authors used Bentler and Bonett's normed-fit index (NFI). The NFI values varied between 0 and 1, and an acceptable model fit to the data was shown by the 0.90 values (20). Finally, the authors used a comparative fit index (CFI) (21). Researchers usually accept a cutoff value of 0.90 for the CFI as consistent with the moderate model fit (21), and believe that a good model fit is indicated by a cutoff value which is close to 0.95. Since the fit indices values become distorted when the distribution of the scale items is not normal, the study also reported the skewness values.

Exploratory Factor Analysis

When the observed factor structure does not fit with the theoretical structure, then the EFA can be employed to improve the model. In order to describe an applicable factor structure, the authors did an EFA in the second phase of the analysis. They also did an EFA to identify the factor sub-scales of the 15 items in the scale employing a principal component method with varimax rotation. The study determined the number of sub-scales that had Eigen values bigger than 1.0 for retaining the factor. However, the study retained items with factor loads greater than or equal to 0.40 (including the values rounded to 0.40), and also retained those that loaded on only one factor. The authors excluded from the scale items that did not fit these criteria one by one. They did the factor analyses over and over again until they found a solution that made all the scale items meet all of the criteria. Cronbach's alpha was used to evaluate the internal consistency reliability and the structure of the new factors.

Results

Table I illustrates the descriptive statistics such as mean, standard deviation and skewness values of the study sample. The authors evaluated the study data using the skewness values by univariate normality. The table indicates that mean skewness value was -0.976 [(range= -2.386 – (-0.290)], and none of the items was showing a bigger skewness value than the cutoffs of |3| that was suggested (22). The univariate normality of the items were advocated by these findings.

Confirmatory Factor Analysis

The study tested a one-factor model according to the original conceptualization of SSES-C. The criteria of model fit evaluation are presented in Table II. Some of these criteria were not acceptable for a good fit. However, the others showed an acceptable or nearly acceptable model fit. These points can also be seen in Table II. According to the study

data, an adequate model fit was revealed by the CFA, and this model fit was only based on Bentler's CFI criterion (0.9028). There was a moderate fit based on GFI (0.8704), adjusted GFI (0.8271); RMSEA (0.0776) and NFI (0.8249). However, there was only one fit index that indicated poor fit: χ^2 (90)=179.329, p=0.0001. The authors could not acquire an acceptable fit from any of the fit statistics. There was only one fit statistic that showed a nearly reasonable model fit. Four other fit statistics showed a moderate fit with the model. Thus, the authors determined that since the CFA failed to confirm the original factor structure, it was necessary to improve the fit between the model and the data and to use the EFA to modify the model.

Exploratory Factor Analysis

In order to analyze the 15 items in the scale, the authors used the maximum likelihood extraction method and also made use of a varimax rotation. They also identified two factors that had eigenvalues above 1.00. The numbers of factors to be retained and rotated were determined using the scree test. This test also recommended a two-factor solution. The authors examined many other criteria to determine the number of factors. These criteria included Tucker and Lewis's reliability coefficient (TLC) (23), which takes values between 0 and 1.0 with a higher TLC value indicating more acceptable reliability like Akaike's information criterion (AIC) (24); and Schwarz's Bayesian criterion (SBC) (25). It is accepted that the best factor solution is the factor number that produces the smallest value of AIC and SBC or the largest value of TLC. The authors rotated and examined many factor solutions to decide on a right factor solution which is theoretically meaningful and fits the retention rules. In the end, the authors selected the two-factor solution since all three criteria were met by this solution. Compared to the other factor solutions, the four-factor and three-factor solutions in particular, AIC and SBC reached their smallest values in their two common factors, and TLC also reached its highest value (TLC=0.958) in these factors. For this reason, it is certain that the two-factor solution is the best for these data. After the authors decided on the two-factor solution, they arranged the factor loads from the greatest to the smallest. This arrangement is shown in Table III. All of the items were kept in the original 15-item measure of the scale according to the criteria that were determined beforehand. The authors assumed that all items were loaded on one single factor since the factor loads of the items were equal to or below 0.40. In the end, the EFA generated a 15-item measurement which had a two-factor solution. Then, the authors interpreted each item by examining their contents and coefficient patterns. These two factors were respectively classified as "self-management of seizures" and "the influence of the environment in the management of seizure." The authors eventually used Cronbach's alpha coefficient to determine the internal consistency reliability

Table I. Summary statistics and comparison of mean item (n=166)

Item	Mean ± SD	Skewness
I can manage my seizure condition by making good choices about which activities I do.	3.23±1.51	-0.290
I can manage my seizure condition so I don't have to miss school or other activities.	3.89±1.34	-0.926
I can keep from doing things that might make my seizure condition worse, even if I get pressure from my friends.	4.08±1.24	-1.223
I can manage my seizure condition when I am at school.	3.65±1.55	-0.732
I can manage my seizure condition even if I am angry or sad.	3.18±1.47	-0.294
I can manage my seizure condition even if there are things to worry about in my family.	3.61±1.49	-0.635
I can manage my seizure condition even if I am at a friend's, on vacation, or on a school trip.	3.84±1.47	-0.837
I can talk to the doctor or nurse if I have questions about my seizure condition.	4.12±1.28	-1.434
I can keep from being afraid after a seizure in order to manage the situation.	3.54±1.54	-0.572
I can talk to my parents if I have problems with my seizure condition.	4.55±1.01	-2.386
I can manage my seizure condition by making sure I get enough rest.	4.08±1.14	-1.193
I can manage my seizure condition by staying away from things that can make it worse.	3.92±1.27	-1.065
I can manage my feelings about my seizure condition by reminding myself of my good qualities.	3.66±1.44	-0.768
I can do the things my doctor told me to do to manage my seizure condition.	4.30±1.09	-1.679
I can manage my seizure condition because I can handle any problems it can cause.	3.56±1.29	-0.608

SD: Standard deviation

Table II. Goodness of fit indices for the Seizure Self-Efficacy Scale for Children factor model

Index	Children with epilepsy
GFI	0.8704
GFI adjusted for degrees of freedom (AGFI)	0.8271
Chi-square	179.3290
Chi-square DF	90
Pr >chi-square	<0.0001
RMSEA estimate	0.0776
RMSEA 90% lower confidence limit	0.0609
RMSEA 90% upper confidence limit	0.0941
Bentler's comparative fit index	0.9028
Bentler & Bonett's (1980) non-normed index	0.8867
Bentler & Bonett's (1980) NFI	0.8249

GFI: Goodness of fit index, AGFI: Adjusted goodness of fit index, RMSEA: Root mean square error of approximation, NFI: Normed-fit index, DF: Degrees of freedom

of both scales. There was a scale homogeneity that varied between 0.63 and 0.89. Thus, the subscales that were identified by EFA had internal consistency. Total SSES-C's alpha coefficient was quite high (0.90). This value shows that the internal reliability was excellent since it far exceeded the accepted limit, which was 0.70. This also implies that the questions in the scale were adequate for the Turkish culture.

Table III. Two factors with factor loading for our sample

Items of SSES-C	Self-management of seizures (F1)	The influence of the environment in the management of seizures (F2)
(1) I can manage my seizure condition by making good choices about which activities I do.	0.60	
(2) I can manage my seizure condition so I don't have to miss school or other activities.	0.51	
(4) I can manage my seizure condition when I am at school.	0.69	
(5) I can manage my seizure condition even if I am angry or sad.	0.75	
(6) I can manage my seizure condition even if there are things to worry about in my family.	0.78	
(7) I can manage my seizure condition even if I am at a friend's, on vacation, or on a school trip.	0.76	
(9) I can keep from being afraid after a seizure in order to manage the situation.	0.43	
(11) I can manage my seizure condition by making sure I get enough rest.	0.69	
(12) I can manage my seizure condition by staying away from things that can make it worse.	0.49	
(13) I can manage my feelings about my seizure condition by reminding myself of my good qualities.	0.59	
(15) I can manage my seizure condition because I can handle any problems it can cause.	0.75	
(3) I can keep from doing things that might make my seizure condition worse, even if I get pressure from my friends.		0.56
(8) I can talk to the doctor or nurse if I have questions about my seizure condition.		0.67
(10) I can talk to my parents if I have problems with my seizure condition.		0.56
(14) I can do the things my doctor told me to do to manage my seizure condition.		0.76
Cronbach's alfa	0.89	0.63
Variance explained %	32.79	16.87
Cumulative variance	32.79	49.67

Discussion

In the past few years, the context of self-efficacy in individuals with epilepsy has become increasingly important. The perceived self-efficacy of the patient is quite important in the management of epilepsy to be able to understand the process of decision-making. In our study, we aimed to examine the psychometric aspects of the Turkish version of the SSES-C. The ages of the children and adolescents in the sample ranged between 9 and 17. Their average age was 13.46±2.57.

Current research indicates that the factor structure of the SSES-C was examined for the first time in this study with a relatively large Turkish sample that includes children with epilepsy when the CFA did not confirm the original factor structure. In the authors' opinion, this study will make remarkable contributions to the relevant literature when the SSES-C is adapted to Turkish culture. It is essential that the psychometric aspects of the scale be used for measurement and gaining information in terms of understanding the nature of the attitude of individuals with epilepsy towards self-efficacy.

As indicated by the results of the CFA, the factor structure, which was derived from and confirmed by US patients, was not confirmed by the Turkish sample. For this reason, the US and Turkish samples had different dimensionality in their beliefs in self-efficacy, as shown by the findings of the CFA. In this study, the authors employed EFA to gain a new modified factor structure for the Turkish sample. This operation aimed to obtain accurate cross-cultural comparisons. The EFA generated a new factor structure, or model with the two separate dimensions of self-efficacy in Turkish culture. This situation is different from the original one-dimension factor structure, which claims that every factor can be taken into account independently when scoring the SSES-C. It is generally accepted that this model represents the distinctiveness of two dimensions of self-efficacy. The subscale "self-management of seizures" includes the items that explain how a child can control or manage epileptic seizures on his or her own (e.g. "I can manage my seizure condition by selecting my activities correctly"). The other subscale includes the statements that focus on the effect of the environment on seizure management, rather than on the child's individual control (e.g. "I can speak to my physician or a nurse when I have a question about my seizure condition"). The authors established the factor structure of SSES-C for the sample that included children with epilepsy. Then, the internal consistency of the instrument was determined. According to the findings of this study, the modified factor structure of the SSES-C has desired psychometric aspects for the Turkish sample. The study used the Cronbach's alpha coefficient to

determine the reliability of the instrument. The estimated alpha of the SSES-C (0.89) was slightly lower than the one reported in the original study, which was conducted with a US sample (0.93) (12), but it was still higher than the result (0.85) of other studies (26). Eventually, the study findings had a strong reliability and a solid internal consistency.

Study Limitations

This study had several limitations. In the relevant literature, the SSES-C is the only tool available to examine the self-efficacy of children with epilepsy. However, there are no foreign studies which aimed to validate the SSES-C by the administration of CFA and EFA. Moreover, there are also no other studies conducted in Turkey to examine the self-efficacy of children with epilepsy. Therefore, the authors recommend that further studies be conducted to test the SSES-C with different samples.

Conclusion

In terms of the factor structure of the SSES-C, there are certain differences between the US and Turkish samples. According to the study results, the best and most effective use of the measurement will be performed by summing the subscale scores instead of the total score. This finding is consistent with the theoretical opinion that multi-dimensionality is the best way to conceptualize self-efficacy. This tool was proved to be valid and reliable to measure self-efficacy in children with epilepsy. For this reason, the authors suggest that researchers use the SSES-C when it is necessary to measure the self-efficacy of epileptic children. The children are capable of evaluating their own self-efficacy, which makes it easier to manage the illness and adjust it to the treatment. Moreover, the awareness of health professionals working with children who have epilepsy can be increased by the application of SSES-C. To conclude, this study proves that SSES-C can be applied to make use of the differences between the sub-samples included both in a single structure and in different cultures.

Acknowledgments

The authors obtained via e-mail, the consent of Joan K. Austin, the creator of the SSES-C, to translate it into Turkish. They also obtained the approval of their Institutional Review Board's Ethics Committee.

The authors would like to thank all participants in this study. This research was supported by the Akdeniz University, Scientific Research Projects Management Unit.

Ethics

Ethics Committee Approval: The study was approved by the Akdeniz University Local Ethics Committee (approval number: B.30.2.AKD.0.20.05.05/39).

Informed Consent: Written consent was obtained from the children and their parents who participated in the study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Concept: Ş.T.G., M.Z.F., A.İ.D., Design: Ş.T.G., M.Z.F., A.İ.D., Data Collection or Processing: Ş.T.G., Analysis or Interpretation: Ş.T.G., M.Z.F., Literature Search: Ş.T.G., M.Z.F., Writing: Ş.T.G., M.Z.F., A.İ.D.

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. Rodgers CC. The Child with Cerebral Dysfunction. In: Hockenberry MJ, Wilson D, (eds). Wong's Nursing Care of Infants and Children, 10th ed. Elsevier/Mosby, 2015;1425-83.
2. Epilepsy Action Australia. Facts and Statistics About Epilepsy [cited 2015 September 17] Available from: URL: https://www.epilepsy.org.au/resources/for-media/facts-statistics-about-epilepsy Date of Access: 09/17/2015.
3. Topbaş M, Özgün Ş, Sönmez MF, et al. Epilepsy prevalence in the 0-17 age group in Trabzon, Turkey. Iran J Pediatr 2012;22:344-50.
4. Dharmadhikari AS, Sinha VK. Psychiatric comorbidity in children with epilepsy: a cross-sectional 5 years rural prevalence study. J Neurosci Rural Pract 2017;8:179-84.
5. Tutar Güven Ş, İşler A. Importance of Seizure Self-efficacy in Children with Epilepsy for Disease Management. Epilepsi 2014;20:103-6.
6. Wohlrab GC, Rinnert S, Bettendorf U, et al. Famoses: a modular educational program for children with epilepsy and their parents. Epilepsy Behav 2007;10:44-8.
7. Chen HF, Tsai YF, Lin YP, Shih MS, Chen JC. The relationships among medicine symptom distress, self-efficacy, patient-provider relationship, and medication compliance in patients with epilepsy. Epilepsy Behav 2010;19:43-9.
8. Tutar Güven Ş, Işler A. Validity and reliability of the seizure self-efficacy scale for children with epilepsy. Noro Psikiyatr Ars 2015;52:47-53.
9. Amtmann D, Bamer AM, Cook KF, Askew RL, Noonan VK, Brockway JA. University of Washington self-efficacy scale: a new self-efficacy scale for people with disabilities. Arch Phys Med Rehabil 2012;93:1757-65.
10. Wagner JL, Smith G, Ferguson PL, Horton S, Wilson E. Hopelessness model of depressive symptoms in youth with epilepsy. J Pediatr Psychol 2009;34:89-96.
11. Wagner JL, Smith G, Ferguson PL, van Bakergem G, Hrisko S. Pilot study of an integrated cognitive-behavioral and self-management intervention for youth with epilepsy and caregivers: Coping Openly and Personally with Epilepsy (COPE). Epilepsy Behav 2010;18:280-5.
12. Caplin D, Austin JK, Dunn DW, Shen J, Perkins S. Development of a self- efficacy scale for children and adolescents with epilepsy. Children's Health Care 2002;31:295-309.
13. Kääriäinen M, Kanste O, Elo S, Pölkki T, Miettunen J, Kyngäs H. Testing and verifying nursing theory by confirmatory factor analysis. J Adv Nurs 2011;1163-72.

14. Stevens JP. Applied Multivariate Statistics for the Social Sciences. 4th ed. Hamilton, New Jersey, Printing Company, 2002;325-81.
15. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Structural Equation Modeling 1999;6:1-55.
16. McRae RR, Zonderman AB, Costa PT, Bond MH, Paunonen SV. Evaluating replicability of factors in the revised NEO personality inventory: confirmatory factor analysis versus pro-crustean rotation. J Pers Soc Psychol 1996;70:552-66.
17. Vassend O, Skrondal A. Validation of the NEO Personality Inventory and the five-factor model. Can findings from exploratory and confirmatory factor analysis be reconciled? European Journal of Personality 1997;11:147-66.
18. McDonald RP, Marsh HW. Choosing a multivariate model: noncentrality and goodness of fit. Psychological Bulletin 1990;107:247-55.
19. Browne MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, eds. Testing Structural Equation Models Sage. Newbury Park CA, 1993;136-60.
20. Bollen KA. Structural equations with latent variables. New York, Wiley, 1989;80-148.
21. Bentler PM. Comparative fit indices in structural models. Psychological Bulletin 1990;107:238-46.
22. Kline RB. Principles and practice of structural equation modeling. New York, Guilford Press, 2005;124-49.
23. Tucker LR, Lewis C. A reliability coefficient for maximum likelihood factor analysis. Psychometrika 1973;38:1-10.
24. Akaike H. Factor analysis and AIC. Psychometrika 1987;52:317-32.
25. Schwarz G. Estimating the dimension of a model. The Annals of Statistics 1978;6:461-4.
26. Wagner JL, Smith G, Ferguson P. Self-efficacy for seizure management and youth depressive symptoms: Caregiver and youth perspectives. Seizure 2012;21:334-9.

