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Güncel Pediatri

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Olgu Sunumları / Case Reports

Güncel Pediatri Dergisi
Bursa Uludağ Üniversitesi Tıp Fakültesi,
Çocuk Sağlığı ve Hastalıkları Anabilim Dalı
tarafından yayınlanmaktadır.

The Journal of Current Pediatrics is published by Bursa Uludağ University Faculty of Medicine Pediatrics Department.

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Amaç ve Kapsam

Güncel Pediatri Dergisi, çocuk sağlığı ve hastalıkları konulu, yayın dili hem Türkçe hem İngilizce olan, bağımsız ve bilimsel çift-kör hakemlik (peer-review) ilkelerine dayanan uluslararası, periyodik olarak yayınlanan bir dergidir. Dergi Nisan, Ağustos ve Aralık aylarında, yılda 3 sayı olmak üzere elektronik olarak yayınlanır.

Güncel Pediatri Dergisi'nin hedefi uluslararası düzeyde nitelikli, sürekli ve çocuk sağlığı ve hastalıkları konusunda özgün bir periyodik olarak, klinik ve bilimsel açıdan en üst düzeyde orijinal araştırmaları yayınlamaktır. Bununla birlikte eğitim ile ilgili temel yenilikleri kapsayan derlemeler, editöryel kısa yazılar, olgu sunumları, orijinal görüntüler ve geniş çocuk sağlığı ve hastalıkları kesimlerinin deneyimlerini ve eleştirilerini içeren mektuplar ve sosyal çocuk sağlığı ve hastalıkları konulu yazılar yayınlamaktır.

Güncel Pediatri Dergisi'nde makale başvuru ücreti veya makale işlem ücreti uygulamamaktadır.

Yayın politikaları, Uluslararası Tıp Dergisi Editörleri Komitesi (2013, http://www.icmje.org/ adresinde arşivlenmiştir) ve "Tıp Dergilerinde Bilimsel Çalışmalarda Bilimsel Çalışmaların Yapılması, Raporlanması, Düzenlenmesi ve Yayınlanması için Tavsiyeler" e dayanmaktadır.

Güncel Pediatri Dergisi, **Emerging Sources Citation Index (ESCI), Scopus, EBSCO, CINAHL, Embase, Gale, Proquest, J-GATE, Türk Medline** ve **Türkiye Atıf Dizini** tarafından indekslenmektedir.

Açık Erişim Politikası

Bu dergi, kamuoyunda serbestçe araştırma yapmanın daha büyük bir küresel bilgi alışverişini desteklediği ilkesi ile içeriğine anında erişim sağlar.

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.

İzin Talepleri

Bu dergi, araştırmaların kamuoyuna ücretsiz olarak sunulmasının daha büyük bir küresel bilgi alışverişini desteklediği ilkesine dayanarak içeriğine anında açık erişim sağlar.

Açık Erişim Politikası, Budapeşte Açık Erişim Girişimi (BOAI) http://www.budapestopenaccessinitiative.org/ kurallarına dayanmaktadır.

[Hakem denetimli araştırma literatürüne] "açık erişim" ile, herhangi bir kullanıcının bu makalelerin tam metinlerini okumasına, indirmesine, kopyalamasına, dağıtmasına, yazdırmasına, aramasına veya bağlantı vermesine izin veren, kamuya açık internette ücretsiz olarak erişilebilirliğini kastediyoruz, bunları dizine eklemek için tarayın, yazılıma veri olarak iletin veya internete erişmenin ayrılmaz bir parçası olmayanlar dışında finansal, yasal veya teknik engeller olmaksızın başka herhangi bir yasal amaç için kullanın. Çoğaltma ve dağıtım üzerindeki tek kısıtlama ve bu alandaki telif hakkının tek rolü, yazarlara çalışmalarının bütünlüğü üzerinde kontrol ve uygun şekilde tanınma ve alıntılanma hakkı vermek olmalıdır.

Telif Hakkı

Yazar(lar) makalesinin telif hakkını, makalenin yayına kabul edilip edilmediği durumlarda geçerli olacak şekilde Güncel Pediatri Dergisi'ne devreder. Telif hakkı, herhangi bir çoğaltma biçiminde (baskı, elektronik ortam veya başka herhangi bir şekilde) makalenin çoğaltılması ve dağıtılması için münhasır ve sınırsız hakları kapsar; ayrıca tüm diller ve ülkeler için çeviri haklarını da kapsar. ABD yazarları için telif hakkı devredilebilecek ölçüde devredilmiştir.

Yayın kararını aldıktan ve kabul ettikten sonra, başvurulara "Telif Hakkı Devir Bildirimi" eşlik etmelidir. Form, derginin makale gönderme ve değerlendirme sitesinden indirilebilir. Telif hakkı devir formu katkıda bulunan tüm yazarlar tarafından imzalanmalı ve ıslak imzalı belgenin taranmış bir sürümü sunulmalıdır.

Materyal Sorumluluk Reddi

Güncel Pediatri Dergisi'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve Editör, Editöryel Kurul ya da Yayıncı'nın görüşü değildir; Editör, Editöryel Kurul ve Yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

Dergi İletişim

Ömer Faruk Tarım

Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Endokrinoloji Bilim Dalı, Bursa, Türkiye

E-posta: drotarim@gmail.com

Yayınevi Yazışma Adresi

Galenos Yayınevi Tic. Ltd. Şti.

Adres: Molla Gürani Mah. Kaçamak Sk. No: 21/1, 34093 İstanbul, Türkiye

Tel.: +90 212 621 99 25

Faks: +90 212 621 99 27

E-posta: info@galenos.com.tr

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Aims and Scope

The Journal of Current Pediatrics is an international, nonbiased, peer-reviewed, independent periodical journal published in Turkish and English languages in pediatrics. It is published electronically in April, August, December.

The Journal of Current Pediatrics aims to publish a perpetual, original journal of international standing with original research articles of the highest standard in the field of both clinical and scientific pediatrics. The journal's content is intended to encompass reviews of new developments in education, brief editorial manuscripts, case reports, original photographs, letters concerning experiences in the field of child health and diseases (pediatrics), and particular feature articles in the field of social pediatrics.

The Journal of Current Pediatrics does not charge any fee for article submission or processing.

The editorial policies are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/) rules.

The Journal of Current Pediatrics is indexed in **Emerging Sources Citation Index (ESCI), Scopus, EBSCO, CINAHL, Embase, Gale, Proquest, J-GATE, Türk Medline** and **Turkish Citation Index.**

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The author is defined as a contributor who has participated in the work to the extent that he takes responsibility for a meaningful share of the manuscript's content published in the Journal of Current Pediatrics. Editor, Editorial Board or Publisher don't share the responsibility.

Journal Contact

Ömer Faruk Tarım

Bursa Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Endokrinoloji Bilim Dalı, Bursa, Türkiye

E-mail: drotarim@gmail.com

Publisher Corresponding Address

Galenos Yayınevi Tic. Ltd. Şti.

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey

Phone: +90 212 621 99 25

Fax: +90 212 621 99 27

Web page: www.galenos.com.tr

E-mail: info@galenos.com.tr

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YAZARLARA BİLGİ

GENEL KURALLAR

1. Yazıların dergide yayınlanmak üzere kabul edilmesi için; önemli, orijinal, bilimsel ve akademik üst düzeyde olması ön koşuldur.

2. Yayınlanan bütün yazıların içerikleri yazarların görüşlerini yansıtır, hiçbir şekilde editörler, yayın kurulu ve yayıncı sorumlu değildir. Dergiye gönderilen yazılara telif hakkı ödenmez. Yazarlardan, başvuru ve yayın aşamalarında herhangi bir ücret talep edilmemektedir.

3. Yayınlanmak üzere gönderilen bütün makalelerin dergimizin yazım kurallarına titizlikle uyularak hazırlanmış olması gerekir. Yayınlanmak üzere gönderilen yazılar en az iki hakem tarafından değerlendirildikten sonra yayınlanması uygun görülürse dergide basılır. Editör konunun özelliğine göre gerekli gördüğünde, yazıyı yayın kurulunda yer alan hakemler dışında hakemlere gönderebilir.

4. Yayın Kurulu yayın koşullarına uymayan yazıları yayınlamamak, düzeltmek veya kısaltmak üzere yazarlara geri göndermek, ayrıca yazıları biçim olarak düzenlemek yetkilerine sahiptir. Yazarlar; Türkçe ve İngilizce dili açısından, metinde anlam değişikliği yapmamak kaydı ile düzeltmelerin gereğinde editörlerce de yapılmasını kabul etmiş sayılır.

5. Derginin yayın dili Türkçe ve İngilizce'dir. Tüm Türkçe yazı içeriklerinde Türk Dil Kurumu "yazım kılavuzu" kurallarına sadık kalınması esastır (www.tdk.gov.tr). Sayılarda kesirler virgül ile ayrılır (örnek; 15,2 veya 5,26). Anatomik terimlerin Latinceleri kullanılmalıdır. Gündelik tıp diline yerleşmiş terimler ise okundukları gibi Türkçe yazım kurallarına göre yazılmalıdır. Yazar tarafından yabancı dildeki şekli ile yazılması istenen terimler tırnak içinde belirtilmelidir. Kısaltmalar yazı içinde ilk geçtiği yerde açıklandıktan sonra yazı içinde kısaltma şeklinde verilebilir. Kısaltmalar, özet ve/veya ana metin içerisinde ilk geçtiğinde ve açıklandığında kısaltma şeklinde verilebilir.

6. Yazılar Word dosyasına, standart A4 ebatında, 11 punto ile Times News Roman karakterinde, çift aralıklı olarak yazılmalı; sayfanın her iki tarafında 2,5 cm boşluk bırakılmalı, sayfalara başlık sayfasından başlayarak sırayla numara verilmelidir. Sayfa numarası her sayfanın alt kısmına yazılmalıdır. Tablo, grafik ve fotoğraflarla birlikte online makale sistemine yüklenmelidir.

7. Özet, tablolar ve kaynaklar hariç, araştırma makaleleri ve derlemeler 5000 kelimeyi, olgu bildirimleri 3500 ve editöre mektuplar 2000 kelimeyi geçmemelidir.

8. Derginin bir sayısında, ilk isim olarak bir yazarın ikiden fazla eseri basılamaz.

9. Deneysel, klinik ve ilaç araştırmaları için uluslararası anlaşmalara uygun etik kurul kararı alınmalıdır. Ayrıca birey veya velisinden izin alınmış olduğu belirtilmelidir. Araştırmalara yapılan kısmi de olsa nakdi ya da ayni yardımların hangi kurum, kuruluş veya ilaç-gereç firmalarınca yapıldığı dip not olarak belirtilmelidir. (Genişletilecek)

10. Deneysel ve klinik çalışmalar, ilaç araştırmaları ve bazı olgu sunumları için WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects ve Guide for the Care and Use of Laboratory Animals çerçevesinde hazırlanmış etik komisyon raporu gerekmektedir. Gerekli görülmesi halinde etik komisyon raporu veya eşdeğeri olan resmi bir yazı da yazarlardan talep edilebilir. Deneysel çalışmaların sonuçlarını bildiren yazılarda, çalışmanın yapıldığı kişilere uygulanan prosedürlerin niteliği tümüyle açıklandıktan sonra, onaylarının alındığına ilişkin bir açıklamaya metin içinde yer verilmelidir. Hayvanlar üzerinde yapılan çalışmalarda ağrı, acı ve rahatsızlık verilmemesi için yapılanlar açık bir şekilde belirtilmelidir. Hasta onamları, etik kurulun adı, onay belgesinin numarası ve tarihi tam metin dosyasında yer alan Yöntemler başlığı altına yazılmalıdır.

Etik Kurul Raporu veya Aydınlatılmış Onam Formu eklenmelidir.

11. Dergiye yayınlanmak üzere yazı gönderilirken editöre başvuru yazısında yazının daha önce başka yerde yayınlanmamış veya yayınlanmak üzere gönderilmemiş olduğu belirtilmelidir. Yayınlanması kabul edilen yazıların dergiye baskısı öncesinde dergi sekreterliğinden bir "Telif Hakkı Devri" (yazarların hakları korunarak hazırlanmış) formu tüm yazarlara imza için gönderilecektir.

YAZI BÖLÜMLERİ

A. Başlık Sayfası

- Yazının Türkçe ve İngilizce başlığı metne uygun ve kısa olmalıdır.

- Ayrıca 40 karakteri geçmeyen Türkçe bir kısa başlık yazılmalıdır.

- Tüm yazarların açık adı ve soyadları yazılmalı, akademik ünvanları ise dipnot halinde gerekirse yıldız koyularak belirtilmelidir.

- Çalışmanın yapıldığı kurum, klinik, enstitü veya kuruluşun adı ve adresi belirtilmelidir.

- Çalışma, daha önce bir kongre ya da sempozyumda bildiri olarak sunulmuş ise belirtilmelidir.

- Yazışma adresi: Yazışmaların yapılacağı kişinin adı ve soyadı, posta adresi, sabit ve mobil telefon ve elektronik posta adresi yazılmalıdır.

- Gerek duyuluyor ise teşekkür yazısı bu kısımda verilmelidir.

- Tüm yazarların ORCID ID bilgileri Başlık sayfasında bulunmalıdır.

B. Türkçe ve İngilizce Özet Sayfası

Özgün araştırma, olgu sunumu ve derleme yazılarında 300 kelimeyi geçmeyen Türkçe ve İngilizce özet yazılmalıdır. Türkçe ve İngilizce başlık 150 karakteri geçmemelidir. İngilizce başlık ve özet, Türkçe başlık ve özetle eş anlamlı olmalıdır. Özet, çalışma ve araştırmanın amacını ve kullanılan yöntemleri kısaca belirtmeli, ana bulgular varılan sonucu destekleyecek ölçüde ayrıntılarla belirtilmelidir. Özgün araştırmaların Türkçe özetinde giriş, gereç ve yöntem, bulgular, sonuç, İngilizce özetlerde ise "Introduction, materials and methods, results, conclusions" alt başlıklarını içermelidir. Olgu sunumlarında ise; giriş, olgu sunumu, tartışma alt başlıklarını içermelidir.

Olgu sunumlarının İngilizce özetinde ise;Introduction, case report, conclusions" alt başlıklarını içermelidir. Derleme yazılarında özet konunun içeriğini açıklayacak şekilde olmalıdır.

Anahtar kelimeler: Türkçe ve İngilizce özetin altında "Medical Subject Headings" e (MeSH) uygun olarak en fazla beş adet olmalıdır. MeSH içeriğinde yeni terimler yoksa var olan terimler kullanılabilir.

C. Ana Metin

Özgün araştırmalarda giriş, gereç ve yöntem(ler), bulgular, tartışma, kaynaklar; olgu sunumlarında giriş, olgu (ların) sunumu, tartışma, kaynaklar bölümleri yer almalıdır. Derlemelerde konuya uygun alt başlıklar ve kaynaklar yer almalıdır.

Araştırma Makaleleri

1- Giriş: Makalenin amacı, çalışma veya gözlemin gerekçesi belirtilmeli, çalışmanın verilerine veya varılan sonuçlarına burada yer verilmemelidir.

2- Gereç ve Yöntem: Deneysel ve klinik araştırmalar için etik kurul kararı varlığı belirtilmelidir. Yerleşmiş yöntemler için kaynak gösterilmeli, yeni yöntemler için kısa açıklama verilmelidir.

İstatistiksel Analiz: Yöntem bölümünün son paragrafında, kullanılan istatistiksel analizler ayrıntılı olarak belirtilmelidir.

3- Bulgular: Elde edilen bulgular açık bir şekilde metinde verilmeli ve gereğinde kullanılan istatistiksel yöntemler belirtilmelidir. Metin içinde tablonun tamamının aynen tekrarı yazılmamalıdır. Tablo veya şekiller (çizim,

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YAZARLARA BİLGİ

grafik ve fotoğraflar), başlık ve dipnotları ile birlikte her biri ayrı bir sayfaya yazılmalıdır. Metin içinde geçtikleri sıraya göre numaralanmalıdır. Standart olmayan kısaltmalar dipnotlarla açıklanmalıdır. Bir başka yazarın daha önceki yayınından aynen alındı ise kaynak belirtilmeli ve yazılı baskı izni birlikte yollanmalıdır.

4- Tartışma: Elde edilen bulgular daha önceki mevcut literatür bilgileri, çalışma sonuçları veya orijinal hipotezler ile ilgisi vurgulanarak karşılaştırılmalı ve yorumları yapılmalıdır.

5- Çalışmanın kısıtlılıkları: Bu bölümde çalışma sürecinde yapılamayanlar ile sınırları ifade edilmeli ve gelecek çalışmalara ilişkin öneriler sunulmalıdır.

6- Sonuç: Çalışmadan elde edilen sonuç vurgulanmalıdır.

D. Kaynaklar

Yararlanılan kaynaklar yazıdaki geçiş sırasına göre parantez içerisinde verilmeli, kaynaklar yazının alındığı dilde aşağıdaki gibi düzenlenmelidir. Kullanılacak kısaltmalar Index Medicus'a ve Science Citation Index'e uygun olmalıdır.

Periyodik Yayınlar

Periyodiklerin kısaltmaları Index Medicus'un her yılın Ocak sayısına göre yapılır. Yazar sayısı altı ve daha az olan makalelerde tüm yazarlar yazılır. Yazar sayısı yedi ve fazla ise ilk altısı yazılır ve et al. ilave edilir. Yazar isimlerinden sonra, o yazının tam başlığı, dergi ismi (kısaltma kurallarına uygun olarak), yıl, cilt ve sayfalar sıralanır.

Örnek 1: Meszaros A, Orosz M, Mesko A, Vincze Z. Evaluation of asthma knowledge and quality of life in Hungarian asthmatics. Allergy 2003;58:624-8.

Örnek 2: Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy 2009;64(2):183-93.

Kitaplar

Kitap bölümü: Kaynaklar şu sırayı takip etmelidir: İlk üç yazarın ismi, bölüm başlığı, editörler, kitap başlığı, varsa cilt ve baskı sayısı, şehir, yayınevi, yıl ve ilgili sayfalar.

Örnek: Jane JA, Persing JA. Neurosurgical treatment of craniosynostosis. In: Cohen MM, Kim D (eds). Craniosynostosis: Diagnosis and Management. 2nd edition. New York: Raven Press; 1986. p.249-95.

Örnek: Norman IJ, Redfern SJ, (eds). Mental Health Care for Elderly People. 3rd edition. New York: Churchill Livingstone; 1996.

Tek yazarlı kitap için özgün sayfa numarası kullanılır.

Örnek: Cohn PF: Silent Myocardial Ischemia and Infarction. 3rd ed. New York: Marcel Dekker; 1993. p.33.

Kongre bildirileri; aşağıdaki örnekte olduğu gibi verilmelidir:

Ildırım İ, Köksal N, Canıtez Y: Yenidoğan döneminde Salmonella typhimurium enfeksiyonu. XXXV. Milli Pediatri Kongresi, 12-15 Kasım 1991, Adana, Bildiri Özet Kitabı, s.38, 1991.

Tez: Kanpolat Y. Trigeminal Gangliona Deneysel Perkütan Giriş ve Radyofrekans Termik Lezyonun Histopatolojik Değerlendirilmesi (Doçentlik Tezi). Ankara: Ankara Üniversitesi; 1978.

Yayınlanmamış gözlemler ve kişisel görüşmeler kaynak olarak kullanılmaz. Yayına kabul edilmiş ancak henüz yayınlanmamış yazılara kaynaklarda "baskıda" sözcüğü belirtilerek yer verilebilir. Diğer çeşitli kaynak yazımları konusundaki geniş bilgi "International Commitee of Medical Journal Editors" web sitesinden edinilebilir (www. icmje.org).

E. Tablolar, Şekiller ve Fotoğraflar

Tablolar metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalıdır. Tablo, şekil ve grafikler tasarım ve çizim olarak anlaşılır olmalı, fotoğraflar uygun baskı kalitesi için yeterli olmalıdır. Tablo içinde geçen kısaltmalar, tablo altında dipnot olarak açıklanmalıdır.

EK KURALLAR

1- **Derlemeler:** En son yenilikleri kapsayacak şekilde ve/veya literatür bilgilerine dayalı olarak yazılmalıdır. Türkçe ve İngilizce özet 300 kelimeyi geçmemeli, İngilizce başlık ve özet, Türkçe başlık ve özetle eş anlamlı olmalıdır.

2- Olgu Sunumları: Özellikli ve eğitici olmalıdır. Türkçe ve İngilizce özet 300 kelimeyi geçmemeli, İngilizce başlık ve özet, Türkçe başlık ve özetle eş anlamlı olmalıdır.

Yazı metni; giriş, olgu (ların) sunumu, tartışma alt başlıklarını içermelidir.

3- Editöre Mektuplar: Yayınlanan bir yazının önemini, gözden kaçan bir yönünü ya da eksikliğini tartışır. Başlık ve bölümleri yoktur, 5'ten fazla kaynak gösterilmez. Sonunda yazarın adı ve tam adresi bulunur. Mektuplara cevap değerlendirmesini orijinal yazının yazarları ve/veya doğrudan editör kararlaştırır.

4- Tüm yazarların iletişim bilgileri ve ORCID numaraları eksiksiz olarak başlık sayfasında yer almalıdır.

5- Tüm yollanan çalışmalar intihal programı tarafından tarandıktan sonra hakemlere yollanmaktadır.

6- TR dizin 2020 yılı kurallarına göre, çalışmalardan Etik Kurul İzin Formu istenmektedir.

7- Etik Kurul izni gerektiren araştırmalar aşağıdaki gibidir.

Anket, mülakat, odak grup çalışması, gözlem, deney, görüşme teknikleri kullanılarak katılımcılardan veri toplanmasını gerektiren nitel ya da nicel yaklaşımlarla yürütülen her türlü araştırmalar:

İnsan ve hayvanların (materyal/veriler dahil) deneysel ya da diğer bilimsel amaçlarla kullanılması,

İnsanlar üzerinde yapılan klinik araştırmalar,

Hayvanlar üzerinde yapılan araştırmalar,

Kişisel verilerin korunması kanunu gereğince retrospektif çalışmalar,

Ayrıca;

Olgu sunumlarında "Aydınlatılmış Onam Formu"nun alındığının belirtilmesi,

Başkalarına ait ölçek, anket, fotoğrafların kullanımı için sahiplerinden izin alınması ve belirtilmesi,

Kullanılan fikir ve sanat eserleri için telif hakları düzenlemelerine uyulduğunun belirtilmesi.

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INSTRUCTIONS TO AUTHORS

GENERAL RULES

1- For the articles to be accepted for publication in the journal, the article should be original, scientific, and at a high academic level.

2- The contents of all published articles indicate that the views of the authors. Editors, editorial board members or publishers are not responsible. No copyright is paid to the articles submitted to the journal.

3- All articles submitted for publication must be prepared meticulously, complying with our journal's spelling rules. Manuscripts submitted for publication are published in the journal if considered appropriate after evaluation by at least two reviewers. When the editor considers it necessary according to the sort of the subject, can send the article to the reviewers other than the reviewers in the editorial board.

4- The Editorial Board has the authority not to publish the articles that do not comply with the publication provisions, convey them to the authors for revision or editing, and edit the articles in construction. The authors are considered to have accepted that the revisions are executed by the editors if required, provided that they do not change the meaning of the text in terms of Turkish and English language.

5- The publication languages of the journal are both Turkish and English. It is essential to adhere to the Turkish Language Association "spelling guide" rules in all Turkish writing content (www.tdk.gov.tr). Fractions in numbers are ordered by commas (e.g. 15.2 or 5.26). Anatomical terms should be used in the Latin language. Terms that are settled in the standard medical language should be written according to the Turkish spelling rules as they are spelt. Terms that are requested by the author to be written as in a foreign language should be specified in quotation marks. Abbreviations can be presented as abbreviations after they are first explained in the text.

6- Manuscripts should be written in a Word file, in a standard A4 size, 11 font size, Times News Roman, double-spaced; There should be a space of 2.5 cm on both sides of the page, and the pages should be numbered in order, starting from the title page. The number of the page should be written at the bottom of each page. The file should be sent by e-mail, along with tables, graphics and images.

7- Except for abstracts, tables and references, original articles and reviews should not exceed 5000 words, case reports should not exceed 3500 and letters to the editor should not exceed 2000 words.

8- In an issue of the journal, more than two works of an author cannot be published as the first name.

9- Ethics committee decisions should be taken for experimental, clinical, and drug research according to international agreements. In addition, it should be stated that permission has been obtained from the individuals or their parents. It should be stated as a footnote by which institutions, organizations or pharmaceutical equipment companies, albeit partial, in cash or in-kind aids to research.

10- If the study includes human experimentation, the authors should state in the manuscript that it complies with the ethical standards (institutional and national) for human experimentation and the 1964 Helsinki Declaration, which was revised in 2013, and the consent of the patients was obtained. In experimental animal research, the authors should declare that the practices (procedures) comply with animal rights (Guide for the care and use of laboratory animals; www.nap.edu/catalog/5140.html), ethics committee approval should be obtained.

Ethics Committee Form or Informed Consent Form should be attached.

11- When sending an article to the journal for publication, it should be stated in the application letter to the editor that the article has not been published or sent for publication elsewhere before. Before the articles accepted for publication are published in the journal, a Copyright Transfer Form (preserving the authors' rights) will be sent to all authors for signature from the journal secretariat.

MANUSCRİPT ORGANİZATİON

A. Title Page

- The Turkish and English titles of the article should be appropriate and brief.

- In addition, a short Turkish title that is not exceeding 40 characters should be written.

- All authors' full names and surnames should be noted, and their academic titles should be indicated in footnotes, with an asterisk if required.

- The name and address of the clinic, institute or institution where the scientific research was done should be defined.

- It should be stated if the study has been presented as a paper in a congress or symposium before.

- All authors' ORCID ID information must be available on the Title page.

B. Turkish and English Abstract Page

Turkish and English abstracts not exceeding 300 words should be written in original research, case reports and reviews. Turkish and English titles should not exceed 150 characters. The English title and abstract must be synonymous with the Turkish title and abstract. The abstract should briefly state the purpose of the study and research and the methods used, and the main findings should be stated in detail to support the result obtained. The Turkish summary of the original research should include the subheadings of "giriş, gereç ve yöntem, bulgular, sonuç" and "Introduction, materials and methods, results, conclusions" in English abstracts. Case reports should include an "giriş, olgu sunumu, tartışma sub-titles."

The English summary of the case reports should include the subtitles "Introduction, case report, conclusions". In Reviews, the abstract should be explanatory about the content of the subject.

Keywords: There should be a maximum of five in accordance with the "Medical Subject Headings" (MeSH) under the Turkish and English abstract. If there are no new terms in the MeSH content, existing terms can be accepted.

C. Main Text

Original studies should include an introduction, material and method(s), findings, discussion, and references. In case reports, introduction, case(s) presentation, discussion, references sections should be involved.

Compilations should include appropriate subtitles and resources.

Original Research

1- Introduction: The purpose of the article, the aim of the study or observation should be stated, the data or conclusions of the study should not be stated in this section.

2- Materials and Methods: For experimental and clinical research, the ethics committee decision should be indicated. References should be presented for established methods, and a short explanation should be provided for new methods.

Statistical Analysis: In the last paragraph of the Method section, the statistical analysis should be detailed.

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INSTRUCTIONS TO AUTHORS

3- Result: The findings should be stated clearly in the text, and the statistical methods used should be stated if necessary. The full repetition of the table should not be written in the text. Tables or figures (drawings, graphics and images) should be represented on a separate page with headings and footnotes. They should be numbered according to the order in which they appear in the text. Non-standard abbreviations should be explained with footnotes. If taken precisely from a previously published publication of another author, the source should be indicated and sent with written permission to print.

4- Discussion: Obtained findings should be compared and interpreted by emphasizing their relevance with previous literature, study results or original hypotheses.

5- Study of Limitations: In this section, what could not be done during the study process and the study's limits should be stated, and suggestions for future studies should be presented.

6- Conclusion: The results achieved from the study should be emphasized.

D. References

The references used should be given in parentheses according to the order in the article, and the references should be arranged in the language of the article as follows. The abbreviations to be used should be in accordance with the Index Medicus and the Science Citation Index.

Periodical Publications

Periodic abbreviations are made according to the January issue of Index Medicus of each year. In articles with six or fewer authors, all authors are listed. If the number of authors is seven or more, the first six are written, and et al. is added. After the authors' names, the full title of the article, the journal name (according to the abbreviation rules), year, volume and pages are listed.

Example 1: Meszaros A, Orosz M, Mesko A, Vincze Z. Evaluation of asthma knowledge and quality of life in Hungarian asthmatics. Allergy 2003;58:624-8.

Example 2: Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy 2009;64(2):183-93.

Books

Book Sections: References should follow the following order: Names of the first three authors, chapter title, editors, book title, volume and edition number, city, publisher, year and relevant pages.

Example: Jane JA, Persing JA. Neurosurgical treatment of craniosynostosis. In: Cohen MM, Kim D (eds). Craniosynostosis: Diagnosis and Management. 2nd edition. New York: Raven Press; 1986. p.249-95.

Example: Norman IJ, Redfern SJ, (eds). Mental Health Care for Elderly People. 3rd edition. New York: Churchill Livingstone; 1996.

For a single-authored book, the original page number is used.

Example: Cohn PF: Silent Myocardial Ischemia and Infarction. 3rd ed. New York: Marcel Dekker; 1993. p.33.

Congress papers; It should be given as in the example below:

Ildırım İ, Köksal N, Canıtez Y: Yenidoğan döneminde Salmonella typhimurium enfeksiyonu. XXXV. Milli Pediatri Kongresi, 12-15 Kasım 1991, Adana, Bildiri Özet Kitabı, s.38, 1991.

Thesis: Kanpolat Y. Trigeminal Gangliona Deneysel Perkütan Giriş ve Radyofrekans Termik Lezyonun Histopatolojik Değerlendirilmesi (Doçentlik Tezi). Ankara: Ankara Üniversitesi; 1978. Unpublished observations and personal interviews are not used as sources. Articles accepted for publication but not yet published can be included in the references by specifying the word "in the press". Extensive information on various other manuscripts can be obtained from the "International Committee of Medical Journal Editors" website (www.icmje.org).

E-Tables, Figures and Photos

Tables should be prepared with the aim of making the text descriptive and clear.

Tables, figures and graphics should be evident as design and drawing, photographs should be sufficient for appropriate print quality. The abbreviations used must be explained below as footnotes.

ADDITIONAL TERMS

1- Reviews: It should be written to cover the latest innovations and/ or based on literature information. The Turkish and English titles and abstracts should not exceed 300 words. The English title and abstract must be synonymous.

2- Case Reports: They should be specific and educational. The Turkish and English abstract should not exceed 300 words. The English title and abstract must be synonymous with the Turkish title and abstract. The text should include introduction, case(s) presentation, discussion subheadings.

3- Letter to the Editor: Discusses the significance, matters not provided or deficiency of a published article. There are no titles and chapters, and more than five sources are not shown. At the end are the author's name and complete address. The authors of the original article and/ or the editor decide the evaluation of the response to the letters.

4- All authors' contact information and ORCID numbers should be included on the title page.

5- All submitted works are sent to the reviewers after being checked by the plagiarism checker.

6- According to the TR index 2020 rules, an Ethics Committee Permission Form is requested from the studies.

7- Studies that require the approval of the Ethics Committee are as follows.

All kinds of research are conducted with qualitative or quantitative approaches that require data collection from the participants using survey, interview, focus group work, observation, experiment, and interview techniques.

Use of humans and animals (including material/data) for experimental or other scientific purposes,

Clinical studies on humans,

research on animals,

Retrospective studies by the personal data protection law,

Also;

Indicating that an "informed consent form" has been received in case reports,

Obtaining and specifying permission from the owners for the use of scales, questionnaires, images belonging to others,

Indication of compliance with copyright regulations for the intellectual and artistic works used.

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HAKEM DEĞERLENDİRMESİ VE ETİK

Hakem Değerlendirmesi

Derginin Yayın ilkeleri "Council of Science Editors (Bilim Editörleri Konseyi)" ve "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" (http://www.icmje.org/) tarafından önerilen kurallara göre yürütülür.

Güncel Pediatri Dergisi çift-kör hakemlik ilkeleri çerçevesinde yayın yapan süreli yayın bir organıdır. Hakemler, yazının konusuyla ilgili uluslararası literatürde yayınları ve atıfları olan bağımsız uzmanlar arasından seçilmektedir. Makale baş editöre ulaşınca değerlendirilir ve bölüm editörüne gönderilir. Bölüm editörü makaleyi 2 hakeme gönderir. Hakemler 21 gün içinde kararlarını belirtmelidirler. Yardımcı editör hakem kararlarına kendi değerlendirme ve önerisini ekleyerek baş editöre gönderir. Hakemlerin kararları çatışıyorsa dergi editörü yeni hakem atayabilir. Dergide yayınlanacak yazıları değerlendiren hakemler dergide belirtilen bilimsel kurul ve gerekirse yurt içi/dışı konu ile ilgili uzmanlar arasından seçilir. Tüm yazılar, baş editör, editörler ve hakemler tarafından incelenir.

Gönderilen yazılar, iThenticate tarafından intihal, tekrarlanan yayın olup olmadığı taramasına tabi tutulur. Yazarlar tam çalışma sonuçlarını veya bir kısmının özeti şeklinde teslim etmek zorundadırlar.

Kabul edilen makalelerin yazarları, editör ve yardımcı editörlerin metinde temel anlam değişikliği yapmadan, yazım kurallarına değişiklik yapmamak kaydı ile düzeltmeler yapabileceğini kabul etmelidir.

Format Biyomedikal Dergilere Gönderilen makaleler "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" (http://www.icmje.org/) yazma ve düzenleme kurallarına uygun olmalıdır.

Etik

Dergiye yayınlanmak amacıyla gönderilen ve etik kurul onayı alınması zorunluluğu olan deneysel, klinik ve ilaç araştırmaları için uluslararası anlaşmalara ve 2008'de 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.

Yazarlar, kurum, finansal veya maddi destek bildirim, yardım arasında çıkar çatışması beyanı yazması zorunludur ve beyan yazının sonunda görünmelidir. Hakemler olası çıkar çatışmasını, hakem, yazarlar ve kurumların arasında olup olmadığını raporla bildirilmek zorundadır.

Toplanan hiçbir veri üçüncü parti şahıslarla veya organizasyonlarla paylaşılmayacaktır. Yazarların kişisel bilgileri (sorumlu yazar hariç; bilgiler makalenin ilk sayfasında belirtilecektir) korunacaktır. Hastaların kişisel bilgileri açıklanmayacaktır.

İntihal: Başka bir yazarın yayınının içeriğini tamamen veya kısmen, bir referans vermeden, kendi yayını gibi yeniden yayımlamak.

Fabrikasyon: Mevcut olmayan veri ve bulguları/sonuçları yayımlamak.

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Salamisation/Yanıltma: Doğal olmayan yollarla yapılmış bir çalışmanın sonuçlarını bölerek birden fazla yayın oluşturmak.

İntihal kontrolü için makale yayınlanmadan önce Crossref Smilarity Check powered by "iThenticate" kullanılmaktadır. İntihal, uydurma, teksir ve yanıltma gibi etik olmayan uygulamalar ve makale inceleme sürecini etkileme çabası ile hediye yazarlık katkıları gibi uygunsuz teşekkür bildirim ve kaynak gösterimler onaylanmamaktadır. Şüphe durumunda yazarlardan ek açıklamalar istenecektir. Tüm eylemler COPE Flowchart'lara göre yapılacaktır.

Ayrıca, yazarlar çalışmaya katkıda bulunanların gizlilik haklarına saygı duymalıdır. Diğer taraftan, kongre kitaplarında yayınlanan ve 400 kelimeyi aşmayan kısa özetler ve elektronik ortamda önceden yayınlanmış ön araştırma ve mevcut veriler işlem için kabul edilmez. Bu durumda yazarların, makalenin ilk sayfası ve kapak mektubunda bu durumu bildirmeleri gerekir (COPE: http://publicationethics.org)

İntihal Tespiti

İntihal tıbbi yazıyı etkileyen en yaygın etik sorundur. Güncel Pediatri Dergisi hiçbir şekilde intihale izin vermemektedir. Dergi politikamıza uygun olarak, gönderilen makaleler en az iki kez (değerlendirme sürecinde ve kabul sonrasında) çakışan ve benzeri metin (iThenticate) durumlarını tespit etmek için intihal yazılımı ile taranmaktadır.

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PEER REVİEW AND ETHICS

Peer-review

Editorial policies of the journal are conducted according to the rules advised by the Council of Science Editors and reflected in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/).

The Journal of Current Pediatrics is a periodical that publishes within the framework of double-blind peer-review principles. Reviewers are selected from among independent experts who have publications and citations in the international literature on the relevant field of the article. When the editor-in-chief receives the article, it is evaluated and sent to the section editor. The section editor sends the article to 2 reviewers. Reviewers must state their decision within 21 days. The assistant editor adds his comment and suggestion to the reviewer's decisions and sends them to the editor-in-chief. And the reviewer makes the final decision. If the reviewers' decisions conflict, the journal editor may assign a new reviewer. The reviewers who evaluate the articles published in the journal are selected from the scientific committee specified in the journal and, if necessary, among the national or international experts related to the subject. All manuscripts are reviewed by the editor, associate editors and internal and external reviewers.

Submitted manuscripts are also subjected to evaluate plagiarism, duplicate publication by Crossref Similarity Check powered by iThenticate. Authors are obliged to acknowledge if they published study results in whole or in part in the form of abstracts.

The authors of the accepted manuscripts should consent that the editor and associate editors could make corrections without changing the paper's main text. The manuscript format should be by Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/).

Ethics

For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (Helsinki Declaration revised 2008 (www.wma.net/e/policy/b3.html) are required. In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights (Guide for the care and use of laboratory animals, www.nap.edu.catalog/5140.html), and they should obtain animal ethics committee approval.

The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

The collected data will not be shared with third parties or organizations. The authors' personal information (excluding the responsible author; information will be stated on the first page of the article) will be protected. Personal information of patients will not be exposed.

Plagiarism: To re-publish whole or in part the contents of another author's publication as one's own without providing a reference. Fabrication: To publish data and findings/results that do not exist.

Fabrication: Publish data and findings/results that are not available.

Duplication: Use of data from another publication, which includes re-publishing a manuscript in different languages.

Salamisation: To create more than one publication by dividing the results of a study preternaturally. We disapprove of such unethical practices as plagiarism, fabrication, duplication, and salamisation and efforts to influence the review process with such practices as gifting authorship, inappropriate acknowledgements, and references.

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Additionally, authors must respect participants right to privacy. On the other hand, short abstracts published in congress books that do not exceed 400 words and present preliminary research data and those presented in an electronic environment are not accepted pre-published work. Authors in such a situation must declare this status on the first page of the manuscript and the cover letter. (The COPE flowchart is available at: http://publicationethics.org)

Plagiarism Detection

Plagiarism is a severe problem and the most common ethical issue afflicting medical writing. The Journal of Current Pediatrics does not allow any form of plagiarism. Under our journal policy, submitted manuscripts are screened with plagiarism software to detect instances of overlapping and similar text (iThenticate) at least two times (during the evaluation process and after acceptance).