J Pediatr Res 2017;4(4):227-31
DOI: 10.4274/jpr.53244

Original Article / Orijinal Araştırma

Assessment of the Awareness of Prematurity and Related Problems

Prematürelik ve Sorunları Konusunda Farkındalık Düzeyinin Değerlendirilmesi

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ABSTRACT

Aim: Prematurity is an important health problem affecting all segments of society. In this study, we aimed to evaluate the level of awareness of prematurity and related problems.

Materials and Methods: A questionnaire consisting of fifteen questions was administered to medical faculty students, pediatric residents, and to laypersons by face to face interviews. The questionnaire applied in the scope of the study had 8 open-ended questions and 7 "yes-no" questions.

Results: Of the 150 people who answered the questionnaire, 92 were health workers and the remaining 54 were people from the public. The groups with and without health workers had a similar rate of awareness of the World Prematurity Awareness Day (58.7% vs. 58.6% respectively, p=0.30). All of the health care workers defined prematurity correctly while 89.7% of the laypersons gave the correct definition (p<0.05). People from the public expected the survival of babies with higher birth weight and gestational age and this group was less informed about the short and long-term problems related to prematurity. In both groups, the awareness of physicians specializing in newborn care was low (17.4% vs. 13.8%, p=0.13). The level of awareness of the shortage of specialized physicians and nurses in neonatal care was significantly lower among laypersons than that of health care workers (p values <0.05).

Conclusion: Although our study population knew what prematurity was, they lacked knowledge about the complications of prematurity, and the quality and adequacy of the health care teams involved in the care of premature babies.

Keywords: Newborns, preterm, awareness, mortality, morbidity

ÖZ

Amaç: Prematürite toplumun tüm kesimlerini etkileyen önemli bir sağlık sorunudur. Bu çalışmada prematürite ve ilişkili sorunlar konusunda farkındalık düzeyinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: On beş sorudan oluşan anket tıp fakültesi öğrencileri, pediatri asistanları ve halktan kişilere yüz yüze görüşme yöntemi ile uygulanmıştır. Çalışma kapsamında uygulanan anket 8 adet açık uçlu, 7 adet "evet-hayır" şeklinde yanıtlanan soru içermekteydi.

Bulgular: Anketi yanıtlayan 150 kişinin 92'si sağlık çalışanı geri kalan 54'ü ise halktan kişilerdi. Dünya Prematürite Farkındalık Günü'nünden sağlık çalışanı olan ve olmayan gruplar benzer oranda haberdardı (sırasıyla %58,7'ye karşı %58,6, p=0,30). Prematüreliği sağlık çalışanları %100 oranda; diğerleri ise %89,7 oranında doğru tanımladı (p<0,05). Halktan kişiler daha büyük doğum ağırlığı ve gestasyonel yaştaki bebeklerin yaşatılabileceğini düşünürken; bu grubun prematürelerin erken ve uzun dönem sorunları konusunda bilgileri daha kısıtlıydı. Her iki grupta da yenidoğan bakımında uzmanlaşmış hekimler konusunda farkındalık düşüktü (%17,4'e karşı %13,8, p=0,135). Yenidoğan bakımında uzmanlaşmış hekim ve hemşire açığı konusunda halktan kişilerin farkındalık düzeyi sağlık çalışanlarından anlamlı olarak düşüktü (p değerleri <0,05).

Sonuç: Prematüreliğin ne olduğu bilinmesine rağmen; bu bebekleri bekleyen sorunlar, bakımında görev alacak ekiplerin nitelik ve yeterliliği konusunda toplumda henüz bilgilenme olmadığı anlaşılmıştır.

Anahtar Kelimeler: Yenidoğan, prematüre, farkındalık, mortalite, morbidite

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Received/Geliş tarihi: *21.05.2017* **Accepted/Kabul tarihi:** *03.10.2017*

Introduction

In the year 2012, the number of live premature births before 37 weeks of gestation was 15.1 million; 1 million newborns died due to direct complications of premature birth and 1.47 million newborns lost their lives due to conditions related to prematurity (1). According to the UNICEF 2014 report, the etiology of neonatal deaths around the world is listed as prematurity and its complications (35%, 1 million deaths), complications related to birth (24%, 0.7 million deaths) and sepsis (15%, 0.6 million deaths) (2).

The premature birth rate among 184 countries changes between 5-18%; the average rate is estimated to be 10% both in our country and in the world. It is also estimated that 3/4 of deaths related to prematurity is preventable by cost effective measures (3).

In the last 20 years with the scientific and technological developments observed in the field of neonatology, the survival rate of premature infants has significantly increased. However, the mortality and morbidity of very low birth weight (VLBW <1500 gr) infants is still very high. The most important reasons of mortality in newborns with birth weights less than 1000 grams are respiratory failure, infections, and congenital malformations.

Some of the survivors have sequelae such as learning disabilities, visual and auditory problems (4). Premature births are responsible for 70% of neonatal mortality, 36% of infant mortality, and 25-50% of long-term neurological disabilities.

All around the world every year 15 million babies are born prematurely; 13 million of prematurely born babies survive, but 345.000 (2.7%) such babies survive with moderate to severe neurological sequel, and 567.000 (4,4%) babies survive with mild sequelae. In addition to that, 185.000 premature babies live with retinopathy of prematurity (ROP), and 32.000 have severe visual problems including blindness. In USA, the cost of premature births was calculated as 26.2 million dollars, and more than 51.000 dollars per baby for the year 2006. Premature births bring a heavy burden to the health care system.

"Awareness Day for Prematurity", which has important results, was first celebrated in 2008 with European family associations. Since 2011, November 17th has been celebrated as "World Prematurity Awareness Day" internationally (5). Family associations, health care workers, politicians, hospitals and organizations try to raise awareness of prematurity by press release campaigns, local events and other activities. In the last few years Turkish Neonatal Society and all neonatology units have also started to celebrate this day with the families of premature infants, and efforts to raise awareness have increased.

To raise awareness of prematurity we interviewed a group of 150 people by a questionnaire consisting of 15 simple questions about prematurity before 17th November 2015. Our study carries importance since it is the first sectional study aiming to attract attention to prematurity.

Materials and Methods

On 10-11th November 2015, a questionnaire with 15 questions was applied to medical faculty students, residents in pediatrics, families of preterm and term infants, and laypersons to evaluate their knowledge about prematurity. The questionnaire applied in the scope of the study had 8 open-ended questions and 7 "yes-no" questions. The interviews were done one by one in a face to face manner. Data obtained from these interviews were analyzed by SPSS for Windows 19.0 software, International Business Machines Corporation, Armonk, New York. Ethics committee approval was not obtained since the study was done by a questionnaire.

Results

Among the 150 people who answered the questionnaire 93 (62%) were female and 57 (38%) were male. In this group 58 were laymen, 74 were medical faculty students, and 18 were residents in pediatrics. The questions and the answers obtained from health care workers and medical students compared to those of people from the public are given in detail in Table I and Table II.

Fifty four of 92 (58,7%) health care workers, and 34 of 58 (58,6%) laypersons were aware that 17th November was celebrated as "World Prematurity Awareness Day" (p=0.30). Prematurity was correctly defined by all in the health care group while the correct answer was given by 52 (nearly 90%) laymen. When limits of viability were asked, in the health care workers group the average expected limits were 600 gr and 24 weeks; in the other group these limits were higher as 1000 gr and 28 weeks. The health care group had more knowledge about early and late problems of preterm infants, as expected.

The necessary qualifications, and the quantity of doctors and nurses giving health care to preterm newborns were also asked in the questionnaire. The knowledge about the specially trained doctors in the field of neonatology was low in both groups (Table II). The knowledge about the availability of neonatologists in the care of premature infants in Turkey was lower in the non-health care group.

Discussion

European Foundation for the Care of Newborn Infants (EFCNI) had their first meeting on 17th November 2008 in Rome. In this meeting it was decided to celebrate a day to raise awareness of prematurity (5). The 1st World Prematurity Awareness Day was celebrated by EFCNI and other organizations in Europe on 17th November 2009. In 2010 "The March of Dimes" from USA and "Little Big Souls" from Africa joined EFCNI for a larger celebration of the 2nd World Prematurity Awareness Day all around the world. Because purple represents hope, courage, sensitivity, kindness, unity, and helping people, the symbol color for

World Prematurity Awareness Day was decided to be purple (6). In our study, half of both groups were knowledgeable about the celebration of 17th November as World Prematurity Awareness Day, which shows that both groups need more information on this special day.

According to the definition of World Health Organization, newborns born before 37 weeks (259 days) are considered as premature (3). This definition of prematurity was widely known in both of the groups who answered our questionnaire. However, health care workers defined prematurity more correctly (100% vs. 89.7%; p<0.05).

Table I. The percentage of correct answers in study groups about prematurity and related problems

	Health care worker (n=92)	Others (n=58)	p
What special day was set on November 17th in the world and in Turkey?	54 (58.7%)	34 (58.6%)	0.30
What does "premature" mean?	92 (%100%)	52 (89.7%)	<0.05
What is the smallest birth weight that a baby can survive?	600 grams	1000 grams	<0.05
What is the smallest gestational age that a baby can survive?	24 weeks	28 weeks	<0.05
What is the name of the special care device where premature babies are heated and taken care of?	66 (71.7%)	45 (77.6%)	0.380
What are the most serious problems that lead to premature infant deaths?			
Respiratory problems	65 (70.7%)	16 (27.6%)	<0.05
Infectious diseases	12 (13%)	11 (19%)	<0.05
Is there a disease that can lead to loss of vision in premature babies?	89 (96.7%)	36 (62.1%)	<0.05
Is the milk of the mothers who delivered premature infants different from the ones who delivered at term?	69 (75.0%)	30 (51.7%)	<0.05
Since premature babies are born smaller than term babies; can they catch-up their peers in the future?	85 (92.4%)	47 (81.0%)	0.05
Do premature babies have less intelligence than normal?	86 (93.5%)	49 (84.5%)	0.09
Can breast milk increase the intelligence of premature babies?	75 (81.5%)	44 (75.9%)	0.11
What is the name given to the procedure of holding the naked premature babies on mothers' chests?	44 (47.8%)	15 (25.9%)	0.02

Table II. The percentage of correct answers in study groups about the health care given to premature infants

	Health care worker (n=92)	Others (n=58)	p
What is the name given to specially trained doctors who look after premature babies?	16 (17.4%)	8 (13.8%)	0.13
Do you think there are enough specially trained doctors in Turkey for premature babies?	84 (91.3%)	35 (60.3%)	<0.05
Do you think there are enough specially trained nurses in Turkey for premature babies?	90 (97.8%)	38 (65.5%)	<0.05

Data from different centers in Turkey showed the frequency of preterm births around 10%, this means nearly 1 out of every 10 newborns are premature in our country. These premature babies can only find a chance to live if cared in neonatal intensive care units with developed facilities, and with experienced neonatal doctors and nurses. The special care device where premature babies are heated and taken care of was defined correctly as "incubator" by a high percentage of health care workers and laypersons who answered our questionnaire.

Newborns with gestational ages below 28 weeks comprise the highest risk group for mortality with rates over 95% if they do not receive specialized care. Newborns with gestational ages between 32-37 weeks have a 7 times increased neonatal mortality rate and 2.5 times increased mortality rate when compared to term newborns. In high-income countries (in which neonatal mortality rate is <5/1000 live births) enough maternal and neonatal care is provided; more than 80% of newborns with gestational ages over 28 weeks survive. Mortality and sequelae risks exist in newborns delivered before 26 weeks of gestation. The chance of sequelae free survival is very slim for newborns delivered before 24 weeks (7). In medium income countries that are decreasing neonatal deaths (neonatal mortality rate 5-15/1000 live births), maternal and neonatal care is provided to a certain extent but the sequelae rate among surviving babies between 28-32 weeks is twice as high compared to high income countries. Therefore, improving the quality of care in these countries is very important. In the countries with low income and high neonatal mortality (neonatal mortality rate ≥15/1000 live births) birth complications and perinatal asphyxia are high due to inadequate obstetric and neonatal emergency care services. On the other hand, there are few prematurity related long-term complications as highest risk babies with gestational age below 28 weeks have a low chance of survival (1).

Even in late preterm newborns whose gestational ages are between 34-36 weeks, infection, hyperbilirubinemia, feeding difficulties are more common than term babies. Also increased neonatal mortality and morbidity have been reported in late preterm infants compared to term infants (8-11). Kalyoncu et al. (12) have reported 2.3% mortality and 11 times more respiratory distress syndrome (RDS), 14 times more feeding problems, 11 times more hypoglycemia and 2.5 times more rehospitalization in late preterm infants of 34-37 weeks compared to term babies.

In the United States (US), between 1990 and 2000, no improvement was detected in the prognosis of infants between 500 and 1500 grams (13). However, according to the US data for 2006, the chances of surviving for those under 1500 grams reached 92.6%, and for those under 1000 grams approached 85%, and it has become similar

to what Japan has been doing for many years in the world (14). According to the data from Turkish Neonatal Society, the overall mortality in neonatal intensive units, particularly neonatal mortality under 1500 grams and 32 weeks has been decreasing over the years. The mortality rate was 18.8% for newborns with gestational ages <32 weeks, and 23.9% for VLBW in 2014 (15).

Neonatal mortality rate is 71% for 22-24 weeks, and 42.8% for 25-26 weeks, whereas mortality decreases to 20% for 27-28 weeks. The high mortality rate of 62.8% for 500-750-gram newborns decreases to 28.2% for those over 750 grams. Unfortunately, while the survival rate increases after 750 grams and 26 gestational weeks, brain, lung and eye complications are more frequently expected in these earlier weeks. In our survey, for the question about the smallest infant that can survive, the health care workers agreed on over 600 grams and the laypersons agreed on over 1000 grams.

The Infant Death Monitoring System records of the Ministry of Health of the Republic of Turkey in 2008 show that 56.5% of deaths were defined as "early neonatal deaths", 19.5% as "late neonatal deaths", 76% as neonatal deaths, and 24% as post neonatal infant deaths. It was observed that prematurity ranked first as the major cause of death; prematurity and RDS were the most common intermediate causes, and RDS was the most common final cause of death. It has been determined that about 60% of infant deaths are of premature infants and low birth weight infants (16).

Ling et al. (17) have conducted a survey on parental knowledge about prematurity and related issues in Singapore. Their survey has shown that the majority of responders had enough general knowledge to pass the T-score defined by the researchers, but the median scores were low. Although this above mentioned survey is structured in a different way, we compared our results with this study when appropriate.

According to the health workers who answered our questionnaire the most important problems leading to the death of premature infants were respiratory problems (70.7%) and infection problems (13.0%). These two main reasons were naturally much less known in the other group. Tendency for infection and difficulty in breathing were the most commonly known problems of prematurity in the survey conducted in Singapore (17).

ROP is a major health problem, especially in very premature infants, and can lead to loss of vision (18). An illness that may lead to loss of vision in premature babies was correctly expressed by nearly all the health care workers and by 61% of the ordinary people. Less than half of the responders in Ling et al. (17) survey were aware of the parental eye problems of premature infants.

Breast milks of mothers who have given birth to premature babies contain more protein and sodium in the first 4-6 weeks to allow the rapid growth of the premature infant (19). When this information was asked in the questionnaire, 75% of health workers, and 51% of people from the public expressed this content difference correctly. Premature babies catch up within 2 years of age if they are fed adequately (19). Our survey showed that 92.4% of health workers and 81% of laypersons thought that premature babies could catch up with their peers (p=0.049).

Nearly half of the health workers and one-quarter of the other group defined "Kangaroo care" as premature babies lying naked on the mother's breast, but interestingly, 13 people in this second group had had babies admitted to our newborn intensive care unit where kangaroo care is a routinely applied procedure.

There were very few people in both groups who knew that the specially trained doctors who looked after premature babies were called "neonatologists" or "newborn specialists" (%17,4 and %13,8; p=0,135). While a large number of health workers knew the inadequate number of neonatologists and neonatal nurses who can take care of premature infants competently, the rates of those who had the correct answer on this subject were 60% and 65% in the other group.

With the results of this survey it has been understood that although the definition and incubator need of premature babies are commonly known, there is a lack of information in society about the problems awaiting these infants due to the lack of qualifications, and insufficiency of the teams in charge of their care. It is important to reduce the number of premature births and the mortality related to prematurity in our country in order to reduce infant mortality rate, which is a sign of the level of our development. For this purpose, it is not enough to provide only medical devices, it is necessary to quickly resolve the deficits for specialized physicians and nurses in neonatal medicine both qualitatively and quantitatively. It is essential to inform each section of society not only about prematurity but also about the short and long-term problems related to it, and the presentation of health services.

Study Limitations

This study was conducted in a single center, thus has limitations for generalization of data among different centers.

Conclusion

World Prematurity Day Awareness activities must be more widely supported by family associations, politicians, and social organization groups to increase public awareness since this awareness is the prerequisite of searching and finding solutions to this big problem.

Ethics

Ethics Committee Approval: Ethics committee approval was not obtained since the study was done by a questionnaire.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., M.A., Concept: N.K., Design: N.K., Data Collection or Processing: S.K., E.K.,

Analysis or Interpretation: S.K., E.K., Ö.A.K., N.K., Literature Search: S.K., Ö.A.K, N.K., Writing: S.K., Ö.A.K, N.K.

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. Lawn JE, Blencowe H, Oza S, et al. Every Newborn: progress, priorities, and potential beyond survival. Lancet 2014;384:189-205.
2. Levels & Trends in Child Mortality Report 2014: Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation. UNICEF, World Health Organization, The World Bank, United Nations; 2014.
3. World Health Organization Facts Sheets: Preterm Birth. Available at: http://www.who.int/mediacentre/factsheets/fs363/en/.
4. No authors listed. Practice Bulletin No. 159: Management of Preterm Labor. Obstet Gynecol 2016;127:29-38.
5. History of world prematurity day. Available at: http://www.efcni.org/index.php?id=2150.
6. World Prematurity Day. Available at: https://en.wikipedia.org/wiki/World_Prematurity_Day.
7. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443-56.
8. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, Barfield W, Weiss J, Evans S. Risk factors for neonatal morbidity and mortality among "healthy," late preterm newborns. Semin Perinatol 2006;30:54-60.
9. McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 2008;111:35-41.
10. De Luca R, Boulvain M, Irion O, Berner M, Pfister RE. Incidence of early neonatal mortality and morbidity after late-preterm and term cesarean delivery. Pediatrics 2009;123:1064-71.
11. Araujo BF, Zatti H, Madi JM, Coelho MB, Olmi FB, Canabarro CT. Analysis of neonatal morbidity and mortality in late-preterm newborn infants. J Pediatr (Rio J) 2012;88:259-66.
12. Kalyoncu O, Aygün C, Cetinoğlu E, Kücüködük S. Neonatal morbidity and mortality of late-preterm babies. J Matern Fetal Neonatal Med 2010;23:607-12.
13. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196:147.
14. Vermont Oxford Network Very Low Birth Weight Database. Available at: https://public.vtoxford.org/databases/very-low-birth-weight/.
15. Türkiye'deki yenidoğan merkezlerinde mortalite verileri. Türk Neonatoloji Derneği Bülteni 2015;27:51-2.
16. Korkmaz A, Aydın Ş, Duyan Çamurdan A, et al. Türkiye'de bebek ölüm nedenlerinin ve ulusal kayıt sisteminin değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları Dergisi 2013;56:105-21.
17. Ling ZJ, Lian WB, Ho SK, Yeo CL. Parental knowledge of prematurity and related issues. Singapore Med J 2009;50:270-7.
18. Bas AY, Koc E, Dilmen U; ROP Neonaal Study Group. Incidence and severity of retinopathy of prematurity in Turkey. Br J Ophthalmol 2015;99:1311-4.
19. Kültürsay N, Bilgen H, Türkyılmaz C. Türk Neonatoloji Derneği Prematüre ve Hasta Term Bebeğin Beslenmesi Rehberi, 2014.

J Pediatr Res 2017;4(4):232-8
DOI: 10.4274/jpr.78055

Orijinal Araştırma / Original Article

Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeğinin Türkçe Geçerlilik Güvenirliği ve Yenidoğana Uyarlanması

Turkish Validity Reliability of the Pediatric Peripheral Intravenous Infiltration Scale and Its Adaptation to Newborns

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ÖZ

Amaç: Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği'nin Türkçe geçerlilik güvenirliğinin incelenmesi ve yenidoğanlarda kullanımının uyarlanması amacıyla planlanmıştır.

Gereç ve Yöntemler: Metodolojik tipte olan bu çalışma prospektif ve gözlemsel özelliktedir. Elli dört yenidoğanda, 2 gözlemcinin eş zamanlı değerlendirme sonuçları ile yürütülmüştür. Her bebek damar yolu değiştirildiği andan itibaren, saatlik gözlemler ile 8 kez izlenmiş ve toplam 864 gözlem sonucu ölçek ile değerlendirilmiştir. İstatistiksel değerlendirmeler için SPSS programı kullanılmıştır.

Bulgular: Çalışmaya toplam 54 hasta ve 864 gözlem sonucu alınmış olup yenidoğan yoğun bakım ünitesinde her bir bakım düzeyindeki olguların oranları benzerdir (1. düzey: 16 hasta; 2. düzey: 23 hasta; 3. düzey 15 hasta, (p=0,348). En fazla kullanılan sıvı cinsi %63'lük oranla %10 dekstroz ve %26'lık oranla total parenteral nütrisyon sıvısı olarak bulunmuştur. Postnatal ortanca 3. günden (minimum: 1, maksimum: 27) itibaren takip yapılmıştır. Toplam 864 gözlem yapılan 54 bebeğin (n=19) %35'inde birinci gözlem sonrasında damar yolu değiştirilmiştir. Damar yolu değiştirilen bebeklerin ölçeğe göre n=11'i (%69) birinci evrede (1 puan), n=5'i (%25) ikinci evrede (2 puan) tespit edilmiş ve damar yolları yenilenmiştir. İki değerlendirici arasındaki uyumu gösteren Krippendorff alfa güvenirlik katsayısı 1,00 olarak hesaplanmıştır (p<0,001).

ABSTRACT

Aim: The aim of this study is to determine the Turkish validity reliability and newborns' adaptation to Pediatric Peripheral Intravenous Infiltration Scale.

Materials and Methods: This study is methodological and was conducted on 54 newborns with the simultaneous evaluation of two observers. Each infant was monitored 8 times with hourly observations from when the vein path was changed, and a total of 864 observational outcomes were assessed with scale. SPSS program was used for statistical evaluations.

Results: A total of 54 newborns were taken into the study and the proportions of cases at each care level in neonatal intensive care unit were similar (level 1: 16 patients, level 2: 23 patients, level 3: 15 patients (p=0.348). The most commonly used fluid was found to be dextrose 10% in 63%, and total parenteral nutritional fluid in 26%. The newborns' postnatal age was median 3 days (minimum: 1, maximum: 27). A total of 864 observations were made for 8 hours and in the 35% (n=19) of 54 babies, the vein pathway was changed after the first observation. 69% of the infants whose vascular accesses were changed, were identified in the first stage (1 point), 25% in the second stage (2 points), and vascular accesses were renewed. The Krippendorff's alpha reliability coefficient showing the integration between the two evaluators was 1.00 (p<0.001). This result shows "full agreement" between the two

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Geliş tarihi/Received: *17.09.2017* **Kabul tarihi/Accepted:** *03.10.2017*
4 Nisan 2016, 24. Ulusal Neonatoloji Kongresi'nde poster bildiri (PB-023) olarak sunulmuştur.

Bu sonuç iki değerlendirici arasında "tam uyumu" göstermektedir. Ölçümler arasındaki güvenirliği gösteren sınıf içi korelasyon katsayısı ise r=0,99 (p<0,001) bulunmuştur. Bu katsayısı da ölçümlerin yüksek düzeyde güvenilir olduğunu ifade etmektedir.

Sonuç: İntravenöz infiltrasyon ve ekstravazasyonlar yenidoğanlarda önlenebilir komplikasyonlardır ve düzenli aralıklarla bir ölçek yardımı ile değerlendirilmelidir. Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği Türkçe olarak geçerli güvenilir bir ölçek olup yenidoğanlarda kullanımı uygundur.

Anahtar Kelimeler: İnfiltrasyon, yenidoğan, ölçek

evaluators. Intra-class correlation coefficient showing reliability between measurements was r=0.99 (p<0.001). This coefficient also indicates that the measurements are highly reliable.

Conclusion: Intravenous infiltration and extravasations are preventable complications in neonates and should be assessed with the aid of a scale at regular intervals. Pediatric Peripheral Intravenous Infiltration Scale can be used in newborns and also in Turkish.

Keywords: Infiltration, newborn, scale

Giriş

Hastanede yatan yenidoğanların bakım ve takiplerinde yenidoğan hemşireleri çok önemli sorumluluklara sahiptir. Bunların en önemlilerinden biri de periferik venöz kateterizasyon (PVK) işlemi ve takibidir. Yenidoğan hemşirelerinin PVK alanını yakından izlemesi ve saatlik kayıt alması ile intravenöz infiltrasyon ve ekstravazasyonların önlenmesi mümkün olabilmektedir (1).

Yenidoğan bakımında deneyim sahibi, profesyonel hemşireler için bile damar dışına çıkan bir sıvının tespit edilmesi bazen zor olabilmektedir. İnfiltrasyon ve ekstravazasyonların tanımlanmasında bazı fizyolojik ve davranışsal bulgular klinisyen için yol gösterici olmalıdır. Bebeğin kalp atım hızında artma, oksijen satürasyonlarında düşme, apne, ağlama ve ajitasyon gibi fizyolojik ve davranışsal değişiklikler önemli göstergeler olabilmektedir (2).

İntravenöz infiltrasyon; damar içine verilen irritan ve vezikan olmayan ilacın damar dışına sızması durumudur. İnfiltrasyonlar çoğunlukla bölgede kızarıklık, şişlik ve büller oluşturur. Herhangi bir doku kaybı gelişmez (1,3,4).

Ekstravazasyon; damar içine verilen, irritan ve vezikan ilacın damar dışına sızması sonucu gelişen durumdur. İlaç ekstravazasyonlarında infiltrasyondan daha ağır bir tablo vardır. Şişlik, kızarıklık, solukluk, soğukluk, morarma, ağrı bulgularıyla birlikte deri bütünlüğü bozulabilir, dokuda hasar meydana gelebilir (1,3,4).

Bebeğin damar yolunun temizlenmesi ya da yıkanması işlemi sırasında kaçınma hareketleri ve bebeğin ağlaması (özellikle ağrı bulgusu olarak), deride soğukluk, kırmızılık, şişlik görülmesi söz konusudur. Periferik kateter çıkarıldığında düzelme gözlenir. İntravenöz sıvının yerleşim yerinden ayrılması, tespit altından sızıntı olması da infiltrasyon bulguları arasındadır. Ancak bazı durumlarda komplikasyonlar daha fazla olabilir, deride kabarıklık, solukluk, kapiller dolum zamanında uzama ve dokuda nekroz görülebilir (4-6).

İnfiltrasyon ve ekstravazasyonların önlenmesinde yenidoğan hemşirelerinin temel anatomi ve fizyoloji bilgileri yanı sıra; vasküler anatomi, güvenli infüzyon kuralları ve enfeksiyon kontrolünü de içeren detaylı bilgiye sahip olmaları gerekmektedir (1,3,4). İnfiltrasyon ve ekstravazasyonlar her ne kadar tıbbi bakım hizmetlerinin birer komplikasyonu gibi kabul edilse de birçok kez daha ağır komplikasyonlara yol açabilmekte ve hukuki davalara konu olabilmektedir.

Yenidoğan yoğun bakım ünitelerinde intravenöz infiltrasyon ve ekstravazasyonların önlenmesine yönelik; vasküler yapının korunması, infüzyon bölgesi yer seçimi, vasküler yaralanmaları azaltıcı tedbirler, yüksek risk içeren irritan ve vezikan ilaçlar ve infüzyon tedavisi hazırlanması ilkelerinin yer aldığı kanıta dayalı hemşirelik girişim protokolleri bulunmalıdır (7).

Bu protokollerin uygulanmasında kullanılacak çeşitli rehber ve ölçekler uygulama ve takiplerin daha güvenli yapılmasına yardımcı olmaktadır. İnfiltrasyon ölçümünde yenidoğanlar ve çocuklarda kullanılan ölçeklerin daha ayrıcalıklı olması gerekmektedir. Çünkü yetişkin hastalar için kullanılan ölçüm araçlarında ödem boyutu "inç veya santimetre" olarak ölçülmektedir. Yenidoğanların 500 gr ile 5000 gr arasında değişebildiği düşünüldüğünde santimetre ya da inç ölçümlerinin güvenli olmadığı aşikardır. Bu ölçüm özellikle bebekler ve yenidoğanlar için uygun olmadığından, ödem bulgusu; etkilenen ekstremitede kapsadığı alan olarak (yüzde) değerlendirilmelidir (3).

Bu çalışma, erişkin dahil tüm hastalarda kullanılmak üzere İnfüzyon Hemşireler Birliği tarafından 1998 yılında geliştirilen ve 2012 yılında Simona (3) tarafından pediatrik hastalarda kullanılmak üzere revize edilen "Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği"nin (Tablo I) Türkçe geçerlilik güvenirliğinin yapılması ve yenidoğanlarda kullanımının uygunluğunu araştırmak amacıyla planlanmıştır. Ölçek beş (0-1-2-3-4) düzeyli puanlama sisteminden oluşmaktadır. Ölçek, PVK takiplerinde damar yollarının gözlemlenmesi için hazırlanmış olup kullanımı oldukça kolaydır.

Gereç ve Yöntem

Araştırmanın Türü ve Yeri

Metodolojik, prospektif ve gözlemsel bir çalışmadır.

Etik Kurul ve İzinler

Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği'nin Türkçe geçerlilik, güvenirlik ve yenidoğana uyarlanmasının yapılabilmesi için çalışma öncesinde ölçeğin geliştiricisi "Children's Medical Center Dallas ve PhD. RN Rodika Simona Pop'tan" e-posta yolu ile izin alınmıştır. Etik Kurul Onayı Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi Klinik

Araştırmalar Etik Kurulu'ndan alınmıştır (onay numarası: 22, tarih: 06.03.2015). Araştırmaya dahil edilen bebeklerin annelerinden sözlü olarak aydınlatılmış onam alınmıştır.

Araştırma Evreni ve Örneklem Seçimi

Araştırmanın evreni Sağlık Bilimleri Üniversitesi Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi Neonatoloji Kliniği'nde yatan ve intravenöz sıvı-ilaç tedavisi alan, daha önce intravenöz infiltrasyon ve ekstravazasyon bulgusu olmayan, dolaşım bozukluğu ve sepsis tanısı almayan bebeklerin tamamı çalışmaya alınmıştır.

Araştırmanın örneklemi ise 2014-2015 yılları arasında klinikte yatan ve intravenöz sıvı-ilaç tedavisi alan, rastgele seçilen 54 bebekte uygulanan 864 gözlem sonucundan oluşmaktadır.

Tablo I. Pediatrik Periferal İnfiltrasyon Ölçeği'nin özgün formu

	Pediatric Peripheral Intravenous Infiltration Scale
Grade	**Characteristics**
0	No symptoms
	Flushes with ease
1	Localized swelling (1-10%)
	Flushes with difficulty
	Pain at site
2	Slight swelling at site (up to 1/4 of the extremity above or below site, or 10-25% of the extremity above or below site)
	Presence of redness
	Pain at the site
3	Moderate swelling at site (1/4 to 1/2 of the extremity above or below site, or 25-50% of the extremity above or below site)
	Pain at site
	Skin cool to touch
	Blanching
	Diminished pulse below site
4	Severe swelling at site (more than 1/2 of extremity above or below site, or more than 50% of the extremity above or below site)
	Infiltration of blood products, irritants, and/or vesicants (any amount of swelling)
	Skin cool to touch
	Blanching
	Skin breakdown/necrosis
	Blistering
	Diminished or absent pulse
	Pain at site
	Capillary refill >4 seconds

Simona (3), 2012

Ölçeklerde gözlem sayısı ya da örneklem sayısına karar verme ile ilgili çeşitli görüşler, öneriler mevcuttur. Bu önerilerden bir tanesi ölçekteki madde sayısına göre; minimum 1:5 (madde başı 5 örneklem), maksimum 1:30 (madde başı 30 örneklem) olmakla birlikte genellikle 1:10 ilkesi kullanılmaktadır (8). Diğer bir öneri ise mutlak gözlem sayısına yöneliktir. Buna göre 50 çok zayıf, 100 zayıf, 200 kararsız, 300 iyi, 500 çok iyi, 1000 ve üzeri ideal kabul edilir (9).

Özellikle gözlemciler arası uyumun değerlendirildiği çalışmalarda ise gözlenen özne sayısının en az 30 olması gerektiği bildirilmiştir (10). Bu veriler doğrultusunda çalışmamızda 54 bebek ve 864 gözlem sonucunun değerlendirilmesi örnek büyüklüğü açısından yeterli olduğunu düşündürmektedir.

Veri Toplama Süreci

Dil Geçerliliği

Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği'nin Türkçe'ye çevirisi için ilk aşamada dil üzerinde çalışıldı. İlk olarak dil çeviri sürecinde ölçek orijinal dilinden üç bağımsız çevirmen tarafından Türkçe'ye çevrildi. Çeviri İngilizce'ye ve konuya hakim iki akademisyen tarafından birleştirildi ve üzerinde uzlaşılan tek araç haline getirildi. Türkçe hali bağımsız bir çevirmen tarafından orijinal dili olan İngilizce'ye geri çevrildi. Geri çevrilen ölçek İngilizce orijinali ile karşılaştırıldı ve Türkçe versiyonu üzerinde tartışılarak Türkçe ölçeğin düzeltmeleri gerçekleştirildi.