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İçindekiler / *Contents*

Özgün Araştırmalar / Original Articles

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İçindekiler / *Contents*

Olgu Sunumları / Case Reports

ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Çocukluk Çağı Akut Lenfoblastik Lösemi Hastalarında Tedavi Sırasında Gelişen Akut Endokrin ve Metabolik Komplikasyonların Retrospektif Değerlendirilmesi

Acute Endocrine and Metabolic Complications During Treatment in Childhood Acute Lymphoblastic Leukemia Patients: Retrospective Study

Melike Sezgin Evim* (0000-0002-4792-269X), Zeynep Tobcu (0000-0003-1714-6017), Salih Güler* (0000-0002-2398-0959), Yasemin Denkboy Öngen*** (0000-0002-5657-4260), Adalet Meral Güneş* (0000-0002-0686-7129)**

*Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Hematoloji Bilim Dalı, Bursa, Türkiye

**Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Bursa, Türkiye

***Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Endokrinoloji Bilim Dalı, Bursa, Türkiye

Öz

Giriş: Akut lösemiler, çocukluk çağının en sık görülen malignitesi olup, akut lenfoblastik lösemi (ALL) en sık alt tipidir. Bu çalışmada yeni tanı almış ALL hastalarının tedavileri sırasında gelişen akut endokrin ve metabolik komplikasyonların sıklığı ve risk faktörlerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Uludağ Üniversitesi Tıp Fakültesi Çocuk Hematoloji Bilim Dalı'nda Ocak 2007-Aralık 2017 tarihleri arasında, yaşı 1 ile 18 yıl arası olan, yeni ALL tanısı almış 293 hastada gelişen akut endokrin ve metabolik komplikasyonlar incelendi. Hastaların yaşları, cinsiyetleri, risk grupları, lösemi alt tipleri ve endokrin komplikasyonların geliştiği dönemdeki kemoterapi fazları not edildi.

Bulgular: Toplamda 250 hasta B-ALL, 43 hasta T-ALL tanısı ile izlendi ve çalışmaya alınan hastaların %64'ü (n=188) erkek ve %36'sı kadındır. Hastaların %36,4'ü yüksek riskli olup 10 hasta risk grubu belirlenemeden kaybedildi. İki yıl süren tedavi boyunca en az bir endokrin komplikasyon gelişen hastaların oranını %83 olarak saptadık. Tanı anında 10 yaşından büyük olan hastalarda hiperglisemi, osteoporoz ve avasküler nekroz daha fazla gözlendi. Cinsiyetler arasında fark sadece D vitamininde saptandı ve kızlarda daha düşüktü. Regresyon analizinde sadece hastaların yüksek riskli olması endokrin komplikasyon gelişmesi açısından anlamlı bulundu.

Sonuç: Günümüzde kullanılan kemoterapötikler, sağkalımı süresini uzatmış olsa da komplikasyon görülme sıklığında artışa sebep olmuştur. Risk faktörlerini önceden belirleyerek bu komplikasyonların azaltılabileceğini düşünmekteyiz.

Anahtar kelimeler
Pediatrik ALL, endokrin komplikasyon, kemoterapi

Keywords
Pediatric ALL, endocrine complication, chemotherapy

Abstract

Introduction: Acute leukemias are the most common malignancy of childhood, and acute lymphoblastic leukemia (ALL) is the most common subtype. In this study; we aimed to asses to acute endocrine and metabolic complications which occurs during treatment. Newly diagnosed ALL patients were included in the study.

Materials and Methods: The endocrine and metabolic complication of 293 patients aged 1-18 years old who were newly diagnosed ALL between January 2007 and December 2017 in Uludağ University Faculty, Department of Pediatric Hematology were analyzed. Patients' age, gender, risk groups, leukemia subtypes, and chemotherapy phases at the time of endocrine complications were noted.

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Yazışma Adresi/Address for Correspondence: Dr. Melike Sezgin Evim, Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Hematoloji Bilim Dalı, Bursa, Türkiye
Tel.: +90 224 295 06 04
E-posta: melikevim@yahoo.com

Results: In total, 250 patients were follow-up with B-ALL and 43 patients with T-ALL. 64% (n=188) of patients were male and 36% (n=105) were female. In our study, 36.4% of patients were in the high risk group but ten of the patients died before the risk group could be determined. During the two-year treatment, We found that 83% of the patients developed at least one endocrine complication. Hyperglycemia, osteoporosis and avascular necrosis were observed more frequently in patients older than 10 years at the time of diagnosis. The difference between the sexes was found only in vitamin D and was lower in girls. In regression analysis, only to be high risk group were found to be effective for the development of endocrine complications.
Conclusion: Although the chemotherapeutics used today have prolonged the survival time, they have caused an increase in the incidence of complications. We think that these complications can be reduced by determining the risk factors in advance.

Giriş

Akut lösemiler, çocukluk çağı malignitelerinin yaklaşık %30'unu oluşturur ve çocuklarda en sık görülen malignitedir (1). Akut lösemiler arasında da akut lenfoblastik lösemi (ALL), yaklaşık %70-80 oranla çocuklarda en sık görülen lösemi alt tipidir (2,3). Çocuk çağı lösemilerinin etiyolojisi kesin olarak bilinmemekle birlikte kalıtsal ve çevresel faktörlerin rol aldığı düşünülmektedir (4-6). ALL tanısı; fizik muayene, tam kan sayımı, periferik yayma incelenmesi, kemik iliği ve beyin omurilik sıvısının sitolojik olarak incelenmesi ile konulmaktadır (7).

Bugün çoklu kemoterapi protokolleriyle hastaların %80'inden fazlasında kür sağlanabilmektedir (8,9). ALL'li hastalarda günümüzde izlenen sağkalım oranlarındaki bu artış, tedavi ile ilişkili mortalite ve morbidite risklerini de beraberinde getirmiştir (10). Hastalığın kendisine veya tedaviye bağlı, erken veya geç dönem komplikasyonlar gözlenebilmektedir. Enfeksiyonlar, karaciğer ve böbrek fonksiyonlarında bozulma, pıhtılaşma bozuklukları, kanama, hiperkalsemi, tümör lizis sendromu, tiflit, hipertansiyon, pankreatit, endokrinolojik ve metabolik sorunlar, nöropati, avasküler nekroz, alerjik reaksiyonlar, mukozit önde gelen erken dönem yan etkiler arasındadır (11). Kardiyomiyopati, lökoensefalopati, infertilite, böbrek fonksiyon bozuklukları, işitme kaybı, obezite ise diğer bazı geç dönem komplikasyonlardandır (12).

Literatürde çok sayıda çocukluk çağı lösemisinin geç dönem tedavi komplikasyonlarını inceleyen çalışma vardır (13,14). Akut dönem tedavi komplikasyonlarını inceleyen çalışmalar belli komplikasyonlar için tek tek çalışılmış olup bütüncül bakışla yapılan çalışmalar oldukça azdır. Çalışmamızda tedavi sırasında gelişen akut endokrin ve metabolik komplikasyonları bütünüyle değerlendirmeyi amaçladık.

Gereç ve Yöntem

Uludağ Üniversitesi Tıp Fakültesi Hastanesi, Çocuk Hematoloji Bilim Dalı'nda Ocak 2007- Aralık 2017 tarihleri arasında yeni ALL tanısı alan 293 hastanın tıbbi verileri geriye dönük incelendi. Down sendromu olan, infant lösemi tanısı olan hastalar, tedavisi devam ederken refrakter ALL tanısı alan hastalar çalışma dışı bırakıldı. Tedavi sırasında nüks gelişen hastaların nüksün geliştiği tarihten itibaren, kemikiliği nakli (KİT) olan hastaların ise KİT'in yapıldığı tarihten itibaren gelişen komplikasyonları, tedavi protokollerinin değişmiş olması nedeniyle çalışmaya alınmadı. Tanı anında tümör lizis nedenli gelişen metabolik komplikasyonlar çalışma dışı bırakıldı. ALL tanısı almadan önce endokrinolojik bir hastalık tanısı alan olgular, ilgili parametre için çalışma dışı bırakıldı. ALL tedavisi iki yılı bulan, indüksiyon (Protokol I-A), erken intensifikasyon (Protokol I-B), konsolidasyon (Protokol-M ya da yüksek risk blokları), reindüksiyon (Protokol II) ve idame fazı olmak üzere beş fazdan oluşur. Üniversitemizde BFM bazlı kemoterapi protokolleri (ALL-BFM 2002, ALLIC-BFM 2009) kullanılmakta olup, risk gruplaması ve kemoterapi standarttır (8,9). Standart risk ve orta risk protokolleri arasındaki fark; indüksiyonda standart riske 2 doz daunorubicine verilirken, orta riske 4 doz daunorubicine verilmesi ve Protokol M'de B-ALL'de metotreksatın 5 gr ya da 2 gr randomize edilmesi olup, biz standart risk grubundaki hastalarımızda bu randomizasyonlar yapılmadı, her iki gruba da aynı tedavi protokolü uygulandı.

Gelişen endokrin yan etkilerden hiperglisemi ve hipoglisemi, Common Term Criteria for Adverse Events (CTCAE) versiyon 4'e göre; hipokalsemi, hiperkalsemi ve total kolesterol, CTCAE versiyon 5'e göre sınıflandırılmış ve sadece evre 3 ve evre 4 komplikasyonlar çalışmaya alındı (15) (Tablo 1). D vitamini için belirlediği değerler referans alınmış,

Tablo 1. Kan şekeri, kan kalsiyumu ve total kolesterol değerlerinin CTCAE'ye göre evrelemesi (15)		
	Evre 3	Evre 4
Hipoglisemi	40-30 mg/dL	<30 mg/dL
Hiperglisemi	250-500 mg/dL	>500 mg/dL
Hipokalsemi	7,0-6,0 mg/dL	<6,0 mg/dL
Hiperkalsemi	12,5-13,5 mg/dL	>12,5 mg/dL
Total kolesterol	400-500 mg/dL	>500 mg/dL

25-OH-D vitamini düzeyi <20 ng/mL olanlara düşük, >20 ng/mL olan değerler normal olarak kabul edildi (16). Hiperparatiroidi için Uludağ Üniversitesi Tıp Fakültesi Biyokimya Anabilim Dalının sınırı olan 65 pg/mL'nin üstündeki değerler yüksek olarak kabul edildi. Kemik mineral dansitesi ölçümünde dual energy X-ray absorbsiyometri (DEXA) yöntemi ile bakılan Z skoru ≤-2 ise osteoporoz var olarak değerlendirildi. Avasküler nekroz tanısı klinik bulgular ve radyolojik değerlendirmelerde uyumlu bulgu saptanması ile kondu. Tiroid fonksiyon testlerinden yaşa göre sT4 normal, TSH yüksek olan hastalar subklinik hipotiroidi; sT4 düşüklüğü ve TSH yüksekliği olan hastalar primer hipotiroidi; sT4 düşüklüğü ile beraber TSH düşüklüğü de olan hastalar sekonder ya da tersiyer hipotiroidi kabul edildi. Trigliserid için 2021 Türkiye Endokrin ve Metabolizma Derneğinin Kılavuzundaki referans değerler kullanıldı. Buna göre <150 mg/dL normal, 150-499 mg/dL hafif y üksek, 500-1000 mg/dL arası orta yüksek, >1000 mg/dL şiddetli yüksek olarak sınıflandırıldı (17). Olcay Neyzi persentil cetvellerine göre en az bir kez >97 p üzerinde kilosunun olması obezite varlığı olarak kabul edildi (18).

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İstatistiksel Analiz

SPSS versiyon 23.0 kullanılarak yapıldı. Ölçümsel değişkenlerin normal dağılıma uygunluğu görsel (histogram) ve analitik yöntemlerle (Kolmogorov-Smirnov/Shapiro-Wilk testleri) incelendi. Kategorik değişkenlerin karşılaştırılmasında ki-kare veya Fisher testi kullanıldı. Çoklu karşılaştırmalarda anlamlılığın hangi iki alt grup arasından kaynaklandığını tespit etmek için Bonferroni düzeltmesi uygulanarak ikili karşılaştırmalar yapıldı. Çok değişkenli analizde, önceki analizlerde belirlenen olası faktörler kullanılarak erken komplikasyon gelişimini öngörmedeki bağımsız prediktörler lojistik regresyon analizi kullanılarak incelendi. P değerinin 0,05'in altında olduğu durumlar istatistiksel olarak anlamlı olarak değerlendirildi.

Bulgular

Kritelere uyan 293 hastanın tıbbi verileri geriye dönük incelendi. Hastaların 105'i (%36) kız, 188'i (%64) erkekti. Tanı aldığındaki ortalama yaşları 83±57,4 ay idi. Hastaların %16,7'sinde (n=49/293) hiçbir komplikasyon görülmezken, 85 hastada hiperglisemi, 86 hastada parathormon yüksekliği, 31 hastada kalsiyum düşüklüğü, 20 hastada D vitamini düşüklüğü, 11 hastada hipoglisemi saptandı. Hastalarda gelişen endokrin komplikasyonlar arasında cinsiyet bakımından sadece D vitamini düşüklüğü açısından fark saptandı. Kız cinsiyetteki bu düşüklük istatistiksel olarak anlamlıydı (p≤0,001) (Tablo 2). B-ALL tanısı alan hastaların %61'i, T-ALL tanısı alan hastaların ise %81,4'ü erkekti ve B-ALL tanısı alan hastaların %82,7'si ile T-ALL tanısı alan hastaların %60,5'inin tanı yaşları 10'dan küçüktü. Cinsiyet ve tanı alma yaşları açısıdan olan bu fark istatistiksel olarak anlamlı bulundu (p=0,01, p=0,001). B-ALL ve T-ALL olarak iki grupta hastalar incelendiğinde, sadece hiperglisemi, hipokalsemi, hiperparotiroidi T-ALL hastalarında sık görülürken, diğer parametreler açısından anlamlı farklılık saptanmadı (Tablo 2).

Hastaların tanı anındaki yaşları ≥10 yaş ve <10 yaş olmak üzere iki grupta incelendi. Hastalarda gelişen endokrin komplikasyonlar değerlendirildiğinde hiperglisemi, osteoporoz ve avasküler nekroz gelişen grubun ≥10 yaş olan yaş olan grupta fazla olduğu saptandı. Diğer parametrelerde yaş grupları arasında fark görülmedi (Tablo 3).

Risk grubu açısından analizler; standart ve orta risk grubu bir grup, yüksek risk grubu ise diğer bir grup kabul edilerek yapıldı. Hiperglisemi ve hipokalsemi varlığı açısından risk grupları arasında fark bulunurken, diğer parametrelerde fark saptanmadı. T-ALL olan hastalarda yüksek risk görülme oranı daha yüksek bulundu (p=0,005) (Tablo 3).

Hiperglisemi gelişen hastaların sadece üçünde, kısa süreli olarak insülin tedavisi gerekmiş olup, diğer hastalarda dekstroz içermeyen mailerin kullanılması,

diyet uygulaması yapıldı. Hipertrigliseridemi için sadece iki hastada insülün tamponize mai, diyet ve orta zincirli yağ asitleri ile tedavi gerekirken, diğer hastalar ise sadece yağdan fakir diyet ile tedavi edildi. Avasküler nekroz için iki hastaya tek taraflı kalça replasmanı yapıldı.

Logistik regresyon analiz sonucuna göre tanı yaşı, cinsiyet ve löseminin tipi ile endokrin komplikasyon gelişimi arasında istatistiksel olarak anlamlı bir ilişki bulunmadı. Yüksek riskli olmak, endokrin komplikasyon gelişim riski açısından anlamlı bulundu (Tablo 4). Tablo 5'de gelişen komplikasyonların hangi kemoterapi fazında geliştiği sayıları ile birlikte gösterildi. Komplikasyonların en sık görüldüğü dönemler indüksiyon ve yüksek risk blokları idi.

Tartışma

Akut lenfoblastik lösemi tanılı hastalarda günümüzde izlenen sağkalım oranlarında belirgin artış görülmektedir (19). Hunger ve ark.'nın (20) yaptığı bir çalışmada sağkalım %90,4 olarak bildirilirken, Güneş ve ark.'nın (21) Türkiye'den iki merkezden 343 hasta ile yaptığı, çalışmada ise sağkalım oranı %85 olarak bildirilmiştir. Sağkalım oranlarında izlenen artış, tedavi ile ilişkili mortalite ve morbidite risklerini de beraberinde getirmiştir.

ALL tedavisinde görülen endokrin ve metabolik komplikasyonlar tedavi sırasında, tedavinin hemen sonrasında ve uzun dönemde izlemlerde görülebilmektedir (22). Biz çalışmada tedavi sırasında görülen akut komplikasyonları değerlendirdik ve 293 hastanın 244'ünde en az bir endokrin ve/veya

Tablo 2. Cinsiyetin ve lösemi tipinin endokrin komplikasyon gelişimi üzerindeki rolü

	Kız n (%)	Erkek n (%)	p	B-ALL n (%)	T-ALL n (%)	p
Hiperglisemi						
Var	35 (33,7)	50 (26,6)	0,204	65 (26,2)	20 (46,5)	**0,007**
Yok	69 (66,3)	138 (73,4)	-	184 (73,8)	23 (53,5)	-
Hipokalsemi						
Var	8 (7,6)	23 (12,2)	0,218	18 (7,2)	13 (30,2)	**≤0,001**
Yok	97 (92,4)	165 (87,8)	-	232(92,8)	30 (69,8)	-
D vitamini düşüklüğü						
Var	14 (16,1)	6 (3,6)	**≤0,001**	18 (8,0)	2 (6,7)	1,0
Yok	73 (83,9)	162 (96,4)	-	207 (92,0)	28 (93,3)	-
Hiperparatiroidi						
Var	35 (42,7)	51 (32,9)	0,307	75 (35,5)	11 (44,0)	**0,021**
Yok	47 (57,3)	104 (67,1)	-	137 (64,5)	14 (56,0)	-
Tiroid patolojisi						
Var	13 (14,3)	23 (14,1)	0,969	34 (15,5)	2 (6,1)	0,188
Yok	78 (85,7)	140 (85,9)	-	187 (84,5)	31 (93,9)	-
Osteoporoz						
Var	21 (30,9)	27 (25,0)	0,394	43 (27,6)	5 (26,3)	0,908
Yok	47 (69,1)	81 (75,0)	-	114 (72,4)	14 (73,7)	-
Avasküler nekroz						
Var	4 (3,8)	3 (1,6)	0,294	5 (2,2)	2 (4,7)	0,295
Yok	101 (96,2)	185 (98,4)	-	245 (97,8)	41 (95,3)	-
Obezite						
Var	10 (9,5)	24 (12,8)	0,406	29 (11,6)	5 (11,6)	0,997
Yok	95 (90,5)	164 (87,2)	-	221 (88,4)	38 (88,4)	-

ALL: Akut lenfoblastik lösemi

metabolik komplikasyon geliştiğini saptadık. Gelişen komplikasyonların başında hiperglisemi (n=85) ve hiperparatiroidi (n=86) yer almaktadır. Literatürde endokrin komplikasyon sıklığı ile ilgili yeterli veri olmayıp, Öztürk'ün (23), 110 hasta ile yaptıkları bir çalışmada; ALL tedavisi sırasında 23 endokrin

Tablo 3. Hastaların tanı anındaki yaşlarının 10 yaş altı ve üstü olmasının ve risk grubunun endokrin komplikasyon gelişimi üzerindeki rolü

	≥10 yaş n (%)	<10 yaş n (%)	p	Yüksek risk n (%)	Standart/orta risk n (%)	p
Cinsiyet						
Kız	16 (26,7)	89 (38,2)	0,097	39 (36,8)	62 (35,2)	0,931
Erkek	44 (73,3)	144 (61,8)	-	68 (63,2)	114 (34,8)	-
Risk grubu						
Yüksek risk	24 (39)	83 (35,6)	0,220	-	-	-
Standart/orta risk	32 (54,2)	144 (61,8)	-	-	-	-
Belirlenememiş	4 (6,8)	6 (2,6)	-	-	-	-
Flow						
B-ALL	43 (71,7)	207 (88,8)	**0,001**	84 (78,1)	160 (90,9)	0,005
T-ALL	17 (28,3)	26 (11,2)	**-**	23 (21,9)	16 (9,1)	-
Hiperglisemi						
Var	30 (50,0)	55 (23,7)	**≤0,001**	49 (45,7)	33 (18,8)	**≤0,001**
Yok	30 (50,0)	177 (76,3)	-	58 (54,3)	143 (81,3)	-
Hipokalsemi						
Var	8 (13,3)	23 (9,9)	0,480	19 (17,9)	11 (6,3)	**0,002**
Yok	52 (86,7)	210 (90,1)	-	88 (82,1)	165 (93,8)	-
D vitamini düşüklüğü						
Var	4 (8,3)	16 (7,7)	1,0	10 (12,5)	10 (5,7)	0,061
Yok	44 (91,7)	191 (92,3)	-	71 (87,5)	165 (94,3)	-
Hiperparatiroidi						
Var	15 (36,6)	71 (36,2)	0,836	26 (35,2)	61 (36,7)	0,882
Yok	26 (63,4)	125 (63,8)	-	46 (64,8)	105 (94,3)	-
Tiroid patolojisi						
Var	4 (8,3)	32 (15,5)	0,198	12 (14,3)	24 (14,2)	0,986
Yok	44 (91,7)	174 (84,5)	-	73 (84,7)	146 (85,8)	-
Osteoporoz						
Var	14 (48,3)	34 (23,1)	**0,005**	8 (17,8)	40 (30,5)	0,097
Yok	15 (51,7)	113 (76,9)	-	38 (82,2)	91 (69,5)	-
Avasküler nekroz						
Var	6 (10,0)	1 (0,4)	**≤0,001**	2 (1,9)	5 (2,8)	0,715
Yok	54 (90,0)	232 (99,6)	-	105 (98,1)	171 (97,2)	-
Obezite						
Var	6 (10,0)	28 (12,0)	0,664	15 (14,2)	19 (10,8)	0,402
Yok	54 (90,0)	205 (88,0)	-	92 (85,8)	157 (89,2)	-

ALL: Akut lenfoblastik lösemi

komplikasyon geliştiği bildirilmiştir. Zawitkowska ve ark.'nın (24) ALL'li 1872 hasta ile yaptığı bir başka çalışmada ise en sık görülen komplikasyonun enfeksiyonlar olduğu, son sırada ise %1,5'ten az bir oran ile avasküler nekroz görüldüğü belirtilmiştir. Karbuz ve ark.'nın (25) yaptığı çalışmada endokrin komplikasyonlardan da en sık %23 oran ile hiperglisemi saptanmıştır. Aynı çalışmada dislipidemi ve osteoporoz saptanan diğer endokrin komplikasyonlardandır ancak yüzde konusunda bilgi verilmemiştir. Öztürk'ün (26) çalışmasında ise metabolik ve endokrin komplikasyon oranı %15,2 olarak bildirilmiştir. Literatürde daha çok akut lösemi tedavisinin geç komplikasyonları değerlendirilmiş olup, tedavi sırasında gelişen akut endokrin komplikasyonlarla ilgili veri oldukça azdır. Belli endokrin komplikasyonlar tek tek çalışılmış olması nedeniyle literatürdeki endokrin komplikasyon oranı bizim çalışmamıza göre daha düşüktür.

Tablo 4. Endokrin komplikasyon gelişmesi ile tanı yaşı, cinsiyet, flow ve risk grubunun logistik regresyon analizi

	OR (%95 GA)	p
Tanı yaşı		
≥10 yaş	1	0,364
<10 yaş	0,658 (0,267-1,624)	-
Cinsiyet		
Kız	1	-
Erkek	0,637 (0,310-1,309)	0,220
Flow		
B-ALL	1	-
T-ALL	1,207 (0,408-3,573)	0,734
Risk grubu		
Yüksek risk	1	**0,021**
Orta/standart risk	2,385 (1,140-4,988)	-

GA: Güven aralığı

Literatürde çocukluk çağı ALL hastalarında erkek cinsiyet hakimiyeti olup (27), bizim çalışmamızda da çalışmaya dahil edilen hastaların %64'ü erkek idi. Çalışmamızda cinsiyet bakımından karşılaştırma yapıldığında; sadece D vitamini kızlarda erkeklere göre anlamlı derecede düşüktü (p≤0,001). Bayram'ın (28) yaptığı çalışmada D vitamini yetersizliği/eksikliği dahil olmak üzere endokrin komplikasyon gelişmesi ve cinsiyet arasında fark saptanmamıştır. Bhattacharya ve ark.'nın (29) çalışmasında da bizim çalışmamıza benzer şekilde kızlarda D vitamini düzeyi daha düşük bulunmuştur.

En sık görülen komplikasyon hiperglisemi olmakla birlikte çalışmamızda 11 hastada hipoglisemi saptanmış olup bu hastaların 8'i erken intensifikasyon ve idame fazında idi. Hipoglisemi gelişen hastalarda bu etkinin 6-merkaptopurin kullanımına bağlı olduğu ve bu ilacın glukoneogenezi bozabildiği bildirilmiştir (30,31). Özellikle küçük çocuklarda bu etki daha sık görüldüğü için hipoglisemi bulguları için uyanık olunması ve ailenin eğitilmesi gereklidir.

Çalışmamızda toplam 250 (%85,3) hasta B-ALL, 43 (%14,7) hasta T-ALL tanısı ile izlendi. Literatürde de B-ALL, T-ALL'ye göre daha fazla gözlenmektedir (6,32). Hasta grubumuzda T-ALL tanılı hastalarda, B-ALL tanılı hastalara göre hiperglisemi, hipokalsemi ve hiperparatiroidiyi daha fazla saptadık (p=0,007, p≤0,001, p=0,021). Diğer parametreler için anlamlı fark saptanmadı. Literatürde T ve B-ALL hastalarının akut endokrin komplikasyonlarının arasındaki farkı araştıran bir yayına rastlanılmadı. Çalışmamızda T-ALL grubundaki hastaların B-ALL olan hastalara göre, daha sık yüksek risk grubunda olması ve 10 yaşın üzerinde olması endokrin komplikasyonların daha sık görülmesini açıklayabilir.

Tablo 5. Kemoterapi protokolleri sırasında gelişen komplikasyon sayıları

Komplikasyon	Protokol 1a n=293	Protokol 1b n=283	Protokol-M n=176	HR blokları n=107	Protokol-2 n=250	İdame n=237
Hiperglisemi	36	7	7	38	14	10
Hipoglisemi	3	3	0	0	0	5
Hipokalsemi	9	6	3	13	1	2
D vitamini düşüklüğü	3	1	0	3	4	9
Hiperparatiroidi	1	0	0	0	36	49
Hipertrigliseridemi	19	5	4	8	30	14
Tiroid patolojisi	5	2	0	0	22	7

Bayram'ın (28) yaptığı çalışmada endokrin komplikasyon gelişmesi ve yaş arasında anlamlı farklılık bulunmamıştır. Bizim çalışmamızda tek değişkenli analizlerde tanı yaşı 10 yaşından büyük olan hastalarda hiperglisemi, osteoporoz ve avasküler nekroz daha fazla gözlenmiş olup (p≤0,001, p=0,005, p≤0,001), çoklu regresyon analizi ile değerlendirme yapıldığında yaş, endokrin komplikasyon gelişmesi için risk faktörü olarak bulunmadı. Diğer çalışmalarda da bizim bulgularımıza benzer olarak 10 yaş üstündeki çocuklarda hiperglisemi gelişiminin daha sık olduğu bulunmuştur (33,34). Mattano ve ark.'nın (35) yaptığı çalışmada avasküler nekroz bizim çalışmamızda olduğu gibi 10 yaş üzerinde sık görülürken bizim çalışmamızdan farklı olarak kız cinsiyet hakimiyeti bildirilmiştir.

Risk sınıflamasına göre yüksek riskli olan hastalarda, hiperglisemi ve hipokalsemi daha fazla saptandı (p≤0,001, p=0,002). Çalışmamızda regresyon analizinde sadece yüksek riskli olmanın endokrin komplikasyon gelişiminde etkili olduğu bulundu. Yüksek risk bloklarındaki hastaların yaşlarının daha büyük olması, yüksek risk bloklarında yüksek doz deksametazon kullanılması ve ek doz L-asparaginaz almaları etkilidir (36).

Sonuç

Akut lenfoblastik lösemi tedavisi sırasında hastalığın kendisine veya tedaviye bağlı birçok komplikasyona rastlanmaktadır. Endokrin komplikasyonlar da ALL tedavisinin sık görülen komplikasyonları arasında yer almaktadır. Düzenli ve yakından izlenen hastalarda bu komplikasyonlar erken tanındığında etkin olarak tedavi edilerek azaltılabilmektedir. Tedavinin farklı dönemlerinde gelişebilecek olası komplikasyonlara karşı hazırlıklı olmak, ilgili semptomları erken tanımak ve erken müdehale etmek tedavi sürekliliği açısından önem arz etmektedir. Bu çalışma ALL tedavisi almakta olan hastalarda gelişebilecek endokrin komplikasyonlara ışık tutmayı amaçlamaktadır. Benzeri çalışmaların yapılması, ALL tedavisinde karşılaşılabilecek sorunların erken tanınması, tedavilerin sorunsuz devam edebilmesi ve hastaların tedavi sonrası dönemde ek problemler ile karşılaşmamaları için literatüre katkı sağlayacaktır.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Investigation of the Relationship Between Maternal & Neonatal Vitamin B12 Deficiency and Neonatal Hyperbilirubinemia: A Prospective Controlled Study

Neonatal Hiperbilirübinemi ve Maternal & Neonatal Vitamin B12 Eksikliği Arasındaki İlişkinin Araştırılması: Prospektif Kontrollü Çalışma

Meltem Turan* (0000-0002-1690-1511), Hilal Özkan (0000-0001-5454-5119), Melike Sezgin Evim*** (0000-0002-4792-269X), Nilgün Köksal** (0000-0002-6067-3886)**

*Uludag University Faculty of Medicine, Department of Pediatric, Bursa, Turkey

**Uludag University Faculty of Medicine, Department of Pediatric, Division of Neonatology, Bursa, Turkey

***Uludag University Faculty of Medicine, Department of Pediatric, Division of Hematology, Bursa, Turkey

Abstract

Introduction: The aim in this study was to investigate the role of vitamin B12 deficiency in neonatal hyperbilirubinemia.

Materials and Methods: Term newborns who were breastfed and with hyperbilirubinemia were included in this prospective study. Those with hyperbilirubinemia were assigned to a patient group, and those without hyperbilirubinemia were assigned to a control group. The vitamin B12 levels of all newborns and their mothers were checked.

Results: A total of 154 newborns were included in the study. Vitamin B12 deficiency was significantly higher in the patient group in comparison to the control group. Similarly, vitamin B12 levels of mothers were significantly lower in the patient group. The mean bilirubin level and phototherapy need were found to be significantly higher in patients with vitamin B12 deficiency.

Conclusion: This study showed that vitamin B12 deficiency in the mother is related to vitamin B12 deficiency in the newborn, which significantly leads to neonatal hyperbilirubinemia.

Keywords
Breast milk, hyperbilirubinemia, newborn, vitamin B12 deficiency

Öz

Giriş: Bu çalışmada neonatal hiperbilirubinemi olgularında vitamin B12 eksikliğinin rolünün araşatırılması amaçlandı.

Gereç ve Yöntem: Bu prospektif çalışmaya yenidoğan sarılığı olan ve anne sütü ile beslenen term bebekler dahil edildi. Sarılığı olan olgular hasta, sarılığı olmayan olgular kontrol grubu olarak tanımlandı. Tüm bebekler ve annelerinde vitamin B12 düzeyi bakıldı.

Bulgular: Toplam 154 bebek çalışmaya dahil edildi. Vitamin B12 eksikliği hasta grubunda, kontrol grubuna kıyasla anlamlı olarak yüksek bulundu. Benzer şekilde hasta grubunun annelerinde de vitamin B12 düzeyi anlamlı düşük idi. Hasta grubunda ortalama bilirubin düzeyi ve fototerapi ihitiyacı vitamin B12 eksikliği saptanan bebeklerde anlamlı olarak yüksek olduğu görüldü.

Sonuç: Bu çalışmada annelerdeki vitamin B12 eksikliğinin yenidoğan bebeklerde vitamin B12 eksikliği ile ilişkili olduğu ve bebeklerdeki bu eksikliğin yenidoğan sarılığı gelişimine yol açtığı gösterildi.

Anahtar kelimeler
Anne sütü, sarılık, yenidoğan, vitamin B12 eksikliği

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Address for Correspondence/Yazışma Adresi: Prof. Hilal Özkan MD, Uludag University Faculty of Medicine, Department of Pediatric, Division of Neonatology, Bursa, Turkey
Phone: +90 532 760 80 83
E-mail: hiozkan@hotmail.com

Introduction

Neonatal hyperbilirubinemia (NH) is one of the most common clinical findings in newborns (1). It is found in about 60% of term newborns in the first week of life (2). Although it is usually temporary, NH is one of the most common causes of hospitalization in newborns.

NH etiology especially includes blood type incompatibility, enzyme deficiencies, erythrocyte membrane defects, metabolic diseases and breast milk jaundice, as well as a variety of risk factors such as race, ethnicity, sex and low birth weight, but in most cases, the underlying cause cannot be identified (1).

Vitamin B12 dissolves in water, is synthesized by microorganisms and has a symmetrical and complex structure. Among all vitamins, it is the largest and has the most complex structure. Vitamin B12 is essential for DNA synthesis and for cellular energy production. The system that is most sensitive to B12 deficiency is the hematopoietic system, especially erythropoietic series, where the cell proliferation rate is high. Red blood cell destruction causes excessive amounts of heme production, resulting in hyperbilirubinemia (3-5).

Maternal vitamin B12 deficiency has been shown to cause vitamin B12 deficiency in newborn babies (6-8). There are, however, few studies exploring the association between vitamin B12 deficiency and neonatal jaundice development.

The aim in this study was to check vitamin B12 levels in NH patients and their mothers and examine the role of vitamin B12 deficiency in NH and its impact on the severity of the disease.

Materials and Methods

Term newborns admitted to the hospital between 1 February 2018 and 31 May 2019 were included in this prospective study. The study protocol was approved by the Uludağ University Ethics Committee on the decision date of 11 January 2018 date and with the decision number of 2018-1/13. Informed parental consent was obtained for all babies.

Study Population

This study included 211 full term neonates divided into 2 groups;

Patient group: Patients with significant hyperbilirubinemia in infants ≥35 weeks gestational age (GA) is defined as a TB >95th percentile on the hour-specific Bhutani nomogram.

Control group: The control group who did not have hyperbilirubinemia consisted of sex- and age-matched healthy subjects from our clinic. Health status was determined through the subjects' medical history and parental report.

Inclusion criteria

- Gestational age 37-42 week
- Postnatal age 3-7 days
- Birth weight from 2500 gm to 3700 gm
- Good general condition
- Breast milk feeding
- Normal platelet count and WBCs and no other signs of infection

Exclusion criteria

- Blood type incompatibility
- Glucose-6-phosphate dehydrogenase (G6PDH) deficiency
- Pyruvate kinase (PK) deficiency
- Hypothyroidism
- Direct hyperbilirubinemia
- Dehydration

Clinical Features

Neonatal and maternal demographic characteristics, ages at the time of admission, phototherapy or blood exchange needs and hospitalization stays were recorded for all cases. Birth weight and body weight at admission recorded.

Laboratory Tests

Complete blood count (CBC), direct coombs, peripheral blood smears, reticulocyte and serum total bilirubin levels of all cases, as well as maternal and infant vitamin B12 levels, were checked.

Serum total and direct bilirubin levels were measured by using the spectrophotometric measurement method on an Abbott Architect C16000 device. Vitamin B12 levels were checked by using the chemiluminescent microparticle immunoassay (CMIA) method on an Abbott Architect I2000 device.

Reference Values

The total bilirubin levels of the cases were classified according to the bilirubin nomograms based on values

defined by the American Academy of Pediatrics. Those with a vitamin B12 level below 250 ng/L were considered to have vitamin B12 deficiency (9).

Treatment Protocol and Follow-up

The total bilirubin levels of all patients in the patient group were followed up. The newborns and their mothers who were diagnosed to have vitamin B12 deficiency were treated for vitamin B12.

The dose was administered as 1 drop (330 microgram) for newborns and 1 puff (1000 microgram) sublingually for their mothers every day for the first two weeks and then 3 days a week. Total bilirubin levels were checked on day 7 of the treatment, and vitamin B12 levels were checked after 1 month of treatment. Treatment was planned to be maintained.

Statistical Analysis

The SPSS SPSS program (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.), program was used for data analysis. The descriptive statistics are presented in frequencies and percentages. The relationships between categorical variables were examined by running chi-squared tests and Fisher's Exact tests. The results were evaluated in a 95% confidence interval, and $p<0.05$ was considered significant.

Results

A total of 154 term newborns, 104 in the patient group and 50 in the control group, were included in the study.

No significant difference was found between the patient and control groups when the groups were compared in terms of their demographic characteristics (Table 1).

Vitamin B12 deficiency was found in 63.5% (n=66) of the patient group and 32% (n=16) of the control group, and the difference was significant (p=0.0001). Similarly, the mean vitamin B12 level of the patient group was also significantly lower than the control group (p=0.002). Vitamin B12 levels of the mothers in the patient group were also found to be significantly lower compared to the control group (p=0.01). Similarly, the vitamin B12 levels of the

Table 1. Demographic characteristics and laboratory tests

Demographic characteristics	Patient group n=104	Control group n=50	p
Maternal age (years), mean ± SD	28.7±5.2	28.2±5.7	0.6
Male, n (%)	47 (45.2)	30 (60)	0.6
Gestational week, mean ± SD	38.2±0.9	38.5±1.03	0.2
Birth weight (g), mean ± SD	3228±448	3316±503	0.2
Cesarean, n (%)	63 (60.6)	33 (66)	0.3
APGAR 1, median (min-max)	9 (7-10)	9 (8-10)	0.1
APGAR 5, median (min-max)	10 (8-10)	10 (9-10)	0.1
Postnatal age, mean ± SD	5.0±1.9	4.7±2.2	0.4
Laboratory tests			
Total bilirubin (mg/dL), mean ± SD	14±2.7	10.1±3.2	**0.0001**
Total bilirubin above 2 SD, n (%)	64 (61.5)	0 (0)	-
Hemoglobin (g/dL), infant, mean ± SD	15.9±2.4	16.3±1.8	0.2
Reticulocyte count (%), mean ± SD	1.5±1	0.9±0.34	**0.02**
Hemoglobin (g/dL), mother, mean ± SD	12.2±1.6	10±0	0.153
Vitamin B12 deficiency, infant n (%)	66 (63.5)	16 (32)	**0.0001**
Vitamin B12 level (ng/L), infant, mean ± SD	259±154	346±169	**0.002**
Vitamin B12 deficiency, mother n (%)	50 (48)	14 (21.9)	**0.01**
Vitamin B12 level (ng/L), mother, mean ± SD	280±136	322±138	0.07

SD: Standard deviation

mothers were found to be low in the patient group in comparison to the control group. While there was no significant difference between the groups in terms of the hemoglobin levels, the reticulocyte counts were significantly higher in the patient group (p=0.02) (Table 1).