İçerik/Kapsam Geçerliliği

Uzman görüşü: Ölçeğin Türkçe son hali ve özgün formu; yenidoğan alanında uzman klinik hemşire, hekim ve akademisyen (toplam 7 kişi) tarafından değerlendirildi. Çalışmanın özgün hali ve Türkçe'ye çevrilmiş hali uzmanlara gönderilerek anlaşılırlık ve içerik yönünden değerlendirilmesi istendi. Buna göre her bir madde 1'den 4'e kadar puanlandı (1: Uygun değil, 2: Biraz uygun, 3: Oldukça uygun, 4: Çok uygun). Uzman görüşü önerileri doğrultusunda ölçek yeniden düzenlendi. Uzman görüşleri ölçeği tam olarak uygun bulduğundan görüş sonrasında bir düzenleme yapılmasına gerek kalmadı. Ölçeğin son hali çalışma verilerini toplamak için kullanıldı. Kapsam geçerlik indeksi 0,99 olarak hesaplandı. Çalışmaya başlamadan önce 5 bebekte araştırmaya dahil olmayan klinik hemşireler tarafından pilot çalışma yapıldı.

Ölçeğin Güvenirliği

İki değerlendirici arasındaki uyumu göstermek için Krippendorff alfa güvenirlik katsayısı hesaplandı. Ölçümler arasındaki güvenirliği değerlendirmek için sınıf içi korelasyon katsayısı kullanıldı.

Verilerin Toplanması

Araştırma verileri; Türkçe'ye çevrilen Pediatrik İntravenöz İnfiltrasyon Ölçeği ve Veri Toplama Formu kullanılarak 2 klinik

hemşire tarafından (eş zamanlı ve birbirinden bağımsız olarak) toplandı. Klinikte intravenöz sıvı-ilaç tedavisi alan yenidoğanlar arasından rastgele örneklem seçimi ile belirlenen bebeklerin damar yolları 08:00-16:00 saatleri arasında 8 saat boyunca saatte bir defa, iki gözlemci tarafından infiltrasyon ölçeği kullanılarak değerlendirildi. Her gözlem için ölçek puanlaması yapıldı. Türkçe'ye çevrilen ve yenidoğanların sıvı-ilaç takiplerinde kullanılan intravenöz infiltrasyon ölçeği Tablo II'de gösterilmiştir.

Ölçek maddeleri gözlemsel verileri içerdiğinden genel olarak gözlemcilerin eş zamanlı ve birbirinden bağımsız değerlendirme puanlamaları esas alındı.

Özellikle ödem ölçümü ölçeğin orijinalinde önerildiği şekilde etkilenen ekstremitede kapladığı alan olarak değerlendirildi. Örneğin; %1-10 (1. derece), %10-25 (2. derece), %25-50 (3. derece) olarak değerlendirildi.

Bebeğin damar yolunun temizlenmesi ya da yıkanması işlemi sırasında kaçınma hareketleri ve bebeğin ağlaması ağrı bulgusu olarak değerlendirildi (ünitede ayrıca standart ağrı ölçeği kullanılmaktadır).

Veri Toplama Formları

Hasta Tanılama Formu

Yenidoğanların temel demografik verilerini (doğum tarihi, doğum tartısı, gebelik haftası, cinsiyet, tanı, doğum şekli, hasta bakım düzeyi, kullanılan sıvı cinsi vb.) içermektedir.

Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği

Simona (3) tarafından 2012 yılında pediatrik hastalarda kullanım için geliştirilmiş ve geçerlik güvenirliği yapılmıştır. Ölçeğin özgün hali; infiltrasyon ve ekstravazasyon derecesini belirleyen 5 düzeyden ve bunlara ait bulgulardan oluşmaktadır. Birinci düzey en hafif, beşinci düzey en ağır infiltrasyon/ekstravazasyon durumunu ifade etmektedir (Tablo I). İnfiltrasyon ölçeğinin kullanım şekli; sıvı tedavisi alan her hastanın/yenidoğanın saatte bir defa bulgular açısından kontrol edilmesi ve düzeyin kaydedilmesi esasına dayanmaktadır. Ölçek puanı yükseldikçe komplikasyon riski artmaktadır. Ölçeğin Cohen kappa değeri intravenöz ekip hemşireleri için 0,80 ($p<0,001$) olup Pearson korelasyon katsayısı $r=0,95$ ($p<0,001$) olarak belirtilmiştir.

İstatistiksel Analiz

Çalışmadaki verilerin tanımlayıcı istatistikleri hesaplanmıştır. Değerlendiriciler arasındaki uyum (agreement) Krippendorff alfa güvenirlik katsayısı ile incelenmiştir. Ölçümler arasındaki güvenirliği değerlendirmek için sınıf içi korelasyon katsayısı hesaplanmıştır. İstatistiksel değerlendirmeler için SPSS v.22 programından yararlanılmıştır. $P<0,05$ istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

Araştırmaya dahil edilen bebeklerin ortanca doğum ağırlığı 2075 gram (minimum: 650 - maksimum: 4200), ortanca gebelik haftaları 35 hafta (minimum: 24 - maksimum: 41) ve ortanca postnatal günü 3. gün (minimum: 1 - maksimum: 27) olarak tespit edilmiştir. Bebeklerin bireysel özellikleri Tablo III'te verilmiştir.

Tablo II. Pediatrik Periferal İnfiltrasyon Ölçeği

İnfiltrasyon düzeyi	Bulgular	Girişimler
Düzey 0	Semptom yok Yıkama kolay (damar yolu yıkama/sıvı geçişi)	Saatte bir infüzyon hız ve total volümü kontrol edilir. İnfüzyon hızı her değiştiğinde hız ve total volümü kontrol edilir.
Düzey 1	Ödem <%1-10 (etkilenen ekstremitede kapladığı alan) Yıkama zor (Damar yolu yıkama/sıvı geçişi) Ağrı	Düzey 0 girişimlerine ek olarak; İnfüzyon cihazından infüzyon seti çıkarılmadan önce tüm klempleri kapatılır. İntravenöz sıvı dikkatli ve nazikçe bebekten ayrılır. Ekstremite eleve edilir. Salin solüsyon ile bölgeye kompres yapılır. Yapılan işlem hemşire gözlem formuna kaydedilir.
Düzey 2	Ödem %10-25 (Bölgenin altında/üstünde ekstemitenin 1/4'üne kadar ya da %10-25'ini kapsıyor) Kızarıklık Ağrı	Düzey 0-1 girişimlerine ek olarak; Ağrı kesici non-farmakolojik bir yöntem kullanılır.
Düzey 3	Ödem %25-50 (Bölgenin altında/üstünde ekstremitenin 1/2, 1/4'ünü ya da %25-50'sini kapsıyor) Ağrı Dokunulduğunda soğuk deri Renk değişimi, deride solukluk, şeffaflık Nabız azalması (etkilenen bölgenin altında)	Düzey 0-1-2 girişimlerine ek olarak; Ağrı kesici olarak medikal tedavi de kullanılabilir.
Düzey 4	Ödem >%50 (Bölgenin altında/üstünde ekstremitenin 1/2'sinden ya da %50'sinden fazla alan kapsıyor) Kan ürünü, vezikan veya irritan ilaç sızıntısı Dokunulduğunda soğuk deri Renk değişimi, deride solukluk, şeffaflık Deri bütünlüğünde bozulma/nekroz Bül (içi sıvı dolu kabarcıklar) Nabız azalmış ya da yok (etkilenen bölgenin altında) Ağrı Kapiller dolum >4 sn	Düzey 0-1-2-3 girişimlerine ek olarak; İlaç ya da sıvının vezikan-irritan olması durumunda ekstravazasyon prosedürüne uygun hareket edilmelidir.

Tablo III. Bebeklerin bireysel özelliklerine göre dağılım tablosu		
	Kişi sayısı (n=54)	**%**
Cinsiyet		
Erkek	33	61,1
Kız	21	38,9
Doğum şekli		
NSD	15	27,8
Sezaryen	39	72,2
Tanı		
Preterm	17	31,5
Preterm + ek sorun	6	11,1
Yenidoğanın geçici taşipnesi	20	37,0
Hiperbilirubinemi	3	5,6
Polisitemi	5	9,3
Diğer	3	5,6
Bakım düzeyi		
1	16	29,6
2	23	42,6
3	15	27,8
NSD: Normal spontan doğum		

Çalışmaya toplam 54 hasta alınmış olup yenidoğan yoğun bakım ünitesinde her bir bakım düzeyindeki olguların oranları benzerdir. 1. düzey: 16 hasta; 2. düzey: 23 hasta; 3. düzey 15 hasta, (p=0,348). Doğum şekli sezaryen olanların oranı anlamlı düzeyde yüksektir (p=0,001). Çalışmaya alınan bebeklerin term n=31 (%57) ve preterm n=23 (%43) olma durumları birbirine benzer idi (p>0,05). En fazla kullanılan sıvı cinsi %63'lük oranla %10 dekstroz ve %26'lık oranla total parenteral nütrisyon sıvısı olarak bulunmuştur (p<0,001). Toplam 864 gözlem yapılan 54 bebeğin %35'inde (n=19) birinci gözlem sonrasında damar yolu değiştirilmiştir. Damar yolu değiştirilen bebeklerin %69'u (n=11) birinci evrede (1 puan), %25'i (n=5) ikinci evrede (2 puan) belirlenmiş ve damar yolları yenilenmiştir.

İki değerlendirici arasındaki uyumu gösteren Krippendorff alfa katsayısı 100 olarak hesaplanmıştır (p<0,001). Bu sonuç iki değerlendirici arasında "tam uyumu" göstermektedir. Ölçümler arasındaki güvenirliği gösteren sınıf içi korelasyon katsayısı ise r=0,99 (p<0,001) bulunmuştur.

Tartışma

PVK'ler hastaneye yatışlarda; ilaç tedavisi, sıvı desteği ya da parenteral beslenme amacı ile genellikle rutin olarak kullanılır. PVK'lerin %95'i tıkanıklık, sızıntı ve infiltrasyon nedeniyle çıkartılırlar. Hastaların çoğunda karşılaşılan en genel komplikasyon ise infiltrasyonlardır.

Yenidoğan hasta popülasyonu; intravenöz infiltrasyonlar açısından en hassas hasta gruplarındandır. Özellikle yenidoğan yoğun bakım ünitelerinde takip edilen prematüre bebekler damar yollarına kateter uygulanması ve takip edilmesinde komplikasyonlar açısından yüksek risk taşımaktadır. İntravenöz infiltrasyon ve ekstravazasyonlar dikkatli bir şekilde takip edildiğinde önlenebilir komplikasyonlardır. İntravenöz infiltrasyonların tanımlanmasında çeşitli ölçek ve rehberler kullanılmaktadır (3,4,7).

Simona'nın (3) yaptığı çalışmada Pediatrik Periferik İnfiltrasyon Ölçeği değerlendirme sonuçlarına göre infiltrasyonların %37,1'i 1. evrede, %31,4'ü 2. evrede, %10,8'i 3. evrede belirlenmiştir. Jeong ve ark. (11) Kore'de bir çocuk hastanesinde yaptıkları çalışmada ise deney grubu çocuklarda kateterizasyon alanı şeffaf bir koruyucu ile kapatılarak bir gözlem penceresi oluşturulmuştur. Çalışma sonunda gözlem penceresi uygulanarak gözlenen çocuklarda 2. evrede infiltrasyon gelişiminin %44 azaltıldığı vurgulanmıştır (11).

Pediatrik Periferik İnfiltrasyon Ölçeği kullanılarak yenidoğanlarda yaptığımız bizim çalışmamızda da infiltrasyon gelişen bebeklerin %69'unun 1. evrede, %25'inin 2. evrede damar yolu değiştirilmiş olup değerlendirme araçlarının hatta sadece gözlemin kendisinin bile infiltrasyonları erken dönemde belirlemedeki önemini ortaya koymaktadır.

Yenidoğanlarda intravenöz infiltrasyon sıklığı %50-75 arasında, ekstravazasyonlar ise daha düşük oranlarda olup %11-23 arasında bildirilmektedir (2,12). Bu çalışmada intravenöz infiltrasyon oranı %35, ekstravazasyon oranı ise %6 olarak tespit edilmiş olup periferik intravenöz infiltrasyon ölçeğinin kullanımına bağlı olarak değişikliklerin erken dönemde tespit edildiği düşünülmektedir.

Ölçek geliştirmenin zorlukları bilindiğinden daha önce geliştirilmiş uluslararası ölçeklerin ilgili toplum ve gruplarda uyarlanarak kullanılması oldukça yaygın bir uygulamadır. Uluslararası geçerlilik güvenirliği belirlenmiş bir ölçeğin başka topluma uyarlanmasında öncelikle dil geçerliliği sonrasında ise konusunda uzman kişilerin görüş önerilerini içerek kapsam geçerliliğinin yapılması önerilmektedir (10). Çalışmada dil geçerliliği ve kapsam geçerliliği (7 uzman görüşü) aşamaları uygulanmıştır.

İntravenöz infiltrasyonların önlenmesi ve komplikasyonların azaltılmasında damar yollarının saatlik olarak gözlenmesi aynı zamanda infüzyon pompasında sıvının gittiğine dair işaretlerin kaydedilmesi gerekmektedir. İnfüzyon alanının gözlenmesinde; kızarıklık, ağrı, şişlik, renkte değişiklik, solukluk, ödem, sızıntı gibi bulguların mutlaka bir ölçek yardımı ile sistematik olarak gözlenmesi ve değerlendirilmesi gerekmektedir (3,13-16).

Çalışmada ölçek verileri gözlemsel değerlendirme kriterlerini içermektedir. Tek yönlü gözleme dayalı verilere dışardan gözlem tanımlaması yapılmış olup bu çalışmalarda ilgili olayın birden fazla gözlemci tarafından aynı zamanda gözlenmesi önerilmektedir (17).

Gözleme dayalı ölçeklerin güvenirliğinin belirlenmesinde ise; bağımsız gözlemler arası uyum sıklıkla aranan özelliklerden birisidir. Gözlemciler arası uyumda farklı uygulayıcıların aynı

zamanda aynı ölçme araçlarını kullandıklarında elde edilen puanların uyumlu olması ile ifade edilir. Birden fazla ölçümcü arasında %70 ve daha yüksek tutarlılık güvenirlik sınaması için uygundur (18).

İki puanlayıcı için hesaplanan uzlaşma katsayıları Cohen'in kappa, Gwet'in AC2, Scott'un pi, Krippendorff'un alfa, Brennan-Prediger gibi testler uzlaşma yüzdesi olarak kullanılabilir (19). Bu çalışmada değerlendiriciler arası uyum hesaplamasında Krippendorff'un alfa güvenirlik katsayısı kullanılmıştır. Krippendorff'un alfa katsayısı 1,00 olarak bulunmuş olup gözlemciler arası uyumun "mükemmel değerde "0,93-1,00" olduğunu göstermektedir. Simona (3) çalışmasında puanlayıcılar arasındaki uyumu ölçmek için Cohen kappa değerini kullanmış olup intravenöz ekip hemşireleri için Cohen kappa 0,80 olarak belirtmiştir.

Bu çalışmada ölçümler arasındaki güvenirliği gösteren sınıf içi korelasyon katsayısı r=0,99 (p<0,001) bulunmuş olup bu değer ölçümlerin yüksek düzeyde güvenilir olduğunu ifade etmektedir. Simona (3); ölçek kullanımında ölçümler arası korelasyon katsayısını intravenöz ekip hemşireleri için r=0,92 (p<0,001), klinik hemşireler için r=0,84 (p<0,001) olarak belirtmiştir.

Pediatrik Periferal İntravenöz İnfiltrasyon Ölçeği'nde infiltrasyon düzeylerinin derecelendirilerek yorumlanması ölçek kullanımını kolaylaştırmakta ve düzeyi belirlemeyi sağlamaktadır. Thigpen Grading ve Revize Grading ölçeklerinde de bizim çalışmamıza benzer şekilde sırasıyla 4 ve 3 düzeyli derecelendirme yapılmıştır (13,14).

İntravenöz infiltrasyon ölçekleri; damar yolu, kateter ve diğer infüzyon araçlarındaki olası problemleri içeren bulgulardan oluşmaktadır. Bunlar genel olarak; ağrı, renk değişikliği, solukluk, şeffaflık, ödem, sızıntı gibi çok önemli göstergelerdir (6,15,16). Çalışmamızda da bu parametreler yer almaktadır.

Ekstravazasyonların önlenmesinde kurumsal stratejiler çok önemlidir. Dünyada kullanılan intravenöz infiltrasyon ölçeklerinde genel olarak infiltrasyon düzeyi gözlemsel bulgulara göre belirlenmektedir (3,16,20-22). Düzey belirlemenin ardından yapılacak işlemler kurum politikalarına göre değişmektedir. Türkçe olarak geçerlilik güvenirliği ve yenidoğanlarda kullanımının uygunluğu incelenen çalışmada, düzey belirlendikten sonra yapılması gereken girişimler, ölçeğe eklenmiştir. Yapılacak girişimlerin ölçek içinde yer alması standardizasyon açısından önemlidir. Böylece hem hızlı bir şekilde düzey tanımlanabilecek hem de yapılması gereken takip ve tedavide zaman kazanılacaktır.