A total of 64 mothers had B12 deficiency. B12 deficiency was found in the babies of 54 of these mothers and 50 of these babies were in the patient group (Figure 1).

When the patient group was categorized based on low and normal vitamin B12 levels, it was found that there was no significant difference in terms of the demographic characteristics (Table 2).

The mean bilirubin levels, severe hyperbilirubinemia (>15 mg/dL) and need for phototherapy were significantly higher in with vitamin B12 deficiency patient. No patient needed exchange transfusion. In the patients with vitamin B12 deficiency, the need for for >48 hours of phototherapy was higher (Table 2).

An ROC analysis was carried out to identify the vitamin B12 level on which jaundice occurred in 154 cases including the patient and control groups. Based on the analysis, the vitamin B12 level cutoff value was

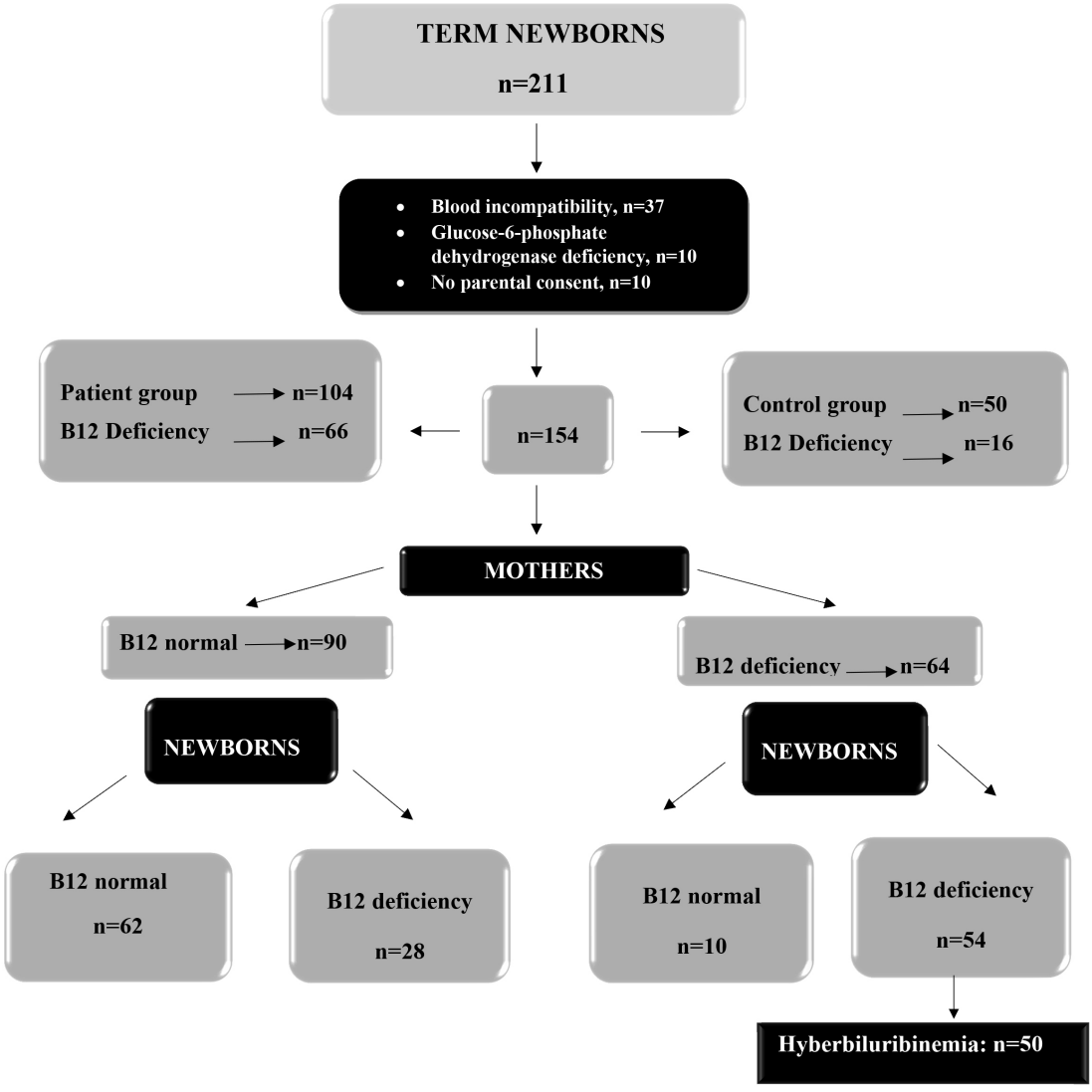

Figure 1. Mothers and newborns distribution.

218 ng/L (p<0.001). There was 53% sensitivity and 76.4% specificity for this value (Table 3).

Accepting that the vitamin B12 level cutoff value was 218 ng/L, the vitamin B12 deficiency in the patient group was again found to be significantly lower (Table 4).

The median median vitamin B12 level was 620 ng/mL in the 1st month after treatment in the patients with vitamin B12 deficiency.

Discussion

NH is one of the most common problems in the neonatal period, and its etiology cannot be determined in most cases. It has been reported in studies conducted in Turkey that the cause of NH could not be determined at a rate of up to 66-78% (10,11). Early diagnosis and treatment may be achieved by conducting etiology studies to prevent possible neurological problems.

Since vitamin B12 plays a role in maturation of erythrocytes and DNA synthesis, it is known that its deficiency leads to an increase in erythrocyte destruction due to ineffective erythropoiesis and hyperbilirubinemia. The studies investigating its frequency in newborns, its role in etiology in NH or its effects on the severity of the disease are very limited. Considering that vitamin B12 deficiency detected in infants based on newborn screenings may be mainly due to their mothers, it is very important that mothers and newborns are assessed together, and the treatment plan is carried out together (12).

In this prospective study, the vitamin B12 levels of mothers and their babies were assessed together in NH, and it was found that vitamin B12 deficiency

Table 2. Comparison of the patient group with normal and low vitamin B12 levels

	Normal vitamin B12 n=37	Low vitamin B12 n=67	p
Maternal age (years), mean ± SD	29.4±4.6	28.2±5.6	0.27
Male, n (%)	16 (43.2)	31 (46.1)	0.4
Gestational week, mean ± SD	38.2±0.8	38.2±1.0	0.1
Birth weight (g), mean ± SD	3202±488	3364±424	0.78
Cesarean, n (%)	25 (67.6)	38 (56.7)	0.1
APGAR 1, median (min-max)	9 (8-10)	9 (9-10)	0.1
APGAR 5, median (min-max)	9 (9-10)	9 (9-10)	0.1
Age of admission (days), mean ± SD	5.3±2.2	4.9±1.8	0.34
Total bilirubin (mg/dL), mean ± SD	13.3±2.6	14.4±2.7	**0.04**
Total bilirubin >15 mg/dL, n (%)	5 (13.5)	22 (32.8)	**0.02**
Hemoglobin (g/dL), infant, mean ± SD	16.3±3.1	15.7±2.6	0.54
Reticulocyte count (%), mean ± SD	1.7±1.2	1.4±0.9	0.24
Vitamin B12 level (ng/L), infant, mean ± SD	402±155	179±79	**0.0001**
Vitamin B12 deficiency, mother n (%)	4 (10.8)	46 (68.6)	**0.0001**

Table 3. Values determined as a result of ROC analysis

	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Vitamin B12 level ≤218 ng/L	53.06	76.47	81.2	45.9

Table 4. Comparison of vitamin B12 deficiency in the patient and control groups according to the new cut-off value

Cut-off=218 ng/L	Patient group n=104	Control group n=50	p
Vitamin B12 deficiency, infant n (%)	58 (55.8)	12 (24)	**0.0001**
Vitamin B12 deficiency, mother n (%)	41 (39.4)	7 (14)	**0.003**

played an important role in the etiology of NH, and deficiency in the infants originated from their mothers.

Finkelstein et al. (6) investigated vitamin B12 levels in pregnant adolescents and their babies, and they found that the vitamin B12 levels of the mothers fell during pregnancy, and this was associated with the vitamin B12 levels of their babies. It was also demonstrated in their study that vitamin B12 levels decreased further as pregnancy progressed. Visentin et al. (7) reported that vitamin B12 deficiency increased further at the late stages of pregnancy, in a similar way, in their study on vitamin B12 levels in Canadian pregnant women. Hay et al. (8) showed that maternal vitamin B12 levels are a strong predictor of infants' blood vitamin B12 levels at birth. They also demonstrated that vitamin B12 supplements used in pregnancy increase umbilical cord blood vitamin B12 levels. Çoban et al. (13) reported that maternal vitamin B12 deficiency is the major cause of vitamin B12 deficiency in newborns, by revealing that the positive correlation between vitamin B12 levels of mothers and newborns is significant.

Onal et al. (10) noted that inadequate animal protein consumption due to low socioeconomic status in pregnancy is an important risk factor for vitamin B12 deficiency in both mothers and newborns. They emphasized the need for the use of parenteral vitamin B12 during pregnancy in developing countries such as Turkey.

In our study, as well, 84.4% of the mothers of the newborns with low vitamin B12 were found to have vitamin B12 deficiency, which was significantly different in comparison to the mothers of the newborns with normal vitamin B12 levels.

Despite the information in the literature on deficiency of vitamin B12 in the mother causing deficiency in the infant, there are no large-scale case studies that explore the role of this condition in NH.

In the only study reported from Turkey, Eroglu et al. (14) found that vitamin B12 deficiency was significantly higher in cases of prolonged jaundice involving 20 patients than in the control group. However, in their study, maternal vitamin B12 levels were not checked (14). In our study, a total of 154 mothers and their newborns were assessed and significantly higher vitamin B12 deficiency was detected in the patient group.

In our study, only babies who were breastfed were included. Vitamin B12 levels have also been found to be low in the milk of mothers with vitamin B12 deficiency in previous studies. Specker et al. (15) found that vitamin B12 was low in the milk of mothers with vitamin B12 deficiency.

The NH patients with normal and low levels of vitamin B12 were found to be similar in terms of the demographic characteristics. The mean bilirubin levels and need for phototherapy were significantly higher in with vitamin B12 deficiency patient. In the only study investigating the relationship between jaundice and vitamin B12 deficiency in the literature, neither the severity of the disease nor the need for treatment was taken into account.

Numerous different cutoff values for vitamin B12 levels have been determined in previous studies. In a study on neonatal cases with hyperbilirubinemia in India, Sukla et al. (16) determined the vitamin B12 cutoff value as 201 pg/mL. In a study by Koc et al. (17) in Şanlıurfa in Turkey, the vitamin B12 cut-off value was determined to be 207 pg/mL. In a study by Hay et al. (8) in Norway, the limit for vitamin B12 levels was determined to be 404 pg/mL.

The reference value in our study was taken to be 250 pg/mL in line with the guidelines (5). However, when an ROC analysis was carried out through our own cases, the cutoff value was determined to be 218 ng/L (1 ng/L=1 pg/mL). There was no difference in the results of the study when the patients were reassessed based on this value.

Conclusion

This study has demonstrated that vitamin B12 deficiency in mothers is related to vitamin B12 deficiency in newborns, and vitamin B12 deficiency in newborns significantly leads to hyperbilirubinemia.

It has been shown that, in NH cases for whom the etiology cannot be determined, vitamin B12 deficiency may have a role at a rate as high as 60%, which demonstrates the importance of assessing vitamin B12 levels in mothers and newborns in the early period.

Ethics

Ethics Committee Approval: The study protocol was approved by the Uludağ University Ethics Committee on the decision date of 11 January 2018 date and with the decision number of 2018-1/13.

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Risk and Prognostic Factors in Neonatal Meningitis

Yenidoğan Menenjitinde Risk Etmenlerinin ve Prognostik Faktörlerin Değerlendirilmesi

Gülşah Parlakay* (0000-0003-0120-0066), Salih Çağrı Çakır (0000-0001-5761-4757), Bayram Ali Dorum** (0000-0002-2823-8454), Hilal Özkan** (0000-0001-5454-5119), Solmaz Çelebi*** (0000-0002-3536-0263), Mustafa Hacımustafaoğlu*** (0000-0003-4646-660X), Nilgün Köksal** (0000-0002-6067-3886)**

*Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Turkey

**Uludağ University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Bursa, Turkey

***Uludağ University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Disease, Bursa, Turkey

Abstract

Introduction: Neonatal meningitis is one of the important causes of mortality and morbidity in newborns. In this study, it was aimed to examine the microbiological factors, biochemical and clinical characteristics of neonatal meningitis cases, to reveal the risk factors, and to investigate the effect on the morbidities associated with meningitis in the first year of life.

Materials and Methods: The files of patients diagnosed with meningitis in the level 3 Neonatal Intensive Care Unit between January 2010 and December 2015 were retrospectively analyzed.

Results: There were 118 patients diagnosed with meningitis. The median gestational age of the patients was 32 weeks (24-40 weeks), and the median birth weight was 1987 grams (690-5020 grams). Most of the meningitis patients (n=106, 90%) were with late sepsis. The diagnosis day of those with poor prognosis was found to be greater [9.7 (2-28) days to 15.5 (3-138) days, p=0.03]. Cerebrospinal fluid (CSF) leukocytes were significantly higher in term babies with abnormal cranial magnetic resonance imaging (MRI) findings (p=0.037) and loss in hearing tests (p=0.045). CSF sugar levels were significantly lower in preterm babies with neuromotor retardation (p=0.001), history of seizures (p=0.003), abnormal cranial MRI findings (p=0.008) and hearing loss (p=0.005).

Conclusion: In the long term, a significant number of cases with neonatal meningitis have neuromotor retarda-tion and hearing problems. Factors that can be used as predictors for poor neurological development; late-onset day, increased CSF leukocyte in all babies, and decreased CSF sugar in preterm babies.

Keywords
Neonatal meningitis, newborn, meningitis sequelae, premature infant

Anahtar kelimeler
Neonatal menenjit, yenidoğan, menenjit sekeli, prematüre bebek

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Address for Correspondence/Yazışma Adresi: Salih Çağrı Çakır MD, Uludağ University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Bursa, Turkey
Phone: +90 533 345 37 39
E-mail: salihcagri@gmail.com

Öz

Giriş: Menenjit, yenidoğanlarda önemli bir mortalite ve morbidite nedenidir. Bu çalışmada, yenidoğan menen-jitlerinin mikrobiyolojik, biyokimyasal ve klinik özelliklerinin incelenmesi ve yaşamın ilk yılındaki morbid-itelere etkili risk faktörlerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Ocak 2010-Aralık 2015 tarihleri arasında 3. Düzey Yenidoğan Yoğun Bakım Ünitesi'nde menenjit tanısı alan hastaların dosyaları geriye dönük olarak incelendi.

Bulgular: Menenjit teşhisi konan 118 hasta vardı. Hastaların ortanca gebelik yaşı 32 hafta (24-40 hafta), ortanca doğum ağırlığı 1987 gram (690-5020 gram) idi. Menenjit hastalarının çoğu (n=106, %90) geç sepsis hastasıydı. Prognozu kötü olanların tanı günü daha fazla [9,7 (2-28) gün ile 15,5 (3-138) gün] olarak bulundu,

p=0,03. Anormal kraniyal manyetik rezonans (MR) bulguları (p=0,037) ve işitme testlerinde kayıp (p=0,045) olan term bebeklerde beyin omurilik sıvısı (BOS) lökositleri anlamlı olarak daha yüksekti. Nöromotor retardasyonu (p=0,001), nöbet öyküsü (p=0,003), anormal kraniyal MR bulguları (p=0,008) ve işitme kaybı (p=0,005) olan erken doğmuş bebeklerde BOS şeker düzeyleri anlamlı olarak daha düşüktü.

Sonuç: Yenidoğan menenjitli olguların önemli bir kısmında uzun dönemde nöromotor gerilik ve işitme sorunları görülmektedir. Tüm bebekler için; geç başlangıç günü ve yüksek BOS lökositi, ayrıca prematüre bebekler için ise düşük BOS şekeri kötü nörolojik gelişimin belirteci olarak değerlendirilebilir.

Introduction

The incidence of neonatal meningitis is reported to be 0.25-0.32 per 1000 live births, and meningitis is associated with a rate of 5-10% in early-onset sepsis cases and 25% in late-onset sepsis cases (1,2). The mortality rate for neonatal meningitis is 10-15% and this rate varies according to the time of diagnosis, the causative agent and the time of treatment onset (3). The incidence of neonatal meningitis and associated mortality rate has decreased in the last 50 years due to better antenatal follow-up, intrapartum antibiotic use, and developments in the neonatal intensive care unit (NICU) (4). Long-term complications in survivors are 20-50%, including visual defects, middle ear disease and behavioral problems (5). Risk factors of neonatal meningitis are low birth weight (<2500 g), preterm delivery, premature rupture of membranes (PROM), septic or traumatic birth, fetal hypoxia and maternal peripartum infection (6). The most common causes of neonatal meningitis include group B *Streptococcus* and *Escherichia coli* (4).

In this study, it was aimed to examine the microbiological factors, biochemical and clinical characteristics of neonatal meningitis cases, to reveal the risk factors and to investigate the effect on the morbidities associated with first-year meningitis.

Materials and Methods

Approval for this study was obtained from the Uludağ University Ethics Committee (2016-21/13). Patients who were admitted to the third level NICU with the diagnosis of early and late sepsis in the six years of time (between 01/01/2010-31/12/2015) were included in the study. These patients were diagnosed with meningitis and were followed up until the age of one after discharge. Maternal infection status, maternal diseases, gestational week, delivery route, apgar scores, birth weight, gender, time of diagnosis, acute phase reactants at the time of diagnosis, cerebrospinal fluid (CSF) findings, CSF culture results, cranial imaging findings and neuromotor, cognitive and auditory morbidities of the first year of follow-up were examined retrospectively from the electronic files of the patients. Neuromotor retardation status of the patients was evaluated by the Denver test.

The diagnosis of sepsis is performed by evaluating the clinical and laboratory findings according to the European Medicines Agency scoring (7). Patients in which the causative agent was documented were considered as proven sepsis. Sepsis occurred in the first 72 hours of life was evaluated as early sepsis, and after the first 72 hour as late sepsis.

Diagnosis of meningitis was performed by positive CSF culture, or CSF protein level >150 mg/dL in preterms, >100 mg/dL in terms and CSF glucose level <20 mg/dL in preterms, <30 mg/dL in terms (or less than 70-80% of the concurrent blood glucose value), or CSF leukocyte count >20-30 cells/mm^3. Patients diagnosed with meningitis accompanying early and late sepsis were evaluated separately (8).

Patients whose Denver test and cranial imaging results were found to be normal and whose antiepileptic drugs were discontinued during the follow-up, although there was a history of seizures, were identified as the group with good prognosis. Patients who died, who had neuromotor and mental retardation, and who continued to use antiepileptic drugs with a diagnosis of epilepsy were identified as the group with poor prognosis.

Statistical Analysis

In the statistical analysis of our study; the compliance of continuous variables to normal distribution was examined by Kolmogorov-Smirnov test. According to the results of normality test, t-test or Mann-Whitney U was used for comparisons between groups. Categorical variables were compared between groups using chi-square or Fisher's exact test. The numerical data were expressed as the mean ± standard deviation (SD) or median (min-max) and the categorical data as frequencies and percentages. SPSS 25.0 (IBM

SPSS Statistics for Windows, Version 25.0) program was used for analysis, and the significance level was determined as $p<0.05$ in statistical comparisons.

Results

The number of patients diagnosed with meningitis in the evaluated six-year period was 118, 18 patients who died before the follow-up was excluded and the morbidity data of 100 patients were examined. The epidemiological and demographic characteristics of the patients are given in Table 1.

Mortality rate was found to be 15.2% in 118 cases diagnosed with meningitis. During the same period, a total of 1360 patients, 326 (23%) early sepsis and 1034 (77%) late sepsis, were followed up with a diagnosis of sepsis. Of the patients diagnosed with meningitis, 12 (10%) were with early sepsis, and 106 (90%) were with late sepsis.

Acute phase reactants and CSF findings were similar in meningitis cases accompanying early sepsis and late sepsis in both term and preterm babies. Blood leukocyte count, CRP, CSF leukocyte count, protein and glucose levels of patients with meningitis accompanying early and late neonatal sepsis are examined in Table 2 for preterm and term infants.

Table 1. Epidemiological and demographic characteristics of the patients	
Preterm delivery, n (%)	77 (77)
Birth weight, gram, median (minimum-maximum)	1987 (690-5020)
Low apgar score at 5 minimum, n (%)	8 (8)
Gestational age at birth, median (minimum-maximum)	32 (24-40)
Cesarean delivery, n (%)	71 (71)
Male gender, n (%)	63 (63)
The day of diagnosis of meningitis, median (minimum-maximum)	11,1 (2-40)
Day of hospitalization, median (minimum-maximum)	45.6 (13-154)
Early sepsis, n (%)	11 (11)
History of PROM, n (%)	13 (13)
History of preeclampsia/eclampsia, n (%)	20 (20)
PROM: Premature rupture of membranes	

Table 2. CSF findings and acute phase reactants in preterm and term meningitis cases with early and late neonatal sepsis			
Preterm babies	Meningitis cases with early neonatal sepsis median (min-max) n=8	Meningitis cases with late neonatal sepsis median (min-max) n=69	p[a]
WBC (K/uL)	10 700 (8,920-20,900)	13 100 (5,170-55,400)	0.350
CRP (mg/dL)	1.44 (0.32-5.33)	0.47 (0.3-12.5)	0.340
CSF leukocyte (/mm^3)	20.14 (10-800)	30 (10-2,470)	0.799
CSF protein (mg/dL)	161.5 (104-392)	157 (30-965)	0.582
CSF glucose (mg/dL)	48.5 (30-82)	48 (10-116)	0.537
Term babies	Meningitis cases with early neonatal sepsis median (min-max) n=3	Meningitis cases with late neonatal sepsis median (min-max) n=20	
WBC (K/uL)	7 930 (6 150-11 600)	13 950 (5 820-19 300)	0.059
CRP (mg/dL)	2.1 (0.46-3.5)	3.12 (0.3-17.6)	0.904
CSF leukocyte (/mm^3)	10 (10-20)	20 (10-190)	0.190
CSF protein (mg/dL)	120 (99-142)	114 (43-256)	0.802
CSF glucose (mg/dL)	55 (45-59)	56 (12-83)	0.574
[a]Mann-Whitney U test, WBC: White blood leukocyte, CRP: C-reactive protein, CSF: Cerebrospinal fluid			

Positive blood culture was determined in 21 (21%) patients and positive CSF culture was determined also in 21 (21%) patients. All patients with positive culture results are cases of late neonatal meningitis with sepsis. None of the early neonatal meningitis cases with sepsis had positive culture. The CSF and blood culture results are detailed in Table 3. Gram positive agents were isolated more frequently than gram negatives in blood (14 vs 3) and CSF (19 vs 1) cultures. The most frequently isolated microorganism in both blood and CSF is *S. epidermidis* (respectively 10 and 11). *Candida* were isolated in five patients' blood (4) and CSF (1) cultures.

The rates and statistical comparisons of neurological morbidities in term and preterm infants are shown in Table 4. Hearing aids were worn in three of the patients with auditory loss during follow-up, and all of these patients were preterm cases. Of the patients with abnormal cranial MR findings, 13 had nonspecific bleeding sequelae, 8 patients had periventricular leukomalacia, 10 patients had hydrocephalus, and 10 patients had cortical atrophy 12 of 22 preterm patients and 4 of 7 term patients with seizures had epileptiform anomaly on EEG. It was determined that all patients with normal EEG and only two of the patients with abnormal EEG did not have seizures persisted and their antiepileptic drug was discontinued after the first year.

Comparison results of neurological morbidities and CSF biochemistry results in term infants are

Table 3. Blood and CSF culture results

	Meningitis cases with late neonatal sepsis (n=89)	
Microorganism	CSF culture n (%)	Blood culture n (%)
Gram positive cocci	19 (90.5)	14 (66.5)
Staphylococcus Epidermidis	11 (52)	10 (47.5)
Staphylococcus Haemolyticus	3 (14)	1 (4.7)
Enterococcus Faecium	2 (9.5)	1 (4.7)
Staphylococcus Capitis	-	1 (4.7)
Staphylococcus Chromogenes	-	1 (4.7)
Streptococcus Mitis	1 (4.7)	-
Micrococcus Luteus	1 (4.7)	-
Staphylococcus Hyicus	1 (4.7)	-
Gram negative bacilli	1 (4.7)	3 (14)
Klebsiella Pneumoniae	1 (4.7)	1 (4.7)
Serratia Marcescens	-	1 (4.7)
Stenotrophomonas Maltophilia	-	1 (4.7)
Candida Parapsilosis	-	3 (14)
Candida Albicans	1 (4.7)	1 (4.7)
Total	21 (100)	21 (100)

CSF: Cerebrospinal fluid

Table 4. Comparison of the neurological results of the cases

Neurological morbidities	Preterm cases (n=77) n (%)	Term cases (n=23) n (%)	p[a]
Abnormal cranial MRI findings	25 (32.4)	6 (26)	0.562
Abnormal ABR	20 (25.9)	5 (21.7)	0.681
Retardation in Denver test	18 (23.3)	3 (13)	0.286
History of seizures	22 (28.5)	7 (30.4)	0.861

[a]Chi-square test, MRI: Magnetic resonance imaging, ABR: Auditory brainstem response

shown in Table 5. Comparison results of neurological morbidities and CSF biochemistry results, birth weight and gestational week in preterm infants are shown in Table 6.

The effect of CSF findings, the day of diagnosis, delivery type, low birth weight and gender on mortality and neurological prognosis are given in Table 7. It was determined that CRP, CSF leukocyte count levels and the day of diagnosis were significantly higher in cases with poor prognosis.

Discussion

Although neonatal meningitis is more common in cases with late sepsis, it is also seen in cases with early sepsis. Tan et al. (8) showed in their study in 2015 that there were 12.5% cases of neonatal meningitis accompanying early sepsis. Similarly, 89% of the cases in our study were determined as neonatal meningitis with late sepsis, 11% as neonatal meningitis with early sepsis. Median day of diagnosis was found 11.1 in our

Table 5. Association between CSF biochemistry findings and neurological morbidities in term infants

Neurological morbidities		CSF protein median (min-max)	CSF leukocyte median (min-max)	CSF glucose median (min-max)
Abnormal cranial MRI findings	Yes, 6	126 (54-233)	25 (10-190)	42 (12-74)
	No, 17	99 (43-256)	15 (10-40)	58 (45-83)
	p[a]	0.674	0.037	0.141
Abnormal ABR	Yes, 5	128 (71-233)	20 (20-40)	51 (46-83)
	No,18	109 (43-256)	10 (10-190)	56 (12-82)
	p[a]	0.297	0.045	0.737
Retardation in Denver test	Yes, 3	161 (123-167)	20 (10-190)	51 (29-60)
	No, 20	86.5 (43-256)	15 (10-40)	56.5 (12-83)
	p[a]	0.144	0.672	0.437
History of seizures	Yes, 7	130 (85-256)	20 (10-190)	48 (12-82)
	No, 16	73 (43-174)	15 (10-40)	58 (45-83)
	p[a]	0.124	0.629	0.160

[a]Mann-Whitney U test, CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, ABR: Auditory brainstem response

Table 6. Association between CSF biochemistry findings and neurological morbidities in preterm infants

Neurological morbidities		Birth weight Mean ± SD	Gestational age at birth mean ± SD	CSF protein mean ± SD	CSF leukocyte mean ± SD	CSF glucose mean ± SD
Abnormal cranial MRI findings	Yes, 25	1307 (780-2660)	30±2.8 29 (26-36)	144 (71-965)	20 (10-1300)	38 (10-97)
	No, 52	1515 (690-3680)	31 (24-36)	164 (30-392)	10 (10-2470)	50 (10-116)
	p[a]	0.352	0.029	0.125	0.234	0.008
Abnormal ABR	Yes, 20	1320 (690-2320)	30 (26-35)	150 (71-965)	20 (10-330)	39 (14-116)
	No, 57	1500 (780-3680)	30 (24-36)	159 (30-392)	10 (10-2470)	51 (10-112)
	p[a]	0.231	0.231	0.862	0.768	0.005
Retardation in Denver test	Yes, 18	1292 (780-2320)	29 (24-35)	143 (105-965)	10 (10-1300)	32 (10-69)
	No, 59	1530 (690-3680)	31 (26-36)	161 (30-392)	20 (10-2470)	51 (10-116)
	p[a]	0.115	0.055	0.527	0.951	0.001
History of seizures	Yes, 22	1367 (780-3680)	31 (24-36)	151 (85-965)	10 (10-1300)	36 (10-112)
	No, 55	1470 (690-2660)	30 (26-36)	160 (30-392)	20 (10-2470)	51 (23-116)
	p[a]	0.830	0.188	0.960	0.155	0.003

[a]Mann-Whitney U test, CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, ABR: Auditory brainstem response, SD: Standard deviation

Table 7. Comparison of cases with good and poor prognosis			
	Cases with good prognosis n=70	Cases with poor prognosis n=48	p
Male gender, n (%)	44 (62)	19 (39)	0.162[a]
Birth weight <2500 g, n (%)	51 (72)	34 (70)	0.861[a]
Cesarean delivery, n (%)	51 (72)	34 (70)	0.782[a]
Day of prognosis of meningitis, median (min-max)	9.7 (2-28)	15.5 (3-138)	0.030[b]
WBC (K/uL), median (min-max)	13 555 (5 170-33 600)	15 270 (5 820-55 400)	0.584[b]
CRP (mg/dl), median (min-max)	1.48 (0.33-11)	2.6 (0.3-17.6)	0.040[b]
CSF leukocyte (/mm^3), median (min-max)	48 (0-800)	130 (0-2470)	<0.001[b]
CSF protein (mg/dL), median (min-max)	148 (43-392)	198 (91-965)	0.622[b]
CSF glucose (mg/dL), median (min-max)	56 (24-116)	42 (10-120)	0.761[b]
[a]Chi-square test, [b]Mann-Whitney U test, WBC: White blood leukocyte, CRP: C-reactive protein, CSF: Cerebrospinal fluid			

study similar to the literature. Kumar et al. (9) also found mean day of diagnosis of menengitis 11 in their study published in 2017.

In the literature, risk factors for neonatal meningitis are low birth weight (<2500 g), premature birth, premature rupture of membranes, septic or traumatic labor, fetal hypoxia, and maternal peripartum infection (10). In our study, among these risk factors; prematurity rate was 74%, the history of PROM in the mother was 13%, male gender was 63%, cesarean section was 71% and the median birth weight was 1987 g. Since there was no control group, only descriptive analysis could be done in terms of risk factors.

In our study, any microorganism could not be isolated in the CSF culture in cases diagnosed with neonatal meningitis accompanying early sepsis. In a single center study conducted by Kavuncuoğlu et al. (11) in Turkey, they found the positive culture rate as 18% and the most frequently isolated microorganism as *S. epidermidis*, and gram positive agents were isolated more frequently than gram negatives. Similarly in our study, the positive CSF culture rate in cases of neonatal meningitis with late sepsis was found to be 17.7%, and the most common isolated agent was *S. epidermidis*. It has been observed that gram positive agents are isolated at a higher rate. In a long-term cross-sectional study conducted by Mashau et al. (12), it was stated that the frequency of gram-negative agents increased and antibiotic sensitivity decreased. In addition, *Ureaplasma species* are also reported as the causative agent of neonatal meningitis (13). Therefore, when the routine microbiological tests and conventional treatments are negative, other relevant pathogens can be diagnosed using metagenomic next-generation sequencing and polymerase chain reaction tests (13).

Different results have been reported in the literature regarding the effect of the day of diagnosis of meningitis on prognosis. Tatishvili et al. (14) found a relationship between poor prognosis and neonatal meningitis with early sepsis. However in their study, Kumar et al. (9) found no difference in terms of prognosis in cases diagnosed with neonatal meningitis accompanying both early and late sepsis. In our study, it was observed that the median diagnosis day of the patients with poor prognosis was significantly high.

In the prognostic examination of CSF findings on neurological morbidities; it was observed that high CSF leukocyte levels in term infants and low CSF glucose levels in preterm infants were significantly associated with the development of neurological morbidities. High levels CRP and CSF leukocyte count and the late day of diagnosis were found as prognostic factor for poor prognosis. However, Tan et al. (8) reported higher CSF protein levels in neonatal meningitis cases with poor prognosis and showed that CSF protein levels remained high in these cases after two weeks of treatment. Many newborns with negative CSF culture are considered to have central nervous system infection. The data mentioned above support that CSF biochemistry parameters can be used alone or in combination as both diagnostic and prognostic markers in cases with negative CSF culture. Rajial et al. (15) reported that CSF procalcitonin values could be used to diagnose neonatal meningitis.

Neonatal meningitis continues to be an important cause of morbidity and mortality for newborns. It

causes neuromotor retardation and hearing problems in the long term in a significant part of the patients living. Most of the patients are premature babies whose hospitalization continues in the neonatal clinics, and reducing nosocomial infections will also reduce neonatal meningitis.

The weakness of our study is that the rate of microbiologically confirmed cases is low, there is no control group, and it is a retrospective study. Other limitations of this study are that clinical findings at the time of diagnosis and the predominance of multinucleated cells in CSF were not evaluated in the study.

Conclusion

In neonatal meningitis cases; late diagnosis day, high CSF leukocyte levels in term infants, low CSF glucose levels in preterm infants can be used as a predictor for poor neurological development. Studies examining prognostic factors, risk factors and CSF findings in neonatal meningitis prospectively are needed.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Uludağ University Ethics Committee (decision no: 2016-21/13, date: 27.12.2016).

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Comparison of Maternal Attachment Level, Post-traumatic Stress Disorder, Anxiety and Depression Risk, and Related Factors in Mothers of Preterm Babies with Mothers of Term Babies

Erken Doğum Yapan Annelerde Maternal Bağlanma Düzeyi, Travma Sonrası Stres Bozukluğu, Kaygı, Depresyon Riski ve İlişkili Faktörlerin Zamanında Doğum Yapan Annelerle Karşılaştırılması

Barış Güller* (0000-0001-7911-4614), Erbu Yarcı (0000-0003-4434-0958), Ferhat Yaylacı* (0000-0002-1360-7771)**

*Dörtçelik Children's Hospital, Clinic of Child and Adolescent Psychiatry, Bursa, Turkey

**Dörtçelik Children's Hospital, Clinic of Neonatology, Bursa, Turkey

Abstract

Introduction: The aim of this study is to compare the level of attachment, post-traumatic stress disorder (PTSD), depression, anxiety risk levels, and related factors in mothers with preterm infants followed in the neonatal intensive care unit and mothers who gave birth at term in the first six months.

Materials and Methods: There were 72 mothers who gave birth prematurely and 66 mothers who gave birth at term included in the study. Hospital Anxiety Depression Scale (HADS), Perinatal Post Traumatic Stress Disorder Scale-II (PPQ-II), Maternal Attachment Inventory (MAI), and Parental Bonding Instrument (PBI) were filled in by the mothers.

Results: The number of days after birth was 76.79±43.01 in preterm babies and 78.57±36.48 in term babies. There was no significant difference between the two groups regarding the days after birth (p=0.548). The mean maternal age of preterm babies was 29.36±6.17 years. There was no significant difference between the two groups regarding the mean maternal age (p=0.717). In mothers who gave birth prematurely, the rate of having less than a high school education level was higher (p=0.036) and the monthly income level was lower (p=0.012). The mean scores of MAI (p=0.026), PPQ-II (p=0.018), and HADS depression scores were higher in mothers who gave birth prematurely (p=0.018). A significant negative correlation was found between PPQ-II and the baby's birth weight (r=-0.186; p=0.029). A negative correlation was found between HADS depression scores and the birth week (r=-0.188; p=0.027), baby's birth weight (r=-0.262; p=0.002), maternal age (r=-0.190; p=0.025), maternal education level (r=-0.227; p=0.007) and monthly income level (r=-0.168; p=0.049).

Conclusion: Our study provides important data that the risk level of PTSD and depression is high in mothers who gave birth prematurely, and factors such as maternal age, education level, socioeconomic level, birth week, and baby's weight are associated with these risks. It is also noteworthy that the level of attachment to the baby is higher in mothers who gave birth prematurely. Our results emphasize the importance of investigating the psychological reactions of mothers in the early postpartum period, receiving post-natal support, and having a social worker and psychologist in neonatal intensive care units.

Keywords
Premature birth, maternal attachment, post-traumatic stress disorder, maternal mental health

Anahtar kelimeler
Erken doğum, maternal bağlanma, travma sonrası stres bozukluğu, anne ruh sağlığı

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Address for Correspondence/Yazışma Adresi: Barış Güller MD, Dörtçelik Child Hospital, Clinic of Children's and Adolescent Psychiatry, Bursa, Turkey
Phone: +90 224 275 20 00
E-mail: drbarisguller@gmail.com

Öz

Giriş: Çalışmanın amacı yenidoğan yoğun bakım servisinde takip edilmiş erken doğan bebek sahibi anneler ile hastanemize doğum sonrası bebeğini rutin kontrol için getiren zamanında doğum yapan annelerde bağlanma düzeyi, travma sonrası stres bozukluğu (TSSB), depresyon, kaygı risk düzeylerinin ve ilişkili faktörlerin karşılaştırılmasıdır.

Gereç ve Yöntem: Çalışmaya dahil edilen erken doğum yapan anne sayısı 72, zamanında doğum yapan anne sayısı ise 66 idi. Anneler tarafından Hastane Anksiyete Depresyon Ölçeği (HADÖ), Perinatal Travma Sonrası Stres Bozukluğu Ölçeği-II (PTÖ-II), Maternal Bağlanma Ölçeği (MBÖ) ve Ana Babaya Bağlanma Ölçeği (ABBÖ) doldurudu.

Bulgular: Erken doğan bebeklerde doğum sonrası geçen gün sayısı 76,79±43,01, zamanında doğan bebeklerde 78,57±36,48 idi. Doğum sonrası geçen gün için iki grup arasında anlamlı farklılık yoktu (p=0,548). Erken doğan bebeklerin anne yaş ortalaması 29,36±6,17 yıl bulundu. Anne yaş ortalamaları için iki grup arasında anlamlı farklılık yoktu (p=0,717). Erken doğum yapan annelerde lise altı eğitim düzeyine sahip olmak daha yüksek (p=0,036), aylık gelir düzeyi daha düşüktü (p=0,012). Erken doğum yapan annelerde MBÖ (p=0,026), PTÖ-II (p=0,018) ve HADÖ depresyon puan ortalaması daha yüksekti (p=0,018). PTÖ-II ile bebeğin doğum kilosu arasında negatif korelasyon saptandı. (r=-0,186; p=0,029). HADÖ depresyon ile doğum haftası (r=-0,188; p=0,027), bebeğin doğum kilosu (r=-0,262; p=0,002), anne yaşı (r=-0,190; p=0,025), anne eğitim düzeyi (r=-0,227; p=0,007) ve aylık gelir düzeyi (r=-0,168; p=0,049) arasında negatif korelasyon bulundu.