Çalışmanın Kısıtlılıkları

Araştırma tek merkezde yapılmış olup sadece 2 kişi tarafından veriler toplanmıştır. Merkez sayısı ve araştırmada veri toplayan kişi sayısının az olması araştırmanın kısıtlılığı olarak ifade edilebilir.

Sonuç

İntravenöz infiltrasyon ve ekstravazasyonlar yenidoğanlarda önlenebilir komplikasyonlardır ve mutlaka düzenli aralıklarla bir ölçek yardımı ile değerlendirilmelidir. Ayrıca, sadece infiltrasyon durumunun tanılanması değil gerekli girişimlerin de planlanması gereklidir. Bu bağlamda Pediatrik Periferal İnfiltrasyon Ölçeği Türkçe olarak yenidoğanlarda kullanılabilecek geçerli ve güvenli bir araçtır.

Ülkemizde yenidoğan döneminde kullanılması komplikasyonların önlenmesine, bunlarla ilişkili hukuki sorunların azalmasına yenidoğan ünitelerinden taburcu olan çocukların daha sağlıklı bir hayat sürmelerine katkı sağlayacak niteliktedir.

Etik

Etik Kurul Onayı: Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (onay numarası: 22, tarih: 06.03.2015).

Hasta Onayı: Araştırmaya dahil edilen bebeklerin annelerinden sözlü olarak aydınlatılmış onam alınmıştır.

Hakem Değerlendirmesi: Editörler kurulu ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Konsept: E.T., A.K., Dizayn: G.K., F.O., Veri Toplama veya İşleme: Ö.E., E.T., Ş.C., Analiz veya Yorumlama: Ş.C., E.T., Literatür Arama: A.K., E.T., Ö.E., Yazan: E.T., A.K.

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. Infusion Nurses Society. Infusion nursing standards of practice. J Infus Nurs 2011;34(1 Suppl):65-7.
2. Temizsoy E. Neonatal Ekstravazasyon Rehberi. Tıbbi yayınlar Merkezi, İstanbul, 2017;61:65-95.
3. Simona R. A pediatric peripheral intravenous infiltration assessment tool. J Infus Nurs 2012;35:243-8.
4. Amjad I, Murphy T, Nylander-Housholder L, Ranft A. A new approach to management of intravenous infiltration in pediatric patients. J Infus Nurs 2011;34:242-9.
5. Intravenous Nurses Society. Revised intravenous nursing standards of practice. J Intraven Nurs 1998;21(Suppl 1):36-7.
6. Groll D, Davies B, Donald J, Nelson S, Virani T. Evaluation of the psychometric properties of the phlebitis and infiltration scales for the assessment of complications of peripheral vascular access devices. J Infus Nurs 2010;33:385-90.
7. Wilkins CE, Emmerson AJ. Extravasation injuries on regional neonatal units. Arch Dis Child Fetal Neonatal Ed 2004;89:274-5.
8. Gorusch RL. Factor Analysis. In: Hillsdale NJ, 2nd ed. Lawrence Erlbaum Associates. 1983;332.

9. Comfrey AL, Lee HB. A First Course in Factor Analysis. In: Hillsdale NJ. Lawrence Erlbaum Associates, 1992.
10. Erefe İ. Veri toplama araçlarının niteliği. Hemşirelikte Araştırma İlke Süreç ve Yöntemler. İçinde: Erefe İ. Odak ofset, 3. Baskı, 2004;173.
11. Jeong IS, Park SM, Park KJ. Effect of Observation Window at Peripheral Intravenous Catheter Site on Early Recognition of Infiltration among Hospitalized Children. J Korean Acad Nurs 2016;46:534-41.
12. McCullen KL, Pieper B. A retrospectif chart review of risk factors for extravasation among neonates receiving peripheral intravascular fluids. J Wound Ostomy Continence Nurs 2006;33:113-39.
13. Thigpen JL. Peripheral intravenous extravasation: nursing procedure for initial treatment. Neonatal Netw 2007;26:379-84.
14. Lund CH, Kuller JM. Integumentary system. In: Kenner C, Lott JW, eds. Comprehensive Neonatal Care: An Interdisciplinary Approach. 4th ed. Philadelphia, PA: Elsevier/ Saunders, 2007:65-91.
15. Fırat C, Erbatur S, Aytekin AH. Management of extravasation injuries: a retrospective study. J Plast Surg Hand Surg 2013;47:60-5.
16. Khan MS, Holmes JD. Reducing the morbidity from extravasation injuries. Ann Plast Surg 2002;48:628-32.
17. Erdoğan S. Nitel Araştırmalar. Hemşirelikte Araştırma. İçinde: Erdoğan S, Nahcıvan N, Esin N. Nobel Tıp Kitapevi, İstanbul, 2014;149.
18. Aksayan S, Gozum S. A quide for transcultural adapdation of the scale. Journal of Hemar Gemas 2002;4:9-14.
19. Ada S. Klasik test kuramına göre sözel alanlar için puanlama güvenliğinin kayıp veri kapsamında değerlendirilmesi. Gazi üniversitesi Eğitim Bilimleri Enstitüsü Yüksek Lisans Tezi, 2015. (Danışman: İsmail Karakaya)
20. Kostogloudis N, Demiri E, Tsimponis A, et al. Severe Extravasation Injuries in Neonates: A Report of 34 Cases. Pediatr Dermatol 2015;32:830-5.
21. İrving V. Neonatal iatrogenic skin injuries: a nursing perspective. J Neonatal Nurs 1999;5:10-3.
22. Wilkins CE, Emmerson AJ. Extravasation injuries on regional neonatal units. Arch Dis Child Fetal Neonatal Ed 2004;89:274-5.

J Pediatr Res 2017;4(4):239-41
DOI: 10.4274/jpr.96658

Olgu Sunumu / Case Report

Gastrik By-pass Cerrahisi Sonrası Gelişen Polinöropati

Polyneuropathy After Gastric By-pass Surgery

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ÖZ

Günümüzde hızla artış gösteren obezite önemli derecede mortalite ve morbiditeye neden olmaktadır. Diyete ve egzersize rağmen önüne geçilemeyen kilo artışı ve beraberinde getirdiği hastalıklar nedeniyle tedavide gastrik by-pass uygulaması sıkça kullanılmaktadır. Kısa sürede sonuç alınan bu yöntemin komplikasyonlarından başlıcaları ise sonrasında oluşabilecek nütrisyonel eksiklikler ve bu eksiklikler sonucunda ortaya çıkan klinik tablolardır. Morbid obezite nedeniyle gastrik by-pass uygulanmış ve sonrasında polinöropati gelişen bir hastayı sunmayı amaçladık.

Anahtar Kelimeler: Tiamin, gastrik by-pass, polinöropati

ABSTRACT

Today rapidly increasing obesity causes significant morbidity and mortality. Gastric by-pass is frequently used for the treatment of morbid obesity, which cannot be controlled with diet and exercise. Although this treatment modality achieves rapid success, it also has several complications such as nutritional deficiency and its clinical results. We aimed to present a patient with polyneuropathy after having undergone gastric by-pass surgery for morbid obesity.

Keywords: Tiamine, gastric by-pass, polyneuropathy

Giriş

Obezite cerrahisi sonrası operasyona bağlı cerrahi komplikasyonların yanı sıra ilerleyen süreçte nütrisyonel eksikliklere bağlı klinik durumlarla da karşılaşılmaktadır (1). Bu hastalarda operasyon sonrası by-pass edilen bölgeden emilimi gerçekleşen vitamin, mineral ve eser elementlerin günlük idame tedavilerinin verilmesi gerekmektedir (1). Gastrik cerrrahi sonrası periferal nöropati en sık görülen nörolojik komplikasyondur ve yapılan çalışmalarda %5-16 arası değişmektedir (2). Bunun nedeni olarak B12, tiamin, bakır eksiklikleri sayılabilir (2).

Tiamin duodenum ve jejunumdan emilir, kısıtlı miktarda depolanması ve yarı ömrünün kısa olması nedeniyle, alım ve emilim yetersizliklerinde eksikliği sıkça görülebilir ve polinöropati, kardiyak yetmezlik hatta postoperatif Wernicke ensefalopatisine yol açabilir (3,4). Tiamin eksikliğine bağlı polinöropati sıklıkla 6 hafta-6 ay arasında gelişir. İlk yakınmalar ayaklarda karıncalanma, hissizleşme olup sonrasında kas güçsüzlüğü tabloya eklenir (2,4). Otonomik disfonksiyonlar, nörojenik mesane, konstipasyon gibi bulgular da ilerleyen zamanlarda eşlik edebilir (4). Tedavi ile tiamin eksikliğine bağlı nörolojik bulgular da hızlı düzelme gözlenir (4,5). Burada gastrik by-pass sonrası polinöropati gelişen bir olgu bilgilendirilmiş onam formu alınarak sunulmuştur.

Olgu Sunumu

On yedi yaşında kız hasta yürüyememe, ayaklarında ağrı ve uyuşma şikayeti ile başvurdu. Hastanın öz geçmişinde 4 ay önce morbid obezite nedeniyle gastrik by-pass operasyonu geçirdiği, operasyondan bugüne kadar

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Geliş tarihi/Received: *27.02.2016* **Kabul tarihi/Accepted:** *23.05.2016*

toplam 45 kilo kaybı olduğu ve son bir aydır olan ayaklarda uyuşma, ağrı nedeniyle başvurduğu merkezde yapılan tetkiklerinde B12, folik asit, karaciğer ve böbrek testlerinin, lipit profilinin normal olduğu, romatolojik hastalıklara yönelik yapılan tetkiklerinde ANA, ANCA, C3-C4 testlerinin normal olduğu ve elektromiyelografisinde (EMG) sensorimotor polinöropati saptanması üzerine gabapentin, vitamin B1+B6+B12 kompleksi tedavisi başlanıldığı öğrenildi. Hasta kas güçsüzlüğünün artması ve yürüyememesi nedeniyle kliniğimize başvurdu. Hastanın fizik muayenesinde vücut ağırlığı 129 kg (97p↑), boyu 186 cm (97↑) bulundu. Nörolojik bakıda alt ekstremitelerin distalinde kas güçsüzlüğü (3/5), alt ekstremitelerde arefleksi, her iki alt ekstremitede dize kadar hipoestezi saptandı. Hasta oturduğu yerden kalkamamakta ve ayakkabısız yürüyememekteydi. Ayrıca sistemik bakısında bilateral nistagmus, akantozis, hirsutizm, gövde ön ve yan yüzlerinde beyaz striaları mevcuttu. Hastada olası spinal kanal basısının dışlanması amaçlı çekilen spinal manyetik rezonans görüntülemesi normal bulundu. Periferik yaymasında eritrosit morfolojisi normaldi. Serum tiamin düzeyi 91,8 (25-75) mcg/L bulundu. Ancak hasta bir aydır oral tiamin kullanmaktaydı. Bu nedenle tiamin eksikliğine bağlı nöropati dışlanamayacağından hastaya 100 mg/gün tiamin intravenöz (i.v.) başlandı. Tedavinin 4. gününde hasta yürümeye başladı, i.v. tiamin tedavisine yedi gün devam edildi. İzlemde tiamin 10 mg/gün ağızdan devam edildi. Hastada gastrik by-pass sonrasında gelişen nöropati, olası diğer nedenlerin dışlanması ve tiamin tedavisine belirgin yanıt alınması nedeniyle tiamin nöropatisi olarak değerlendirildi. Hasta ve ailesinden aydınlatılmış onam alındı.

Tartışma

Tiaminin aktif hali olan tiamin pirofosfat karbonhidrat metabolizmasında α-ketoasid dekarboksilasyonunda ve pentoz monofosfat yolunda transketolaz için koenzim olarak görev yapar (6). Bu yüzden yüksek karbonhidrat alımında ve metabolik ihtiyacın arttığı durumlarda tiamin ihtiyacı artar. Vücutta depolanan tiamin miktarının oldukça kısıtlı (yaklaşık 30 mg) ve yarılanma ömrünün 9-18 gün gibi kısa oluşu nedeniyle hiç alınmadığı takdirde tiamin eksiklik bulguları yaklaşık 3-4 hafta içinde çıkar (6). Gastrik cerrahi sonrası, alkolizm, kronik malnütrisyon, uzun süre parenteral nütrisyon kullanımı, malignite, Tip I diabetes mellitus (ketoasidozlara sekonder), uzun süreli furosemid kullanımı, kronik böbrek yetmezliği-diyaliz, anoreksiya nervosa varlığı tiamin eksikliği açısından risk faktörleridir (6).

Tiamin eksikliği, küçük çocuklarda kusma-ishal, laktik asidoz, sepsis benzeri bulgular, kardiyak yetmezlik, pulmoner hipertansiyon, infantil beriberi gibi semptom ve bulgularla ortaya çıkarken daha büyük çocuklarda Wernicke ensefalopatisi, Korsakoff psikozu ve polinöropatiye yol açabilir (7). Gastrik cerrahi sonrası en sık görülen nörolojik komplikasyon periferik nöropatidir (5).

Tiamin eksikliğine bağlı nöropati operasyondan yaklaşık 6-8 ay sonra en sık alt ekstremitelerde güçsüzlük, miyalji şeklinde başlar. Sonrasında ayaklarda yanma hissi görülür. Simetriktir ve olguların %25'inde asendan yayılım gözlenir. Bu özelliği ile Guillain-Barre sendromu ile karışabilir. Nadiren hızlı gelişen olgular olmasına rağmen tiamin eksikliğine bağlı nöropati subakut gelişmektedir (8). Hastalarda üst motor nöron bulguları saptanmaz, ancak kraniyal sinir tutulumu ve otonomik disfonksiyon görülebilir (2,3). Hastamızda otonomik disfonksiyon ya da kraniyal sinir tutulumu yoktu.

Tanıda altın standart eritrositlerde transketolaz aktivitesinin bakılmasıdır, ancak pahalı ve ulaşılması zor bir tetkiktir. Serum tiamin düzeyinin 25 mg/L'nin altında olması da tanıda yol gösterir. Hastamızın 75 mg/L saptanmasına karşın, gastrik by-pass sonrası gelişen subakut gelişimli polinöropatinin tiamin eksikliğine bağlı olduğu düşünüldü. Tiamin tedavisi ile hastada klinik düzelme olması da tanıyı desteklemektedir.

EMG; aksonal dejenerasyon, motor ve duysal aksiyon potansiyellerinin amplütüdlerinde azalma, sinir iletim hızlarında ılımlı yavaşlama, distal latanslarda ılımlı uzama görülebilir. Sural sinir biyopsilerinde ise hem myelinize hem de myelinize olmayan liflerde kayıp, subperinöral ödem görülür (2,3,5). Hastamızda tedavi almakta iken bakılan tiamin değeri normal saptanmıştı, ancak risk faktörleri, hastanın kliniği ve EMG bulguları değerlendirildiğinde hasta tiamin eksikliğine bağlı periferal nöropati olarak değerlendirildi.

Tedavide tiamin replasmanı önerilmektedir. İlk 3-7 gün; 100-200 mg/gün olacak şekilde i.v. yüksek doz tedaviler sonrasında 10-20 mg/gün olacak şekilde ağızdan 2-3 ay süre ile idame tedavisi önerilmektedir. Gastrik by-passlı hastalarda ise idame tedavisi ömür boyu önerilmektedir (1,9). Hastamızda 100 mg/gün 7 gün boyunca i.v., sonrasında 10 mg/gün ağızdan tiamin tedavisi devam edildi.

Genelde iyileşme 15 gün-6 ay arası gerçekleşiyor. Kas güçsüzlüğü tedavi başlangıcından 1 hafta, mesane disfonksiyonu 2-3 haftada düzeliyor. Eğer hastaların tiamin eksikliğine bağlı kalp yetmezliği var ise kardiyomegali ve aritmi replasmandan birkaç gün sonra düzeliyor. Hastaların %85'i 6 ay içinde sekelsiz yürüyor, ancak duyu kaybı 2 yıla kadar sürebiliyor (9). Bizim hastamız da replasmandan 4 gün sonra ayağa kalktı ve yürümeye başladı, ancak 1 ayın sonunda halen güçsüzlüğü ve uyuşma şikayetleri azalmakla birlikte devam ediyordu.

Bu olgu ile gastrik cerrahi sonrası gelişen nöropati bulgularının idame nütrisyonel destek eksikliğine bağlı olabileceği ve fark edildiğinde kolay tedavi ile yüz güldürücü sonuçları olduğu hatırlatılmak istenmiştir.

Etik

Hasta Onayı: Çalışmamıza dahil edilen tüm hastalardan bilgilendirilmiş onam formu alınmıştır.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: H.G.T., S.G., S.Y., Konsept: H.G.T., H.T., Dizayn: H.G.T., H.T., Veri Toplama veya İşleme:

H.G.T., S.Y., Analiz veya Yorumlama: S.G., G.S., Literatür Arama: H.G.T., Yazan: H.G.T.