Sonuç: Çalışmamız erken doğum yapan annelerde TSSB ve depresyon risk düzeyinin yüksek olduğu, anne yaşı, eğitim düzeyi, sosyoekonomik düzey, bebeğin doğum haftası ve ağırlığı gibi faktörlerin bu riskler ile ilişkili faktörler olduğu şeklinde önemli veriler sunmaktadır. Ayrıca erken doğum yapan annelerde bebeğe bağlanma düzeyinin daha yüksek bulunması da dikkat çekicidir. Sonuçlarımız, erken doğum sonrası annelerin psikolojik tepkilerinin erken dönemde araştırılmasının ve doğum sonrası destek almasının, yenidoğan yoğun bakım ünitelerinde sosyal çalışma uzmanı ve psikolog bulundurulmasının önemini vurgulamaktadır.

Introduction

The World Health Organization (WHO) defines births that occur before the 37th gestational week as preterm birth. According to research supported by the American Psychiatric Association and WHO; 15 million babies were born prematurely in 2010 (1). Premature babies are at high risk for neurodevelopmental, gastrointestinal, and respiratory problems. It has been reported that mothers who gave birth prematurely may experience more stress, and financial and relationship difficulties compared to those who gave birth on time due to existing risks and care problems (2). Attachment is a strong bond that develops between the baby and the mother (primary caregiver) and creates a sense of trust (3). In addition, the secure attachment of the mother to her own parents may also positively affect the bond she will establish with her baby (4). Besides, the level of attachment of the mother to her own parents may affect the postnatal mental health of the mother (5). The postpartum period is a source of stress for most mothers. In preterm birth, factors such as the threats to the health of the baby, separation from the baby due to the intensive care process, and the risk of retardation in the baby's physical development can be counted amongst stressful life events. For all these reasons, mothers who gave birth prematurely have a higher risk of mental health deterioration than those who gave birth on time (6). In the literature, high PTSD, anxiety, and depression symptoms have been reported in mothers who gave birth prematurely in the first 6 months postpartum (7,8). Mental health deterioration in mothers who gave birth prematurely may also lead to attachment problems by reducing accessibility for the baby (9). In addition, it has been shown that the risk of postpartum depression is higher in mothers with insecure attachments when compared to mothers who have a secure attachment with their babies (10).

In our country, although some studies investigate mental health symptoms and mother-infant attachment in mothers with preterm babies, the number of studies evaluating a mother's attachment to her own parents and baby, as well as PTSD, depression, and anxiety risk levels is limited.

The aim of this study is to compare the level of attachment, PTSD, depression, anxiety risk levels, and related factors in the first six months of mothers with preterm infants who were hospitalized in the neonatal intensive care unit of a secondary-level children's hospital and mothers with term infants who were brought to the same hospital for routine controls. The hypotheses of the study include that preterm birth will negatively affect the attachment between the mother and the baby, and the unhealthy attachment relationship of the mother with her own parents may increase this risk. In addition, it was found that the risk levels of PTSD, depression, and anxiety were higher in mothers

who gave birth prematurely. It is also predicted that increasing maternal and infant-related characteristics such as maternal education level, socioeconomic status, week of birth, and baby weight may also protect maternal mental health.

Materials and Methods

In the study, 77 mothers with preterm babies who were treated in the neonatal intensive care unit of a secondary-level regional pediatric hospital and 74 mothers with term babies who were brought to outpatient clinics other than child psychiatry in the same hospital for routine postnatal check-ups were contacted. Among the mothers who gave birth prematurely and whose babies were hospitalized in the neonatal intensive care unit between June 2021 and March 2022, and met the inclusion criteria were included in the study. The mothers who gave birth prematurely were contacted via the contact information in their files and informed about the study. They filled in the forms when they brought their babies to the hospital for routine control and if the babies had already been routinely checked, they were invited to the hospital to fill in the forms. Moreover, mothers who gave term births filled out the forms after being directed to the child psychiatry outpatient clinic during their application for routine control in other hospital departments. Among the mothers who gave birth prematurely, the ones who gave birth one to six months ago were included in the study.

The mothers who were illiterate, who had a baby with congenital anomalies, and congenital neurological and motor deficits were excluded from the study. Stage 1-2-3 hypoxic-ischemic encephalopathy patients who were diagnosed with perinatal asphyxia and treated for hypothermia due to the disease and those who were followed up with the diagnosis of acute bilirubin encephalopathy due to indirect hyperbilirubinemia were excluded from the study. Five mothers who gave birth prematurely and eight who gave birth at term were excluded from the study due to missing data and incorrect form filling. As a result, the number of mothers with preterm babies included in the analysis was 72 and the number of mothers with term babies was 66. After being included and informed about the study, the mothers completed the sociodemographic data form, HADS to determine the risk of depression and anxiety, PPQ-II to measure how often the symptoms of PTSD were experienced in the postpartum period, MAI to measure maternal attachment to their babies, and PBI to measure the attachment pattern to their own parents. Ethical approval was obtained for the study from Uludağ University Clinical Research Ethics Committee dated 26.05.2021 and numbered 2021-6/25.

Assessment Tools

Sociodemographic Data Form

Regarding the parents, there were questions in the form such as the age of the mother and father, their education level, their working status, occupations, current number of children, the presence of a known health problem or a chronic disease in the mother, whether the mother has had a past or present psychiatric disorder, if the parents were together or separated, and the monthly income level of the family. The monthly income level of the family was evaluated in Turkish lira, and statistical analyzes were made by dividing them into two groups according to the income level as the minimum wage and below and above the minimum wage. Regarding the pregnancy process of the mother, questions including whether there was a previous miscarriage or child loss, whether assisted reproductive techniques (in vitro fertilization) were used in the last pregnancy, whether any intervention was applied in the last birth to assist the birth (such as the use of vacuum, forceps), the last type of delivery (normal, cesarean delivery), whether there was a history of a problematic or risky pregnancy were asked. The mothers were informed that the presence of conditions such as having a pregnancy under the age of 18, the mother being overweight, having diseases prior to the pregnancy such as cardiac diseases, diabetes mellitus, hypertension, and epilepsy, having an overweight baby, history of ectopic pregnancy, history of multiple pregnancies such as twins or triplets and retardation in the baby's development were considered as risky pregnancies and they were then asked to indicate if any of these conditions were present. The form also included questions regarding the baby's date of birth, birth week, birth weight, the timing of the birth (preterm, term), the baby's gender, feeding style (bottle or breastfeeding), and feeding type (breast milk, formula, mixed).

Maternal Attachment Inventory (MAI)

Maternal attachment on the 26-item scale was tested in two phases. The first phase occurs around a month after birth, includes physical recovery, and the time when the mother is busy with the care of herself and her baby, and the second phase, which is completed in the fourth or fifth months after the birth, is when the maternal identity is gained and the feeling of attachment to the baby and maternal competence is at the highest level. A high score indicates high maternal attachment. In the scale development study, Cronbach's alpha was found to be 0.76 in the fourth month after birth, and 0.85 in the eighth month. The MAI is a self-administered scale that can be filled in by literate women. In the Turkish validity and reliability study conducted by Kavlak and Şirin (12), the MAI was found to be valid and reliable in mothers who had a baby of at least one month old (11).

Perinatal Post-traumatic Stress Disorder Scale-II (PPQ-II)

It measures the frequency of post-traumatic symptoms related to the birth experience, such as disturbing thoughts, re-experiencing, avoidance behaviors, hyperarousal, numbness, and feelings of guilt, within one year after birth. High scores obtained from the scale indicate a high level of perinatal trauma symptoms (13). The Turkish validity and reliability study was performed by Komurcu Akik and Durak Batigun (14). The analysis revealed that the PPQ-II is a valid and reliable scale for measuring the symptoms of perinatal post-traumatic stress experienced by the mother (14).

Parental Bonding Instrument (PBI)

The individual is asked to indicate how much the items reflect the behaviors of her mother or father regarding the first 16 years of her life. It can be filled by male or female adult individuals. No age range has been reported for it. A high score in the care dimension indicates the warm, understanding, and accepting perception of the concerned parent. The high scores obtained from the over-protection sub-dimension indicate that parents exhibit an attitude that is not overprotective or against autonomy. The increase in the total score and sub-dimensions indicates positive attachment (15). Turkish validity and reliability study was performed by Kapçı and Küçüker (16).

Hospital Anxiety and Depression Scale (HADS)

It was developed to determine the risk of anxiety and depression in patients and to measure its level and change in severity (17). The Turkish validity and reliability study of the scale was conducted in a group of 213 healthy university students aged 18-28 and a group of 136 patients (66 males and 70 females) aged 17-79 years, who had any physical illness, and it was reported that it was a valid and reliable scale in both groups. The cut-off points were determined as 10 for the anxiety subscale and 7 for the depression subscale. The Turkish validity and reliability study was performed by Aydemir et al. (18).

Statistical Analysis

SPSS statistical package program (SPSS for Windows, 25.0) was used for data entry and analysis. Data obtained by measurement are shown as arithmetic mean ± standard deviation, and data obtained by counting as a percentage (%). Kolmogorov Smirnov test was used to evaluate the fit of numerical variables to normal distribution. Categorical variables such as children's gender, parental education levels, and monthly income level were compared with chi-square analysis and Fisher's Exact test. The mean scores of MAI, PPQ-II, PBI, and HADS were compared with the Mann-Whitney U test because the data were not normally distributed. Spearman correlation analysis was used for non-normally distributed data while comparing the relationships between MAI, PPQ-II, PBI, and HADS subscales and monthly family income, maternal education level, and birth week. Statistical significance was accepted as $p<0.05$ at the 95% confidence interval.

Results

There were 72 mothers who gave preterm births and 66 mothers who gave term births who filled out the forms completely. The number of days after birth was 76.79±43.01 in preterm babies and 78.57±36.48 in term babies. There was no significant difference between the two groups regarding the days after birth ($p=0.548$). Female babies consisted of 54.2% of preterm babies and 43.9% of term babies. There was no significant difference between the two groups regarding the genders of the babies ($p=0.230$). The mean age of mothers of preterm babies was

29.36±6.17 years, and the mean age of the fathers of these preterm babies was 33.51±6.52 years. The mean age of mothers of term babies was 29.83±5.54 years, and the mean age of fathers of these term babies was 33.30±5.88 years. There was no significant difference between the two groups regarding the mean age of the mother and father (the p-value for the mean age of the mother=0.717, the p-value for the mean age of the father=0.829). While 44.4% of mothers who gave birth prematurely had an education level below high school, this level was found to be 27.3% in mothers who gave birth at term. The mothers who gave birth prematurely were more likely to have an education level below high school (p=0.036). Besides, the monthly income level was significantly lower in this group of mothers (p=0.012). No significant difference was seen between the two groups in comparisons regarding the father's education level (p=0.637), mother's employment status (p=0.961), father's employment status (p=0.227), presence of siblings of the baby (p=0.483) and parental marital status (p=0.227) (Table 1).

In mothers who gave preterm birth, having a history of risky pregnancy in the past was significantly higher (p=0.007) while feeding the baby with breast milk (p=0.026) and breastfeeding (p=0.011) rates were significantly lower. Also, no significant difference was found between the two groups in the comparisons regarding whether there was a previous loss of children (p=0.682), whether assisted reproductive technology was used for pregnancy (p=1.000), whether there was an assisted intervention during labor (p=0.368), whether the mother had a physical illness (p=0.068), the presence of psychiatric disease in the mother (p=0.497), and type of delivery (p=0.103) (Table 2).

The mean MAI score in mothers who gave birth prematurely (99.05±6.67) was significantly higher than in mothers who gave birth at term (97.30±5.58) (p=0.026). The mean PBI over protection control

Table 1. Socio-demographic features

		Preterm birth n (%)	Term birth n (%)	p
Days after birth (mean ± SD)		76.79 (±43.01)	78.57 (±36.48)	0.548**
Baby's gender	Female	39 (54.2)	29 (43.9)	0.230*
	Male	33 (45.8)	37 (56,1)	
Birth week (mean ± SD)		34.38 (±1.91)	38.45 (±1,67)	<0.001**
Birth weight (mean ± SD) (gram)		2461.37 (±691.22)	3283,39 (±596.16)	<0.001**
Mother's age (mean ± SD) (year)		29.36 (±6.17)	29.83 (±5.54)	0.717**
Father's age (mean ± SD) (year)		33.51(±6.52)	33.30 (±5.88)	0.829**
Mother's educational level	Below high school	32 (44.4)	18 (27.3)	0.036
	High school and above	40 (55.6)	48 (72.7)	
Father's educational level	Below high school	29 (59.7)	24 (36.4)	0.637*
	High school and above	43 (40,3)	42 (63.6)	
Mother's working status	Working	21 (29.2)	19 (28.8)	0.961*
	Not working	51 (70.8)	47 (71.2)	
Father's working status	Working	72 (100)	64 (97)	0.227***
	Not working	0 (0)	2 (3)	
Monthly income level	Minimum wage or below	53 (73.6)	35 (53.0)	0.012*
	Above the minimum wage	19 (26.4)	31 (47.0)	
Siblings	Yes	53 (73.6)	45 (68.2)	0.483*
	No	19 (26.4)	21(31.8)	
Marital status	Married	72 (100)	64 (97)	0.227***
	Divorced	0 (0)	2 (3)	

*Chi-square tests, **Mann-Whitney U Test, ***Fisher's Exact test, n: Number, %: Percentage, SD: Standard deviation

dimension score in mothers who gave birth prematurely (24.31±5.73) was significantly lower than in mothers who gave birth at term (26.19±5.57) (p=0.048). The mean PBI care dimension score was found to be 23.61±7.58 in mothers who gave birth prematurely, and 23.86±6.34 in mothers who gave birth at term. In addition, while the mean PBI total score was 47.93±11.69 in mothers who gave birth prematurely, it was 50.21±10.01 in mothers who gave birth at term. There was no significant difference between the two groups for the mean PBI care dimension and PBI total score (p=0.843 and p=0.289, respectively). The mean PPQ-II score (16.40±6.67) in mothers who gave birth prematurely was found to be significantly higher compared to mothers who gave birth at term (12.34 ±7.03) (p=0.018). In addition, the mean HADS depression subscale score in mothers who gave birth prematurely (7.47±3.39) was significantly higher than in mothers who gave birth at term (5.95±3.10) (p=0.018). Although the mean HADS anxiety subscale score (8.52±4.14) was higher in mothers who gave birth prematurely compared to mothers who gave birth at term (7.28±4.19), this difference was not statistically significant (p=0.085) (Table 3).

In our study, correlation analyzes were performed for PBI, MAI, PPQ-II, HADS, week of birth, birth weight, maternal age, maternal education level, and family monthly income. A significant positive correlation was found between PPQ-II and HADS-A (r=0.565; p=0.000) and between PPQ-II and HADS-D (r=0.413; p<0.001). There was also a significant positive correlation between HADS-A and HADS-D subscales (r=0.585; p<0.001). A significant negative correlation was found between PPQ-II and the baby's birth weight (r=-0.186; p=0.029). A significant negative correlation was found between the HADS-D subscale and birth week (r=-0.188; p=0.027), birth weight of the baby (r=-0.262; p=0.002), maternal age (r=-0.190; p=0.025), maternal education level (r=-0.227; p=0.007) and the monthly income level of the family (r=-0.168; p=0.049) (Table 4).

Table 2. Birth and postnatal characteristics of the mother and the baby

		Preterm birth n (%)	Term birth n (%)	p
Ever lost a child before?	Yes	4 (5.6)	2 (3)	0.682**
	No	68 (94.4)	64 (97)	
Ever had a high-risk pregnancy?	Yes	24 (33.3)	9 (13.6)	0.007*
	No	48 (66.7)	57 (86.4)	
Was there any assisted reproductive technique in the last pregnancy?	Yes	2 (2.8)	2 (3.0)	1.000**
	No	70 (97.2)	64 (97.0)	
Was there an assisted intervention in child birth?	Yes	4 (5.6)	1 (1.5)	0.368**
	No	68 (94.4)	65 (98.5)	
The birth method	Normal	23 (31.9)	30 (45.5)	0.103*
	C-Section	49 (68.1)	36 (54.5)	
Method of feeding the baby	Bottle	23 (31.9)	9 (13.6)	0.011*
	Breastfeeding	49 (68.1)	57 (86.4)	
Baby's feeding type	Breastmilk	35 (48.6)	47 (71.2)	0.026*
	Formula	10 (13.9)	5 (7.6)	
	Mixed (formula + breastmilk)	27 (37.5)	14 (21.2)	
Presence of a physical illness in the mother	Yes	13 (18.1)	5 (7.6)	0.068*
	No	59 (81.9)	61 (92.4)	
Presence of a known psychiatric illness in the mother	Yes	6 (8.3)	3 (4.5)	0.497**
	No	66 (91.7)	63 (95.5)	

*Chi-square tests, **Fisher's Exact test, n: Number, %: Percentage

Discussion

Our study in which we compared the attachment level, risk levels for PTSD, depression, anxiety disorder, and related factors of mothers with preterm babies followed up in the neonatal intensive care unit of a secondary care pediatric hospital with mothers with term babies in the first six months after birth, provides important data stating that PTSD and depression risk levels are high in mothers who gave birth prematurely, and factors such as maternal education level, maternal age, socioeconomic level, baby's birth weight and birth week are associated with these risk levels. Moreover, it is remarkable that only the birth weight of the baby was found to be associated with the PTSD risk level in the mother among the factors related to the baby and the mother.

Table 3. Comparison of MAI, PBI, PPQ-II, and HADS scores in mothers

	Mean ± SD		p*
	Preterm birth	Term birth	
Maternal attachment inventory	99.05 (±6.67)	97.30 (±5.58)	0.026
Perinatal post-traumatic stress disorder scale-II	16.40 (±6.67)	12.34 (±7.03)	0.018
Parental bonding instrument care dimension	23.61 (±7.58)	23.86 (±6.34)	0.843
Parental bonding instrument over protection control dimension	24.31 (±5.73)	26.19 (5.57)	0.048
Parental bonding instrument total score	47.93 (±11.69)	50.21 (±10.01)	0.289
HADS anxiety scale	8.52 (±4.14)	7.28 (±4.19)	0.085
HADS depression scale	7.47 (±3.39)	5.95 (±3.10)	0.018

MAI: Maternal attachment inventory, PBI: Parental Bonding Instrument, PPQ-II: Perinatal post-traumatic stress disorder scale-II, HADS: Hospital anxiety and depression scale,*Mann-Whitney U test, SD: Standard deviation

Table 4. Correlations between the birth week of children, income level, maternal education level, PBI, MAI, PPQ-II and HADS

	PBI	MAI	PPQ-II	HADS-A	HADS-D
PBI					
MAI	0.034 (p=0.690)	-	-	-	-
PPQ-II	-0.100 (p=0.245)	-0.118 (p=0.167)	-	-	-
HADS-A	-0.028 (p=0.743)	0.001 (p=0.988)	0.565 (p=0.000)	-	-
HADS-D	-0,147 (p=0.085)	-0,110 (p=0.201)	0,413 (p<0.001)	0.585 (p<0.001)	-
Birth week	0.105 (p=0.218)	-0.104 (p=0.224)	-0.129 (p=0.130)	-0.009 (p=0.912)	-0.188 (p=0.027)
Birth weight	0.069 (p=0.421)	-0.018 (p=0.838)	-0.186 (p=0.029)	-0.097 (p=0.258)	-0.262 (p=0.002)
Maternal age	0.017 (p=0.844)	-0.023 (p=0.792)	-0.022 (p=0.802)	0.001 (p=0,992)	-0.190 (p=0.025)
Maternal education level	0.266 (p=0.002)	-0.115 (p=0.180)	0.053 (p=0.538)	0.138 (p=0.107)	-0.227 (p=0.007)
Monthly income level	0.236 (p=0.005)	-0.194 (p=0.023)	0.074 (p=0.386)	-0.050 (p=0.563)	-0.168 (p=0.049)

Spearman's correlation analysis, MAI: Maternal attachment inventory, PBI: Parental bonding instrument, PPQ-II: Perinatal post-traumatic stress disorder scale-II, HADS: Hospital anxiety and depression scale

In a study conducted with mothers whose babies were followed up in the neonatal intensive care unit, a positive correlation was found between the birth week and breastfeeding self-efficacy, which is defined as the mother's sense of efficacy to breastfeed (19). Additionally, there are studies reporting fewer depressive symptoms in mothers who feed their babies with breastmilk or breastfeed after birth compared to mothers who feed them with formula (20,21). The fact that feeding the baby with breastmilk and breastfeeding rates were lower in mothers who gave birth prematurely, and that HADS depression scores were higher in mothers who gave birth prematurely in our study is compatible with the literature. Considering the positive effects of breastfeeding on maternal mental health and the relationship with the baby, it is important to try to bring the baby together with the mother as early and frequently as possible during the period of stay in the neonatal intensive care unit. In our study, mothers who gave birth prematurely had a higher rate of education level below high school and a lower monthly income. In a study conducted in 2014, low socioeconomic level and low education level were counted among the risk factors for preterm birth (22). Considering the literature data and our study findings, it is seen that close follow-up of those living in socioeconomically disadvantaged regions during pregnancy is important due to the risk of preterm birth.

In a 2013 study, the mean MAI score of 140 mothers whose babies were between 1-4 months old and were treated in the neonatal intensive care unit was found to be 87.19±5.46 (23). The mean MAI score being higher in our study compared to the 2013 study may be explained by the inclusion of mothers whose babies were discharged from the intensive care unit. The increase in mothers' chances of establishing physical intimacy with their babies in the post-discharge period may have increased the MAI scores. While there are studies in the literature showing that preterm birth poses a problem in mother-infant attachment, there are also studies that indicate preterm babies and mothers can be securely attached. In a study conducted with 50 mothers with preterm babies and 30 mothers with term babies in 2006, it was found that only 20% of mothers who gave birth prematurely had a secure attachment 6 months after the birth, while this rate was 53% in those who gave birth at term (24). In another study from 2008, no significant difference was found between the attachment levels of 38 mothers of preterm babies and 45 mothers of term babies. In the same study, it was reported that mothers who gave birth prematurely had the same chance of establishing a secure attachment as mothers who gave birth on time (25). In our study, there was no relationship between maternal age and education level, and mother-child attachment level. In another study investigating the effects of prenatal, perinatal, and postnatal factors on mother-infant attachment, no relationship was found between attachment level and maternal age and education level (26). In the study of Kinsey et al. (27), postpartum attachment scores were found to be lower in older, more educated mothers. Our findings and literature data show that many factors other than socioeconomic level and education level can be effective in the attachment between the mother and the child. In addition, the risk level in many areas such as retardation in fine and gross motor skills, speech delay, learning difficulties, attention deficit, and behavioral problems is higher in preterm children compared to term children (28). It is reported that the level of attachment between the mother and the baby is effective in the emotional, cognitive and physical development of the baby (29). From this point of view, high maternal attachment in mothers who gave birth prematurely in our study can be seen as a protective factor against neurodevelopmental problems in preterm infants.

Although there is data in the literature showing that the mother's level of attachment to her own parents is a predictor of the level of attachment to her baby and the mother's postpartum mental health symptoms, there was no relationship between PBI and MAI, PPQ-II and HADS scales in our study. In addition, there was no significant difference between mothers who delivered prematurely and at term regarding the total mean score of PBI (4,5). One reason for our study findings being different from the literature may be the difficulties experienced by mothers in remembering their relationships with their parents retrospectively, given the stressful postpartum period. In addition, mothers who give birth prematurely may need intensive support from their parents, especially in the postpartum period. In our study, data were collected after the discharge of preterm infants from our hospital. This may have caused bias in their assessment of their attachment levels to their parents.

In the literature, high levels of PTSD have been reported in the first 6 months postpartum in mothers who gave birth prematurely (7). In another study conducted with mothers who gave birth prematurely, it has been reported that on the 1-3 days, 14th day, and 14th month postpartum, they scored higher in questions about traumatic experience compared to the mothers who gave birth at term and that there was no significant decrease in PTSD symptoms on the 14th month (30). The fact that the mean PPQ-II score was higher in mothers who gave birth prematurely in our study is consistent with the literature data. In a study investigating the factors affecting PTSD in mothers with newborn children, factors such as gestational age, baby gender, length of hospital stay, feeding the baby, and mode of delivery were not found to be associated with PTSD. As a result of the study, it was emphasized that preterm birth is traumatic for all parents, regardless of sociodemographic characteristics or the health status of the baby (31). In our study, only a negative correlation was found between the baby's birth weight and PPQ-II. One of the conditions for the newborn to be discharged from the intensive care unit is that the baby reaches an adaptable weight. Even after a long time after birth, parents may be concerned about the baby's weight. The fact that traumatic reactions due to preterm birth were mostly associated with the weight of the baby in a 2014 study, is consistent with the finding we obtained from the study (32).

A 2019 meta-analysis and review study investigated preterm birth as a risk factor for postpartum depression over the past 10 years. It was concluded that although there are methodological differences between the studies, the existence of a relationship between postpartum depression and preterm birth was reported in the majority of the studies (33). In a study investigating postpartum stress and related factors, the risk of depression was reported to be twice as high in mothers who gave birth prematurely compared to mothers who gave birth at term. The risk was found to be higher in mothers who are younger, less educated, and have a lower income (34). In our study, a significant negative correlation was found between the HADS-D subscale and birth week, birth weight, maternal age, maternal education level, and monthly income level. In a study examining the long-term effects of postpartum depression in mothers who gave birth prematurely, 181 mothers and babies were evaluated at five separate times. Although mothers' depression levels decreased over time, symptoms decreased more slowly in those with babies with lower birth weight and in those with lower education and income level (35). The experience that emerged with the increase in parental age may have made it easier for the mother to make sense of the difficulties she faces and to cope with them more easily. Considering the fact that mothers who give birth prematurely are often from regions with low socioeconomic and educational levels and it is more difficult for those living in these regions to reach psychosocial support, the support that can be provided during pregnancy for those living in these regions may contribute to better management of the postpartum period.

Stress is a psychological phenomenon that can manifest in the form of anxiety, depression, and trauma reactions. Although the comorbidity of anxiety and depression in post-traumatic stress reactions is well known, information on the comorbidity of PTSD after preterm birth is more limited (30). In our study, a positive correlation was found between PPQ-II, HADS-A, and HADS-D scales. In a study evaluating the mental health of mothers who gave birth prematurely, the prevalences of post-traumatic stress reactions, depression and anxiety were found to be 52%, 28%, and 17%, respectively. In the same study, it was emphasized that preterm birth can be an important trauma factor for the mother, and the prevalence of depression and anxiety is lower in the mother compared to post-traumatic stress reactions (36). In a study investigating the stress level of mothers who gave birth prematurely, it was reported that there was a relationship between high-level PTSD symptoms (>33%) and high-level depression (>53%) symptoms (37). Providing support to mothers in the early post partum period is critical for reducing depression, anxiety, and traumatic stress levels. This support may include providing information about the condition of preterm babies and helping the mother make sense of her feelings.

Study Limitations

The strengths of the study are the presence of a control group, the evaluation of mothers' attachment levels to both their parents and their babies, and the use of scales that separately assess the risk of anxiety, depression, and PTSD. Despite its strengths, some

limitations can also be mentioned. The limitations of our study include the fact that only self-report scales were filled, the study was conducted in a single center, separate statistics were not made by grouping preterm infants as early, medium, late, and preterm, and the length of stay in the intensive care unit was not reported.

Conclusion

One of the remarkable results of our study is that the mean score of MAI was higher in mothers who gave birth prematurely than in mothers who gave birth at term. In addition, no relationship was found between factors such as maternal age, education level, and the level of attachment between the mother and the baby. Although there have been similar results in the literature, multicenter studies with larger samples will be useful in terms of generalizing these results. Our study provides important data that the risk level of PTSD and depression is high in mothers who gave birth prematurely, and factors such as maternal age, education level, socioeconomic level, birth week and weight of the baby are associated with these risks. Studies aiming to identify mothers at risk for postpartum depression in particular have been a growing area of research that contributes to the prevention and early detection of mental health deterioration (38). Our results emphasize the importance of investigating the psychological reactions of mothers in the early postpartum period, receiving postnatal support, and having a social worker and psychologist in neonatal intensive care units.

Ethics

Ethics Committee Approval: Ethical approval was obtained for the study from Uludağ University Clinical Research Ethics Committee dated 26.05.2021 and numbered 2021-6/25.

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Acute Organ Toxicity, Biochemical and Metabolic Changes in Pediatric Oncology Patients

Çocuk Onkoloji Hastalarında Akut Organ Toksisiteleri, Biyokimyasal ve Metabolik Değişikliklerin Değerlendirilmesi

Hasan Türkmen* (0000-0001-5501-6905), Metin Demirkaya (0000-0001-6547-1872), Betül Sevinir*** (0000-0002-3232-7652)**

*Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Turkey

**Biruni University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Oncology, İstanbul, Turkey

***Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Oncology, Bursa, Turkey

Abstract

Introduction: Organ toxicity is common in childhood cancers and can cause delays in chemotherapy and worsening of prognosis. In this study, we aimed to evaluate organ toxicities, biochemical and metabolic abnormalities associated with the tumor and/or chemotherapy in the acute phase of treatment in children with cancer.

Materials and Methods: The data of 305 patients with lymphoma and solid tumors who received chemotherapy between 01.01.2010 and 31.12.2015 in a tertiary healthcare facility were retrospectively evaluated. The effects of age, gender, cancer stage, chemotherapy group, surgery and radiotherapy on organ toxicity in the first 30 days of treatment were analyzed.

Results: The mean age of the patients at admission was 97 months, and the male/female ratio was 1.5. The most common diagnoses were lymphomas (27.6%), CNS and spinal canal tumors (12.5%) and neuroblastoma (11.8%). Chemotherapy was applied to all the patients, surgery to 61.3% (n=187), and radiotherapy to 13.1% (n=40). Organ toxicity was detected in 59% (n=180) of the patients. The use of alkylating agents, antimetabolites, plant products, and no surgery were risk factors for hepatotoxicity ($p<0.05$). The only risk factor for nephrotoxicity was antimetabolite drug use ($p<0.05$). The most common electrolyte disorder was hyponatremia, observed in 56.7% (n=173) of the patients. Two patients died during the study period, which were not due to organ toxicity, metabolic disease, or electrolyte disturbance.

Conclusion: The rate of organ toxicity as well as biochemical, electrolyte, and metabolic abnormalities were found to be high. These high rates were thought to be related to the excessive tumor burden and organ involvement and the intensity of the combined chemotherapies applied. No associated mortality was observed despite these high rates. Early detection of these pathologies, close follow-up and immediate treatment with the multidisciplinary approach to treatment were described as the reason for the absence of mortality.

Öz

Giriş: Çocukluk çağı kanserlerinde organ toksisiteleri yüksek oranda görülmekte olup, kemoterapinin aksamasına ve prognozun giderek kötüleşmesine yol açabilirler. Bu çalışmada; kanserli çocuklarda tedavinin akut döneminde tümör ve/veya kemoterapi ile ilişkili görülen organ toksisiteleri, biyokimyasal ve metabolik anormalliklerin değerlendirilmesi amaçlanmıştır.

Keywords
Childhood cancers, chemotherapy, hepatotoxicity, nephrotoxicity, electrolyte imbalance

Anahtar kelimeler
Çocukluk çağı kanserleri, kemoterapi, hepatotoksisite, nefrotoksisite, elektrolit dengesizliği

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Address for Correspondence/Yazışma Adresi: Hasan Türkmen MD, Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Turkey
Phone: +90 224 295 04 54
E-mail: hasanturkmen28@gmail.com

Gereç ve Yöntem: Üçüncü basamak bir sağlık kuruluşunda 01.01.2010-31.12.2015 tarihleri arasında kemoterapi alan 305 lenfoma ve solid tümörlü hastanın verileri retrospektif olarak değerlendirildi. Yaş, cinsiyet, kanser evresi, kemoterapi grubu, cerrahi ve radyoterapinin, tedavinin ilk 30 gün içindeki organ toksisitesi üzerine etkileri analiz edildi.
Bulgular: Hastaların başvurudaki yaş ortalaması 97 ay, erkek/kız oranı 1,5 idi. En sık görülen tanılar sırasıyla lenfomalar (%27,6), SSS ve spinal kanal tümörleri (%12,5) ve nöroblastomdu (%11,8). Hastaların tümüne kemoterapi, %61,3'üne (n=187) cerrahi, %13,1'ine (n=40) radyoterapi uygulandı. Hastaların %59'unda (n=180) organ toksisitesi saptandı. Alkilleyici ajan, antimetabolit ve bitki kökenli ilaç kullanımı ve cerrahi uygulanmaması hepatotoksisite için risk faktörleriydi (p<0,05). Nefrotoksisite için tek risk faktörü antimetabolit ilaç kullanımıydı. En sık görülen elektrolit bozukluğu, hastaların %56,7'sinde (n=173) görülen hiponatremiydi. Çalışma döneminde organ toksisitesi, metabolik bozukluk ya da elektrolit dengesizliği ile ilişkisiz olarak 2 hasta kaybedildi.
Sonuç: Organ toksisitesi, biyokimyasal, elektrolit ve metabolik anormalliklerin oranının oldukça yüksek olduğu saptandı. Bu oranların yüksekliğinin tümör yükünün ve organ tutulumunun fazlalığı ve uygulanan kombine kemoterapilerin yoğunluğu ile ilişkili olduğu düşünüldü. Bu oranların yüksek olmasına rağmen, ilişkili mortalite gözlenmedi. Bu patolojilerin erken saptanması, yakın takibi ve buna yönelik tedavilerin multidisipliner yaklaşımla hemen uygulanması mortalite gözlenmeme nedeni olarak açıklandı.

Introduction

Antineoplastic drugs are the main components of cancer treatment. While they can prevent the proliferation of cancer cells and destroy them, they can also cause organ toxicity by affecting the liver, kidney, heart, respiratory system, nervous system as well as rapidly growing cells such as bone marrow, mucosa, and hair cells (1,2). Also organ toxicity can be seen due to disease involvement or additional treatments. Although the severity and frequency of the toxicity of chemotherapy drugs differ, failure to control the side effects may lead to a reduction or termination of the treatment dose or the patients abandoning the treatment. In this study, organ toxicities, biochemical and metabolic abnormalities associated with tumor and/or chemotherapy were evaluated in the acute treatment phase of children with cancer.

Materials and Methods

Patients aged 0-18 years with lymphoma and solid tumors who received chemotherapy at a tertiary healthcare facility, between 01.01.2010 and 31.12.2015 were included in this study. Patients with benign tumors, those who received only radiotherapy and/or surgery but did not receive chemotherapy, those who had a history of organ toxicity, chronic kidney or liver disease, those whose chemotherapy was started in another hospital and those with a history of an additional chronic disease (diabetes insipidus, etc.) were excluded. The records of 356 patients were reviewed retrospectively. Fifty-one patients who did not meet the inclusion criteria were excluded from the study, and the data of 305 patients were evaluated.

The patients' identity information, demographic data (date of birth, gender, and admission age), diagnosis, tumor location and organ involvement, tumor stage, chemotherapy protocol, drugs applied, chemotherapy start date, and surgery or radiotherapy were obtained from the hospital records.

The diagnoses were grouped as Hodgkin lymphoma, non-Hodgkin lymphomas, central nervous system (CNS) and spinal canal tumors, neuroblastoma and other peripheral nerve tumors, kidney tumors, liver tumors, bone tumors, soft tissue sarcomas and germ cell tumors, according to the International Classification of Cancer (ICCC-3). Malign epithelial neoplasms, melanomas, retinoblastoma, carcinomas, and histiocytoses were included in the "other" group, since they are seen with a low frequency in childhood. The tumor stage was classified as early (stages 1-2, non-metastatic) and advanced (stages 3-4, metastatic). Furthermore, the surgical method was divided into three groups, such as liver mass excision, nephrectomy, and mass excision in other regions. Chemotherapy drugs were classified into six groups as alkylating agents, antimetabolites, antitumor antibiotics, plant products, tyrosine kinase inhibitors, and others. Liver and kidney involvements were determined according to laboratory and imaging methods.

The patients' blood glucose, serum urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), serum electrolytes (sodium, potassium, chlorine, calcium, magnesium, phosphorus) and blood gas analysis results at admission and within one month from the start of chemotherapy were

compared with normal reference ranges for age, and they were classified as normal, low, or high (3).

The liver and kidney toxicities were determined and staged according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria (4). Based on these criteria, increases in liver transaminases up to three times the upper limit for age were considered as stage 1 hepatotoxicity, those for three to five times the upper limit for age as stage 2 hepatotoxicity, those between five and 20 times the upper limit for age as stage 3 hepatotoxicity, and those over 20 times the upper limit for age as stage 4 hepatotoxicity. Moreover, acute kidney injury was evaluated according to the increase in serum creatinine. Increases in serum creatinine by 1.5 times or more than the baseline were considered significant. Additionally, increases in serum creatinine by 1.5-2 times were considered as stage 1, increases by 2-3 times as stage 2, increases by more than 3 times as stage 3, patients with dialysis as stage 4, and death occurrence owing to renal failure as stage 5.

The collected data were compared statistically according to age, gender, cancer stage, chemotherapy drug, surgery, and/or radiotherapy application.

The study protocol was approved by Uludağ University Ethics Committee (approval number: 2016-15/17, date: 09.08.2016).

Statistical Analysis

The data were analyzed using SPSS software version 23.0 (IBM Inc., Chicago, IL, USA), and the results are given as mean ± SD, number, and percentage. Shapiro-Wilk test was performed to test for data normality. Additionally, t-test was used to compare continuous variables that conformed to the normal distribution, whereas the Mann-Whitney U test was used to compare continuous variables that did not conform to the normal distribution. Differences between categorical variables were analyzed using chi-square test, and the statistical significance level was set to $p<0.05$.

Results

The mean age of the 305 patients was 97.51±6.03 months (1 day-214 months), of which 60.0% (n=183) were male. Moreover, 10.5% (n=32) of the patients were one year old and younger, 27.9% (n=85) were between one and five years old, and 61.6% (n=188) were over five years old. The most common disease group was lymphomas [Hodgkin lymphoma, 14.1% (n=43); non-Hodgkin lymphomas, 13.5% (n=41)]. The second most common disease groups were CNS and spinal canal tumors, which accounted for 12.5% (n=38). Cancer staging was done for 176 patients, and 85 patients (48.3%) were evaluated as early stage and 91 patients (51.7%) as advanced stage.

Primary kidney tumor or metastasis to the kidney was found in 14.1% (n=43) of the patients, liver tumor or metastasis to the liver in 6.9% (n=21), and primary or metastatic tumor association of the liver and kidney in 0.7% (n=2).

The most commonly used antineoplastic drugs were plant products (91.1%, n=278), antitumor antibiotics (67.9%, n=207) and alkylating agents (67.2%, n=205), respectively. The patient characteristics are described in Table 1.

Surgery was performed on 61.3% (n=187) of the patients at admission or in the first month. Undamaged organ mass excision was performed on 51.5% (n=157), nephrectomy on 9.2% (n=28), liver mass excision on 0.3% (n=1), and primary mass and liver mass excision on 0.3% (n=1).

Radiotherapy was also performed on 13.1% (n=40) of the patients before chemotherapy and/or in the first month of chemotherapy.

Organ toxicity was detected in 59% (n=180) of the patients, of which 2.6% of the patients (n=8) had only nephrotoxicity, 48.5% (n=148) had only hepatotoxicity, and 7.9% (n=24) had both hepatotoxicity and nephrotoxicity. Two (0.7%) of the patients died in the first month, one due to progressive disease and the other due to septicemia.

The hepatotoxicity and nephrotoxicity rates are given according to the stages in Table 2. Stage 1 hepatotoxicity (32.1%, n=98) was the most common, whereas stage 4 hepatotoxicity (4.3%, n=13) was the least common. Nephrotoxicity was also detected in 10.5% (n=32) of the patients, of which stage 1 was the most common (8.5%, n=26) and stage 4 (requiring dialysis) was observed in two patients (0.7%).

At least one electrolyte disorder was found in 87.5% (n=267) of the patients. The most common electrolyte abnormality was hyponatremia with a rate of 56.7% (n=173). Table 3 gives the rates of biochemical abnormalities and electrolyte disturbances.

The blood gas of 79 patients was analyzed, and 21 patients (26.6%) had metabolic acidosis, 9 patients (11.4%) had metabolic alkalosis, 13 patients (16.5%)

Table 1. Characteristics of the patients	
Age [month, mean ± SD (range)]	97.51±6.03 (0.03-214)
Gender [n, (%)]	
Male	183 (60.0)
Female	122 (40.0)
Primary disease [n, (%)]	
Hodgkin lymphoma	43 (14.1)
Non-Hodgkin lymphomas	41 (13.5)
B-cell lymphomas	32 (10.5)
T-cell lymphomas	9 (3.0)
CNS and spinal canal tumors	38 (12.5)
Neuroblastoma and other peripheral nerve tumors	36 (11.8)
Kidney tumors	28 (9.2)
Liver tumors	3 (1.0)
Bone tumors	28 (9.2)
Soft tissue sarcomas	26 (8.5)
Germ cell tumors	33 (10.8)
Other	29 (9.5)
Chemotherapy drug group [n, (%)]	
Alkylating agents	205 (67.2)
Antimetabolites	59 (19.3)
Antitumor antibiotics	207 (67.9)
Plant products	278 (91.1)
Tyrosine kinase inhibitors	1 (0.3)
Other	49 (16.1)

CNS: Central nervous system, SD: Standard deviation

Table 2. Hepatotoxicity and nephrotoxicity rates according to the stage	
Hepatotoxicity [n, (%)]	
None	133 (43.6)
Stage 1	98 (32.1)
Stage 2	24 (7.9)
Stage 3	37 (12.1)
Stage 4	13 (4.3)
Nephrotoxicity [n, (%)]	
None	273 (89.5)
Stage 1	26 (8.5)
Stage 2	0 (0.0)
Stage 3	4 (1.3)
Stage 4	2 (0.7)

had respiratory acidosis, and 25 patients (31.6%) had respiratory alkalosis.

The organ toxicity rates of the patients were compared according to gender, age, cancer stage, whether radiotherapy was applied, whether surgery was performed, and the chemotherapy groups they received.

Table 3. Prevalence of biochemical abnormalities and electrolyte imbalances	
Biochemical abnormality [n, (%)]	
Hypoglycemia	35 (18.2)
Hyperglycemia	46 (24.0)
High uric acid	59 (20.1)
Hypoalbuminemia	111 (39.5)
Hyperbilirubinemia	71 (26.6)
High ALP	23 (21.5)
High GGT	10 (38.5)
Electrolyte imbalance [n, (%)]	
Hyponatremia	173 (56.7)
Hypernatremia	16 (5.2)
Hypokalemia	91 (29.8)
Hyperkalemia	144 (47.2)
Hypochloremia	99 (32.7)
Hyperchloremia	148 (48.8)
Hypocalcemia	115 (38.5)
Hypercalcemia	16 (5.4)
Hypomagnesemia	41 (17.7)
Hypermagnesemia	76 (32.9)
Hypophosphatemia	97 (39.0)
Hyperphosphatemia	30 (12.0)

ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Since the number of patients receiving tyrosine kinase inhibitors in the first month of treatment was insufficient (n=1, 0.3%), it was excluded from the statistical analysis.

It was observed that gender, age, cancer stage, and radiotherapy intake did not make any significant difference when risk factors for hepatotoxicity and nephrotoxicity were compared. Hepatotoxicity was significantly higher in patients who did not undergo surgery (66.9%) than those who received surgery (49.7%) (Table 4).

Hepatotoxicity was significantly higher in patients who received alkylating agents (64.4%) compared to those who did not (40%), patients who received antimetabolite drugs (94.9%) compared to those who did not (47.2%), and patients who received "other" chemotherapy (84.7%) compared to those who did not (50.8%) (Table 5). There was also no significant difference in hepatotoxicity between patients who received plant products and those who did not, as well as between patients who received antitumor antibiotic drugs and those who did not. The rate of nephrotoxicity was found to be significantly higher in patients who received antimetabolite drugs (23.7%) compared to those who did not (7.3%) ($p<0.05$). There was no significant difference in the rate of nephrotoxicity between those who used alkylating agents, plant products, antitumor antibiotics and "other" group chemotherapy and those who did not.

Discussion

In this study, organ toxicity and biochemical, electrolyte, and metabolic abnormalities in the first month of chemotherapy were evaluated in childhood

Table 4. Comparison of risk factors for hepatotoxicity and nephrotoxicity

	Hepatotoxicity [n, (%)]		p value	Nephrotoxicity [n, (%)]		p value	Total [n, (%)]
	Yes	No		Yes	No		
Male Female	109 (59.60) 63 (51.60)	74 (40.40) 59 (48.40)	0.17	24 (13.10) 8 (6.60)	159 (86.90) 114 (93.40)	0.06	183 (100.00) 122 (100.00)
≤5 age >5 age	63 (53.80) 109 (58.00)	54 (46.20) 79 (42.00)	0.47	13 (11.10) 19 (10.10)	104 (88.90) 169 (89.90)	0.78	117 (100.00) 188 (100.00)
Early stage Late stage	49 (57.60) 59 (64.80)	36 (42.40) 32 (35.20)	0.32	8 (9.40) 9 (9.90)	77 (90.60) 82 (90.10)	0.91	85 (100.00) 91 (100.00)
RT (-) RT (+)	155 (58.50) 17 (42.50)	110 (41.50) 23 (57.50)	0.05	28 (10.60) 4 (10.00)	237 (89.40) 36 (90.00)	0.91	265 (100.00) 40 (100.00)
Surgery (-) Surgery (+)	79 (66.90) 93 (49.70)	39 (33.10) 94 (50.30)	0.003*	17 (14.40) 15 (8.00)	101 (85.60) 172 (92.00)	0.07	118 (100.00) 187 (100.00)

*p<0.05, RT (-): Those who do not receive radiotherapy, RT (+): Those who receive radiotherapy, Surgery (-): Those who do not undergo surgery, Surgery (+): Those who undergo surgery

Table 5. Comparison of hepatotoxicity and nephrotoxicity rates by chemotherapy group

	Hepatotoxicity [n, (%)]		p value	Nephrotoxicity [n, (%)]		p value	Total [n, (%)]
	Yes	No		Yes	No		
Alkylating (-) Alkylating (+)	40 (40.00) 132 (64.40)	60 (60.00) 73 (36.60)	<0.001*	7 (7.00) 25 (12.20)	93 (93.00) 180 (87.80)	0.16	100 (100.00) 205 (100.00)
A.M. (-) A.M. (+)	116 (47.20) 56 (94.90)	130 (52.80) 3 (5.10)	<0.001*	18 (7.30) 14 (23.70)	228 (92.70) 45 (76.30)	<0.001*	246 (100.00) 59 (100.00)
P.P. (-) P.P. (+)	20 (74.10) 152 (54.70)	7 (25.90) 126 (45.30)	0.05	5 (18.50) 27 (9.70)	22 (81.50) 251 (90.30)	0.15	27 (100.00) 278 (100.00)
A.A (-) A.A (+)	56 (57.10) 116 (56.00)	42 (42.90) 91 (44.00)	0.86	13 (13.30) 19 (9.20)	85 (86.70) 188 (90.80)	0.27	98 (100.00) 207 (100.00)
Other (-) Other (+)	130 (50.80) 42 (84.70)	126 (49.20) 7 (14.30)	<0.001*	23 (9.00) 9 (18.40)	233 (91.00) 40 (81.60)	0.05	256 (100.00) 49 (100.00)

*p<0.05, A.M.: Antimetabolites, P.P.: Plant-products, A.A.: Antitumor antibiotics

lymphoma and solid tumors, and these abnormalities were found to be at a high rate. No associated mortality was observed despite these high rates.

Hepatotoxicity can manifest itself in a wide spectrum from mild elevation of transaminase levels to severe hepatic insufficiency and coma. In our study, the rate of hepatotoxicity was significantly higher in patients who did not undergo surgery as well as those who received alkalinizing agents, antimetabolite drugs, and "other" chemotherapy. Meanwhile, age group, gender, cancer stage, and radiotherapy did not affect the hepatotoxicity rate.

The hepatotoxicity rate (64.4%) was significantly higher in patients who received alkylating drugs compared to those who did not. Mcdonald et al. (5) reported hepatotoxicity in 16% of 147 patients with adult leukemia and lymphoma who received cyclophosphamide, and De Vita et al. (6) reported hepatotoxicity in 15% of adult patients with lymphoma and solid tumors who received carmustine. In our study, hepatotoxicity was significantly higher in patients who received antimetabolite group chemotherapy (94.9%) compared to those who did not. In the study by Weber et al. (7) with 40 children with leukemia who received high-dose methotrexate, liver transaminase levels were found to be high in 33% in the first cycle and 100% in the fifth cycle. It was observed that the liver transaminase levels returned to normal within two weeks after the drug was discontinued. Oğuz et al. (8) detected an elevation of transaminase levels between stages 1 and 3 in 10 pediatric patients with Burkitt's lymphoma who received methotrexate, and the transaminase levels returned to normal within 2-11 days in nine of the 10 patients. The hepatotoxicity rate performed with methotrexate, a drug with known liver toxicity, in the study was similar to the hepatotoxicity of the antimetabolite group in our study.

In the present study, hepatotoxicity in patients who received antitumor antibiotics was not significantly different from those who did not. Damodar et al. (9) found hepatotoxicity in 30.4% of 46 adult breast cancer patients who received doxorubicin. Green et al. (10) found hepatotoxicity in 13% of 37 patients with Wilms' tumor who received dactinomycin and vincristine treatment. Bisogno et al. (11) found hepatotoxicity in 8% of 511 Wilms' tumor patients who received dactinomycin and vincristine.

Moreover, 54.7% of the patients in our study who took plant-based antineoplastic drugs had hepatotoxicity, and no significant difference was found compared to those who did not. Chen et al. (12) reported hepatotoxicity in 8.9% of 45 patients who received paclitaxel and lobaplatin due to esophageal squamous cell carcinoma.

The hepatotoxicity rate was significantly higher in patients who received "other" chemotherapy (L-asparaginase, corticosteroids) compared to those who did not. Oettgen et al. (13) reported increased transaminase levels in 46% of the children and 63% of the adults in their study of 131 children and 143 adults diagnosed with leukemia, lymphoma, and solid tumors who received chemotherapy combined with L-asparaginase. During the first two months of follow-up of 57 patients diagnosed with acute lymphoblastic leukemia (ALL) who received induction chemotherapy, Christ et al. (14) reported stages 3-4 hepatotoxicity in 60% of patients receiving PEG-asparaginase and 33% of patients receiving L-asparaginase. Wolff et al. (15) found that when dexamethasone was administered with high-dose methotrexate in patients with brain tumors, methotrexate toxicity increased. In our study, unlike other studies, drugs were examined in groups rather than individually due to combined chemotherapy application. The fact that our hepatotoxicity rate was higher than that of other studies was thought to be due to the examination of drugs in groups.

Cancer and chemotherapy-related nephrotoxicity can be seen as obstructive uropathy, prerenal azotemia due to hypovolemia, renal parenchymal damage due to chemotherapy or organ involvement, or mass effect. The rate of nephrotoxicity was 10.5% in our study, and it did not significantly differ according to age group, gender, cancer stage, surgery, and radiotherapy. Nephrotoxicity rate was higher in patients taking antimetabolite drugs than those who did not.

When the nephrotoxicity rates were examined according to the chemotherapy group, there was no significant difference in nephrotoxicity detected in 12.2% of patients who used alkylating agents compared to those who did not. Kiu et al. (16) reported nephrotoxicity in two patients (9.5%) after two cycles of chemotherapy in their study with 21 adults with malignant glioma who received carmustine and cisplatin after surgery and radiotherapy. Kobayashi et

al. (17) reported 13.7% nephrotoxicity in 4-7 days after the first course in 219 patients who received cisplatin. In this study, there was no difference between male and female patients in terms of toxicity rate. The rate of nephrotoxicity in our study was similar to the rate in this study, and there was no gender difference in terms of nephrotoxicity. Khalil et al. (18) reported acute renal failure in 31.8% of 365 adults diagnosed with lymphoma who underwent cyclophosphamide, vincristine, prednisolone (CVP), adriamycin, bleomycin, vinblastine, dacarbazine (ABVD), and cyclophosphamide, daunorubicin, oncovin, prednisone (CHOP) chemotherapy protocols, and this rate is higher than that in our study. In our study, nephrotoxicity was more frequent in patients using antimetabolite drugs (23.7%) compared to those using other chemotherapy agents. Moreover, hematuria was significantly more common in patients who took antimetabolite drugs (49.1%) compared to those who did not. Kaya et al. (19) found nephrotoxicity in 13% of 42 children with ALL who received high-dose methotrexate treatment, Widemann et al. (20) found nephrotoxicity in 1.8% of 3,887 patients diagnosed with osteosarcoma who received high-dose methotrexate, and reported that 4.4% of patients who developed kidney damage died.

In this study, nephrotoxicity was observed in 9.2% of patients who received antitumor antibiotics, and there was no significant difference in nephrotoxicity or urinalysis results between these patients and those who did not. There are very few studies in the literature that showed that antitumor drugs cause nephrotoxicity. Meanwhile, animal studies show that anthracyclines can cause kidney failure through free radical damage. Since antitumor antibiotics were used in combination with other chemotherapy drugs in our study, we could not determine whether they caused only nephrotoxicity.

Nephrotoxicity was also observed in 9.7% of patients who took plant products, and there was no significant difference in the rates of nephrotoxicity or urinalysis results for these patients compared to those who did not. Agaliotis et al. (21) reported nephrotoxicity in 48% of 131 patients who received ifosfamide, carboplatin, etoposide (ICE) protocol. Yahanda et al. (22) reported nephrotoxicity in 12% of 72 patients who took etoposide and cyclosporine, and the rate of nephrotoxicity in their study is similar to that of our study. However, the relationship between plant products and nephrotoxicity could not be determined due to combined chemotherapy use in this study.

Nephrotoxicity was also observed in 18.4% of patients who received "other" chemotherapy, and there was no significant difference in the rates of nephrotoxicity or urinalysis results for these patients compared to those who did not. Haskell et al. (23) reported acute renal failure in two (3.6%) of 55 patients with leukemia and solid tumors who received L-asparaginase in the third week of treatment. Meanwhile, there are few studies in the literature that reported all-trans retinoic acid (ATRA) nephrotoxicity. Yaralı et al. (24) reported acute glomerulonephritis in a patient who received ATRA for acute promyelocytic leukemia. Elsayed et al. (25) reported that ATRA increased the nephrotoxic effect of cisplatin in mouse experiments.

At least one electrolyte imbalance was found in 87.5% (n=267) of patients participating in the study. The most common electrolyte imbalance was hyponatremia (56.7%). Alsirafy et al. (26) reported at least one electrolyte disorder in 78.7% of 750 patients diagnosed with cancer. In this study, the most common electrolyte imbalance was hyponatremia (59%), and the rates coincide with our study. Milionis et al. (27) reported at least one electrolyte and acid-base imbalance in 62% of 66 patients with leukemia, and hypopotassemia was the most common electrolyte disorder (63%).

Blood gas analysis was performed for only 79 patients in our study, and 31.6% of the patients had respiratory alkalosis, 26.6% had metabolic acidosis, 16.5% had respiratory acidosis, and 11.4% had metabolic alkalosis. Milionis et al. (27) found that 9% of 66 patients with acute leukemia had metabolic acidosis, 6% had metabolic alkalosis, 4.5% had respiratory alkalosis, and 3% had respiratory acidosis. In the study, patients who took corticosteroids, diuretics, aminoglycoside, amphotericin, and supplementary drugs (such as potassium, magnesium, and phosphorus) that may affect their acid-base balance were excluded from the study; hence, the acid-base imbalance rates were lower than those in our study.

The strengths of our study are large number of patients involved and the diversity of diagnosis, organ toxicity, electrolyte disorders, acid-base imbalances and the simultaneous evaluation of biochemical abnormalities. However, one of its limitations is

that it is a retrospective study. Moreover, the lack of evaluation of other conditions (sepsis, antibiotic use, diuretic use, etc.) affecting fluid-electrolyte balance and organ functions are the weaknesses of this study.

Conclusion

In this study, in which the first month of treatment of pediatric oncology patients receiving chemotherapy was evaluated, the rate of organ toxicity, biochemical, electrolyte, and metabolic abnormalities were found to be high. These high rates were thought to be related to the excessive tumor burden and organ involvement and the intensity of the combined chemotherapies applied. No associated mortality was observed despite these high rates. The early detection of these pathologies, their close follow-up, and the immediate application of treatment with a multidisciplinary approach were explained as the reason for not having mortality. The side effect rates can be further reduced with up-to-date and good knowledge of the tumor or chemotherapy-related toxicities by physicians treating oncology patients, with an early multidisciplinary approach and appropriate supportive treatment.

Ethics

Ethics Committee Approval: The study protocol was approved by Uludağ University Ethics Committee (approval number: 2016-15/17, date: 09.08.2016).

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

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Pediatrik Behçet Hastalarında Ek İmmünsüpresif Tedavi Gereksiniminin Tahmin Edilmesi

Predicting the Need for Additional Immunosuppressive Treatment in Pediatric Behçet's Patients

Seher Şener* (0000-0003-1564-8996), Sermin Dalarslan (0000-0002-8363-576X), Ezgi Deniz Batu* (0000-0003-1065-2363)**

*Hacettepe Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Romatoloji Bilim Dalı, Ankara, Türkiye
**Hacettepe Üniversitesi Tıp Fakültesi, Ankara, Türkiye

Öz

Giriş: Çalışmamızda pediatrik Behçet hastalığı (BH) tanılı hastaların demografik ve klinik özellikleri ile hastalardaki tedavi yaklaşımlarımızı değerlendirdik. Ek olarak BH'de tedavide kolşisin ve kısa süreli kortikosteroid tedavisi dışında ek immünsüpresif tedavi ihtiyacı olan hastalarda öngörücü faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 2004-2022 yılları arasında BH tanısıyla izlenen pediatrik hastalar dahil edildi. Hastalar, tedavide kolşisin ve/veya kısa süreli kortikosteroid alanlar (grup A) ile ek immünosüpresif tedavilere ihtiyaç duyanlar (grup B) olmak üzere iki ayrı gruba ayrıldı.

Bulgular: Yüz üç hastanın 57'si (%55,3) BH, 46'sı (%44,7) ise inkomplet BH tanısı ile izlenmekteydi. Tedavide en çok tercih edilen ilaç kolşisindi (%92,2). Kortikosteroidler ise (%55,3) sıklıkla majör organ tutulumu olan hastalarda ek immünsüpresif ajanlarla birlikte tercih edilmişti. Diğer immünsüpresif tedavilere dirençli 15 (%14,6) hastada biyolojik ajanlar kullanıldı. Grup A'da 56 ve grup B'de ise 47 hasta vardı. Grup B'de göz tutulumu ve venöz tromboz daha sıktı. Ek olarak grup B'de tanı anındaki akut faz reaktanları ile BHAAF skorları da grup A'daki hastalara göre daha yüksekti. Çok değişkenli analiz sonucunda göz tutulumu [odds oranı (OR) 4,045, %95 GA 6,205-525,470; p=0,001], venöz tromboz (OR 2,497, %95 GA 3,048-48,358; p=0,001) ve akut faz reaktanlarında yükseklik (OR 1,312, %95 GA 0,086-0,842; p=0,024) ek immünsüpresif tedavi ihtiyacı öngören bağımsız faktörler olarak belirlendi.

Sonuç: Pediatrik BH olgularının doğru yönetimi, gelişebilecek komplikasyonların önüne geçebilmek adına oldukça önemlidir. Sonuçlarımız, başvuruda göz veya vasküler tutulum, yüksek akut faz reaktanı ve BHAAF skoruna sahip hastalarda ek immünsüpresif tedavi ihtiyacı olabileceğini gösterdi. Tedavi ihtiyacını tahmin eden faktörlerin belirlenmesi, hastalarda uygun tedavi ve takip planının yapılmasına önemlidir.

Anahtar kelimeler
Behçet hastalığı, pediatrik, immünsüpresif tedavi

Keywords
Behçet's disease, pediatric, immunosuppressive treatment

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Yazışma Adresi/Address for Correspondence: Dr. Ezgi Deniz Batu, Hacettepe Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Romatoloji Bilim Dalı, Ankara, Türkiye
Tel.: +90 312 305 18 63
E-posta: ezgidenizbatu@yahoo.com

Abstract

Introduction: In our study, we evaluated the demographic and clinical characteristics of patients with pediatric Behçet's disease (BD) and our treatment approaches in these patients. In addition, we aimed to determine the predictive factors in patients who need additional immunosuppressive therapy in addition to colchicine and short-term corticosteroid therapy in the treatment of BD.

Materials and Methods: Pediatric patients followed up with BD between 2004-2022 were included in the study. The patients were divided into two groups: those receiving colchicine and/or short-term corticosteroids (group A) and those needing additional immunosuppressive treatments (group B).

Results: Of a total of 103 patients, 57 (55.3%) were being followed up with a diagnosis of BD, and 46 (44.7%) with a diagnosis of incomplete BD. The most preferred drug in the treatment was colchicine (92.2%). Corticosteroids (55.3%) were often preferred with additional immunosuppressive agents in patients with major organ involvement. Biologic agents were used in 15 (14.6%) patients who were resistant to other immunosuppressive treatments. There were 56 patients in group A and 47 patients in group B. Ocular involvement and venous thrombosis were more common in group B. In addition, acute phase reactants and BHAAF scores at the diagnosis were higher in group B than in group A patients. As a result of multivariate analysis, ocular involvement [odds ratio (OR) 4,045, 95% CI 6,205-525,470; p=0.001], venous thrombosis (OR 2,497, 95% CI 3.048-48.358; p=0.001) and elevated acute phase reactants (OR 1.312, 95% CI 0.086-0.842; p=0.024) were identified as independent factors predicting the need for additional immunosuppressive therapy.

Conclusion: Correct management of pediatric BD cases is very important in order to prevent complications that may develop. Our results showed that patients with ocular or vascular involvement, high acute phase reactants, and BHAAF scores may need additional immunosuppressive therapy at admission. Determining the factors that predict the need for treatment is important in making the appropriate treatment and follow-up plan for patients.

Giriş

Behçet hastalığı (BH) ilk olarak Hulusi Behçet tarafından 1937 yılında üç hastada oral ülser, genital ülser ve üveit birlikteliği ile giden bir hastalık olarak tanımlamıştır (1). Günümüzde ise bu bulgulara ek cilt bulguları, kas iskelet sistemi, gastrointestinal sistem (GİS) ve nörolojik sistem tutulumu yapabilen bir sistemik vaskülit tablosu olduğu bilinmektedir (2,3).

BH tanısı için spesifik bir tanı testinin olmaması nedeniyle hastalık tanısı klinik bulgulara göre konulmaktadır (4). Çocukluk çağı BH için önerilmiş tek ölçüt seti 2015 yılında "Pediatric Behçet's Disease Group (PEDBD)" tarafından önerilen kriterlerdir (5). Bu ölçüte göre; tekrarlayan oral aft (yılda en az 3 kez), genital ülserasyon veya aft (iz bırakan), cilt tutulumu (nekrotik folikülit, akne benzeri lezyonlar, eritema nodozum), göz tutulumu (ön üveit, arka üveit, retinal vaskülit), nörolojik (izole baş ağrısı hariç) ile vasküler bulgulardan (venöz tromboz, arteriyel tromboz, arteriyel anevrizma) üç ve daha fazla kritere sahip olan hastalar Behçet hastası olarak sınıflanmaktadır.

BH'de ileri dönemde komplikasyon gelişimini engellemek için erken tanı ve tedavi oldukça önemlidir. Tedavide temel amaç hastalığın erken tanımlanması, enflamasyonun etkin bir şekilde baskılanması ve hastalık alevlenmelerinin engellenmesi olmalıdır. BH multisistemik tutulum yapabilen bir sistemik vaskülit olduğu için hastalar multisistemik bir yaklaşım ile yönetilmelidir. Kolsişin, BH'nin hemen hemen tüm bulguları için kullanılan birinci basamak tedavidir (6). Kortikosteroidler, genital lezyonları iyileştirmek amaçlı kısa süreli veya ciddi organ tutulumlarında uzun süreli kullanılabilir. Göz tutulumunda ise topikal kortikosteroidler oldukça etkilidir. Azatioprin, metotreksat, siklofosfamid, biyolojik ilaçlar gibi diğer immünsüpresif tedaviler ise majör organ tutulumu olduğunda veya klasik tedaviye dirençli Behçet hastalarında tercih edilirler (6).

Çalışmamızda pediatrik Behçet hastaların genel özelliklerinin yanı sıra hastalarda kolşisin ve kısa süreli kortikosteroid tedavisi dışında ek immünsüpresif tedavi ihtiyacını öngören faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem

Hacettepe Üniversitesi Tıp Fakültesi Çocuk Nefroloji ve Romatoloji Bilim Dalları'nda 2004-2022 yılları arasında BH veya inkomplet BH tanısıyla izlenen hastalar çalışmaya dahil edildi. Hasta dosyaları ve elektronik kayıtları geriye dönük incelendi. 2015 yılında yayınlanan PEDBD kriterlerine (5) göre üç ve daha fazla kritere sahip olan hastalar Behçet hastası olarak sınıflandı. İki kritere sahip hastalar ise inkomplet Behçet hastası olarak sınıflandı. Hastaların demografik özellikleri, semptom başlangıcı ile tanı anındaki yaşları, aile öyküleri, klinik bulguları, laboratuvar bulguları [eritrosit sedimentasyon hızı (ESH), C-reaktif protein (CRP), Human Leucocyte Antigen (HLA)-B5-51], paterji testi sonuçları, aldıkları tedaviler ve tedavi yanıtları değerlendirildi. Behçet hastaları, tedavide kolşisin ve/veya kısa süreli kortikosteroid alanlar (grup A) ile ek immünosüpresif tedavilere ihtiyaç duyanlar (grup B) olmak üzere iki ayrı gruba ayrılarak, bu iki grup arasındaki farklılıklar karşılaştırıldı. Ek immünsüpresif tedavilere ihtiyaç duyan hastalar için, ek tedavi ihtiyacını öngörücü faktörler belirlendi. Klinik bulgulardaki değişiklikler tanıda ve son vizitte Behçet Hastalığı Anlık Aktivite Formu (BHAAF) kullanılarak değerlendirildi (7). Hastaların klinik ve laboratuvar bulgularının düzelmesi

(akut faz reaktanlarının normal olması) remisyon olarak değerlendirildi.

İstatistiksel Analiz

SPSS software kullanılarak veri tabanı oluşturuldu ve analiz edildi. Değişkenlerin normal dağılıma uygunluğu görsel (histogram ile olasılık grafikleri) ve analitik yöntemlerle (Kolmogorov-Smirnov/ Shapiro-Wilks) incelendi. Tanımlayıcı analizlerde, normal dağılıma uymayan ve ordinal değişkenler için ortanca (minimum-maksimum) değer kullanıldı. Kategorik değişkenleri karşılaştırmak için ki-kare testi veya Fisher'in kesin testi, normal dağılmayan sürekli değişkenleri karşılaştırmak için Mann-Whitney U testi kullanıldı. Farklı değişkenlerin ek immünsüpresif tedavi gereksinimi üzerindeki etkileri, her biri için tek değişkenli analizde hesaplandı. Lojistik regresyon analizinde düzeltilmemiş p değeri <0,10 olan değişkenler potansiyel öngörücü belirteçler olarak tanımlandı ve tam modele dahil edildi. Geriye dönük elemede ise, çok değişkenli lojistik regresyon analizlerini kullanarak modeli küçültüldü. P değerinin <0,05 olması anlamlı kabul edildi ve güven aralığı (GA) %95 idi.

Çalışma üniversitemizin etik kurulu tarafından onaylandı (GO 21/967). Çalışmaya dahil edilmeden önce tüm ebeveynlerden/hastalardan bilgilendirilmiş onam alındı. Çalışma, 1964 Helsinki Bildirgesi'nde ve daha sonraki değişikliklerde belirtilen etik standartlar izlenerek gerçekleştirildi.

Bulgular

Çalışmaya 103 pediatrik Behçet hastası dahil edildi (%56,3'sı kız) (Tablo 1). Hastaların 57'si (%55,3) PEDBD kriterlerine göre BH, 46'sı (%44,7) ise inkomplet BH tanısı ile takipliydi. Elli yedi hastanın 19'u (%33,3) ise başlangıçta inkomplet BH ile izlenmekte iken zamanla gelişen ek semptomlar sonucu BH tanısı almıştı.

Hastalarda en sık başvuru yakınması tekrarlayan oral aftlardı (%96,1). İlk başvuruda sadece sekiz hastada (%7,7) üveit varken, ilerleyen dönemde 12 hastada (%11,6) üveit gelişmişti. Ek olarak 11 hastada (%10,7) nörolojik, dokuz hastada (%8,7) GİS, iki hastada pulmoner (%1,9) ve bir hastada da (%0,9) kardiyak tutulum mevcuttu. Nörolojik tutulumu saptanan 11 hastadan ikisinde parankimal tutulum, dokuzunda ise non-parankimal tutulum vardı. Vasküler tutulumu olan 25 hastanın (%24,2), 22'sinde venöz, ikisinde arteriyel ve üçünde de hem arteriyel hem de venöz tutulum mevcuttu. Tedavide kolşisin en çok tercih edilen ilaçtı (%92,2) ve mukokütanöz tutulumu (tekrarlayan oral aft, genital aft/ülser, çeşitli cilt lezyonları gibi) olan olgularda en sık tercih edilen tedavi protokolüydü. Kortikosteroidler ise sıklıkla nörolojik, GİS, kardiyopulmoner tutulum gibi ağır klinik bulguları olan hastalarda uzun süreli veya genital ülseri olan hastalarda kısa süreli olarak tercih edilmişti (n=57, %55,3). Azatiyoprin ise üveit olgularının nerdeyse tamamında (%95) kullanılmıştı. Vasküler tutulumu olan hastaların hepsine ek olarak antikoagülan tedavi de verilmişti. Sinus ven trombüsü olan iki hasta ile pulmoner arter anevrizması saptanan iki hasta yüksek doz kortikosteroid tedavisine ek olarak intravenöz siklofosfamid ile tedavi edilmişti. Tüm bu immünsüpresif tedavilere dirençli 15 hastada (%14,6) ise anti tümör nekroz faktör (TNF) alfa ajanlar kullanılmıştı. En sık tercih edilen anti TNF alfa ajan ise adalimumab idi (%12,6).

Tedavide kolşisin ve/veya kısa süreli kortikosteroid alan (grup A, n=56) ve ek immünosüpresif tedavilere ihtiyaç duyan (grup B, n=47) hastaların ortanca tanı yaşları sırasıyla 13,8 (2-17,9) ile 13 (1,1-17,5) idi. Grup A'da kız cinsiyet oranı daha fazlaydı (%42,6 karşı %67,8'e, p=0,010). Grup A'daki hastalarda bir hastada göz tutulumu dışında majör organ tutulumu yoktu. Grup B'de göz tutulumu (özellikle panüveit, p=<0,001) ve venöz tromboz (sıklıkla alt ekstremite yerleşimli derin ven trombozları, p=<0,001) daha sıktı. Ek olarak grup B'de tanı anındaki CRP (p=0,026) ve ESH (p=0,019) değerleri ile BHAAF skorları (p=<0,001) grup B'deki hastalara göre daha yüksekti. Kısmi remisyon oranları ise grup A'daki daha yüksek oranda görülürken (p=0,027), tam remisyon oranları arasında istatistiksel olarak anlamlı bir fark yoktu (p=0,116).

GİS tutulumu, nörolojik tutulum, pulmoner ve kardiyak tutulum gibi ciddi organ tutulumlarının yanı sıra majör organları etkileyen tromboz durumlarında hastaların hepsinin ek immünsüpresif ajan ihtiyacı olduğu için bu değişkenler regresyon analizine dahil edilmedi. Ek tedavi ihtiyacını değerlendirirken kullanılan tek değişkenli ve çok değişkenli regresyon analiz sonuçları Tablo 2'de sunuldu. Çok değişkenli analiz sonucunda göz tutulumu [odds oranı (OR) 4,045, %95 GA 6,205-525,470; p=0,001], venöz tromboz

Tablo 1. Pediatrik Behçet hastalarının genel özellikleri ile grup A ve grup B'deki hastaların karşılaştırılması				
	Tüm hastalar (n=103)	Grup A (n=56)	Grup B (n=47)	p değeri
Kız, n (%)	58 (56,3)	38 (67,8)	20 (42,6)	0,010*
Semptom başlangıç yaşı, yıl, ortanca (min-maks)	10,8 (0,5-17,1)	11,4 (1,5-17,1)	11,2 (0,5-17)	0,822
Tanı yaşı, yıl, ortanca (min-maks)	12,1 (1,1-17,9)	13,8 (2-17,9)	13 (1,1-17,5)	0,355
Tanı ile semptom başlangıcı arası süre, yıl, ortanca (min-maks)	0,5 (0,1-13,1)	0,5 (0,1-11,5)	0,1 (0,1-13,1)	0,197
PEDBD kriterlerini karşılayan BH olanlar, n (%)	57 (55,3)	27 (48,2)	30 (63,8)	0,163
İnkomplet BH olanlar	46 (44,7)	29 (51,8)	17 (36,2)	0,112
Ailede BH öyküsü, n (%)	36 (34,9)	24 (42,9)	12 (25,6)	0,068
Komorbiditeler, n (%)				
Ailevi Akdeniz ateşi	14 (13,6)	8 (14,3)	6 (12,8)	0,241
Sakroilyit	4 (3,8)	2 (3,6)	2 (4,3)	0,172
IgAV/HSP	2 (1,9)	2 (1,9)	0	0,158
Klinik bulgular, n (%)				
Oral aft (≥3/yıl)	99 (96,1)	53 (94,6)	44 (93,6)	1,000
Genital aft/ülserasyon	58 (56,3)	35 (62,5)	23 (48,9)	0,167
Cilt tutulumu	61 (59,2)	32 (57,1)	29 (61,7)	0,639
Nekrotik folikülit	44 (42,7)	21 (37,5)	23 (48,9)	0,243
Eritema nodozum	31 (30,1)	16 (28,6)	15 (31,9)	0,713
Akne benzeri lezyonlar	42 (40,8)	19 (33,9)	23 (48,9)	0,123
Eklem bulguları	57 (55,3)	33 (58,9)	24 (51,1)	0,424
Göz tutulumu	20 (19,4)	1 (1,8)	19 (40,4)	<0,001*
Ön üveit	6 (5,8)	1 (1,8)	5 (10,6)	0,102
Arka üveit	4 (3,8)	0	4 (8,5)	0,049*
Panüveit	10 (9,7)	0	10 (21,3)	<0,001*
Nörolojik tutulum	11 (10,7)	0	11 (10,7)	<0,001*
GİS tutulumu	9 (8,7)	0	9 (19,1)	0,001*
Pulmoner tutulum	2 (1,9)	0	2 (4,3)	0,227
Kardiyak tutulum	1 (0,9)	0	2 (4,3)	0,227
Vasküler bulgular	25 (24,2)	5 (8,9)	20 (42,6)	<0,001*
Venöz tromboz	22 (21,4)	4 (7,1)	18 (38,3)	<0,001*
Arteriyel tromboz	5 (4,9)	0	5 (10,6)	0,018*
Arteriyel anevrizma	2 (1,9)	0	2 (4,3)	0,227
Pozitif paterji testi, n (%)	21/98 (21,4)	10/53 (18,9)	11/45 (24,4)	0,773
Laboratuvar bulguları				
ESH, mm/saat (normal=0-20), ortanca (min-maks)	8 (2-119)	5 (2-37)	9 (4-119)	0,026*
CRP, mg/dL (normal=0-0,5), ortanca (min-maks)	0,4 (0,1-10,3)	0,2 (0,1-5)	0,6 (0,1-10,3)	0,019*
Pozitif HLA-B5/51, n (%)	52/95 (54,7)	28 (50)	24 (51,1)	0,914
Tedavi, n (%)				
Kolşisin	95 (92,2)	52 (92,8)	43 (91,5)	0,814
Kortikosteroid	57 (55,3)	16 (28,6)	41 (87,2)	<0,001*

Tablo 1. devamı				
	Tüm hastalar (n=103)	Grup A (n=56)	Grup B (n=47)	p değeri
NSAİİ	25 (24,2)	13 (23,2)	12 (25,5)	0,623
Azatiyoprin	44 (42,7)	0	44 (93,6)	<0,001*
Siklofosfamid	4 (3,9)	0	4 (8,5)	0,049*
Metotreksat	2 (1,9)	0	4 (8,5)	0,049*
Salazopirin	2 (1,9)	0	4 (8,5)	0,049*
Hidroksiklorokin	1 (0,9)	0	4 (8,5)	0,049*
Anti-TNF alfa ajan	15 (14,6)	0	4 (8,5)	0,049*
Adalimumab	13 (12,6)	0	4 (8,5)	0,049*
Etanersept	4 (3,9)	0	4 (8,5)	0,049*
İnfliksimab	5 (4,9)	0	4 (8,5)	0,049*
İzlem süresi, yıl, ortanca (min-maks)	3 (0,5-11)	2 (0,5-10)	1 (0,5-9)	0,372
BHAAF, tanıda, ortanca (min-maks)	4 (1-15)	3 (1-9)	5 (2-15)	<0.001*
BHAAF, son vizitte, ortanca (min-maks)	1 (0-12)	0 (0-10)	0 (0-12)	1.000
Son durum, n (%)				
Kısmi remisyon	7 (6,8)	1 (1,8)	6 (12,8)	0,027*
Tam remisyon	96 (93,2)	55 (98,2)	41 (87,2)	0,116

BH: Behçet hastalığı, BHAAF: Behçet Hastalığı Anlık Aktivite Formu, ESH: Eritrosit sedimentasyon hızı, CRP: C-reaktif protein, GİS: Gastrointestinal sistem, HLA: Human Leucocyte Antigen, IgAV/HSP: İmmünoglobulin A vasküliti/Henoch-Schönlein purpura, NSAİİ: Non-steroid anti enflamatuvar ilaçlar, PEDBD: Pediatrik Behçet hastalığı grubu, TNF: Tümör nekroz faktör

(OR 2,497, %95 GA 3,048-48,358; p=0,001) ve tanıda ESR/CRP yükseliği (OR 1,312, %95 GA 0,086-0,842; p=0,024) ek tedavi ihtiyacı öngören bağımsız faktörler olarak belirlendi.