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. John S, Hoegerl C. Nutritional deficiencies after gastric bypass surgery J Am Osteopath Assoc 2009;109:601-4.
2. Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, Norell JE, Dyck PJ. A controlled study of peripheral neuropathy after bariatric surgery. Neurology 2004;63:1462-70.
3. Angstadt JD, Bodziner RA. Peripheral polyneuropathy from thiamine deficiency following laparoscopic Roux-en-Y gastric bypass. Obes Surg 2005;15:890-2.
4. Carvajal T, Franco DL, Martinez A, Pena IM. Wernicke´s encephalopathy and polyneuropathy associated with vitamin B complex deficiency after a bariatric surgery. Biomedica 2012;32:474-84.
5. Koike H, Misu K Hattori N, et al. Postgastrectomy polyneuropathy with thiamine deficiency. J Neurol Neurosurg Psychiatry 2001;71:357-62.
6. Manzetti S, Zhang J, van der Spoel D. Thiamin function, metabolism, uptake, and transport. Biochemistry 2014;53:821-35.
7. Kril JJ. Neuropathology of thiamine deficiency disorders. Metab Brain Dis 1996;11:9-17.
8. Faigle R, Mohme M, Levy M. Dry beriberi mimicking Guillain-Barre syndrome as the first presenting sign of thiamine deficiency. Eur J Neurol 2012;19:14-5.
9. Poitou Bernert C, Ciangura C, Coupaye M, Czernichow S, Bouillot JL, Basdevant A. Nutritional deficiency after gastric bypass: diagnosis, prevention and treatment. Diabetes Metab 2007;33:13-24.

J Pediatr Res 2017;4(4):242-4
DOI: 10.4274/jpr.19484

Case Report / Olgu Sunumu

Oral Ibuprofen Induced Spontaneous Intestinal Perforation in a Preterm Infant

Preterm Bir Bebekte Oral İbuprofenin İndüklediği Spontan İntestinal Perforasyon

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ABSTRACT

Ibuprofen is often used as an alternative for patent ductus arteriosus (PDA) management in preterm infants. The reported side effects are fewer than those of indomethacin. Spontaneous intestinal perforation differs from necrotizing enterocolitis, presents an early clinical picture and usually occurs after corticosteroid treatment in preterm infants. We present a case of a preterm neonate with spontaneous intestinal perforation induced by oral ibuprofen treatment for PDA.

Keywords: Ibuprofen, preterm, spontaneous intestinal perforation

ÖZ

İbuprofen prematüre bebeklerde patent duktus arteriozus (PDA) tedavisinde sıklıkla alternatif olarak kullanılmaktadır. Yan etkileri indometazinden daha az olarak bildirilmektedir. Spontan intestinal perforasyon sıklıkla steroid alımı sonrasında prematüre bebeklerde görülen nekrotizan enterokolitten farklı bir klinik tablodur. Bu olguda PDA tedavisi için oral ibuprofen tedavisi alan prematüre bir yenidoğanda tedavi ile ilişkili spontan intestinal perforasyon olgusu sunuldu.

Anahtar Kelimeler: İbuprofen, prematüre, spontan intestinal perforasyon

Introduction

Spontaneous intestinal perforation (SIP) of the newborn is a single intestinal perforation, characteristically present at the terminal ileum and usually consists in low birth neonates or babies who receive corticosteroid treatment early in life (1-4). We present a case of a neonate without any significant necrotizing enterocolitis (NEC) signs, developing SIP related to oral ibuprofen usage for patent ductus arteriosus (PDA) closure treatment.

Case Report

Twin babies of a Syrian mother without antenatal follow-up were born via cesarean section at the 27th week of gestation. One baby was 1250 grams at birth with an Apgar score of 5 in the first minute. He was intubated and transferred to neonatal intensive care unit (NICU) for respiratory distress. Total parenteral nutrition as well as minimal enteral feeding with breast milk was started on the admission day. On follow-up, oral intake was increased to 20 cc/kg/day and total parenteral nutrition was decreased accordingly. He reached his birth weight on the 7th day of admission and as enteral feeding was well-tolerated, on day 10, full enteral feeding was initiated. He was referred to a pediatric cardiologist for a cardiac murmur detected in routine physical examination and diagnosed with PDA. Therefore, oral ibuprofen treatment was started on day 3. The condition of PDA was outlined by the presence of a minimum of one amongst the subsequent criteria: internal ductal diameter ≥1.5 mm, left-atrium-to-aortic-root ratio >1.6 nonrestrictive, pulsatile transductal flow, reverse or absent diastolic flow within the aorta. On day

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Received/Geliş tarihi: *05.05.2016* **Accepted/Kabul tarihi:** *18.07.2016*

11, physical examination revealed abdominal distention and X-ray investigations showed free air under the diaphragm. The patient was referred to the pediatric surgery department for urgent surgery. The whole abdominal cavity was filled with meconium, and ileum was perforated approximately 15 centimeters away from the proximal ileocecal region. As the perforated area was close to the ileocecal region, ileostomy and colostomy were performed. An area of 30 centimeters was resected. Pathology report confirmed the perforation site. The patient was admitted to NICU and followed closely post-operatively. He was started on vancomycin, meropenem and metronidazole treatments as well as furosemide infusion for acute renal failure. On the 5th day of the operation, ileostomy seemed to be working properly. However, he had recurrent high fever episodes during follow-up, though blood cultures turned out to be negative, and laboratory results showed no pathology except thrombocytopenia and anemia. Treatment was continued. Cranial ultrasonography revealed grade 3 intraventricular hemorrhage. Ophthalmic examination showed grade 1 retinopathy of prematurity. Vancomycin was discontinued on the 10th day. As control acute phase reactants were still elevated (C-reactive protein: 59 mg/dL) on the 14th day of the antibiotic regimen, fluconazole was added to the treatment. Twenty days after the surgery, abdominal distention developed and bloody gastric residuals were noted. Oral intake was stopped. The patient received platelet, erythrocyte and fresh frozen plasma infusions to fix the newly detected anemia and thrombocytopenia. Despite all the treatment, he died of multiple organ failure, and his blood cultures confirmed the suspected fungal sepsis. The informed consent form was obtained from the parents of the case.

Discussion

Gastrointestinal side effects related to ibuprofen are mostly known to occur within the first days of life, late occurrence is rare. In our patient, although full enteral feeding was initiated earlier, abdominal distention developed on the 11th day after birth, without any risk factors or other warning signs of NEC, like nausea or feeding intolerance. Therefore, SIP related to ibuprofen use was the initial diagnosis.

SIP of the newborn is typically found at the terminal ileum (1-5). SIP happens especially in premature infants with very low birth weight (weight <1500 g), and extremely low birth weight (weight <1000 g). SIP is a different clinical entity from NEC, the most severe gastrointestinal complication in premature infants (1,6,7).

In our case, the patient was in the high-risk group as his birth weight was 1210 grams at the 27th gestation week. Our case had no antenatal history of chorioamnionitis.

In a study from the Pediatrix bunch, the organization of antenatal glucocorticoids did not seem to expand the danger of SIP (8). Early organization of postnatal glucocorticoids expands the danger of SIP. However, our case did not receive postnatal or antenatal glucocorticoid treatment (9). In spite of the fact that the postnatal utilization of indomethacin had been already answered to build the danger of SIP, ensuing productions have reported no relationship between indomethacin introduction and SIP (9,10).

NEC normally develops after the first week of life, after the baby has started to bolster, whereas, in our case abdominal distention was detected on the 11th day after birth, long after the initiation of full enteral feeding. Abdominal radiographic images might reveal pneumoperitoneum, however, in our case there was no sign of pneumatosis intestinalis or portal venous gas, which are the radiograph signs of NEC. Imaging exhibits a gasless stomach area in a few patients with SIP. The average age at aperture placement is seven days with a scope of 0 to 15 days. SIP generally starts earlier than NEC. (mean age; 7 vs. 15 days) (8).

Hazard elements for SIP might fluctuate as per the season of presentation. In a Pediatrix investigation of 633 neonates with SIP, the patients were divided into two based upon their time of presentation (10) as newborn children in the main group (n=116), somewhere around zero and three days of life, who were bigger (middle birth weight 1.4 kg) and were less inclined to have gotten antenatal glucocorticoids, indomethacin, surfactant, or mechanical ventilation, and babies in the second group, around 7 and 10 days of life with a mean birth weight of 775 g. In our report, the baby weighed 1210 grams, which is compatible with the second group.

Current treatment of choice for SIP is surgery. Exploratory laparotomy with the resection of the bowel or primary peritoneal drainage (PPD) are the traditional approach. In a previous study, PPD and exploratory laparotomy were compared in the newborns diagnosed with either SIP or NEC, and no difference was found in mortality or prognosis between the two groups (11). In our case, we used exploratory laparotomy with bowel resection in addition to ileostomy and colostomy.

In conclusion, oral ibuprofen treatment for PDA closure may increase the risks for the immature gastrointestinal system. Therefore, intravenous route may be the safer choice for preterm infants.

Ethics

Informed Consent: Consent form was obtained from the parents of the case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.H., S.B., Concept: Ö.B., E.Ö., Design: Ş.H., E.C., Data Collection or Processing: Ş.H., Analysis or Interpretation: Ş.H., E.C., Literature Search: S.B.,Writing: Ş.H.

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. Pumberger W, Mayr M, Kohlhauser C, Weninger M. Spontaneous localized intestinal perforation in very-low-birth-weight infants: a distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg 2002;195:796-803.
2. Attridge JT, Clark R, Walker MW, Gordon PV. New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. J Perinatol 2006;26:93-9.
3. Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. J Perinatol 2003;23:278-85.
4. Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 2001;344:95-101.
5. Uceda JE, Laos CA, Kolni HW, Klein AM. Intestinal perforations in infants with a very low birth weight: a disease of increasing survival? J Pediatr Surg 1995;30:1314-6.
6. Alpan G, Eyal F, Vinograd I, et al. Localized intestinal perforations after enteral administration of indomethacin in premature infants. J Pediatr 1985;106:277-81.
7. Kawase Y, Ishii T, Arai H, Uga N. Gastrointestinal perforation in very low-birthweight infants. Pediatr Int 2006;48:599-603.
8. Attridge JT, Clark R, Gordon PV. New insights into spontaneous intestinal perforation using a national data set (3): antenatal steroids have no adverse association with spontaneous intestinal perforation. J Perinatol 2006;26:667-70.
9. Kelleher J, Salas AA, Bhat R, et al. Prophylactic indomethacin and intestinal perforation in extremely low birth weight infants. Pediatrics 2014;134:1369-77.
10. Attridge JT, Clark R, Walker MW, Gordon PV. New insights into spontaneous intestinal perforation using a national data set: (2) two populations of patients with perforations. J Perinatol 2006;26:185-8.
11. Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants. Cochrane Database Syst Rev 2011:CD006182.

J Pediatr Res 2017;4(4):245-8
DOI: 10.4274/jpr.98700

Olgu Sunumu / Case Report

Diazoksit Yanıtsız Hiperinsülinemik Hipoglisemili Bir Olguda Tedavi ve İzlem

Treatment and Follow-up in a Case with Diazoxide Treatment-Resistant Hyperinsulinemic Hypoglycaemia

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ÖZ

Hiperinsülinemik hipoglisemi (HH) yenidoğan ve süt çocuklarında dirençli ve tekrarlayan hipogliseminin en sık görülen ve en zor yönetilen nedenidir. Burada yaşamının 1. gününde HH tanısı alan ve izlemde diazoksit yanıtsız olması nedeniyle totale yakın pankreatektomi uygulanan bir olgu sunuldu. Olguda, erken tanı ve müdahaleye rağmen, hipoglisemi ve cerrahiye ait komplikasyon gelişti.

Anahtar Kelimeler: Hiperinsülinemik hipoglisemi, pankreatektomi, West sendromu

ABSTRACT

Hyperinsulinemic hypoglycemia (HH) is the most common reason for persistent and recurrent hypoglycemia in the neonatal and infancy periods. We presented a case diagnosed with HH on the first day of life and who underwent near-total pancreatectomy because of the unresponsiveness to the diazoxide treatment. Despite early diagnosis and management, complications developed due to hypoglycemia and surgery.

Keywords: Hyperinsulinemic hypoglycemia, pancreatectomy, West syndrome

Giriş

Hiperinsülinemik hipoglisemi (HH), pankreatik β hücrelerinde kan glukozundan bağımsız olarak düzensiz insülin salınımına bağlı gelişir ve tekrarlayıcı hipoglisemiye neden olur (1,2). Yenidoğan ve süt çocuklarında ısrarlı hipogliseminin en sık sebebidir (2-4). Sporadik ve genetik nedenli HH nadir görülürken (insidansı 1/40000) akraba evliliği sık görülen yerlerde insidans 1/2500'e kadar çıkabilir (2). Hipoglisemi anında alınan kan örneklerinde hipoglisemiyle uygunsuz olarak serum insülin değeri saptanabilir düzeydedir. Tedavide temel amaç hipogliseminin kalıcı nörolojik sekel riskinden korunmak için normoglisemiyi sürdürmektir. HH'de normoglisemiyi sağlamak için yüksek dozda glukoz infüzyonu (>8 mg/kg/dk) gerekir, ancak düzensiz insülin salınımı nedeniyle tedavi oldukça karmaşıktır (1,2). Tedavi medikal, medikal tedaviye yanıtsız olanlarda da pankreatektomidir. Cerrahi sonrasında kür olabilir, HH devam edebilir veya cerrahiye ait komplikasyonlar gelişebilir.

Burada, medikal tedaviye dirençli olması nedeniyle totale yakın pankreatektomi yapılan, ancak sonrasında

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Geliş tarihi/Received: *04.03.2016* **Kabul tarihi/Accepted:** *05.09.2016*

komplikasyonlar gelişen bir HH'li olgunun tedavi izlemi paylaşıldı.

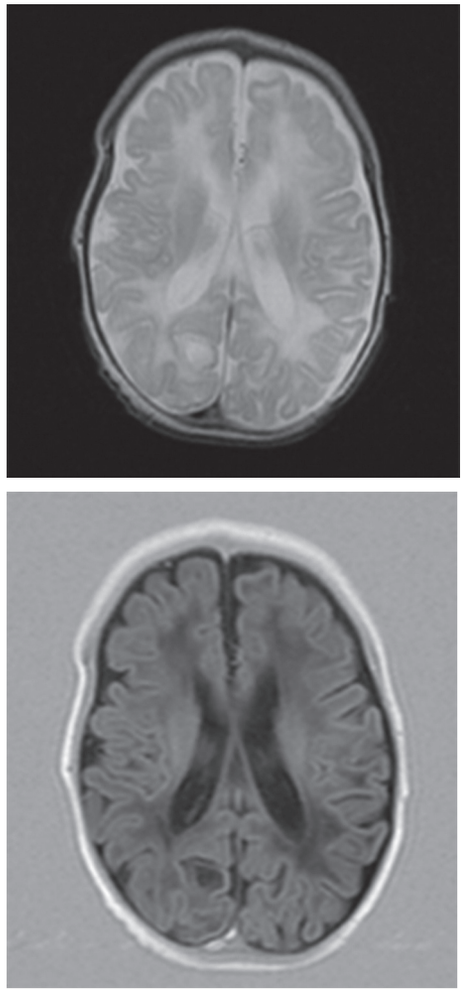
Olgu Sunumu

İki günlük kız bebek yaşamının ikinci saatinde konvülsiyon geçirmesi nedeni ile yönlendirildi. Anne baba arasında akrabalık olmayan, otuz yaşında sağlıklı anneden, zamanında, sezaryenle 3550 gr doğan kız bebek postnatal 2. saatte konvülsiyon geçirmesi nedeniyle ölçülen kapiller kan glukozunun 30 mg/dL bulunarak, 8 mg/kg/dk glukoz infüzyonu başlanıp sevk edildi. Fizik bakıda ağırlık: 3800 gr [1,17 standart deviasyon skoru (SDS)], boy: 50 cm (0,28 SDS), baş çevresi 35,5 cm (1 SDS), fizik bakısı normal, dismorfik görünümü yoktu. Yaşamın ilk saatlerinde başlayan ve ısrarlı hipoglisemileri olan olguda, hiperinsülinik hipoglisemi ön tanısı ile venöz kateter takılarak glukoz infüzyonu 8 mg/kg/dk'den 14 mg/kg/dk'ye arttırıldı ve glukagon perfüzyonu 10 µg/kg/saat başlandı. Serum kan glukozu 33 mg/dL iken hipoglisemi ayırıcı tanısına yönelik tetkikleri alındı (Tablo I). Metabolik hastalık ve sepsis dışlanan olguda hipoglisemi anındaki insülin düzeyi yüksek (45,9 mIU/L), idrar ketonu negatif saptanarak HH tanısı ile, diazoksit 15 mg/kg/g, 3 dozda başlandı. Normoglisemi sağlanamaması üzerine tedaviye oktreotid 10 µg/kg/gün deri altı ve nifedipin 1 mg/kg/gün, eklendi. Moleküler genetik incelemelerinde, K+ (ATP) kanal mutasyonu (*ABCC8/KCNJ11*) ve glukokinaz (*GCK*) gen mutasyonları saptanmadı. Glukoz infüzyonu 15 mg/kg/dk, glukagon infüzyonu 20 µg/kg/saat, diazoksit 20 mg/kg/gün, oktreotid 25 µg/kg/gün, nifedipin 1 mg/kg/gün ve enteral beslenme tedavisi ile glukoz infüzyon hızı hipoglisemi eğilimi nedeni ile azaltılamaladı. Yaşamının 59. gününde totale yakın pankreatektomi uygulandı. Patolojik değerlendirmede; endokrin adacıklarında artış ve hiperplazi yarı sıra endokrin hücrelerinde yer yer pleomorfizm saptandı. Operasyon sonrası glukoz monitorizasyonu açısından sürekli glukoz izlem sistemi uygulandı. Israrlı hiperglisemi (300 mg/dL) nedeniyle 0,05 U/kg/saat insülin infüzyonu başlandı. Yağlı dışkı olması üzerine ekzojen pankreas enzimi (Kreon) ve A, D, E, K vitaminleri tedavisine eklendi. Operasyon sonrası 4. günde sürekli glukoz izlem sistemli insülin infüzyon pompası (Medtronic Veo sistem) takıldı. İzleminde veo insülin infüzyon pompası ile kan şekerleri normal seyreden ve insülin değerleri normal olan olgu, beş aylıktan sonra insülinsiz izleme alındı. Kraniyal manyetik rezonansta hipoglisemi sekeliyle uyumlu olarak her iki parietooksipital bölgede yaygın myelinizasyon gecikmesi ve sağ oksipitalde daha belirgin ensefalomalazi ve gliozis sahası saptandı (Şekil 1). Altı buçuk aylıkken baş düşme şeklinde, gün içinde çok defa tekrarlayan miyoklonik nöbetleri gözlendi. Elektroensefalogramda bilateral temporal alanlarda keskin dalga saptandı ve West