Tartışma

Bu çalışmada, çocuk romatolojinin nispeten nadir bir hastalığı olan pediatrik BH'nin hem tanı hem de tedavisini kolaylaştırmak adına hastalarımızın genel özelliklerini paylaştık. Ek olarak, pediatrik BH'de kolşisin ve kısa süreli kortikosteroid tedavisi dışında ek immünsüpresif tedavi ihtiyacını öngörücü faktörleri belirlemeyi amaçladık. Bu çalışma bildiğimiz kadarıyla bu konuda pediatrik BH'de yapılan ilk çalışmadır.

Hastalarımızda en sık klinik bulgular sırasıyla; oral aft (%96,1), cilt lezyonları (%59,2), genital aft/ülserasyon (%56,3) ve eklem bulgularıydı (%55,3). Tüm çalışmalarda tekrarlayan oral aftlar en sık semptom olmakla beraber diğer bulguların dağılımı değişkenlik göstermektedir. Bununla birlikte, bizim çalışmadaki dört hastada da olduğu gibi BH oral aft olmaksızın da mevcut olabilir. Cilt lezyonları da hastalarımızın yarıdan fazlasında (%59,2) mevcuttu. Genel pediatrik BH popülasyonunda cilt tutulum oranları %32,3-88,9 arasında değişmektedir (8-16). Hastalarımızda en sık görülen üçüncü klinik bulgu olan genital aft/ülserasyon, yapılan çalışmalarda pediatrik BH'de ikinci veya üçüncü en yaygın semptom olarak bildirilmiştir (8-12).

Mukokütanöz belirtiler sıklıkla pediatrik BH'nin erken evresinde genelde meydana gelir, ancak bu her zaman şart değildir (13). Oral aft ve diğer mukokütanöz lezyonlar olmadan BH'yi teşhis etmek oldukça zordur. Çalışmamızda BH ile takipli total 57 hastanın 19'u (%33,3) başlangıçta inkomplet BH ile izlenmekteydi, ancak zamanla gelişen ek semptomlar sonucu BH tanısı almışlardı. Özellikle pediatrik olgularda hastalık özgün olmayan, inkomplet bulgularla seyredebilir ve bu olgular gelişebilecek yeni bulgular açısından dikkatle takip edilmelidir.

BH'de artralji ve artrit sık görülen eklem bulguları arasındadır (13). BH'de görülen artrit eroziv olmayan, asimetrik, deformite bırakmayan özellikte olup, sıklıkla orta ve büyük eklemleri etkilemektedir. Çalışmamızda da 45 hastada (%43,7) artralji ve 24 (%23,3) hastada artrit mevcuttu. Literatürde de genel olarak eklem tutulumu oranı %30,9 ile %63 arasında değişmektedir (8,9,14,15,17).

Tablo 2. Pediatrik Behçet hastalığında ek immünsüpresif tedavi gereksinimini öngörücü faktörler için tek değişkenli ve çok değişkenli regresyon analizi		
Değişkenler	OR (%95 GA)	p değeri
Tek değişkenli (univariate) analiz		
Cinsiyet, kız	1,047 (1,274-6,378)	0,011*
Tanı yaşı, yıl	0,004 (0,995-1,012)	0,397
Kesin BH veya inkomplet BH olma durumu	0,639 (0,239-1,166)	0,114
Ailede BH öyküsü	0,783 (0,197-1,062)	0,069
Komorbidite öyküsü	0,073 (0,466-2,484)	0,865
Oral aft (≥3/yıl)	0,186 (0,160-4,320)	0,825
Genital aft/ülserasyon	0,553 (0,262-1,263)	0,575
Cilt tutulumu	0,189 (0,548-2,666)	0,639
Eklem bulguları	0,101 (0,416-1,966)	0,800
Göz tutulumu	3,620 (4,749-293,326)	0,001*
Venöz tromboz**	2,022 (2,552-22,368)	<0,001*
Tanıda ESR/CRP yükseliği	1,100 (1,296-6,960)	0,010*
Pozitif paterji testi	0,268 (0,121-4,851)	0,776
Pozitif HLA-B5/51	0,75 (0,420-2,051)	0,853
Tanıda BHAAF skoru	0,183 (0,720-0,963)	0,014*
Çok değişkenli (multivariate) analiz		
Göz tutulumu	4,045 (6,205-525,470)	0,001*
Venöz tromboz**	2,497 (3,048-48,358)	0,001*
Tanıda ESR/CRP yükseliği	1,312 (0,086-0,842)	0,024*

BH: Beçet hastalığı, GA: Güven aralığı, CRP: C-reaktif protein, GİS: Gastrointestinal sistem, HLA: Human Leucocyte Antigen, OR: Odds oranı
*Çok değişkenli lojistik regresyon analizlerine dahil edilen, düzeltilmemiş p değeri <0,10 olan değişkenler
**Yaşamı tehdit etmeyen, sıklıkla alt ektremitelerde görülen derin ven trombozları

BH'de en önemli morbidite nedeni ise göz tutulumudur (18,19). Gözde geri dönüşümsüz hasar oluşmaması için erken tanı ve etkin tedavi oldukça önemlidir. Çalışmamızda hastalarımızda göz tutulumu %19,4 oranında görülürken, diğer çalışmalarda genel olarak bu oran %13,3 ile %47 arasında değişmekteydi (8-13). Ek olarak göz bulguları her zaman ilk başvuruda mevcut olmayabilir. Keza bizim hastalarımızın da sadece sekizinde (%7,7) başvuruda üveit varken, ilerleyen dönemde 12 hastada (%11,6) üveit gelişmişti.

Vasküler ve nörolojik belirtiler, pediatrik BH'nin nispeten nadir fakat şiddetli klinik bulgularındandır (13). Özellikle, bu ciddi belirtiler pediatrik inkomplet BH'de atlanmamalı ve dikkatli olunmalıdır. Bizim kohortumuzda hastalarımızın %10,7'sinde nörolojik ve %24,2'sinde ise vasküler tutulum mevcuttu. Çocukluk çağında vasküler tutulum, sıklıkla alt ekstremite yüzeyel ve derin venlerde tutulum şeklinde görülür, arteriyel tutulum daha nadirdir. Bazı vakalarda hem venöz hem arteriyel bölgede tromboz gözlenebilir. Bizim hastalarımızın 20'sinde venöz, ikisinde arteriyel ve üçünde de hem arteriyel hem de venöz tutulum saptanmıştı. Bunun yanı sıra iki hastamızda da pulmoner anevrizma saptanmıştı. Nörolojik tutulumu olan 11 hastamızdan ikisinde parankimal tutulum, dokuzunda ise non-parankimal tutulum vardı. Parankimal olmayan nörolojik tutulum çocuklarda çok daha sık görülürken, parankimal hastalık erişkinlerde daha sıktır (13).

Diğer önemli klinik bulgulardan olan GİS tutulumu ise dokuz hastamızda (%8,7) mevcuttu. Literatürde bildirilen araştırmalarda bu oran (%5,9 ile %58,7) değişkenlik göstermekle birlikte bizdeki bu oran nispeten alt sınırlara yakındı (8,9,14,15,17). Ek olarak erişkin ve çocuk hastaları karşılaştıran çalışmalarda da pediatrik formda, erişkin forma göre önemli ölçüde daha yüksek GİS tutulum oranı olduğu bildirilmiştir (20).

Pozitif paterji testinin BH tanısında yüksek duyarlılık ve özgüllüğe sahip olduğu kabul edilmekte ancak pediatrik tanı kriterleri arasında yer almamaktadır (20,21). HLA-B51 pozitifliği ise, BH için 5,78 kat daha fazla gelişme riskini artıran genetik bir yatkınlık faktörüdür (6,13). Ancak, BH'nin klinik bulguları mevcutsa, HLA-B51'in pozitif olması BH tanısı için sadece destekleyici bir faktördür. Çünkü HLA-B51 pozitifliği sağlıklı popülasyonda da herhangi bir klinik bulgu olmaksızın görülebilir (13).

BH multisistemik bir vaskülittir. Bu nedenle tedavide enflamasyonu kontrol altına almak ve son organ hasarını önlemek temel amaçtır. Pediatrik Behçet hastaların tedavisinde kesin öneriler bulunmamakta olup, temel olarak erişkin tedavi kılavuzlarından yararlanılmaktadır (15). Hastalarımızın tedavisinde kolşisin en çok tercih edilen ilaçtı (%92,2) ve mukokütanöz bulguları kontrol altına almakta oldukça etkiliydi. Kortikosteroidler (%55,3) sıklıkla nörolojik, GİS, kardiyopulmoner tutulum veya genital ülseri olan hastalarda sıklıkla tercih edilirken, azatiyoprin ise (%95) üveit olgularının büyük bir kısmında kullanılmıştı. Ağır nörolojik tutulum veya pulmoner anevrizması olan toplam dört hastada da intravenöz siklofosfamid verilmişti. Tüm bu immünsüpresif tedavilere dirençli 15 hastada (%14,6) ise anti TNF alfa ajanlar kullanılmıştı. Çocuklarda yapılan çalışmalarda dirençli vakalarda tedavide anti TNF ajanlar kullanımı önerilmektedir (14,22). Hu ve ark. (23) tarafından yapılan bir çalışmada (23) dirençli pediatrik BH'ye sahip altı hastada anti TNF alfa ajanlar kullanılmış olup, bu hastalarda oldukça başarılı sonuçlar elde edilmişti.

BH'de kolşisin ve/veya kısa süreli kortikosteroid tedavileri ilk basamak tedavilerden olup, bunlar dışındaki diğer immünsüpresif ajanlar ikinci basamak tedavilerdendir. Literatürde birçok çalışmalarda tedavide genel olarak ciddi organ tutulumu olan ve/veya klasik tedavilere dirençli hastalarda ek immünsüpresif tedavi gerekliliği bildirilmiştir (24-26). Ancak bunlar dışında Behçet hastalarında ek immünsüpresif tedavi gereksinimini öngörebilecek diğer faktörler bilinmemektedir. Bizde bu amaçla hastalarımızı iki gruba ayırdık ve ek immünsüpresif tedavi gereksinimini öngörücü faktörleri belirlemeye çalıştık. Tedavide ek immünosüpresif tedavilere ihtiyaç duyan grup B'de (n=47), kolşisin ve/veya kısa süreli kortikosteroid alan grup A'ya (n=56) göre göz tutulumu ve vasküler bulgular daha sıktı. Grup A'daki hastalarda ise beklediğimiz üzere ciddi bir organ tutulumu yoktu. Önemli bir bulgu olarak grup B'de tanı anındaki CRP ve ESH değerleri ile BHAAF skorları grup A'daki hastalara göre daha yüksekti. Grup B'deki BHAAF skor yüksekliği, bu gruptaki hastaların bir kısmının majör organ tutulumu ile prezente olmalarından kaynaklanıyordu. Tam remisyon oranları açısından iki grup arasında da fark yokken, kısmi remisyon oranları ise grup B'de daha yüksek orandaydı. Bunun nedeni ise yine grup A'da hastaların çoğunun majör organ tutulumu olması nedeniyle tam remisyona ulaşamamasıydı.

Her iki grup arasında da yaptığımız regresyon analizleri sonucunda, göz tutulumu (OR 4,045, %95 GA 6,205-525,470; p=0,001), tromboz (OR 2,497, %95 GA 3,048-48,358; p=0,001) ve tanıda ESR/CRP yükseliği (OR 1,312, %95 GA 0,086-0,842; p=0,024) ek tedavi ihtiyacı öngören bağımsız faktörler olarak saptandı. Göz tutulumunda özellikle ön üveitte başlangıç tedavisi olarak topikal kortikosteroid ve dilate edici göz damlaları ile kontol altına alınabilmektedir. Topikal kortikosteroidlerle kontrol altına alınmayan olgularda sistemik kortikosteroidlerle kısa süre içinde tedavi edilebilir. Ancak dirençli olgularda, arka üveit veya panüveit durumlarında ise daha çok ek immünsüpresif ajanlara ihtiyaç duyulmaktadır (27). BH'de venöz tromboz durumunda ise, son dönemlerde yapılan çalışmalarda relapsın önlenmesi için ek immünosüpresif ajanla kombinasyon halinde kortikosteroid başlangıç tedavisi olarak önerilmektedir (28). Bu nedenle göz tutulumu ve venöz tromboz ile ilgili bulduğumuz sonuçlar bu yaklaşımlarla uyumlu olmakla beraber, bunlara ek olarak özellikle tanıda akut faz reaktanları veya BHAAF skorları yüksek olan hastalarda ek immünsüpresif tedavi ihtiyacı gelişebileceği akılda tutulmalıdır.

Çalışmanın Kısıtlılıkları

Çalışmamızın bazı kısıtlılıkları bulunmaktadır. Çalışmanın geriye dönük tasarımı ve BH tanısı kesin olan kısıtlı hasta sayımızın olması bunların başında sayılabilir. Ayrıca çalışmamızın eski dönemlerde de izlenen çocuk hasta grubunu içermesi ve yıllara göre özellikle tedavi yaklaşımında yenilikler olması nedeniyle elde edilen sonuçlar, bilhassa hastalık yönetimi açısından günümüz durumunu direk yansıtmayabilir.

Sonuç

Bu çalışmada, pediatrik BH prevelansının yüksek olduğu Türkiye'de BH'ye sahip çocuk hastaların klinik özellikleri ile laboratuvar bulgularının yanı sıra tedavi yaklaşımlarını ve sonuçlarını da sunduk. Ek olarak pediatrik BH'de tedavide kolşisin ve kısa süreli kortikosteroid tedavisi dışında ek immünsüpresif tedavi ihtiyacı olan hastalarda öngörücü faktörleri belirlemeye çalıştık. Bulduğumuz sonuçlar doğrultusunda özellikle başvuruda göz veya vasküler tutulumu, yüksek akut faz reaktanları ve BHAAF skoru olan hastalarda ek immünsüpresif tedavi ihtiyacı olabileceği akılda tutulmalıdır.

Pediatrik BH'de erken tanının yanı sıra gerekli durumlarda immünsüpresif tedaviye erken dönemde başlamak da bir takım komplikasyonların önüne geçebilmek adına oldukça mühimdir. Ancak bu tür karmaşık ve bir hastalığı daha iyi anlamak için daha büyük popülasyonlarda yapılacak uzun vadeli kohort çalışmalarına ihtiyaç vardır.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Children with *Stenotrophomonas maltophilia* Bacteremia

Stenotrophomonas maltophilia Bakteriyemili Çocuk Olguların Değerlendirilmesi

Edanur Yeşil* (0000-0002-8926-9959), Solmaz Çelebi (0000-0002-3536-0263), Zeynep Özaslan*** (0000-0003-2641-4140), Arife Özer**** (0000-0001-9232-0084), Duygu Düzcan Kilimci***** (0000-0002-1543-4157), Mustafa Hacımustafaoğlu** (0000-0003-4646-660X)**

*University of Health Science Turkey, Mersin City Hospital, Clinic of Pediatric Infectious Disease, Mersin, Turkey
**Uludag University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Disease, Bursa, Turkey
***Dörtçelik Child Hospital, Clinic of Pediatrics, Bursa, Turkey
****University of Health Science Turkey, Dr. Behçet Uz Children's Hospital, Clinic of Pediatric Infectious Disease, İzmir, Turkey
*****Celal Bayar University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Manisa, Turkey

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Address for Correspondence/Yazışma Adresi: Edanur Yeşil MD, University of Health Science Turkey, Mersin City Hospital, Clinic of Pediatric Infectious Disease, Mersin, Turkey
Phone: +90 532 012 41 28
E-mail: eda_hacettepe@hotmail.com

Abstract

Introduction: *Stenotrophomonas maltophilia* (*S. maltophilia*) is a resistant gram-negative rod that can often cause serious infections, especially in patients with long hospital stays and using broad-spectrum antibiotics. In this study, clinical data, and mortality-related risk factors of patients with *S. maltophilia* bacteremia were evaluated.

Materials and Methods: Patients with *S. maltophilia* bacteremia included in this study and evaluated retrospectively, when hospitalized between 2013 and 2018 in our pediatric wards and intensive care units.

Results: A total of 67 patients had 100 *S. maltophilia* bacteremia in 70 different episodes. Sixty percent (n=40) of the cases were male and their median age were 9 months. Sixty-nine percent (n=46) of the cases were admitted in intensive care units. The most common comorbidity was malignancy. All bacteremias were healthcare associated, and 55% (n=55) were catheter-related. In the total of 70 episodes; 57% (n=37) of the patients had central venous catheters, 47% (n=33) were entubated. Fourty-seven percent (n=33) of the patients had broad spectrum antibiotic use over 14 days. In the blood cultures, 98% of *S. maltophilia*-producing strains were sensitive to trimethoprim-sulfamethoxazole. Ciprofloxacin and trimethoprim-sulfamethoxazole combination therapy had used for treatment. The mortality rate in the first 30 days was 16% (n=11). Mechanical ventilation was found to be significant ($p<0.05$) as a predisposing factor related to mortality.

Conclusion: *Stenotrophomonas maltophilia* is the causative pathogen in healthcare associated bloodstream infections especially in intensive care unit. In our study, 69% of the cases were admitted in the intensive care unit and mechanical ventilation status increased mortality.

Öz

Giriş: *Stenotrophomonas maltophilia* (*S. maltophilia*), uzun süre hastane yatışı olan ve geniş spektrumlu antibiyotik kullanan hastalarda ciddi enfeksiyonlara neden olabilen dirençli bir gram negatif basildir. Bu çalışmada *S. maltophilia* bakteriyemili hastaların klinik verileri ve mortalite ile ilişkili risk faktörleri değerlendirildi.

Gereç ve Yöntem: Çalışmada 2013-2018 yılları arasında pediatri servisleri ve yoğun bakım ünitelerinde yatırılan *S. maltophilia* bakteriyemili çocuk olgular retrospektif olarak değerlendirildi.

Bulgular: Toplam 67 hastada 70 farklı epizodda 100 kan kültüründe *S. maltophilia* üredi. Olguların %60'ı (n=40) erkekti ve ortanca yaşları 9 ay idi. Olguların %69'u (n=46) yoğun bakım ünitelerine yatırıldı. En sık eşlik eden hastalık malignite idi. Tüm bakteriyemiler sağlık hizmetiyle ilişkiliydi ve %55'i (n=55) kateterle ilişkili kan akımı enfeksiyonuydu. Toplam 70 epizodda; hastaların %57'sinde (n=37) santral venöz kateter vardı, %47'si (n=33) entübe idi. Hastaların %47'si (n=33) 14 gün üzerinde geniş spektrumlu antibiyotik kullandı. Kan kültürlerinde üreyen *S. maltophilia* suşlarının %98'i trimetoprim-sülfametoksazole duyarlıydı. Tedavide siprofloksasin ve trimethoprim-sülfametoksazol kombinasyon tedavisi kullanıldı. İlk 30 gün mortalite oranı %16 (n=11) idi. Mekanik ventilasyon mortalite ile ilişkili predispozan faktör olarak anlamlı (p<0,05) bulundu.
Sonuç: *Stenotrophomonas maltophilia*, özellikle yoğun bakımda sağlık hizmeti ilişkili kan dolaşımı enfeksiyonlarında önemli bir etken patojendir. Çalışmamızda olguların %69'u yoğun bakım ünitesine yatırılmış ve mekanik ventilasyon durumunun mortaliteyi artırdığı gösterilmiştir.

Introduction

Stenotrophomonas maltophilia is an opportunistic pathogen, which was previously called *Pseudomonas maltophilia* and later called *Xanthomonas maltophilia*. *Stenotrophomonas maltophilia* is an aerobe, non-fermentative gram-negative bacillus, particularly seen in patients receiving broad spectrum antibiotics such as carbapenem for a long time, and often cause respiratory tract infections, bacteremia, endocarditis, central nervous system and urinary tract infections. It can be isolated from soil, water, animals and hospital equipment. *Stenotrophomonas maltophilia* is capable of adhesion and biofilm formation of foreign substances and therefore can lead to catheter-related bloodstream infections and urinary tract infections.

The reported incidence of *S. maltophilia* infections ranged from 7.1 to 37.7 cases in 10,000 inpatients (1). *Stenotrophomonas maltophilia* has intrinsic resistance to aminoglycosides and beta-lactams including carbapenem (2,3). Although increasing resistance to quinolones had been reported, strains are usually susceptible to trimethoprim-sulfamethoxazole (4).

Risk factors associated with *S. maltophilia* infections include hospitalization in the intensive care unit (ICU), HIV infection, malignancy, cystic fibrosis, neutropenia, mechanical ventilation, central venous catheters indwelling, surgery, trauma and broad-spectrum antibiotics (1,5).

The aim of this study was to evaluate the clinical data of patients with *Stenotrophomonas maltophilia* bacteremia and to determine the risk factors.

Materials and Methods

Sixty-seven patients aged between 0-18 years were included in this study, who were detected *S. maltophilia* in their blood cultures (catheter and peripheral) and hospitalized between January 1, 2013 and January 31, 2018 in our pediatrics wards and intensive care units. Clinical conditions (duration and cause of hospitalization, comorbid disease, diagnosis at admission) and demographic characteristics of these cases, laboratory data (microbiological data), infection risk factors such as central venous catheter indwelling, urinary catheterization, mechanical ventilation, nasogastric tube, total parenteral nutrition, longterm use (>14 days) of broad-spectrum antibiotics, neutropenia status, received immunosuppressant therapy, prolonged hospitalization (≥14 days), *S. maltophilia* related infection rates, mortality rates were evaluated. The clinical and laboratory data of the patients were taken from our hospital electronic database. The use of third-generation cephalosporin, carbapenem, aminoglycoside and glycopeptide were accepted as the use of broad-spectrum antibiotics.

Ethics committee approval was obtained from the Clinical Research Ethics Committee of Uludağ University on July 10, 2018 with the decision numbered 2018-13/20. Participation involved informed consents.

Bacterial identification and antibiotic susceptibility tests are performed in BD Phoenix 100 (Becton Dickinson, USA) system in the bacteriology laboratory of our hospital. Antibiotic susceptibility tests are performed according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations. The best documented clinical response in this system is trimethoprim-sulfamethoxazole, and only the results of this antimicrobial susceptibility are indicated. It is considered as susceptible if the minimal inhibitory concentration of isolate to trimethoprim-sulfamethoxazole ≤4 mg/L, and >4 mg/L concentration is resistant (6,7).

Centers for Disease Control and Prevention (CDC, USA) criteria were used in the definitions (8-10).

Nosocomial infection defined as healthcare-associated infection. An infection is considered a healthcare-associated infection (HA) if the date of event of the National Healthcare Safety Network site-specific infection criterion occurs on or after the 3rd calendar day of admission to an inpatient location where day of admission is calendar day 1. Primary bloodstream infection (BSI) is a laboratory confirmed bloodstream infection that is not secondary to an infection at another body site. Catheher related bloodstream infection is a laboratory confirmed bloodstream infection where an eligible BSI organism is identified and an eligible central line is present on the laboratory confirmed bloodstream infection date of event or the day before (8-10).

Polymicrobial infection defined as combination of two or more microorganisms together cause disease. The presence of one microorganism generates a niche for other pathogenic microorganisms to colonise, one microorganism predisposes the host to colonisation by other microorganisms (11). In this study, isolation of more than one microorganism from the same blood sample in a bacteremia episode was called polymicrobial bacteremia.

Isolation of the same organism from a patient, from the same source, was accepted as a single episode. In this study, when *S. maltophilia* was growth more than once in one patient in a single episode, only one was evaluated. Contamination was defined as the detection of contaminated bacteria in blood culture and also when the patient was lack of clinical significance and determination of negative acute phase reactants. Neutropenia was defined as the absolute neutrophil count <1500/mm^3.

All causes of death were detected within 30 days of the first positive blood culture.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 software (SPSS Inc.; Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). The results were expressed as frequency (percentage) and mean ± standard deviation or median (minimum-maximum and interquartile range). The chi-square or Fisher's Exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups. In statistical analyzes, the significance level was determined as $p<0.05$.

Results

Stenotrophomonas maltophilia was detected in a total of 158 samples (blood, urine, tracheal aspirate fluid and other non-sterile body fluids) in the 5-year period between January 1, 2013 and January 31, 2018 in the pediatric wards and intensive care units in our hospital. In 67 patients with 70 different episodes, *S. maltophilia* detected in 100 (63%) blood culture. In 18 patients, more than one growth detection was found, and the mean number of growths were 2.5±1.1. Sixty percent (n=40) of the cases were male and the median ages were 9 months (mean 45±67, range 0-216 months). Sixty-nine percent (n=46) of the patients were hospitalized in the pediatric and neonatal intensive care unit. *Stenotrophomonas maltophilia* grew in the blood in patients median 14 (mean 28±35, range 1-150) days after hospitalization. There was no growth in a different site (endotracheal aspirate and/or body fluid) in the same episode. The underlying diseases were malignancy (20%), prematurity (18%) and neurological diseases (18%). There were no patients with cystic fibrosis. Patients were admitted to hospital mostly due to sepsis (50%) (Table 1).

Sixteen percent (n=16) of the blood cultures were from the catheter and 84% (n=84) were from the peripheral blood cultures. Fourteen percent (n=14) were considered as contamination. *Stenotrophomonas maltophilia* bacteremia episodes were all healthcare-associated and 55% (n=55) of them were catheter related. Twenty-six percent of all growth detection were polymicrobial and the most common accompanying microorganism was *Ralstonia pickettii*, followed by *Burkholderia cepaciae*.

Sixty-nine percent (n=46) of the 67 cases with *Stenotrophomonas maltophilia* bacteremias were inpatient in intensive care units, of which 78% (n=31) were associated with outbreak.

Sixty-nine percent (n=11/16) of the *S. maltophilia* bacteremias in the neonatal intensive care unit (n=16) were associated with outbreak. In this outbreak in February-April 2014, 20% (11/54) of the neonatal intensive care unit patients were affected and mortality was 45% (5/11). *Stenotrophomonas maltophilia*

isolates were not detected in the hospital equipment screening.

In the pediatric intensive care unit (n=30 patients), 67% (n=20) patients with *S. maltophilia* bacteremia were associated with the outbreak during 2013-2018 period. *Stenotrophomonas maltophilia* was detected in heparin vial in the period of October-December 2015.

Of the 70 episodes, 57% (n=37) had central venous catheter, 50% (n=35) had nasogastric catheter, 30% (n=21) had total parenteral nutrition, 10% (n=7) had urinary catheter, 47% (n=33) patient were intubated and 21% (n=15) were neutropenic. Fourty-seven percent (n=33) of the patients had more than 14 days of broad-spectrum antibiotic use and 20% (n=14) had immunosuppressive treatment (Table 2).

Ninety-eight percent (n=98) of the *S. maltophilia* bacteremia strains were susceptible to trimethoprim-sulfamethoxazole (TMP-SMX). Ciprofloxasin and trimethoprim-sulfamethoxazole combination therapy was used in the treatment. Control blood cultures became negative within 5 days.

Sixteen percent (n=11) of the patients died in the first 30 days. In two patients who had polymicrobial growth and died within first 30 days of growth detection; had concomitant microorganisms which were *B. cepaciae/ Ralstonia spp* in one case and *Staphylococcus aureus*

Table 1. Demographic characteristics of patients with *Stenotrophomonas maltophilia* bacteremia

	Mean ± SD (min-max, med)	n (%)
Total number of patients	-	67 (100)
Total episode	-	70 (100)
Age (month)	45±67 (0-216, 9)	-
Sex (boy)	-	40 (60)
ICU number of inpatients[a]	-	46 (69)
Duration of hospitalization (days)	28±35 (0-150, 14)	-
Major comorbidity (in 67 cases)		
Malignancy[b], n (%)	-	14 (20)
Prematurity, n (%)	-	12 (18)
Neurological[c], n (%)	-	12 (18)
CHD, n (%)	-	9 (13)
Metabolic disease, n (%)	-	8 (12)
Non-comorbid, n (%)	-	6 (9)
Postoperative inpatients[d], n (%)	-	3 (5)
Other (asthma, DM, immunodifeciency), n (%)	-	3 (5)
Diagnosis at admission (70 episodes)		
Sepsis, n (%)	-	35 (50)
Respiratory failure, n (%)	-	18 (26)
Heart failure, n (%)	-	5 (7)
Prematurity, n (%)	-	4 (6)
Liver failure, n (%)	-	3 (4)
Convulsion, n (%)	-	3 (4)
Renal failure, n (%)	-	1 (1.5)
Diabetic ketoacidosis, n (%)	-	1 (1.5)
Mortality in the first 30 days, n (%)	-	11 (16)

[a]Includes the total number of patients in pediatric intensive care unit and neonatal intensive care unit
[b]Includes malignancies, which most of them are hematologic and then oncologic malignancies
[c]Neurological comorbidities includes, cerebral palsy mostly and then epilepsy, spinomuscular atrophy
[d]It contains congenital diaphragmatic hernia and esophageal atresia
Mean: Average, SD: Standard deviation, min: Minimum, max: Maximum, med: Median, ICU: Internal care unit, CHD: Congenital heart disease, DM: Diyabetes mellitus

Table 2. Risk factors in *Stenotrophomonas maltophilia* bacteremia patients (70 episode)	
	n (%)
Use of broad-spectrum antibiotics	60 (90)
Central venous catheter	37 (57)
Nazogastric tube	35 (50)
Use of broad-spectrum antibiotics >14 days	33 (47)
Mechanical ventilation status	33 (47)
Prolonged admission (>14 days)*	29 (43)
Total parenteral nutrition	21 (30)
Neutropenia	15 (21)
Immunosuppressive therapy	14 (20)
Urinary catheterization	7 (10)

*The day of hospitalization at the time of growth detection was taken into consideration

in the other case. Polymicrobial growth was not detected as a mortality risk factor. When the mortality-related risk factors of *S. maltophilia* bacteremia were compared (Table 3), mechanical ventilation was found to increase mortality ($p<0.05$).

In 2013-2018 study period, in our clinic wards (included intensive care units, hematology and oncology clinics, pediatric infectious disease clinic wards and other pediatric clinic wards where the *S. maltophilia* bacteremia inpatients stayed) *S. maltophilia* infection rate was 0.86% (n=67/7764).

Stenotrophomonas maltophilia is one of the organisms isolated from the respiratory tract of patients with cystic fibrosis (CF). It simply colonizes the CF lung, and generally does not contribute to CF lung disease. In this study, there were no patients with cystic fibrosis.

Discussion

Stenotophomonas maltophilia is a gram-negative bacteria with low virulence and is an opportunistic multidrug-resistant pathogen that is usually detected in hospital, particularly in immunocompromised hosts. Risk factors associated with various *S. maltophilia* infection include underlying malignancy, cystic fibrosis, immunosuppressive therapy, the presence of a permanent central venous catheter, and exposure to broad-spectrum antibiotics (4). In this study, malignancy followed by prematurity and neurological diseases were the most common underlying disease in patients with *S. maltophilia* bacteremia. It has been observed as risk factors that broad-spectrum antibiotic use and invazive procedures such as central venous catheterization, nasogastric tube and mechanical ventilation were frequently used.

Most infections caused by *Stenotrophomonas maltophilia* require serious morbidity and long-term intensive care, with a mortality of 13-62% (12-14). In our study, 40% (n=27) of the patients died and the first 30 days mortality attributed to *S. maltophilia* was 16% (n=11). In a pediatric study which was designed by Tokatly Latzer et al. (5), *S. maltophilia* atrributed mortality was %16 which is similar to this study. In an adult study designed by Jeon et al. (15), the first 28 days mortality associated with *S. maltophilia* was found as 36.6% and the most important risk factors affecting the mortality were determined as hematological malignancy, SOFA (Sepsis-related Organ Failure Assessment) score and higher central venous catheter (CVC) indwelling.

In this study, the presence of mechanical ventilation as a predisposing factor related to mortality was found significant in hospital acquired *S. maltophilia* infections ($p<0.05$). In a similar study, long-term antibiotic use (>14 days) and urinary catheter presence were found to be significant (3). In another pediatric study, longer hospitalization, septic shock, mechanical ventilation, central vein catheter indwelling, prior use of steroids and carbapenems were related with mortality ($p<0.05$) (5). Ebara et al. (14) found that mechanical ventilation as a risk factor for mortality, similar to this study. In this study, 90% of the patients used broad-spectrum antibiotics and all clinically significant bacteremia episodes were healthcare associated infections. Another study points out that the use of broad-spectrum antibiotics and in particular carbapenems, increases *S. maltophilia* bacteremia (14).

Some studies have reported that initial administration of inappropriate antibacterial treatment was a significant predictor of mortality (16). In our study longer broad-spectrum antibiotic use did not found as a risk factor contrast to many studies (5,14).

Stenotrophomonas maltophilia infection rates has been increasing over recent years (17). Especially the initial condition of the patient is directly related to mortality (18). Also, several virulence factors of *S. maltophilia* such as forming biofilm on surfaces and extracellular enzymes is the cause of its pathogenity (19).

Table 3. Risk factors associated with mortality in *Stenotrophomonas maltophilia* bacteremia patients (67 patients)			
	Mortality (n=11)	No mortality (n=56)	p
Height	8 (73)	32 (57)	0.50
Age (median, month)	25	9	1
Clinics			
Neonatal intensive care unit, n (%)	5 (45)	11 (20)	0.11
Pediatric intensive care unit, n (%)	5 (45)	25 (45)	1
Neonatal and pediatric ICU[a], n (%)	10 (90)	36 (64)	0.15
Hematology oncology clinic, n (%)	1 (10)	11 (20)	0.67
Other pediatric clinics, n (%)	0 (0)	9 (15)	0.34
HA bloodstream infection[b]			
Bakteriyemi (peripheral blood culture), n (%)	5 (45)	11 (27)	0.12
Catheter-associated bacteremia, n (%)	6 (55)	19 (48)	0.31
Comorbidity			
Sepsis, n (%)	6 (55)	28 (50)	1
Respiratory failure, n (%)	2 (18)	14 (25)	1
Heart failure, n (%)	1 (9)	4 (7)	1
Prematurity, n (%)	1 (9)	3 (5)	0.52
Liver failure, n (%)	0 (0)	3 (5)	1
Convulsion, n (%)	1 (9)	2 (4)	0.42
Renal failure, n (%)	0 (0)	1 (2)	1
Diabetic ketoacidosis, n (%)	0 (0)	1 (2)	1
Risk factors			
Central venous catheter, n (%)	6 (66)	29 (52)	1
TPN[c], n (%)	5 (41)	15 (27)	0.28
Neutropenia, n (%)	5 (26)	10 (18)	0.10
Nasogastric tube, n (%)	9 (60)	25 (45)	0.17
Urinary cathater, n (%)	3 (19)	4 (7)	0.08
Mechanical ventilation, n (%)	10 (78)	20 (36)	**0.0016**
Polymicrobial growth detection, n (%)	2 (15)	15 (27)	0.71
Use of broad-spectrum antibiotic, n (%)	11 (100)	49 (88)	0.59
Use of broad-spectrum antibiotic >14 days, n (%)	8 (73)	25 (45)	0.10
Hospital stays longer than 14 days, n (%)	8 (73)	25 (45)	0.10
Immunosuppressive therapy, n (%)	3 (27)	11 (20)	0.69

[a]ICU: Internal care unit, [b]HA: Healthcare-associated, [c]TPN: Total parenteral nutrition

In the SENTRY antmicorbial surveillance programme TMP-SMX resistance to *S. maltophilia* ranging from 2% to %10 (20). In this study, 98% of the *S. maltophilia* bacteremia strains were susceptible to TMP-SMX. Generally, TMP-SMX and fluoroquinolones are the major options for treatment choice. But in some studies minocycline, ceftazidime, ticarcilin-clavunate found susceptible to *S. maltophilia* *in vitro* and used for treatment (14,16). In this study, we used ciprofloxasin and TMP-SMX combination therapy for *S. maltophilia* bacteremia. There are limited data shown that TMP-SMZ combination with levofloxacin or ciprofloxacin had not change the mortality rate of *S. maltophilia* infections (21).

In this study, *S. maltophilia* infection rate was 0.86% (n=67/7764) during the 5-year period. Tokatly Latzer

et al. (5) found the total incidence of *S. maltophilia* isolation during the 5.5-year period was 0.53% and this was lower according to our study.

Sixty-nine percent (n=46) of patients with *S. maltophilia* bacteremia were hospitalized in intensive care units, of which 67% (n=31) were associated with the outbreak. It is determined that the ratio of patient/nurse is over 3 in intensive care units in epidemic periods. It is aimed to avoid the use of CVC, taking care of catheter care and ensuring that the patient/nurse ratio is 2. In addition, it was ensured that only the same patient could use common samples such as heparin bottles or saline. When this is not possible, sterilization methods have been explained and taught. Infection prevention and control trainings were given to all health personnel in the relevant department. It is aimed to repeat these trainings at certain intervals.

Conclusion

In conclusion, nonfermentative gram-negative bacillus such as *S. maltophilia* are important opportunistic pathogens responsible for severe hospital acquired infections. These pathogens are frequently encountered in hospital-associated bloodstream infections especially in intensive care units. In this study, 69% of the patients were hospitalized in intensive care unit. All strains had nosocomial origin. The presence of mechanical ventilation as a predisposing factor related to mortality in patients with hospital acquired *S. maltophilia* bloodstream infections were found to be significant. Monitoring surveillance of antimicrobial susceptibility of these pathogens and optimal treatment are very important for treatment success.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Clinical Research Ethics Committee of Uludağ University on July 10, 2018 with the decision numbered 2018-13/20.

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Clinical Features, Prognostic Factors and Outcome of Children with Ewing Sarcoma: A Single-center Experience

Ewing Sarkomlu Çocuk Hastaların Klinik Özellikleri, Prognostik Faktörleri ve Tedavi Sonuçları: Tek Merkez Deneyimi

Işık Odaman Al* (0000-0003-4292-1409), Bengü Demirağ (0000-0003-4399-0844), Dündar Sabah*** (0000-0002-3391-2597), Serra Kamer**** (0000-0001-8316-9976), Başak Doğan Avşargil***** (0000-0002-4738-4350), Mehmet Argın****** (0000-0002-3310-8398), Yeşim Oymak** (0000-0002-6908-8309)**

*Medipol University Faculty of Medicine, Department of Pediatric Hematology and Oncology, İstanbul, Turkey

**University of Health Science Turkey, Dr. Behçet Uz Children's Hospital, Clinic of Pediatric Hematology and Oncology İzmir, Turkey

***Ege University Faculty of Medicine, Department of Orthopedics, İzmir, Turkey

****Ege Üniversity Faculty of Medicine, Department of Radiation Oncology, İzmir, Turkey

*****Ege University Faculty of Medicine, Department of Pathology, İzmir, Turkey

******Ege University Faculty of Medicine, Department of Radiodiagnostics, İzmir, Turkey

Abstract

Introduction: Ewing sarcoma (ES) is a rare, aggressive, malignant tumor. It is the second most common malignant bone tumor in children. A total of 20-25% of patients are metastatic at the time of diagnosis. The survival rate for localized disease (LD) is approximately 70-74%. For metastatic disease (MD), it is about 30%. The most important prognostic factor affecting survival is the presence of MD at diagnosis. In this study, we investigated the clinical characteristics, treatment outcome, and factors affecting the prognosis and survival of patients followed up with the diagnosis of ES.

Materials and Methods: Between 2007 and 2020, a total of 24 ES patients aged 0-18 years were retrospectively analyzed.

Results: The most common complaint was pain and swelling in the lesion area (n=9), followed by pain (n=5), swelling (n=3), abdominal pain (n=2), shortness of breath (n=2), facial paralysis (n=1), spinal compression findings (leg pain and walking difficulty) (n=1) and hematuria (n=1). ES was bone-derived in 19 patients (79%). Of these, 14 had LD and 5 had MD at the time of diagnosis. Extraskeletal Ewing sarcomas (EES), was detected in five patients (21%) and derived from the kidney (n=1), rectus abdominis (n=1), left quadriceps femoris muscle (n=1), left upper thoracic region and lumbar region paraspinal muscles (n=2). The rate of MD was 25% (6/24) in the entire patient group. Disease progression was observed in three patients during treatment. Relapse at follow-up was observed in 6 of 19 patients in complete remission. The median time to relapse was 20 months (minimum 13, maximum 34 months) from diagnosis. The median survival of our patients after relapse was 14.5 months (minimum 6-maximum 27 months). Radiological response and histopathological response to induction therapy, presence of relapse or progression, and relapse site were found to be correlated with survival (Fisher's Exact test p=0.02, 0.0047, <0.001, 0.001 respectiveley).

Conclusion: ES is a cancer with high mortality and morbidity. Although the most common symptoms are pain and swelling, the symptoms may vary depending on the region from which the tumor originates. Response to induction therapy and the presence of relapse-progression are factors affecting prognosis. Treatment should be personalized to improve survival.

Keywords
Ewing sarcoma, children, bone tumors, sarcoma

Anahtar kelimeler
Ewing sarkom, çocuk, kemik tümörleri, sarkom

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Address for Correspondence/Yazışma Adresi: Işık Odaman Al MD, Medipol University Faculty of Medicine, Department of Pediatric Hematology and Oncology, İstanbul, Turkey
Phone: +90 507 535 55 62
E-mail: dr.odamanal@gmail.com

Öz

Giriş: Ewing sarkomu nadir görülen, agresif, malign bir tümördür. Çocuklarda görülen ikinci en sık malign kemik tümörüdür ES tanı sırasında lokal (LH) ve metastatik hastalık (MH) olarak karşımıza çıkabilir. %20-25 hasta tanı sırasında metastatiktir. LH'de sağkalım yaklaşık %70-74'tür. MH'de ise %30 civarındadır. Sağkalımı etkileyen en önemli prognostik faktör tanı sırasında MH varlığıdır. Bu çalışmamızda ES tanısı ile takip ettiğimiz hastaların klinik özelliklerini, tedavi yanıtlarını, prognozu etkileyen faktörleri ve sağkalımlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Hastanemizde 2007-2020 yılları arasında ES tanısı ile tedavi gören 0-18 yaş 24 hasta retrospektif olarak değerlendirildi.

Bulgular: Başvuru şikayetleri en sık lezyon bölgesinde ağrı ve şişlik (n=9) iken, ağrı (n=5), şişlik (n=3), karın ağrısı (n=2), nefes darlığı (n=2), yüz felci (n=1), bacaklarda ağrı-yürümede zorluk yakınması ile gelen olgumuzda spinal bası bulguları (n=1) ve hematüri (n=1) hastaneye başvuru nedenleri idi. ES 19 hastada (79%) kemik kaynaklıydı. Bunların 14'ünde tanı sırasında lokal, 5'inde metastatik hastalık mevcuttu. Beş hastada (21%) ise ekstraskeletal saptanmış olup, böbrek (n=1), rektus abdominis (n=1), sol kuadriseps femoris kası (n=1), sol üst torakal bölge ve lomber bölge paraspinal kasları (n=2) kaynaklıydı. Tüm hasta grubunda MH oranı 25% (6/24) idi. Üç hastada tedavi altında progresyon görüldü. Tam remisyona giren 19 hastanın 6'sında (6/19) izlemde relaps gözlendi. Relaps zamanı tanıdan itibaren ise ortanca 20 ay (minimum 13, maksimum 34) idi. Hastalarımızın relaps sonrası yaşam süresi ortanca 14.5 ay (minimum 6-maksimum 27 ay) idi. İndüksiyon tedavisine radyolojik yanıt, indüksiyon tedavisine histopatolojik yanıt, relaps ya da progresyon varlığı ve relaps yeri sağkalım ile ilişkili olarak bulundu (Fisher's exact test p=0,02, 0,0047, <0,001, 0,001).

Sonuç: ES mortalite ve morbiditesi yüksek olan bir kanser türüdür. En sık semptom ağrı ve şişlik olmakla birlikte tümörün kaynaklandığı bölgeye göre semptomlar farklılık gösterebilir. Indüksiyon tedavisine yanıt, relaps-progresyon varlığı prognozu etkileyen faktörlerdir. Sağkalımı artırmak için tedavi kişiselleştirilmelidir.

Introduction

Ewing sarcoma family tumors (ESFTs) are used to identify tumors composed of small, round tumor cells that share common neural histology and genetic mechanisms. The most common of these tumors are bone Ewing sarcomas (ES), extraskeletal Ewing sarcomas (EES), pPNET, and Askin tumors with chest wall-derived pPNET. ES is a rare, aggressive, malignant tumor (1). It was first described by Ewing in 1921. It is the second most common malignant bone tumor in children, adolescents, and young adults accounting for less than 5% of the cancers in this age group (2-5). It is more prevalent in males, and its annual incidence ranges from one to three cases per million (5). Clinically, it often presents as a painful, mass lesion (6). Localization in the long bones is the most common (5). The axial skeletal system is the second most common site. ESFTs can originate from anywhere in the body, and approximately 20% of them are EES cases (2,7). EES is 10 times less common than bone ES, and the incidence is 0.4 per million. Most cases occur at ages younger than 5 years and older than 35 years. Contrary to bone ES, there is no gender relationship in ESS. It most commonly occurs in the upper femoral region, hip, shoulders, and upper arm (7).

ES may present as a local (LD) or metastatic disease (MD) at the time of diagnosis. A total of 20-25% of patients are metastatic at the time of diagnosis. Forty percent of them have isolated lung metastases, and metastases may also occur in bone and bone marrow (BM) (2). The diagnosis is based on histopathologic examination (2). Treatment requires a multidisciplinary approach (8). Treatment modalities include neoadjuvant chemotherapy, surgery, radiotherapy (RT), and autologous stem cell transplantation (ASCT). The survival rate for LD is approximately 70-74% (2,4). For MD, it is about 30% (2). In patients with pulmonary metastases, the 3-year survival rate is 52% (1). The most important prognostic factor affecting survival is the presence of MD at diagnosis (2). For LD, histopathological response to induction treatment and tumor volume and diameter are the most important factors. Other prognostic factors include patient age, tumor location, and lactat dehydrogenase (LDH) level (1).

In this study, we investigated the clinical characteristics, treatments, treatment outcome, and factors affecting the prognosis and survival of patients followed up with the diagnosis of ES.

Materials and Methods

Study Design and Data Collection

Twenty-four patients aged 0-18 years who were treated at our hospital with a diagnosis of ES between 2007 and 2020 were retrospectively evaluated. The patients were divided into 3 groups: 0-10 years, 11-14 years, and 15-18 years. Patient information was retrieved from patient files and electronic recording systems. Demographic and clinical characteristics of the patients, treatments applied and treatment outcomes were recorded.

Diagnosis and Staging

The diagnosis was made according to standard histopathological criteria. Molecular analysis was not performed. Patients were divided into two groups: osseous and extraosseous. Tumor regions were classified as the axial skeleton, extremities, pelvis, and extraosseous. Contrast-enhanced magnetic resonance imaging (MRI) was performed at the tumor site in each patient as an imaging modality. Tumor diameter was classified as <8 cm and ≥ 8 cm considering the largest diameter on MRI examination. Thoracic computed tomography (CT) and whole-body bone scintigraphy were performed on each patient for metastasis screening. Bilateral BM biopsy was performed to detect BM involvement. The patients were divided into those with LD, those with pulmonary and pleural metastases, and those with disseminated disease (pulmonary, bone, bone marrow).

Evaluation of Treatment, Prognosis, and Treatment Outcomes

EICESS 92 and Euro-Ewing 99 were used as chemotherapy protocols. Accordingly, neoadjuvant chemotherapy was administered after the diagnosis and followed by surgery and/or RT in local treatment, while the treatment was completed with adjuvant chemotherapy. While <50% reduction in tumor soft tissue mass was considered a poor response, and >50% reduction was considered a good response, in the post-surgical histopathological evaluation, viable tumor tissue was considered poor if ≥10% and as good response if <10%. Complete disappearance of the tumor was considered a complete response, ≥50% reduction in size was considered a partial response, while <50% reduction or <25% increase in size was considered a stable disease, and ≥25% increase in size was considered progression. Relapse and progression were detected using imaging methods and a histopathological examination was not performed.

Statistical Analysis

Demographic data and descriptive statistics were used. Descriptive statistics were expressed as the number of units (n), percentage (%), mean ± standard deviation (x ≤ ± SD), median values, and minimum-maximum values. Whether the categorical variables were dependent was compared using chi-square, Yates correction (continuity correction), and Fisher's Exact test. P<0.05 was considered statistically significant. All statistical analyzes were conducted using SPSS software for Windows version 25.0 (IBM Corp. Released 2017. Armonk, NY, USA).

Ethics approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital Ethics Committee (approvel number: 2022/04-02, date: 24.02.2022).

Results

Baseline Characteristics

Twenty-four patients (F/M: 14/10) were included in the study. The median age of patients at diagnosis was 12.8 years (min 4.7, max 16.8 years), and the median duration of follow-up was 33 months (min 5, max 151 months). The most common complaint was pain and swelling in the lesion area (n=9), followed by pain (n=5), swelling (n=3), abdominal pain (n=2), shortness of breath (n=2), facial paralysis (n=1), spinal compression findings (leg pain and walking difficulty) (n=1) and hematuria (n=1). The mean time between the onset of the symptoms and admission to the hospital was 8.5±17 months (min 15 days, max 69 months). As the first imaging method, the patients were underwent direct radiography (n=2), CT (n=4), and MRI (n=18). ES was bone-derived in 19 patients (79%). Of these, 14 had LD and 5 had MD at the time of diagnosis (Table 1). EES was detected in five patients (21%) and derived from the kidney (n=1), rectus abdominis (n=1), left quadriceps femoris muscle (n=1), left upper thoracic region and lumbar region paraspinal muscles (n=2). The patient with

renal origin had isolated BM metastasis, and the other 4 patients were staged as LD. The rate of MD was 25% (6/24) in the entire patient group. Of the patients with MD, 3 had lung and pleural metastases, 1 had BM, and 2 had the disseminated disease (bone, BM, and lung). Histopathologic diagnosis was made by tru-cut needle biopsy in 16 patients, open mass biopsy in 6 patients, and total mass excision in 2 patients (rectus abdominis muscle, kidney).

Table 1. Clinical characteristics of the patients

	All patients (n=24)	
Characteristics	No.	%
Age groups (years)		
0-10	3	12.5
11-14	15	62.5
15-18	6	25
Sex		
Female	14	58
Male	10	42
Primary tumor site		
Extremity	9	37.5
Pelvis	4	16.7
Axial	6	25
Extraosseous	5	20.8
Primary tumor source		
Bone	19	79
Soft tissue	5	21
Primary tumor diameter		
<8 cm	12	50
≥8 cm	12	50
Disease spread		
Local	18	75
Lung and pleura metastatic	3	12.5
Isolated bone marrow	1	4.2
Disseminated disease	2	8.3
Chemotherapy protocol		
EICESS 92	21	87.5
Euro-Ewing 99	3	12.5
Local treatment		
Surgery	7	29.2
Radiotherapy	9	37.5
Surgery and radiotherapy	6	25
No treatment	2	8.3
Treatment results		
Complete response	19	79
Disease progression	3	12.5
Sepsis and cardiac toxicity	2	8.3
Relapse		
Yes	6	25
None	18	75
Last event		
Alive	14	58
Deceased	10	42

Treatment

EICESS 92 protocol was initiated in 21 patients, and the Euro-Ewing 99 protocol was initiated in 3 patients. Local treatment to the primary tumor region was applied to 7 patients (29.2%) with surgery, 9 (37.5%) with RT, and 6 (25%) with surgery and RT. One of the 2 patients (8.3%) who could not be treated locally had sacrum, vertebrae, and cranial bone involvement at the time of diagnosis, and the primary tumor region was not clear, and the other died due to sepsis before completion of induction treatment. None of our patients underwent ASCT.

Treatment Results

Radiologic response to induction therapy was poor in 10 patients (41.7%), good in 9 (37.5%), and unclear in 5 (20.8%) because of the quality of radiologic imaging. The postoperative histopathologic response was good in 4 patients (16.7%) and poor in 8 patients (33.3%), and could not be studied in 12 patients (50%). Total excision was performed in 3 of the patients in whom tissue response to treatment could not be assessed. In the remaining 9 patients, only RT was used as a local treatment, while in 2 patients no local treatment could be performed. In one patient with poor response to treatment, treatment with ifosfamide, carboplatin, and etoposide (ICE) was started. Nineteen patients (19/24) achieved a complete response.

Events

Disease progression was observed in three patients during treatment. Progression occurred during neoadjuvant chemotherapy in one and adjuvant chemotherapy period in other two patients. Relapse at follow-up was observed in 6 of 19 patients in complete remission (Table 2). The median time to relapse was 8 months (min 1, max 23 months) from treatment discontinuation and 20 months (min 13, max 34 months) from diagnosis. The median survival of our patients after relapse was 14.5 months (min 6-max 27 months). Rescue treatments applied due to disease progression and relapse are shown in Table 3. Sorafenib (29.2%) was started in seven patients with conventional chemotherapy due to progression and relapse.

Table 2. Clinical characteristics of patients with disease progression and relapse

No	Diagnosis age (years)	Primary region/ Stage	Tm size (cm)	Primary treatment	Induction radiological response	Local treatment in primary diagnosis	*Relapse duration (months)	Relapse/ progression site	Applied treatment	Last event	Time of death (month)
1	13.6	Left hemithorax/ local	<8	EICESS 92	Poor	Surgery + RT	21	Local and lung	ICE 6 courses	Deceased (progression)	33
2	15	Right tibia/ local	≥8	EICESS 92	Poor	Surgery + RT	22	Local	VIT + amputation	Deceased (Progression)	39
3	14.4	Left quadriceps femoris muscle/ local	≥8	EICESS 92	Poor	Surgery + RT	34	Osseous, (tibia)	VIT 6 courses + sorafenib	Alive	43
4	11	Pelvis/metastatic (bone + lung)	≥8	EICESS 92	Good	RT	13	Lung	VIT 6 courses + sorafebib	Deceased (progression)	19
5	10.1	Right femur distal/ local	≥8	EICESS 92	Poor	Surgery	14	Lung	Metastasectomy/ VIT 4 courses/ ICE 1 course/ Sorafenib/lung RT	Deceased (progression)	11
6	11.2	Pelvis/ local	≥8	EICESS 92	Poor	Surgery + RT	19	Lung and bone	Metastasectomy/ VIT 6 courses/ Sorafenib	Deceased (Progression)	19
7	1.9	Right humerus/ local	<8	EICESS 92	Could not be determined	RT	-	Disseminated bone	Topotecan/cyclo-Ice 2 courses-RT/ metronomic	Deceased (progression)	10
8	11.7	Left kidney/ metastatic	≥8	EICESS 92	Could not be determined	RT	-	Disseminated bone	ICE 4 courses	Deceased (progression)	11
9	16.7	Left humerus/ metastatic	≥8	EICESS 92	Poor	Surgery + RT	-	Lung	Treatment rejection	Deceased (progression)	7

*Time since diagnosis

ICE: ifosphamide + carboplatin + etoposide, q3w, every 3 weeks; VIT: vinkristin, irinotecan, temozolimide, ; q3w, every 3 weeks; metronomic treatment: cyclophosphamide, etoposide, celebrex

Table 3. Clinical characteristics of patients with relapsed or primary disease progression		
	All patients (n=9)	
Characteristics	No.	%
Relapse-free interval		
<24 months	2	33.3
24 months	4	66.6
Type of relapse or progression		
Local	2	22.2
Lung	3	33.3
Diffuse bone	2	22.2
Local and lung	1	11.1
Bone and lung	1	11.1
Primary tumor diameter		
<8 cm	2	22.2
≥8 cm	7	77.8
Salvage chemotherapy protocol		
ICE	2	22.2
VIT	4	44.4
ICE-VIT*	1	11.1
Topotecan/cyclo-Ice-metronomic therapy**	1	11.1
Sorafenib	5	55.5
No	1	11.1
Last event		
Alive	1	11
Deceased	8	89

*2 cycles of VIT unresponsive followed by 1 cure of ICE
**cyclophosphamide, etoposide, celebrex
ICE: Ifosfamide + carboplatin + etoposide, q3w, every 3 weeks; VIT: Vincristine, irinotecan, temozolimide; q3w, every 3 weeks

During the follow-up period, 10 patients (41.7%) died. The cause of death was progression in 8 patients (80%), sepsis in one patient (10%), and cardiac toxicity in one patient (10%). One patient developed a secondary tumor of soft tissue origin on the right knee 8 years after discontinuation of treatment. He was diagnosed with round cell sarcoma with rhabdoid differentiation. After mass excision, local RT was applied with 4 cycles of vincristine, irinotecan, and temozolomide (VIT) treatment. The patient is in complete remission.

Factors Associated with Survival

Factors affecting survival were evaluated. Radiological response and histopathological response to induction therapy, presence of relapse or progression, and relapse site were found to be correlated with survival (Fisher's Exact test p=0.02, 0.0047, <0.001, 0.001 respectiveley). On the other hand, there was no correlation between age, sex, tumor region, tumor size, LDH level, local treatment, disease status (local-metastatic), and survival (p=0.847, 0.678, 0.218, 0.214, 0.321, 1, 0.192 respectiveley).

Discussion

The aim of this study was to analyze the clinical admission findings, treatments administered, and treatment responses of our patients and to evaluate the factors affecting the treatment outcomes. ES is a tumor that is more common in children after the age of 10 years (2,3) and tends to be 1.5 times more common in males than in females (5). While 15 of our patients (62.5%) were in the 11-14 age group and were consistent with the literature, our number of female patients was higher, with a female/male ratio of 1.4. The fact that most of our cases were of bone origin was also consistent with the literature. Although the symptoms vary according to the region, size, and stage of the tumor (6), pain and swelling were the most common symptoms in our patient group, in parallel

with other studies. One patient with temporal bone origin presented with facial paralysis, and one patient with kidney origin presented with complaints not suggestive of ES, such as hematuria. Because of the nonspecific presenting symptoms, the establishment of the diagnosis is delayed which affects survival results (6). Therefore, early diagnosis of patients is extremely important (8). In our patient group, the mean time to diagnosis after the onset of symptoms was 8.5±17 months (min 15 days, max 69 months).

The periosteum reaction in ES looks like an onion membrane on direct radiography. It refers to the new bone tissue surrounding the cortical destruction caused by the tumor. Therefore, direct radiography and MRI, thoracic CT, and whole bone scintigraphy should be performed for staging. Today, although not routinely, PET-CT is used in some centers, and because PET-CT is not available in our hospital, it could not be taken.

In diagnosis, tru-cut biopsy is sufficient at >90% to determine the tumor grade and specific subtype (8). A large part of ESFT is positive in the CD 99 membranous pattern. Cytoplasmic pattern positivity can also be seen. ETS-family gene translocations with EWSR1 are characteristic of the ESFT family. Approximately 85% of them are composed of t (11;22), encoding the EWSR1-FLI1 oncoprotein (2). Our patients were diagnosed according to histopathological criteria, and no molecular genetic analysis could be performed on any of them. Although TNM staging (tumor, lymph node, metastasis) is performed as in all bone tumors in staging, two classifications as MD and LD are used, because they are not significant in terms of prognosis (2). In our study, the rate of MD was 25% (6/24).

Treatment of the disease requires a multidisciplinary team (8). The standard initial treatment is systemic chemotherapy. Treatment is based on vincristine, ifosfamide, doxorubicin, actinomycin D, and etoposide. It has not been established that adding topotecan, cyclophosphamide, carboplatin, and cisplatin to the treatment of localized ES is beneficial. The effectiveness of ASCT with high-dose busulfan and melphalan (BuMel) as consolidation therapy in patients with high-risk localized tumors has been studied, and event-free survival was found to be better than that of standard treatment (60.7 vs 47.1%) (9). However, we did not have the opportunity to use the ASCT procedure in our patient group.

The prognosis is poor in relapsed patients. Relapse time is the most important factor affecting prognosis. The survival rate was <10% in patients with relapse within the first 2 years after diagnosis, while it was 30% in patients with relapse after 2 years. Another important factor is the localization of the relapse. The coexistence of local and distant metastases indicates a worse prognosis (4). Some of the treatment options for relapse are topotecan-cyclophosphamide and irinotecan-temozolomide-vincristine. There are publications emphasizing that 30% and 28% of responses are achieved with these treatments, respectively (4). There was a 14% response to gemcitabine at low doses and a 66% response at high doses with the docetaxel combination. In patients who respond to salvage therapy, high-dose chemotherapy with BuMel can be administered (9).

The optimal local treatment after neoadjuvant chemotherapy remains controversial (1). Surgery, RT, or both are applied together. There are no randomized controlled trials comparing local therapies. Controversial and conflicting results have been reported in trials comparing surgery and RT in local treatment. In trials comparing patients treated with surgery and RT together with patients treated with surgery alone, there was no significant difference in event-free survival (EFS) and overall survival (OS) (5). In a study that provided results on overall survival (OS), it was found that there was no significant difference in either group (10). As a result, surgery or RT alone may be the treatment option for local treatment in ES. Tumor location, size, radiologic and histopathologic response to chemotherapy, and patient comorbidity should be considered when deciding on local treatment (11).

In our patient group, RT could not be applied on a patient because she was mentally disabled and RT required daily anesthesia. In this patient an expanded tumor bed excision was performed. When the treatment-related complications were examined; fractures, functional losses, and skin lesions were reported in the bone region in patients RT applied, and functional mechanical disorders were reported most frequently in relation to S (5).

In our patient group, 5 patients had EES. Chemotherapy and local treatment were given to all of them. The efficacy of systemic chemotherapy in EES has been proven and is essential for treatment.

The definitive treatment is neoadjuvant chemotherapy and surgery. Although EES is radiosensitive, RT alone is not sufficient for local control. The definitive indication of RT is tumors that cannot be surgically removed and cases with positive surgical margins and should be applied at 54-55 Gy (7). A negative surgical margin is the most important factor in the local control of tumors. Although the prognosis of EES is better than that of bone tumors, the prognostic factors are the same. Despite the publications stating that BM biopsy is not required for the staging, especially in patients without metastases (12), the presence of BM metastases in our ES patient of kidney origin in the primary diagnosis was notable, although there were no lung or bone metastases, and it was thought that BM biopsy may be important in the diagnosis, particularly for the extraosseous group.

Disease relapse occurs in 30-40% of ES patients. Relapse disease is associated with a poor prognosis. <20% of patients who develop relapse survive in the 5-year follow-up. However, the prognosis may be better in patients with limited local or relapse 2 years after diagnosis (2). In our study, disease recurrence was observed in 6 patients, 5 patients died, and one patient was followed up for 27 months after relapse. While the primary tumor of this patient was of quadriceps femoris origin and EES, relaps was seen in tibia 34 months after the first diagnosis. The median survival of our patients after relapse was 14.5 months (min 6-max 27 months).

There has been an increase in treatment related secondary cancer incidence, especially among children, as a result of improvements in treatment modalities and increased survival rates. ES is one of the disease with the highest risk of secondary cancer. Alkylating agents and anthracyclines used in treatment pose an increased risk for tumor development, such as hematologic malignancies, breast cancer and osteosarcoma (13). The cumulative incidence of treatment-related secondary tumors in surviving patients was 9-10% over 30 years. The incidence has been shown to be lower in patients diagnosed after 1990 compared with previous years, which is related to lower RT doses (14). In our patient group, one patient diagnosed with localized ES from the pelvis developed round cell sarcoma from the soft tissue 8 years after the diagnosis, and this patient continues to live in complete remission with chemotherapy (VIT scheme) and RT.

Over the years, with the changes in treatment protocols and the development of supportive treatments, survival in ES has increased to 70-74% for LD and 30% for MD (2,4). With the addition of ifosfamide and etoposide to the treatment consisting of vincristine, doxorubicin, and cyclophosphamide, improvement in OS and EFS was achieved in LD (61% vs. 72%, 54% vs. 69%, respectively) (15). The most important prognostic factor affecting survival is the presence of MD at diagnosis (2). The prognosis is poor in patients with pelvic tumors, patients without local control, large tumors and poor histologic response. Histologic response to induction therapy is significantly predictive of survival. The disease-free 5-year survival was significantly better in patients with <5% viable tumors than in patients with >30% viable tumors (75% vs 20%, p<0.001) (16). The 5-year EFS has been reported to be 50% in pelvic and sacral tumors. Tumor size and age are other prognostic factors. Tumors ≥8 cm have a poor prognosis. Young patients have a better prognosis (2). In patients with relapse or progression, the prognosis is very poor and the survival rate is around 10-30%. Response to salvage therapy is also a prognostic indicator in this patient group (3). When the factors affecting survival were evaluated in our study, radiological response and histopathologic response to induction therapy, presence of relapse or progression, and relapse site were found to be associated with survival (Fisher's Exact test p=0.02, 0.0047, <0.001, 0.001). On the other hand, there was no relationship between age, sex, tumor region, tumor size, LDH levels, local treatment, local or metastatic disease, and survival (p=0.847, 0.678, 0.218, 0.214, 0.321, 1, 0.192). This can be explained by the low number of patients and especially the lower rate of metastatic patients (6/24 patients).

ASCT can be used in the metastatic patient group when there is a good response to chemotherapy or to eliminate chemotherapy resistance in relapsed-refractory patients. However, the clinical significance is controversial in many studies (3). In our patient group, relapse and/or progression were observed in 9 patients (37.5%) (9/24), 6 of whom had primary LD, and 8 (8/9) died to follow-up (Table 3). None of them underwent ASCT. Studies to improve the prognosis

in relapsed and progressed patients are ongoing. In a phase 2 trial conducted by the pediatric oncology group, 7 different single drugs were tested in relapsed/progressed disease, and the 6-month EFS rate was 12.7%. In this study, the radiological response was evaluated, and it was obtained with docetaxel, but its effect on EFS was not shown (4).

Our study has limitations due to its retrospective design and the small number of patients enrolled.

Conclusion

ES is a cancer with high mortality and morbidity. Although the most common symptoms are pain and swelling, the symptoms may vary depending on the region from which the tumor originates. Response to induction therapy and the presence of relapse-progression are factors affecting prognosis. Treatment should be personalized to improve survival.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital Ethics Committee (approvel number: 2022/04-02, date: 24.02.2022).
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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Yatarak Tedavi Gören Çocuk Hastalarda Malnutrisyon Değerlendirmesi

The Assessment of Malnutrition in Child Inpatients

Süleyman Şahin*(0000-0001-9673-5826), Vesile Meltem Energin(0000-0001-8777-3046)**

*Afyonkarahisar Devlet Hastanesi, Çocuk Nöroloji Kliniği, Afyon, Türkiye

**Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Konya, Türkiye

Öz

Giriş: Çocukluk çağında malnutrisyon ölümlerin %50'den fazlasından sorumlu tutulmaktadır. Hastaneye yatan çocuklarda malnutrisyon ciddi bir durum olup yatış süresi, morbidite, mortalite, hayat kalitesi ve maliyeti olumsuz yönde etkilemektedir. Çalışmamızda hastaneye yatırılan çocukların başvuru sırasında nutrisyonel durumu ve belirlediğimiz sosyo-demografik faktörler ile malnutrisyon ilişkisini incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya Ocak 2015-Mart 2015 tarihleri arasında Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Hastanesi Çocuk Sağlığı ve Hastalıkları servislerinde izlenen 1 ay-18 yaş arası 293 çocuk alındı. Belirlediğimiz sosyo-demografik faktörlerle ilgili anket şeklinde hazırlanmış bilgi formu ailelerinde onamı alınarak doldurduldu. SPSS 16.0 ile istatistiki veriler elde edildi.

Bulgular: İki yüz doksan üç olgunun 117'si (%39,9) kız, 176'sı (%60,1) erkek ve yaş aralığı 1ay-18 yaş olup yaş ortalaması 5,97±5,59 yıl idi. Olguların ağırlık ortalaması 22,46±23,71 kg, boy ortalaması 101,59±37,82 cm, vücut kitle indeksi ortalaması 16,33±3,42 idi. Hiçbir olguda malnutrisyon tanısı belirtilmemişti. İki yüz doksan üç olgunun 154'ünde (%52,5) Gomez sınıflamasına göre yatış anında akut malnutrisyon saptandı. İki yüz doksan üç olgunun 84'ünde (%28,6) Waterlow sınıflamasına göre yatış anında akut malnutrisyon saptandı. İki yüz doksan üç olgunun 131'inde (%44,7) yatış anında kronik malnutrisyon saptandı.

Sonuç: Çocukluk çağında hastanemize yatış sırasında akut malnutrisyon oranı Gomez sınıflamasına göre %52,5, Waterlow sınıflamasına göre %28,6'dır. Yatış sırasında malnutrisyonun en sık görüldüğü yaş grubu 9-18 (%29,4) yaştır. Çocuklarda hastaneye yatış çocuğun nutrisyonel durumunu kötü yönde etkilememekte, morbidite ve mortalitenin en önemli sebebi olan yüksek malnutrisyon sıklığını da maalesef azaltmamaktadır. Bu konuda sağlık çalışanlarının farkındalığının artırılmasına ihtiyaç vardır.

Anahtar kelimeler
Akut, kronik, malnutrisyon, çocuk, Waterlow, Gomez, antropometri

Abstract

Introduction: Malnutrition is held responsible for more than 50% of death in childhood. Malnutrition in children, who is so sick that hospitalization is needed, is much more serious since effecting length of stay, morbidity, mortality, quality of life and costs. In this study, we aimed to examine the relationship between malnutrition and nutritional status of hospitalized children during admission together with some demographic factors set by us.

Materials and Methods: In this study, 293 children aged 1 month to 18 years old who were hospitalized and monitored in Child Health and Disease Department in Meram Medical Faculty Hospital of Necmettin Erbakan University between November 2014 and January 2015 were included. The survey type information form prepared to collect data about the socio-demographic factors was filled with the consent of the family.

Keywords
Acute, chronic, malnutrition, child, Waterlow, Gomez, anthropometry

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Yazışma Adresi/Address for Correspondence: Dr. Süleyman Şahin, Afyonkarahisar Devlet Hastanesi, Çocuk Nöroloji Kliniği, Afyon, Türkiye
Tel.: +90 444 42 34/72 01
E-posta: drsulimen2003@hotmail.com

Results: Of the 293 cases, 117 (39.9%) were girls, 176 (60.1%) were boys, and the age range was 1 month to 18 years, with a mean age of 5.97±5.59 years. The average weight of the patients was 22.46±23.71 kg, the average height was 101.59±37.82 cm, and the average body mass index was 16.33±3.42. Malnutrition was not stated in any case. Out of 293, in 154 (52.5%) cases acute malnutrition according to Gomez classification was detected immediately during admission. Out of 293, in 84 (28.6%) patients acute malnutrition according to Waterlow classification was detected immediately during admission. Out of 293, in 131 (44.7%) patients chronic malnutrition was detected immediately during admission.
Conclusion: The nutritional risk with child patients during their admissions to our hospital is 52.5% according to Gomez classification, and 28.6% according to Waterlow classification. Hospitalization of children does not have a negative impact on their nutritional status, and unfortunately does not reduce the frequency of high malnutrition which is the main cause of morbidity and of mortality. There is a need to raise awareness of the health professionals about this subject.

Giriş

Dünya Sağlık Örgütü, protein-enerjiyi malnutrisyonunu yetersiz protein ve kalori alımının bir sonucu olarak ortaya çıkan enfeksiyonların eşlik ettiği, en sık bebeklerde ve küçük çocuklarda karşılaşılan bir grup patolojik sendrom olarak tanımlar (1). Protein enerji malnutrisyonu gelişmekte olan ülkelerde daha sıklıkla görülmekte ve daha çok 6 ay ile 5 yaş arasındaki çocukları etkilemektedir (2). 2020 yılında 5 yaş altı 45,4 milyon çocuk açlıktan etkilenmiştir (3). Her yıl yaklaşık 5 milyonu bulan beş yaş altı çocuk ölümlerinin %45'i malnutrisyon ilişkili olup bu ölümlerin çoğunluğu gelişmekte olan ülkelerdedir (3). Çocuklarda nutrisyonel durumu etkileyen birçok faktör mevcuttur. Bu faktörler nutrisyonel durumu direkt olarak etkileyen düşük doğum ağırlığı, erken sütten kesme, yetersiz sağlık koşulları olabileceği gibi nutrisyonel durumu dolaylı olarak etkileyen elverişsiz çevre koşulları da olabilir (4). Protein enerji malnutrisyonunun dağılımı ve derecesi o toplumun eğitim düzeyine, hijyen koşullarına, iklim ve mevsimsel özelliklerine, kültürel ve din alışkanlıklarına, emzirme oranlarına, enfeksiyon hastalıkları prevalansına, nutrisyon programlarını uygulama oranı gibi birçok faktöre göre değişmektedir (5,6). Nutrisyonel faktörlerin etkilendiği koşullar olduğu gibi etkilediği birçok durum da bulunmaktadır. Malnutrisyonun özellikle hastanede yatan olgulardaki morbidite, mortalite, yatış süreleri, hayat kalitesi, olası komplikasyonlar ve maliyet üzerinde olumsuz etkileri olduğu bildirilmiştir (7). Hastaneye herhangi bir nedenle yatırılan olgularda hastalığa odaklanırken malnutrisyon genellikle göz ardı edilmektedir. Ancak son yıllarda yatan hastalardaki nutrisyonel durumun tespiti, malnutrisyonun tedavisi ve hastanede yatarken malnutrisyon gelişiminin önlenmesi üzerinde durulmaktadır. Yatarak tedavi edilen hastalarda beslenme desteği tedavinin bir parçası olmalıdır (8). Fransa'da 2 ay-16 yaş arası 280 çocukta hastaneye yatış sırasında malnutrisyon oranı %11 saptanırken bu oran Brezilya'da beş yaş altı 186 çocukta %6,9 bulunmuştur (9,10). Almanya'daki başka bir çalışmada ise taranan 475 çocuğun %24,1'inin malnutre olduğu gösterilmiştir (11). Türkiye'de çocuklarda hastaneye yatırılarak tedavi edilen olguların başvuru sırasında nutrisyonel durumunu gösteren iki çalışmada malnutrisyon oranı %31,8 ve %27,7 olarak bildirilmiştir (12,13). Çalışmamızda ülkemizde çocuklar için önemli bir morbidite ve mortalite nedeni olan malnutrisyonun hastanede yatan çocuklardaki durumunun belirlenmesi amaçlanmıştır. Hastaneye yatışa neden olan hastalık kadar çocuğun nutrisyonel durumuna da dikkat edilmesinin sağlanması, malnutrisyonun erken tanınarak tedavisinin yapılması hatta gelişmeden önlenmesi hastanelerde çocukluk yaş grubuna ait morbidite ve mortaliteyi azaltacaktır.

Çalışmamızda öncelikli olarak hastaneye yatırılan çocukların başvuru sırasında nutrisyonel durumu, ikincil olarak ise nutrisyonel durumların hastalık tanıları, eşlik eden hastalıklar ve belirlediğimiz sosyo-demografik faktörler ile ilişkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem

Çalışmaya Ocak 2015-Mart 2015 tarihleri arasında Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Hastanesi Çocuk Sağlığı ve Hastalıkları servislerinde yatırılarak izlenen 1 ay-18 yaş arası 293 çocuk alındı. Vücut ağırlığında hızlı ve büyük değişikliklere neden olabilecek hastalığı olan çocuklar (Çocuk Yenidoğan, Çocuk Yoğun Bakım, Çocuk Hematoloji ve Onkoloji, Çocuk Acil) ve yatış süresi 24 saatten kısa olanlar çalışma dışı bırakıldı. Hastaların yaşı, cinsiyeti, tanı ve eşlik eden hastalıkları kaydedildi. Olguların hastaneye

yatış sırasında vücut ağırlığı, boyu ölçüldü. Ölçümler aynı doktor tarafından aynı araçlarla yapıldı.

İki yaşın altındaki çocuklar çıplak olarak 16 kg kapasiteli, 10 gr duyarlı dijital bebek tartısında tartılırken iki yaşından büyük çocukların vücut ağırlıkları ise 100 gr duyarlı erişkin ağırlık ölçer ile ölçüldü. İki yaşın altındaki çocukların boyları düz bir zeminde, sırtüstü pozisyonda, başı sabitlenip ayakları birleştirilerek 0,1cm'ye duyarlı 1 m'lik uzunluk ölçer ile; iki yaşından büyük çocukların boyları ise ayakta, dik pozisyonda 0,2 cm'ye duyarlı duvara sabitlenmiş metreler yardımı ile ölçüldü (14). Bunlara ek olarak vücut ağırlığı, boy, boya göre ağırlık, yaşa göre ağırlık, yaşa göre boy, vücut kitle indeksi değerlerinin yüzdelik değerleri ve z-skorları hesaplandı. Olgular akut ve kronik malnutrisyon yönünden değerlendirilmek üzere Waterlow sınıflamasına göre yaşa göre boy ve boya göre ağırlık kriterleri göz önüne alınarak sınıflandırıldı (15). Boya göre ağırlığı %90'ın altında, yaşa göre boyu %95'in üzerinde olan olgular akut malnutrisyon, boya göre ağırlığı %90-110, yaşa göre boyu %95'in altında olan olgular kronik malnutrisyon, boya göre ağırlığı %90'ın ve yaşa göre boyu %95'in altında olan olgular kronik zeminde akut malnutrisyon olarak değerlendirildi (15). Akut malnutrisyon kendi içinde hafif, orta ve ağır olmak üzere üç sınıfa ayrılmaktadır. Boya göre ağırlığı %80-90 arası hafif, %70-80 arası orta, %70 ve altındaki değerler ise ağır malnutrisyonu tanımlamakta kullanılmaktadır (15). Olgularımızda bu sınıflamaya göre gruplandırıldı. Olguların hastaneye yatış sırasındaki nutrisyonel antropometrik verileri karşılaştırıldı.