Tablo I. Serum glukozu 33 mg/dL iken eş zamanlı alınan diğer örnekler ve sonuçları

Laboratuvar	Sonuç	Normal değer*
Kan ve idrar keton	Negatif	-
İndirgen madde	Negatif	-
Amonyak (Umol/L)	50	<70
İdrar organik asit	Normal	-
İnsülin (mIU/L)	45,9	<2
Glukoz/insülin	0,7	<0,4
Kortizol (µg/dL)	7,17	>10
Büyüme hormonu (ng/mL)	37,9	>10
C-peptid (ng/mL)	7,62	<0,6
ACTH (µg/dL)	15,7	>10

*Hipoglisemi anında normal değerler
ACTH: Adrenokortikotropik hormon



Şekil 1. Kraniyal manyetik rezonans. T1 ve T2 sekanslarında aksiyal plan. Her iki parietooksipital bölgede yaygın miyelinizasyon gecikmesi ve sağ oksipitalde daha belirgin ensefalomalazi ve gliozis sahası

sendromu tanısı konarak vigabatrin başlandı. Yedi aylık kontrolünde ise hepatosplenomegali saptandı. Üst glukoz izlem sistemi endoskopisinde özofagusta grade 1-2 varisleri bulundu. Özofagus varislerinin pankreatektomi operasyonuna ikincil gelişen portal ven trombozuna bağlı olduğu düşünüldü ve varislere yönelik propranolol tedavisi başlandı. Yirmi sekiz aylık iken hipo ve hiperglisemi saptanmayan olgu izlenmekte, nöromotor gelişimi geri, portal hipertansiyon mevcut ve konvülsiyonları kontrol altında idi.

Olgunun ailesinden onam alınmıştır.

Tartışma

Yenidoğanda hipoglisemi oldukça sık gözlenen ve farklı nedenlere bağlı ortaya çıkan, mortalite ve morbiditeyi arttıran metabolik bir durumdur. Kan glukozunun 50 mg/dL altında olması hipoglisemi olarak kabul edilir, ancak beyin hasarının hangi değerlerde gelişeceği bilinmemektedir. Hipoglisemi anında müdahale edilirken, etiyolojiye yönelik hipoglisemi tetkikleri alınmalıdır. Hipoglisemi anında ölçülebilir insülin (>2 µU/mL) ve C-peptid değerinin olması, idrar/keton negatifliği saptanması HH tanısını koydurtur. Yenidoğan döneminde glukoz ihtiyacı 4-6 mg/kg/dk olup normoglisemiyi sürdürmek için 8 mg/kg/dk'den fazla glukoza ihtiyaç duyulması HH açısından önemli bir bulgudur (2). Hipoglisemi, genellikle hayatın ilk 3 günü içinde gelişir ve olguların yarısında konvülsiyon gelişir (1). Bazı olgularda zayıf beslenme, letarji, irritabilite gibi spesifik olmayan bulgular olabilir (2). HH, geçici veya kalıcı olabileceği gibi bazı sendromlara eşlik de edebilir. Olgumuz normoglisemiyi sürdürmek için 14 mg/kg/dk glukoz infüzyonu ve glukagon infüzyonu almaktaydı. HH saptanması ile birlikte medikal tedavide ilk seçenek olan diazoksit başlandı. HH'de kullanılan diğer ilaçlar ve dozları Tablo II'de verilmiştir (1,2). HH histolojik olarak fokal ve diffüz olarak ayrılır ve tedavi yaklaşımları diffüz veya fokal hastalık olmasına göre değişir (1,2). Ayırıcı tanı için ^{18}F-Dopa pozitron emisyon tomografisi/bilgisayarlı tomografi kullanılır, ancak bu yöntem henüz Türkiye'de uygulanmamaktadır. Fokal hastalıkta pankreas β hücre hiperplazisi sadece bir alanı etkilediğinden, o alana yönelik parsiyel veya selektif cerrahi ile kür sağlanabilir (1-4). Diffüz hastalıkta ise tüm pankreas β hücrelerinde artış vardır. Medikal tedaviye yanıt oldukça değişkendir. Lord ve ark. (3) yaptığı 223 olguda oluşan seride diffüz hastalıkta (ortalama %98 rezeksiyon) operasyon sonrası %41 olguda hipoglisemi nedeniyle tedaviye gereksinim duyulurken, fokal hastalıkta (ortalama rezeksiyon %27) %94 oranında kür sağlanmıştır.

Fokal β hücre hiperplazisi sporadik veya *ABCC8* ve *KCNJ11* genlerinde (β hücresi potasyum kanalına ait defektler) paternal geçişli mutasyonlarda görülür (1,2,4). Diffüz β hücre hiperplazisinde genetik yapı heterojendir; otozomal resesif (*ABCC8, KCNJ11*) veya otozomal dominant (*ABCC8/KCNJ11, GCK, GLUD1, SLC16A1, HNF4A, HADH*) gen mutasyonları olabilir (1,2). Olguların yarısına genetik olarak tanı konamazken, bilinen en sık neden *ABCC8/KCNJ11* genlerinde otozomal resesif inaktive edici mutasyondur (2,4). *ABCC8/KCNJ11* mutasyonları haricindeki mutasyonlarda çoğunlukla diazoksite yanıt vardır (1,2). Diazoksit, bir potasyum kanal aktivatörüdür. *ABCC8/KCNJ11* gen mutasyonlarında *in vivo* olarak yanıt gözlenemezken *in vitro* olarak potasyum kanalını aktive edebildiği bildirilmektedir (2). Yüksek dozda bu yanıt *in vivo* olarak elde edilebilir, ancak diazoksit yan etki riskini arttırır (2). En sık görülen yan etki hipertrikozdur, ayrıca sodyum ve su retansiyonu, buna bağlı olarak pulmoner ödem, kalp yetmezliği, prematürelerde duktus arteriyozusun tekrar açılmasına neden olabilir. Diazoksit başlandıktan sonra kan glukozu kontrolü ile intravenöz sıvı ve diğer tedaviler kesilir. Art arda 5 gün normogliseminin görülmesi durumunda olgu diazoksit yanıtlı olarak değerlendirilir (1). Diazoksit başlandıktan sonra 24 saat içinde 2 kez kanıtlanmış hipoglisemi görülmesi de diazoksite yanıtsızlık olarak kabul edilir (1). Diazoksit-yanıtsız olgularda pankreatektomi öncesi oktreotid ve nifedipin denenmelidir (1,2). Oktreotid bir

Tablo II. Hiperinsülinemik hipoglisemide kullanılan ilaçlar, dozları, etki mekanizmaları ve yan etkileri

İlaçlar	Kullanım şekli	Dozu	Etki mekanizması	Yan etkileri
Diazoksit	Oral	5-20 mg/kg/g 3 dozda	Potasyum kanal agonisti	Sıvı retansiyonu, hipertrikoz, hiperürisemi, eozinofili, lökopeni, nadir; hipotansiyon
Klortiazid (diazoksit ile)	Oral	7-10 mg/kg/g 2 dozda	Potasyum kanal aktivasyonu	Hiponatremi, hipokalemi
Nifedipin	Oral	0,25-2,5 mg/kg/g 3 dozda	Kalsiyum kanal blokeri	Nadiren hipotansiyon
Glukagon (± oktreotid)	Deri altı veya intravenöz infüzyon	1-20 µg/kg/saat	Adenilat siklaz aktivasyonu, glukoneogenez ve glikojenolizi arttırır	Bulantı, kusma, deri döküntüsü paradoksal insülin salınımında artış (>20 µg/kg/saat)
Oktreotid (± glukagon)	Deri altı veya intravenöz infüzyon	5-25 µg/kg/gün	İnsülin sekresyonunu azaltır, kalsiyum mobilizasyonunu ve asetilkolin aktivitesini azaltır	Anoreksi, bulantı, şişkinlik, karın ağrısı, diyare, safra taşı, GH, ACTH, TSH, glukagon salınımında azalma, büyümede azalma Taşiflaksi

ACTH: Adrenokortikotropik hormon, TSH: Tiroid stimüle edici hormon, GH: Büyüme hormonu

somatostatin analoğudur ve günde 3 veya 4 dozda, deri altı veya deri altı infüzyon yoluyla uygulanır. Gastrointestinal yan etkileri vardır ve cevap olduğunu belirlemek amaçlı en az 48 saat izlenmelidir (1). Oktreotidin diffüz hastalığın medikal tedavisinde uzun dönemde de, enteral beslenme ile uygulanabilir. Diazoksit yanıtsız potasyum kanal defektlerinde 2-5 yaşlarında spontan remisyona uğrayana kadar oktreotidin uzun dönemde başarılı bir şekilde kullanıldığı bildirilmiştir (4). Nifedipin bir kalsiyum kanal antagonistidir ve şimdiye kadar nifedipine yanıtlı sadece birkaç olgu bildirilmiştir (2). Diffüz olgularda cerrahi palyatif bir tedavidir ve oktreotide de yanıt olmadığında uygulanmalıdır (1,2). Genetik olarak tanı konamayan olgumuzda, hiperinsülinizmin fokal mi diffüz mü olduğuna dair elimizde bir verimiz yoktu. Medikal tedavide 5 ilaç altında ve sürekli beslenmeye rağmen hipoglisemi devam ettiği için, 59 günlükken, %95 oranında totale yakın pankreatektomi uygulandı.

Pankreatektomi majör bir operasyondur, sonrasında insülin bağımlı diabetes mellitus (DM), ekzokrin pankreas bozukluğu, enfeksiyon gelişebilir veya hiperinsülinizm devam edebilir. Al-Shanafey'in (5) yaptığı pankreatektomi uygulanan 18 olguluk bir çalışmada, operasyon sonrası izlemde 4 olguda tekrar operasyon, 6 olguda tedavisiz normal kan şekeri kontrolü, 9 olguda medikal tedavi ihtiyacı, 3 olguda da DM geliştiği bildirilmiştir. McAndrew ve ark. (6) 48 olguluk pankreatektomi sonuçlarında ise 44 olguda hiperinsülinizm gerilemiş, ancak olguların sadece 16'sında ilaç tedavisi veya ikinci bir operasyona gerek kalmadığı belirtilmiştir. Ayrıca operasyon esnasında kanama, dalak zedelenmesi, safra kesesi hasarı, operasyon sonrasında safra sızıntısı, safra yolu darlığı, ileus bildirilmiştir (6). Arya ve ark. (7) 45 olguluk totale yakın pankreatektomi deneyiminde ise operasyon sonrası olguların %60'ı medikal tedaviye devam etmiş, %96'sının 11 yıllık izlem sonrasında insülin bağımlı diyabet geliştirdiği, %72'sinde ise ekzokrin pankreas fonksiyon bozukluğu bildirilmiştir. Olgumuzda operasyon sonrası üç ay kadar insülin ihtiyacı oldu. Altı buçuk aylıkken West sendromu tanısı aldı. Hipoglisemik beyin hasarının West sendromuna neden olabileceği literatürde bildirilmektedir, ancak mekanizması tam olarak bilinmemektedir (8-10). Operasyondan 5 ay sonra da pankreatektomiye bağlı portal ven trombozu ve özofagus varisleri gelişti.

Sonuç olarak, HH tanısı konan bebeklerde ilaçlar çoklu başlanıp, glukoz değerlerinin normal/yüksek değerlerde izlenmesi amaçlanabilir. Diazoksit-yanıtsız olgularda pankreatektomi uygulanmalıdır. Olgular pankreatektomi sonrasında da büyüme, gelişme, hipoglisemi, ekzokrin pankreas fonksiyon bozukluğu ve insülin bağımlı diyabet açısından izlenmelidir.

Etik

Hasta Onayı: Çalışmamıza dahil edilen hastanın velisinden bilgilendirilmiş onam formu alınmıştır.

Hakem Değerlendirmesi: Editörler kurulu tarafından değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi Uygulama: A.Ç., Medikal Uygulama: Ş.D., D.G., S.Ö., N.K., M.Y., Ö.A.K., S.Y., N.M., B.E.Y., Patoloji Değerlendirme: Y.E., Konsept: N.M., D.G., S.Ö., Dizayn: N.M., D.G., S.Ö., Veri Toplama veya İşleme: N.M., D.G., S.Ö., Analiz veya Yorumlama: N.M., D.G., S.Ö., Literatür Arama: N.M., Yazan: N.M., D.G., S.Ö.

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. Arnoux JB, de Lonlay P, Ribeiro MJ, et al. Congenital hyperinsulinism. Early Hum Dev 2010;86:287-94.
2. Hussain K. Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. Horm Res 2008;69:2-13.
3. Lord K, Dzata E, Snider KE, Gallagher PR, De León DD. Clinical presentation and management of children with diffuse and focal hyperinsulinism: a review of 223 cases. J Clin Endocrinol Metab 2013;98:1786-9.
4. Yorifuji T. Congenital hyperinsulinism: current status and future perspectives. Ann Pediatr Endocrinol Metab 2014;19:57-68.
5. Al-Shanafey S. Laparoscopic vs open pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy. J Pediatr Surg 2009;44:957-61.
6. McAndrew HF, Smith V, Spitz L. Surgical complications of pancreatectomy for persistent hyperinsulinaemic hypoglycaemia of infancy. J Pediatr Surg 2003;38:13-6.
7. Arya VB, Senniappan S, Demirbilek H, et al. Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. PLoS One 2014;9:e98054.
8. Kumaran A, Kar S, Kapoor RR, Hussain K. The clinical problem of hyperinsulinemic hypoglycemia and resultant infantile spasms. Pediatrics 2010;126:1231-6.
9. Alrifai MT, AlShaya MA, Abulaban A, Alfadhel M. Hereditary neurometabolic causes of infantile spasms in 80 children presenting to a tertiary care center. Pediatr Neurol 2014;51:390-7.
10. Camurdan MO, Cinaz P, Serdaroğlu A, Bideci A, Demirel F. Persistent hyperinsulinemic hypoglycemia presenting with a rare complication: West syndrome. J Pediatr Endocrinol Metab 2004;17:1465-8.

J Pediatr Res 2017;4(4):249-52
DOI: 10.4274/jpr.42650

Case Report / Olgu Sunumu

A Newborn Case of "c" Subgroup Mismatch Presenting with Severe Hemolysis and Anemia

Ağır Hemoliz ve Anemiyle Başvuran "c" Subgrup Uyuşmazlıklı Bir Yenidoğan Olgusu

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ABSTRACT

Hemolysis and jaundice related to Rh incompatibility in the neonatal period has decreased substantially due to the widespread use of anti-D gammaglobulin in recent years. Nevertheless, the rate of subgroup mismatch in the etiology of hemolytic diseases of the newborn has increased significantly. In this article an 8-day-old newborn infant with "c" subgroup incompatibility and presenting with severe anemia, in whom hemolysis could be controlled with intravenous immunoglobulin infusion and subgroup appropriate blood transfusion, has been presented. Scientific studies have demonstrated that the hemolytic disease of patients who don't have major blood group incompatibility but carry anti-C antibodies can be rather serious. Therefore, subgroup mismatch should always be kept in mind for newborns presenting with severe hemolytic anemia, and transfusion or if necessary exchange transfusion should be provided with subgroup matched blood products.

Keywords: Subgroup mismatch, newborn, hemolytic anemia, intravenous immunoglobulin

ÖZ

Son yıllarda anti-D gamaglobulin kullanımının yaygınlaşması ile birlikte yenidoğan döneminde Rh uyuşmazlıklarına bağlı hemoliz ve sarılık büyük ölçüde azalmıştır. Bununla beraber subgrup uyuşmazlıklarının yenidoğanın hemolitik hastalığı etiyolojisindeki oranı önemli ölçüde artmıştır. Bu makalede; postnatal 8. gününde, ağır anemiyle seyreden, intravenöz immünoglobulin ve subgrup uygun kan transfüzyonu ile hemolizi kontrol altına alınan bir subgrup "c" uyuşmazlığı olgusu sunulmuştur. Bilimsel çalışmalar, majör kan grubu uyuşmazlığı bulunmayan, ancak anti-C antikorları taşıyan olgularda hemolitik hastalığın oldukça ciddi seyredebildiğini göstermiştir. Bu nedenle şiddetli hemolitik anemi ile kliniğe başvuran yenidoğanlarda her zaman subgrup uyuşmazlıkları akılda bulundurulmalı, subgrup uygun kan ürünleri ile transfüzyonları ve gerekirse kan değişimleri sağlanmalıdır.

Anahtar Kelimeler: Subgrup uyuşmazlığı, yenidoğan, hemolitik anemi, intravenöz immünoglobulin

Introduction

The formation of antibodies against the erythrocyte antigen in pregnancy is called erythrocyte isoimmunization, and after birth it is called erythrocyte alloimmunization. The perinatal outcome of this process is hemolysis and anemia in the fetus/newborn or hemolysis disease of the fetus/newborn (1). Neonatal hemolytic disease is caused by the formation of maternal antibodies against fetal erythrocyte antigens and these antibodies causing hemolysis in the

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Received/Geliş tarihi: *02.06.2016* **Accepted/Kabul tarihi:** *10.09.2016*
A brief summary of this case was presented as poster at the 24th National Neonatal Congress.

fetus or newborn by passing through the placenta passively. Today with the widespread use of anti-D gammaglobulin, immunohemolytic anemia due to Rh incompatibility, and indirect hyperbilirubinemia have decreased while the rate of subgroup incompatibility in the etiology of newborn hemolytic disease is increasing (2,3).

The most common subgroup incompatibilities are; non-D Rh antigens (c, C, e, E), Kell, Duffy, Kidd and MNS. In the United States of America in 1969, 18.000 prenatal serum for red cell antibodies were screened, and 37.000 were screened in 1996. RhD alloimmunisation causing immunohemolysis in newborns decreased from 16.5 cases per 1000 samples in 1969 to 2.7 per 1000 in 1996 while Kell alloimmunisation increased from 1.6 cases per 1000 in 1969 to 3.2 per 1000 in 1996 (3). Due to subgroup incompatibilities, there may be many clinical findings ranging from subclinical hemolysis to severe hemolysis and blood exchange. The potentiality of the increased antibodies causing severe hemolysis due to these incompatibilities are significantly higher than others in some subgroups (such as "c" incompatibility) (4).

Here, a rare case of severe hemolysis and severe anemia due to "c" subgroup incompatibility is presented.

Case Report

The Apgar score of the 2850-gr-newborn girl of a twenty-five-year-old healthy mother delivered by normal spontaneous vaginal delivery was 8 at the 1st minute, and 10 at the 10th minute; and no parental consanguinity was found. In the antenatal period, ultrasonography (USG) follow-ups had been normal and the mother had had vitamin and iron supplements. On the family history, there was an isolated cleft palate in one sibling and the other one was healthy, neither of whom had newborn jaundice and/or phototherapy history. The patient who had no clinical problems in the early neonatal period was hospitalized on the 8th postnatal day due to palpitations, tachycardia and hepatomegaly in the neonatology policlinic where she came for examination. It was found that the body weight was 2650 gr (3-10 percentile), height was 47.5 cm (10-50 percentile), and the circumference of the head was 33 cm (10 percentile). Vital findings were; heart rate: 190/min; arterial blood pressure: 85/44 (55) mmHg; temperature: 36.7 °C; respiratory rate: 66/min; and SpO_2 was 98% (with 5 Lt/min in oxygen support). In the physical examination it was found that the case was tachypneic and the skin color was pale; had cardiac 2/6 systolic murmur, liver was located 3 cm under the rib, and neonatal reflexes were slightly decreased. In the laboratory tests haemoglobin was found to be 3 g/dL, hematocrit was 15.5%, mean corpuscular volume 139.5 fL, red cell distribution width 18.8%. Leukocyte count was 100260/mm^3, and thrombocyte count was 424000/mm^3. In the peripheral blood smear, mature normoblast increase was apparent, and thrombocytes were sufficient and clustered; atypical cells and blast were not observed. Total bilirubin was found to be 6.1 mg/dL, direct bilirubin was 0.8 mg/dL, lactate dehydrogenase was 2030 IU/L, uric acid was 10 mg/dL, and there was no ion imbalance in the patient who had normal liver and kidney function tests. The maternal and infant blood groups showed A Rh (+), direct coombs +4 positive, and the reticulocyte value was found to be significantly increased by 32%, and the peripheral blood smear supported hemolysis. After conducting tests for anemia, erythrocyte suspension transfusion (ERT) was planned. During blood preparation, appropriate mastitue support and inotropic support were provided, and intravenous immunoglobulin (IVIG) was administered at 1 g/kg considering severe immunohemolytic anemia. Thyroid hormones and glucose-6-phosphate dehydrogenase enzyme levels were found to be normal before transfusion, TORCH and parvo virus serology were negative. Cranial and submucosal USG, which was done to see possible bleeding into closed spaces, was found to be normal. Immune hemolytic anemia was suspected in the infant with +4 positive direct coombs, reticulocytosis, and severe hemolytic findings in the peripheral blood smear. When the etiology of immune hemolysis was examined, there was no AB0, RhD incompatibility between the mother and baby. Antibody screening was performed before transfusion, but antibody detection could not be done due to technical reasons. Because of this, the cause of this severe immunohemolytic anemia could not be detected, and "c" subgroup incompatibility was considered.

Owing to the presence of cardiac insufficiency, the patient was transfused with 10 cc/kg/dose, with A RhD positive, "c" antigen negative, leucocyte-less ERT. IVIG was administered once more at 1 g/kg 12 hours after hospitalization because post-transfusion hemoglobin was 6.7 gr/dL, hematocrit was 22.6%, also oxygen requirement continued, and there was tachycardia retention. With the administration of ERT 10 cc/kg once again, the hemolysis was controlled, oxygen requirement and tachycardia decreased, inotropic support was gradually reduced and cut. When the patient was stabilized, echocardiography was performed due to the possibility of additional cardiac pathology that could lead to cardiac failure; but no symptoms were detected. In the follow-up, the patient, who had no recurrent hemolysis whose vital signs were stable, who had received total oral nutrition and gained weight, was discharged from hospital on the 18th postnatal day to be followed up in the polyclinic. The case was followed up at regular intervals until the age of 1. During that time, hemolysis did not recur, growth and development were consistent with its age group, pathological anemia did not develop, and early iron supplementation was not needed. For this article the family was informed, written and spoken approvals were taken from the family.

Discussion

The most common cause of hemolytic anemia and pathological neonatal jaundice is blood group incompatibility, and the etiopathogenesis is based on the formation of antibodies in the mother against the antigens in the erythrocytes of the newborn. Antibodies causing hemolysis

of the fetus and newborn erythrocytes are most commonly seen in AB0 and RhD incompatibilities. Although approximately 15% of live births present this risk, the syndromes appear only in 0.3% to 2.2% of infants (5).

The most common subgroup incompatibilites are; Kell, Duffy, Kidd and MNS, which are the non-D Rh antigens (c, C, e, E) (3). In a study conducted among 452 women with a positive indirect Coombs test, antibody incidence of fetal haemolytic disease was as follows: anti-D 18.4%, anti-E 14%, anti-C 5.8%, anti-C 4.7%, anti-Kell 22%, anti-MNS 4.7%, Duffy 5.4%, and Jka 1.5% (6). Another study carried out with 507 antibody-positive women in Poland, showed that 106 of them (21%) had non-anti-D antibodies; and in 46 of these (%43) Rh subgroups (C, c, E, e, G, Rh17); in 35 (%33) of them K and k; and in the other 25 (%24) other antigens were detected. Nowadays, all women are screened for blood group and antibody presence on the first prenatal examination in order to be protected from Rh alloimmunisation. Hemolytic disease of the newborn due to maternal isoimmunisation is gradually decreasing with the application of anti-D gammaglobulin prophylactically on the 28th gestational week to all Rh-negative women with no alloimmunization findings; however, there is an increase in the frequency of isoimmunization due to subgroups including anti-E, anti-Kell and anti-C (7).

The pathophysiology of isoimmunisation in subgroup incompatibility is similar to Rh incompatibility; the clinic of the disease may vary widely, ranging from the subclinical hemolysis to severe hemolysis, deep anemia, and hyperbilirubinemia, which requires blood exchange. Among subgroup incompatibilities, anti-c may cause more severe hemolytic disease. The highest levels of bilirubin have been reported in cases with hemolytic disease due to anti-c antibody (8,9). In the study in which Dajak et al. (10) studied 44 newborns with hemolytic disease due to subgroup incompatibility, a severe hemolysis was observed in 14 of them, and it was found that hemolytic disease was more severe in 8 who were anti-c antibody positive. In our case, "c" antigen was positive and severe hemolysis had developed, and this patient applied to our hospital with cardiac insufficiency due to hemolysis.

In the immunohemolytic anemia of the newborn; intravascular hemolysis findings such as indirect hyperbilirubinemia, shortened erythrocyte sedimentation, increased urobilinogen excretion, hemoglobinemia, hemoglobinuria, hemosiderinuria, methemalbuminemia due to erythrocyte destruction; and reticulocytosis, macrocytosis, normoblastemia, leukocytosis and thrombocytosis due to increased erythropoiesis may ocur in the peripheric blood (11). There is erythroid hyperplasia in the bone marrow (11). In our case, significant leukocytosis and mature normoblast increase was seen in the peripheral blood smear.

In the studies carried out, direct coombs test was found to be positive in 33% of the cases in which subgroup disagreement was detected. In cases with hemolytic anemia, the direct coombs test is not always positive or negative, which does not mean there is no incompatibility. This is thought to be due to the poor antigenic properties of subgroup antigens (4). In our case, the direct coombs test was positive +4, which supports severe hemolysis.

In hemolytic diseases due to subgroup incompatibilities, an early high-dose of IVIG, which is thought to demonstrate its effect by altering the expression and function of reticuloendothelial system Fc receptors, and interacting with complex activation, can prevent hemolysis (9). As stated in the Turkish Neonatology Association Jaundice Guide, IVIG can be used in the presence of bilirubin levels close to the blood exchange limit in infants with immunohistochemistry-indirect hyperbilirubinemia such as Coombs (+) AB0 or Rh incompatibility, and subgroup incompatibility. According to the guidelines of the American Academy of Pediatrics, IVIG is given to babies with elevated serum bilirubin levels despite intensive phototherapy, bilirubin levels close to the blood exchange limit, total bilirubin levels at the blood exchange limit at a dose of 0.5 to 1.0 g/kg every 2 hours to be repeated after 12 hours if necessary. However, in a newly published meta-analysis of 463 Rh and 350 AB0 incompatibility cases in 2014, it was reported that the use of IVIG did not reduce the need for blood exchange in neither Rh nor AB0 incompatibility (12). Although there are conflicting publications on the use of IVIG in the hemolytic disease of the newborn, IVIG was administered at a dose of 1gr/kg every 12 hours to our case due to detected anemia requiring transfusion, and clinical benefit was obtained in halting hemolysis.

In some countries, despite the low frequency, non-anti-D-erythrocyte alloimmunisation screening is recommended for gestation because of severe hemolytic disease due to subgroup incompatibility whereas in some others, these screenings are not recommended (13,14). In our country, anti-D administration in pregnancy for Rh incompatibility is adopted as a health policy but screening for subgroup incompatibility in pregnancy is not on the agenda yet (15).

As a result, subgroup incompatibilities should be kept in mind in cases of severe hemolysis as hemolytic disease can be quite severe in cases with subgroup "c" incompatibility even if no major blood group incompatibility is detected in the studies performed; and if blood exchange is required, transfusion and/or blood exchange with the appropriate subgroup of blood should be performed.

Ethics

Informed Consent: Consent form was filled out by the parent's of the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y.E., Concept: Ö.O., Design: Ş.Ç., Data Collection or Processing: E.Y.E., S.A.Ö., Analysis or Interpretation: K.Ç., Literature Search: R.Ç., E.Y.E., Writing: E.Y.E.

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. Moise Kenneth J. Hemolytic disease of the fetus and newborn. Creasy and Resnik's Maternal - Fetal Medicine, Principles and Practice, 2014;558-68.
2. Zipursky A, Bowman JM. Isoimmune hemolytic diseases. In: Nathan DG, Oski FA (eds). Hematology of Infancy and Childhood, 4th ed. Philadelphia, WB Saunders C, 1993;44-73.
3. Moise KJ. Fetal anemia due to non-Rhesus-D red-cell alloimmunization. Semin Fetal Neonatal Med 2008;13:207-14.
4. Özkaya H, Bahar A, Özkan A, Kandemir F, Göçmenİ, Mete Z. Neonatal Period anemia with symptoms that minor blood group (anti-C, anti-E) nonconformity connected Hemolytic Disease. Turk Pediatri Ars 2000;35:30-5.
5. Rath ME, Smits-Wintjens VE, Walther FJ, Lopriore E. Hematological morbidity and management in neonates with hemolytic disease due to red cell alloimmunization. Early Hum Dev 2011;87:583-8.
6. Geifman-Holtzman O, Wojtowycz M, Kosmas E, Artal R. Female alloimmunization with antibodies known to cause hemolytic disease. Obstet Gynecol 1997;89:272-5.
7. Farnault L, Garcia-Meric P, Cortey A, Arnaud F. Fetomaternal anti-RH3, -4 (anti-E and anti-c) rhesus isoimmunization: a case report. Arch Pediatr 2011;18:176-82.
8. Van Dijk BA, Hirasing RA, Overbeeke MA. Hemolytic disease of the newborn and irregular blood group antibodies in the Netherlands: prevalence and morbidity. Ned Tijdschr Geneeskd 1999;143:1465-9.
9. Kubo S, Ariga T, Tsuneta H, Ishii T. Can high-dose immunoglobulin therapy be indicated in neonatal rhesus haemolysis? A successful case of haemolytic disease due to rhesus (c + E) incompatibility. Eur J Pediatr 1991;150:507-8.
10. Dajak S, Culic S, Stefanovic V, Lukacevic J. Relationship between previous maternal transfusions and haemolytic disease of the foetus and newborn mediated by non-RhD antibodies. Blood Transfus 2013;11:528-32.
11. Gökçe İK, Güzoğlu N, Öncel MY, Çalışçı E, Canpolat FE, Dilmen U. A Hemolytic Disease due to Minor Blood Group (Anti-C and Anti-E) Incompatibility Leading to Symptomatic Anemia in the Neonatal Period. Turkish Journal of Pediatric Disease 2014;1:32-4.
12. Louis D, More K, Oberoi S, Shah PS. Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: an updated systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2014;99:325-31.
13. Thakral B, Agrawal SK, Dhawan HK, Saluja K, Dutta S, Marwaha N. First report from India of haemolytic disease of newborn by anti-c and anti-E in Rh (D) positive mothers. Hematology 2007;12:377-80.
14. Wu KH, Chu SL, Chang JG, Shih MC, Peng CT. Haemolytic disease of the newborn due to maternal irregular antibodies in the Chinese population in Taiwan. Transfus Med 2003;13:311-4.
15. Orgun A, Çalkavur Ş, Olukman Ö, et al. Role of minor erythrocyte antigens in alloimmunization during indirect hyperbilirubinemia. Turk Pediatri Ars 2013;48:23-9.

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Yazarlık, Yayın Hakkı Devri, Maddi Yardım ve Teşekkür-Kabul İzni

TEŞEKKÜR VE KABUL BEYANI BÖLÜMÜ, SORUMLU YAZAR TARAFINDAN İMZALANMALI. SON BÖLÜM İSE MAKALEDE İSMİ GEÇEN BÜTÜN YAZARLAR TARAFINDAN İMZALANMALIDIR.

MAKALE BAŞVURUSUNDA FORM DOLDURULARAK ONLİNE SİSTEME YÜKLENMELİDİR.

BU FORM GEREKİRSE, İMZA İÇİN HER BİR YAZAR TARAFINDAN DOLDURULMAK ÜZERE FOTOKOPİ İLE ÇOĞALTILABİLİR.

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Telif hakkı oluşturulmuş olup toplum tarafından kullanıma açıktır. Orijinal olduğunu, daha önce yayınlanmadığını ve yayınlanmak üzere değerlendirme aşamasında olmadığını beyan ederim.

YAYIN HAKKI ŞARTNAMESİ

Bu başvuru ile makalemizin değerlendirme ve düzeltilmesinin, The Journal of Pediatric Research tarafından yapılma haklarını; imza yetkisi, kopyalama ve başka şekillerde çoğaltılmasını da içeren yayın haklarını ve basım haklarını Galenos Yayınevi'ne veriyorum.
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