İstatistiksel Analiz

İstatistiksel değerlendirme SPSS 16.0 programı ile yapıldı. Ölçülebilir değişkenlerin dağılımı için ortalama ve standart sapma değerleri hesaplanarak sayımla belirlenen verilerin gruplandırılmış olarak karşılaştırılması için ki-kare testi, bağımsız iki grubun ölçümlerinin ortalama değerlerinin karşılaştırılması için Mann-Whitney U testi kullanıldı. Bağımlı değişkenlerin karşılaştırılmasında Wilcoxon testi kullanıldı. İstatistiksel değerlendirmede $p<0,05$ anlamlı kabul edildi.

Çalışma Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Klinik ve Laboratuvar Araştırmaları Etik Kurulundan 5 Aralık 2014 tarihli toplantıda onay almıştır (karar no: 2014/55, tarih: 05.12.2014).

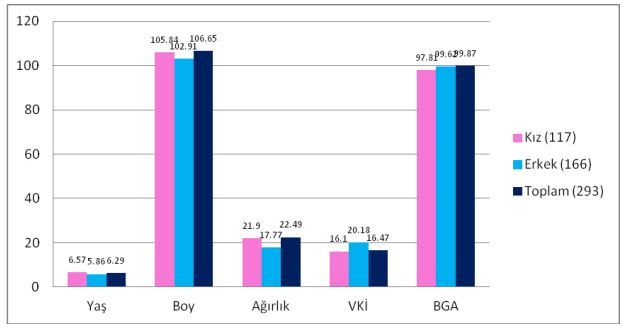
Bulgular

İki yüz doksan üç olgunun 117'si (%39,9) kız, 176'sı (%60,1) erkek ve yaş aralığı 1ay-18 yaş olup yaş ortalaması 5,97 yıl ± 5,59 idi. Olguların 77'si (%26,3) 0-1 yaş, 82'si (%28) 1-4 yaş, 48'i (%16,4) 5-9 yaş, 86'sı (%29,4) 9-18 yaş arasında idi. Olguların ağırlık ortalaması 22,46 kg ± 23,71, boy ortalaması 101,59 cm ± 37,82, vücut kitle indeksi ortalaması 16,33±3,42 idi (Grafik 1).

İki yüz doksan üç hastanın 113'ü göğüs hastalıkları, 53'ü enfeksiyon hastalıkları, 21'i nöroloji, 19'u gastroenteroloji, 19'u endokrinoloji, 18'i genel pediatri, 15'i nefroloji, 14'ü kardiyoloji, 11'i romatoloji, 10'u alerji grubunda hastalardı. Olguların birincil tanılarına ek olarak hiçbir olguda malnutrisyon tanısı belirtilmemişti.

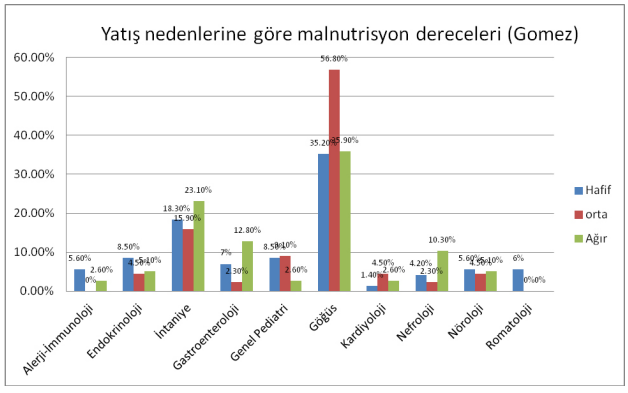
İki yüz doksan üç olgunun 154'ünde (%52,5) Gomez sınıflamasına göre yatış anında malnutrisyon saptandı (Grafik 2). Bunların 86'sı erkek, 68'i kız idi. Kızların %53'ünde hafif, %25,7'sinde orta ve %21,3'ünde ağır derecede malnutrisyon vardı. Erkeklerin ise %41'inde hafif, %30,7'sinde orta ve %28,3'ünde ağır derecede malnutrisyon tespit edildi.

İki yüz doksan üç olgunun 84'ünde (%28,6) Waterlow sınıflamasına göre yatış anında akut malnutrisyon saptandı (Grafik 3). Bunların 44'ü erkek, 40'ı kız idi. Kızların %20,5'inde hafif, %7,7'sinde orta derecede malnutrisyon vardı. Ağır malnutrisyon tespit edilmedi. Erkeklerin ise %23,1'inde hafif, %13'ünde orta ve %9'unda ağır derecede malnutrisyon tespit edildi. %9'luk oran ise aslında sadece 1 hastayı karşılıyordu. Bu oranın fazla olması tanılara göre hastalık grupları oluşturulduğunda grup sayısının fazla olmasından kaynaklı idi. İki yüz doksan üç

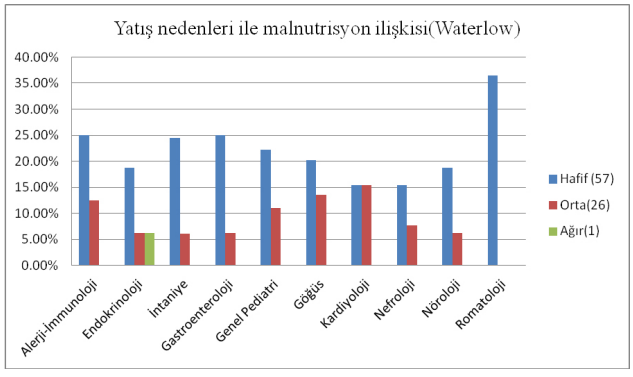


Grafik 1. Yaş, vücut ağırlığı, boy vücut kitle indeksi ve boya göre vücut ağırlıkları durumları.

VKİ: Vücut kitle indeksi, BGA: Boya göre vücut ağırlıkları



Grafik 2. Yatış nedenlerine göre malnutrisyon dereceleri (Gomez).



Grafik 3. Yatış nedenleri ile malnutrisyon ilişkisi (Waterlow).

olgunun 131'inde (%44,7) yatış anında kronik malnutrisyon saptandı. Bunların 79'u erkek, 52'si kız idi. Erkeklerin %20,5'inde hafif, %6,8'inde orta derecede malnutrisyon ve %17,1'inde ağır derecede malnutrisyon vardı. Kızların ise %22,7'sinde hafif, %9,7'sinde orta ve %12,5'inde ağır derecede malnutrisyon tespit edildi. İki yüz doksan üç olgunun 49'unda (%16,7) yatış anında kronik zeminde akut malnutrisyon saptandı. Bunların 28'i erkek, 21'i kız idi. Malnutrisyon sıklığı ve dereceleri yaş aralıklarına göre irdelendiğinde <1 yaş için hafif malnutrisyon sıklığı %19,7, orta malnutrisyon %34,1 ve ağır malnutrisyon %30,8 idi. 1-4 yaş için hafif malnutrisyon %12,8, orta malnutrisyon %29,5 ve ağır malnutrisyon ise %33,8 oranlarında tespit edilmişti. 5-9 yaş aralığında malnutrisyon görülme sayısında hafif bir azalma görülmekle beraber bu yaş aralığında dikkati çeken en önemli bulgu hafif malnutrisyon sıklığını orta ve ağır malnutrisyona göre daha fazla görülmesi idi. Diğer yaş gruplarında orta ve ağır malnutrisyon oranlarının fazlalığı dikkat çekmişti. Bu yaş aralığı için hafif malnutrisyon %23,1, orta malnutrisyon %18,2, ağır malnutrisyon ise %12,7 olarak karşımıza çıktı. Son olarak 9-18 yaş grubunda yani adolesan dönemi de kapsayan olgu grubunda ise hafif malnutrisyon %33,3, orta malnutrisyon %18,2 ve ağır malnutrisyon ise %33,8 sıklığında görüldü. Bu bulgular orta malnutrisyon sıklığının hafif ve ağır malnutrisyona göre daha az görüldüğünü ortaya koydu. Bu da ağır malnutrisyon görülme sıklığının fazla olmasını kronik hastalıklara maruziyet süresinin uzaması ile ilişkili olabileceğini düşündürdü. Yine hafif malnutrisyonda benzer oranlardaki sıklık akla beslenme problemlerini getirmektedir. Okul çocuklarının beslenmesinde diğer bir sorun da erken saatte okula giden çocuklarda kahvaltı öğününün atlanması ve buna bağlı yetersiz besin alımıdır.

Beslenme bozukluğu için uluslararası standart değerler esas alındığında, olguların %74,4'ü normal kilolu, %10,5'i düşük kilolu, %12,6'sı aşırı düşük kilolu bulundu. Yine olguların %76,4'ü normal, %9,2'si boy kısalığı ve %11,9'u patolojik boy kısalığı idi. Çalışmaya alınan çocukların annelerinin %5,8'i örgün eğitim faaliyetleri içerisine hiç dahil olmamış fakat hayatın akışı içerisinde kendi çabalarıyla okuma ve yazma eylemlerini kazanmışlardı. %57,5'i ise ilköğretim düzeyinde eğitim almışlardı. Eğitim düzeyi ile malnutrisyon arasında anlamlı bir ilişki tespit edilmedi. Olgularımızın annelerinin neredeyse tamamı ev hanımı idi. Bu sebeple anne mesleği ile malnutrisyon arasında net bir ilişki bulunamadı. Olguların %17,1'i köyde, %17'si ilçede kalanı da il merkezinde yaşamakta idi. Yerleşke ile malnutrisyon dereceleri arasında anlamlı bir ilişki bulunamadı. Olguların anne sütü alım süreleri sorgulandı. Olguların 96'sı 6 aydan kısa süreli/hiç anne sütü almıştı. 129'u ise en az 6 ay süre ile anne sütü almıştı. Olguların anne sütü alım süreleri ile malnutrisyon ilişkisi değerlendirildi. Ancak anlamlı bir ilişkiye rastlanamadı. Veriler incelendiğinde 6 aydan az anne sütü alımı ya da hiç anne sütü alınmadığında gelişen malnutrisyon dereceleri ve olgu sayıları ile en az 6 ay süre ile anne sütü alan malnutrisyonlu olgular arasında anlamlı bir farklılık yoktu.

Ek gıdaya başlama süreleri değerlendirildi. Kırk dokuz olgunun ek gıdaya başlama zamanı öğrenilemedi. Kalan 244 olgunun %59,7'si 6. ayda

ek gıdaya başlamıştı. %38'i ise 6. aydan önce ek gıdaya başlamıştı. Ek gıdaya başlama süreleri ile malnutrisyon ilişkisi değerlendirildiğinde 6. ayda ek gıdaya başlayan olgularda malnutrisyonun en fazla görüldüğü tespit edildi. Ek gıdaya başlama zamanının malnutrisyonun en fazla görüldüğü grup olan 6. ayda olması ek gıdaya başlama zamanı ile malnutrisyon arasında bir ilişki olmadığını ortaya koydu.

Tartışma

Protein enerji malnutrisyonu gelişmekte olan ülkelerde daha çok görülen yaygın sağlık sorunlarından biridir. Daha çok 6 ay ile beş yaş arasındaki çocuklar etkilenmektedir (2). Her yıl yaklaşık 5 milyonu bulan beş yaş altı çocuk ölümlerinin %45'i malnutrisyon ilişkili olup ağır malnutrisyonu olan çocukların yarısından fazlası kaybedilmektedir (3). Hastaneye yatan olgularda gerek altta yatan hastalıklar gerekse tanıları sebebiyle artmış enerji ihtiyaçlarının karşılanamaması malnutrisyonun yüksek oranda görülmesine sebep olmaktadır (16). Yatırılan olgunun primer hastalığı üzerinde durulurken genelde gözden kaçırılan malnutrisyon tedavi başarısını azaltmakta, hastaneye yatışları ve maliyeti artırmaktadır (11). Daha önceki pediatrik çalışmaların çoğu zihinsel engelli çocukların evde veya bir kurumda beslenme durumunu değerlendirirken çalışmamıza primer hastalıkları sebebiyle yetersiz beslenmiş olabileceği de düşünülen ve hastaneye kabul edilen hastaları dahil ettik. Sonuçlarımız, yalnızca incelenen hasta popülasyonundaki yüksek malnütrisyon prevalansı nedeniyle değil, veri eksikliği sebebiyle çalışmaya kabul edilmeyen ve çalışma grubunun neredeyse 1/3'ü kadarını oluşturan hasta sayısı nedeniyle endişe uyandırmaktadır. Bu son bulgu, profesyonel beslenme destek ekibine sahip büyük bir çocuk hastanesinde bile yetersiz beslenme konusunda bariz bir farkındalık eksikliğine işaret etmektedir. Hastanede yatan çocuklarda eksik temel antropometrik ölçümlerin derecesini ortaya koyan yeterli çalışma olmamakla birlikte yetişkin hastalara ilişkin veriler, bunun yaygın bir sorun olabileceğini gösteriyor. Kondrup, hastanedeki yetişkin hastaların sadece %59'unun beslenme durumu açısından tarandığını bildirmiştir (17). Gomez sınıflaması (18) vücut ağırlığı ölçümüne dayanır ve malnutrisyonun derecesini belirlemede yaygın olarak kullanılmaktadır. Waterlow sınıflamasında (15) malnutrisyon; yaşa göre boy ve boya göre ağırlık oranları kullanılarak zayıf, kısa boylu ve zayıf + kısa boylu olarak 3 gruba ayrılmıştır. Waterlow sınıflaması, toplumlarda malnutrisyon etiyolojisini tanımlamada, sadece yaşa göre ağırlık belirtecinin çok yararlı olmadığı görülerek geliştirilmiştir. Waterlow sınıflaması bu haliyle malnutrisyonu tanımlamada en çok kullanılan sınıflamadır. İki yüz doksan üç olgunun 84'ünde (%28,6) Waterlow sınıflamasına göre yatış anında akut malnutrisyon saptandı. İki yüz doksan üç olgunun 131'inde (%44,7) yatış anında kronik malnutrisyon saptandı. İki yüz doksan üç olgunun 49'unda (%16,7) yatış anında kronik zeminde akut malnutrisyon saptandı. Bunların 28'i erkek, 21'i kız idi. Çalışmamızdaki malnutrisyon sıklığı ülkemizde sağlıklı çocuklarla yapılan toplum taramalarına göre oldukça yüksekti (19). Bu durum çalışmamızdaki çoğu hastanın kronik hastalıklara sahip olması ve malnutrisyona önemli derecede katkıda bulunacak enfeksiyon hastalıkları nedeniyle hastaneye yatırılmış olmasından kaynaklanmaktadır. Pawellek ve ark. (20) hastanede yatan 475 çocukta akut malnutrisyon sıklığını %24,1 olarak bulmuşlardır. Hendricks ve ark. (21) 1995 yılında Amerika Birleşik Devletleri'nde 268 çocukta yaptıkları çalışmada hastane malnutrisyonu sıklığını %24,5 ve Hendrikse ve ark. (22) ise İngiltere'de yaptıkları çalışmada hastanede yatan yaşları yedi ay ile 16 yaş arası değişen 226 çocukta malnutrisyon sıklığını %27 bulmuşlardır. Merritt ve ark. (16) hastaneye yatan çocuklarda akut malnutrisyonu %26, kronik malnutrisyonu %38, akut zeminde kronik malnutrisyonu %10,2 bildirirken Renaudin (23) Afrika'da yaptıkları çalışmada hastanede yatan 0-5 yaş arası çocuklarda malnutrisyon sıklığını %63,1 olduğunu, malnutrisyonlu olguların %37'sinin ise ağır malnutrisyonlu olduğunu göstermişlerdir. Çalışmamızın verileri dünya verileri ile benzerlik göstermektedir.

Ülkemizde çeşitli sınıflamalar ile yapılan hastane malnutrisyonu çalışmalarında Özer ve ark. (24) akut malnutrisyon sıklığını %18,9, kronik malnutrisyon sıklığını %15,4, akut zeminde kronik malnutrisyon sıklığını ise %20,8 olarak bulurken, Genel ve ark. (25) sırasıyla akut, kronik, kronik zeminde akut malnutrisyon sıklığını %21,3, %24,2, %11,9 olarak saptamışlardır. Oztürk ve ark. (13) 2001 yılında çocuk servisine yatış anında malnutrisyon sıklığını %31,8 olarak bulmuşlardır. 0-2 yaş grubunda hastanede yatmakta olan çocuklarda Rocha ve ark. (10) akut

malnutrisyon sıklığını %6,9, Pawellek ve ark. (20) 2-5 yaş arası 164 hastayı içeren çalışmasında %28,1 akut malnutrisyon oranları bulmuşlardır. Genel ve ark. (25) ise 1996 yılında İzmir'de yaptıkları çalışmada hastanede yatan 2-6 yaş grubundaki 67 hastada %52,2 gibi yüksek bir oranda akut malnutrisyon saptamışlardır. Pawellek ve ark. (20) hastanede yatan çocuklarda 6-12 yaş grubunda akut malnutrisyonu %20,4 olarak bulmuşlardır. Çalışmamızda da akut malnutrisyon oranı <1 yaş grubunda %26,3, 1-4 yaş grubunda %28, 5-9 yaş grubunda %16,4 ve 9-18 yaş grubunda %29,4 bulunmuştur. Bu da çocuk izlemi, erken tanı koyma ve zamanında tedavi ile önlenebilecek akut malnutrisyon bulguları açısından dikkat çekicidir. Çalışmamızda %38,6 ile en fazla hasta sayısının olduğu grup göğüs hastalıkları grubu idi. Bu grupta akut malnutrisyon hastaneye yatış sırasında %57,6 bulundu. Malnutrisyon oranları yüksek saptanan bu grup hem altta yatan hastalığı nedeniyle hem de malnutrisyonun enfeksiyonlara yatkınlığı arttırması nedeniyle hastanede yattığı dönemde büyüme ve gelişme açısından risk altındadır (26).

Çalışmamızda ikinci sırada malnutrisyon sıklığının görüldüğü grup %18,1'lik oran ile enfeksiyon hastalıkları olmuştur. Bu grupta akut malnutrisyon oranı %54,7 tespit edilmiştir. Enfeksiyonların malnutrisyon için hazırlayıcı faktör olduğu bilinmektedir (27). Malnutrisyonun da hücresel immüniteyi, fagosit fonksiyonunu, kompleman aktivitesini, sekretuar antikor düzeyini ve sitokin yapımını azaltarak enfeksiyona zemin hazırladığı gösterilmiştir (28). Solunum yolu enfeksiyonları, akut gastroenterit gibi enfeksiyon hastalıklarının, beslenme bozukluğunun önlenmesi ve erken dönemde tanınıp düzeltilmesi ile morbidite ve mortalite oranları belirgin olarak azalmıştır (29). Bulgularımız, literatürde enfeksiyon hastalıklarında daha çok hafif malnutrisyonun görüldüğü bilgisini desteklemektedir (8,26,27). Nörolojik hastalıklara zeka geriliğinin eşlik etmesi ve zekâ geriliğinin derecesi, aile ve sosyo-ekonomik yetersizlikler, tedavi yönetiminden ne kadar fayda gördükleri diğer hastalıklara kıyasla malnutrisyon ile daha yakından ilişkilidir (30). Çalışmamızda nörolojik hastalığı olan çocukların hastaneye yatış anında akut malnutrisyon oranı %38 olarak saptandı. Literatüre bakıldığında hastanede yatmakta olan nörolojik hastalığa sahip gruplarda çalışmamıza kıyasla akut malnutrisyon daha yüksek bulunmuştur. Dogan ve ark.'nın (12) yaptığı çalışmada %42,9, Pawellek ve ark. (20) %40 ve Willig ve ark. (31) %50 sıklıkta akut malnutrisyon tespit etmişlerdir. Türkiye'de çocukluk çağında hastane malnutrisyonu ile ilgili yapılan çalışmalar az sayıda olmakla birlikte bu çalışmaların çoğunda yaşa göre ağırlık yöntemi kullanılarak malnutrisyon oranları belirtildiğinden ülkemizdeki diğer çalışmalar ile çalışmamızdaki malnutrisyon oranlarını karşılaştırabilmek amaçlı bu yöntemle de malnutrisyon oranlarını belirledik. Çalışmamızda hastane başvurusunda yaşa göre ağırlık yöntemiyle belirlenen malnutrisyon %52,5 bulundu. Dogan ve ark. (12), yaşa göre ağırlık yöntemiyle İstanbul ilinde hastanede yatan 1 ay-23 yaş arası hastalarda malnutrisyon oranını %52,4, yine aynı ilde Özer ve ark. (24) aynı yöntem ile yaptıkları çalışmada malnutrisyon oranını %55,1 olarak saptanmıştır. Genel ve ark. (25) ise İzmir ilinde hastanede yatmakta olan 1 ay-6 yaş arası 350 çocuk hastada yaşa göre ağırlık yöntemiyle yaptıkları incelemede %56,6 malnutrisyonlu olgu olduğunu bildirmişlerdir. Her ne kadar ülkemizdeki bu oranlar çok yüksek görünse de yurtdışından bildirilen veriler daha dikkat çekicidir. Ferreira ve ark. (32) malnutrisyon oranını %71,5 bildirirken ve Cortes ve ark. (33) hastanede yatan 450 çocuk olguda bu oranı %72,5 olarak bildirmiştir. Antropometrik ölçümler dışında hastanede yatan çocuklarda malnutrisyonu saptamaktaki bir başka eksiklik doktor ve diğer sağlık personelinin hastanın hastaneye yatırılış nedeni ile ilgilenirken malnutrisyonu gözden kaçırmasıdır. Buna örnek olarak Özer ve ark.'nın (24) yaptıkları çalışma verilebilir. Özer ve ark. (24) yaptıkları çalışmada hastanede yatan 350 olgunun 29'unda (%8,3) ağır malnutrisyon saptamışlar ancak tüm hasta grubunda malnutrisyon tanısı ile yatırılan hasta bulamamışlardır. Çalışma grubumuzda da malnutrisyonlu olgular olmasına rağmen hastaneye yatırılırken yatış tanılarında malnutrisyon tanısının belirtilmemiş olduğu görüldü. Avrupa Pediatrik Gastroenteroloji, Hepatoloji ve Beslenme Derneği pediatri hastanelerinde beslenme destek ekiplerinin kurulmasını, beslenme riski taramasının yapılmasını, beslenme desteğine ihtiyaç duyan hastaların belirlenmesini, yeterli beslenme yönetiminin sağlanmasını, hastane personelinin eğitilmesini ve uygulamaları denetlemesini önermektedir (34). Bu çalışmada belgelenen pediatrik hastalarda kabul

edilemez derecede yüksek malnütrisyon prevalansı, bu önerilerin uygulanmasına yönelik acil ihtiyaca ağırlık katmaktadır. Ülkelerin gelişmişlik düzeyi ile malnutrisyon sıklığı ters orantı göstermektedir (35). Çalışmamız ülkenin sosyo-ekonomik düzeyi nispeten yüksek bir ili olan Konya'daki bir üniversite hastanesinde yapılmıştır. Ülkemizin farklı bölgelerindeki hastanelerde yatış anında çocuklardaki malnutrisyon varlığının farklı oranlarda görülebileceği düşünülebilir.

Sonuç

Kronik hastalığa sekonder gelişen malnutrisyon, mevcut tüm nutrisyonel destek imkanları ve bu konuda yapılmış çalışmalarla iyi bir şekilde ortaya konmuş olmasına rağmen sıklığı yüksektir. Göğüs hastalıkları, enfeksiyon, nörolojik hastalık tanılı çocuklarda malnutrisyon sıklığı yüksektir. Bu gruplarda beslenme desteğine dikkat etmek gerekmektedir. Ancak hastaneye yatışta malnutrisyonun yeterince tanınmadığı da göz önünde bulundurulmalıdır.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Content Analysis of Food Advertisements on TV Channels in Turkey

Türkiye'deki Televizyon Kanallarında Yayımlanan Gıda Reklamlarının İçerik Analizi

Ahmet Ergin* (0000-0001-5236-7507), Caner Özdemir (0000-0003-2940-8694), Betül Özdemir*** (0000-0003-4424-2063)**

*Pamukkale University Faculty of Medicine, Department of Public Health, Denizli, Turkey
**Ankara University Faculty of Medicine, Department of Public Health-Epidemiology Unit, Ankara, Turkey
***Republic of Turkey Ministry of Health, General Directorate of Public Health, Ankara, Turkey

Abstract

Introduction: Childhood obesity is an important public health problem and rising. The spread of unhealthy food advertisements (ads) in media may contribute to obesity. This study aims to perform a content analysis of food ads on TV channels in Turkey.

Materials and Methods: This cross-sectional study included 6 TV channels with the highest ratings according to the Television Monitoring Surveys Joint Stock Company 2016 data. Primetime (PT, 20:00-23:00 and off prime time (OPT, 17:00-19:59) time slots were taken into consideration for data collection. The data was collected between October 13-19, 2017. For standardization, food groupings were based on previously published literature and the Turkey Specific Food and Nutrition Guide. Frequencies and percentages are given for descriptive statistics and chi-square test was used to compare categorical variables.

Results: A total of 2740 food ads were evaluated. 1.732 (63.2%) of them were found to be unhealthy, only 124 (4.5%) were healthy and 884 (32.3%) were other types of food ads. There were more unhealthy food ads in the OPT period (65.5%) than the PT period (60.2%) (p=0.005). The most commonly advertised unhealthy food ads were cakes, cookies, and biscuits. Unhealthy drink ads were coke, carbonated beverages, and aroma sodas.

Conclusion: Two of 3 food ads on Turkish TVs are unhealthy. Any child will be exposed to an average of 96 unhealthy food ads per week in case of only 2 hours of TV viewing per day.

Keywords
Obesity, child, media, food, advertisement

Öz

Giriş: Çocukluk çağı obezitesi önemli bir halk sağlığı sorunudur ve giderek artmaktadır. Medyada sağlıksız gıda reklamlarının yaygınlaşması obeziteye katkıda bulunabilmektedir. Bu çalışma, Türkiye'deki televizyon kanallarında yayımlanan gıda reklamlarının içerik analizini yapmayı amaçlamaktadır.

Gereç ve Yöntem: Kesitsel tipteki bu araştırmaya Televizyon İzleme Araştırmaları Anonim Şirketi 2016 verilerine göre en yüksek reytinge sahip 6 TV kanalı dahil edilmiştir. Zamansal ilişkinin karşılaştırılabilmesi amacıyla primetime (PT, 20:00-23:00) ve off prime time (OPT, 17:00-19:59) zaman dilimleri değerlendirmeye alınmıştır. Veriler 13-19 Ekim 2017 tarihleri arasında toplanmıştır. Standardizasyon için, gıda gruplamaları daha önce yayımlanmış literatüre ve Türkiye'ye Özgü Besin ve Beslenme Rehberi'ne dayanılarak yapılmıştır. Tanımlayıcı istatistikler için frekans ve yüzdeler verilmiş, kategorik değişkenlerin karşılaştırılmasında ki-kare testi kullanılmıştır.

Anahtar kelimeler
Obezite, çocuk, medya, gıda, reklam

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Address for Correspondence/Yazışma Adresi: Caner Özdemir MD, Ankara University Faculty of Medicine, Department of Public Health-Epidemiology Unit, Ankara, Turkey
Phone: +90 507 426 01 01
E-mail: canerozdemir88@hotmail.com

Bulgular: Toplam 2.740 gıda reklamı değerlendirilmiştir. Bunların 1.732'si (%63,2) sağlıksız, sadece 124'ü (%4,5) sağlıklı ve 884'ü (%32,3) diğer gıda reklamı türündedir. OPT döneminde (%65,5) PT döneminden (%60,2) daha fazla sağlıksız gıda reklamı bulunmaktadır (p=0,005). En çok yayımlanan sağlıksız gıda reklamları kek, kurabiye ve bisküvi iken sağlıksız içecek reklamları kola, gazlı içecekler ve aromalı soda reklamlarıdır.
Sonuç: Türkiye'deki televizyon kanallarında yayımlanan her 3 gıda reklamından 2'si sağlıksız gıda reklamıdır. Bir çocuk günde sadece 2 saat televizyon izlemesi durumunda haftada ortalama 96 sağlıksız gıda reklamına maruz kalmaktadır.

Introduction

Obesity is a health problem caused by excessive fat accumulation in the body. The prevalence of childhood obesity on the rise all over the world and in Turkey (1,2). According to World Health Organization (WHO) data, the prevalence of overweight/obesity in the world between 5-19 years has increased over the years; from 4% in 1975 to 18% in 2016. In Turkey, the prevalence of obesity among children and adolescents aged 5-19 has risen dramatically from just 5% in 1975 to 29.5% in 2016 (1).

Genetic, environmental, and behavioral factors play roles in the increase in childhood obesity (3,4). The obesogenic environment has been shown as the main reason for the increase in the frequency of obesity via contributing to weight gain. It is defined as an unsuitable environment for weight loss and the Media plays an important role in the formation of this environment (5). The widespread use of unhealthy food marketing in the Media changes the purchasing and consumption behaviors of families and leads to childhood obesity (4,6-8). While exposed to these unhealthy advertisements at many points of daily life; TV advertising has long been used by the food industry as one of the most important means of publicity as an effective means of reaching children (7). According to the studies, food advertisements mainly affect the knowledge, attitudes, and behaviors of children; these effects can be more prominent in developing countries (7,9,10). For this reason, in 2010, the WHO introduced a series of recommendations regarding the marketing of food and non-alcoholic beverages to children and aimed to reduce the marketing effect of foods containing highly saturated fat, trans-fatty acids, sugar, and salt (11).

The increase in childhood obesity is an important public health problem, given the potential impacts of both adulthood and aging. The content of food advertising to children is not known to TV channels broadcasting in Turkey since there is a very limited number of studies on this subject. In this study, we aim to explain the potential relationship of food advertising with different channels and times, and to provide suggestions for legislation on food advertising on TV.

Materials and Methods

This cross-sectional study constitutes the universe of all television channels broadcasting in Turkey. Six television channels with the highest ratings based on a television viewing research company 2016 data were included in the study. To compare the temporal relationship, 17:00-19:59 [off prime time (OPT)] and 20:00-23:00 [prime time (PT)] times where television was most-watched were evaluated.

Ads are divided into food ads and non-food ads. According to Turkey's Food and Nutrition Guide and studies in the literature, food ads are divided into three categories as unhealthy, healthy, and other (restaurant, supermarket, black coffee/tea, vitamin/mineral supplements, formula, recipe additions, etc.) and thus, advertising categorization form was created. Foods and beverages containing high amounts of fat, sugar and salt are considered unhealthy. Before the data collection process, 12 researcher assistants were given training on forms and the data collection process, and a team of two researcher assistants was assigned for each channel. Data were collected between October 13-19, 2017, with individual notes regarding video recording or advertising content. Individual notes were shared by two researchers responsible for the channel. All ads were evaluated, and duplicate ads were included in the analysis.

The study protocol was approved by Pamukkale University Ethics Committee (approval number: 60116787-020/81512, date: 05.12.2017).

Statistical Analysis

Data were evaluated in SPSS 17.0 package program. Frequency, percentage, and averages were given for descriptive statistics, and the number of advertisements

per channel (food/non-food, unhealthy/healthy/other) was calculated per hour. Chi-square test was used to compare categorical variables, and the significance test of the difference between two means (t-test) was used to compare independent group differences of continuous variables. Statistical significance level (p)<0.05 was considered significant.

Results

A total of 7.662 advertisements were evaluated and 35.8% of them were food advertisements. When food ads were compared according to the channel, day, and time characteristics, a statistically significant difference was observed between channels and the time of the day. The highest food advertising frequency is 43.4% on Channel 2 and more food advertisements are published in the OPT time frame (Table 1).

When the contents of the published food advertisements were analyzed, 1.732 (63.2%) of the 2.740 food advertisements were unhealthy, 124 (4.5%) were healthy, and 884 (32.3%) were other food advertisements (Figure 1). Cake/cookies/biscuits (5%), chocolate/wafers/bars (3.2%), chips/popcorn/salted dried fruits (2.7%) were the most frequently published unhealthy food advertisements. Cola/sparkling/flavored soda (4.1%) was the most frequently published unhealthy beverage advertisement. Only non-sugar dairy products (yogurt, milk, buttermilk, etc.) (1.3%) and water/mineral water (0.2%) were the healthy food/beverages. Restaurant ads constitute 4.4% of all ads. Supermarket (3.4%) and vitamin/mineral supplements (1.7%) was among the most frequently published advertisements (Table 2).

Table 3 shows the comparison of food advertisements according to the channel, day, and time characteristics on which they were televised. The most unhealthy food advertisements were seen in channel 2 (71.9%) and there was a statistically significant difference between the groups (p<0.001). While 64.6% of the weekday advertisements are unhealthy food ads, 59.8% of the weekday advertisements are unhealthy food advertisements. It was determined that there were more unhealthy food advertisements in the

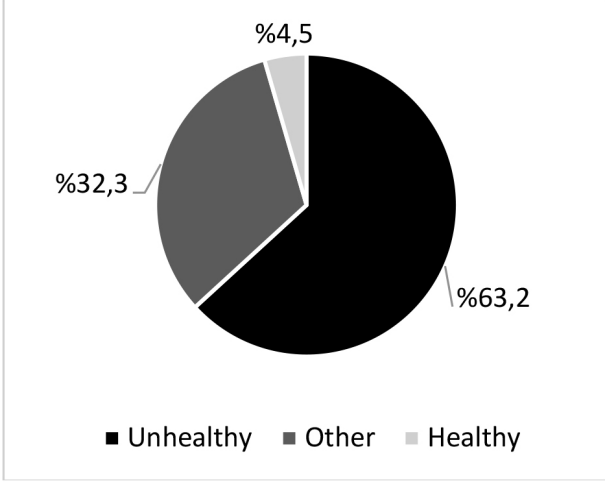

Figure 1. Distribution of food ads by content.

Table 1. Comparison of food and non-food advertisements by channel, day and time characteristics

	Food ads		Non-food ads		p
	n	%	n	%	
Channel*					
Channel 1	412	30.4	945	69.6	
Channel 2	388	43.4	505	56.6	
Channel 3	551	39.2	855	60.8	<0.001
Channel 4	468	36.5	813	63.5	
Channel 5	411	33.1	832	66.9	
Channel 6	510	34.4	972	65.6	
Day of the week					
Weekdays	1.932	35.5	3.504	64.5	0.530
Weekend	808	36.3	1.418	63.7	
Time frame					
Prime time	1.173	34.0	2.280	66.0	0.003
Off prime time	1.567	37.2	2.642	62.8	
Total	2.740	35.8	4.922	64.2	-

*The names of the TV channels were masked to prevent advertisement

OPT period than the PT period (p=0.005). The ratio of the number of advertisements according to channels and hours was determined as 6.87 for unhealthy food advertisements. Weekday (6.93) compared to the weekend (6.70); OPT (8.14) compared to PT (5.60) had statistically significant more unhealthy food advertisements (p<0.001) (Table 4).

Discussion

When compared with the studies in the literature, the frequency of food advertisements in total advertisements was found to be higher in our study. According to our study, in TV channels broadcasting in Turkey one in three ads is food ads. In another study conducted in Malaysia in 2013, it was determined that food advertisements accounted for 23% of all advertisements (7). Li et al. (6) explored the extent and nature of television food advertising in Xi'an, China. They found that 25% of the 5.527 studies they evaluated were food advertisements. In 2012, Ok et al. (12), including three TV channels broadcasting in Turkey, found that 29% of the TV advertisements were food advertising. In 2007, Guran et al. (13) was determined 32% as evaluating ads on 4 TV channels broadcasting in Turkey. In another study from Iran, 4 TV channels were evaluated for a week in 2012, while the frequency of publishing food advertisements was

Table 2. Types of food advertisements and frequency of delivery

Advertisement	n	%
Unhealthy food		
Cakes, cookies, biscuits and so on	383	5.0
Chocolate, wafer, bar and so on	249	3.2
Chips, popcorn, salted dried fruits	208	2.7
Chewing gum	148	1.9
Ice cream	81	1.1
Dairy desserts	77	1.0
Jam, marmalade, cream chocolate, mash etc.	62	0.8
Processed meat products	39	0.5
Frozen foods	35	0.5
Prepared sauces	12	0.2
Prepared soups	6	0.1
High sugar and/or low fiber breakfast cereals	4	0.1
Unhealthy beverage		
Cola, carbonated beverage, flavored soda	315	4.1
Dairy products with added or flavored sugar	38	0.5
Sugar added tea/coffee, cold tea/coffee	28	0.4
Powders for beverages	27	0.4
Energy drink	17	0.2
Fruit juices	3	-
Healthy food/drink		
Unsweetened dairy products (yoghurt, milk, buttermilk etc.)	103	1.3
Water/mineral water	16	0.2
Greengrocery	3	-
Low-sugar, high-fiber breakfast cereals	1	-
Meat/fish/eggs	1	-
Bread/grain/rice/legume	-	-
Other		
Restaurant	336	4.4
Supermarket	260	3.4
Vitamin/mineral supplements	130	1.7
Formula	37	0.5
Recipe additions (broth, oil, condiment, etc.)	35	0.5
Black coffee/tea	20	0.3
Other	66	0.9

found to be 14.9%. In another 11 country study, the frequency of food advertisements was determined to be 18% in 2008 (14,15). In a study conducted on Italian TV channels in 2016-2017, it was determined that 11% of 810 commercials were food advertisements, and 72% of them were sweet/salty snack advertisements (16). Cheung and Louie (17) was determined that 18.4% of 10.348 advertisements were food advertisements in Hong Kong and Kontsevaya et al. (18) was determined that 19.2% of the advertisements broadcast on 5 TV channels were food advertisements in Russia.

According to our findings, two out of three food advertisements were unhealthy food advertisements. Neville et al. (9) reported that 55% of food advertisements broadcast on Australian metropolitan television channels contain foods that were high in fat and/or sugar. In the study conducted in 11 countries, 67% of food advertisements were unhealthy (15). Studies by Ok et al. in 2012 (12) and Guran et al. (13) in 2007 in Turkey was determined the unhealthy food advertising frequency on TV as 81% and 88%, respectively. Similarly, in the study that evaluated the children's channels broadcasting in Argentina in 2014, the frequency of unhealthy advertising was found to be 64% (19). In 2012, unlike our study in China, the percentage of unhealthy food advertising was found to be lower (48%) (6).

It has been determined that the frequency of food ads and the unhealthy food ads within them vary according to the viewing time. This may be due to the lack of standardization as defined by the legislation or the lack of supervision or both. In the OPT period, in which children spent more time at home during the day after school and programs for children, the frequency

Table 3. Comparison of food ads by channel, day and time

	Unhealthy food		Healthy food		Other		p
	n	%	n	%	n	%	
Channel*							
Channel 1	182	44.2	40	9.7	190	46.1	
Channel 2	279	71.9	20	5.2	89	22.9	
Channel 3	325	59.0	22	4.0	204	37.0	**<0.001**
Channel 4	334	71.4	4	0.9	130	27.8	
Channel 5	287	69.8	14	3.4	110	26.8	
Channel 6	325	63.7	24	4.7	161	31.6	
Day of the week							
Weekdays	1249	64.6	82	4.2	601	31.1	0.050
Weekend	483	59.8	42	5.2	283	35.0	
Time frame							
Prime time	706	60.2	49	4.2	418	35.6	**0.005**
Off prime time	1026	65.5	75	4.8	466	29.7	
Total	1732	63.2	124	4.5	884	32.3	-

*The names of the TV Channels were masked in order to prevent advertisement

Table 4. Distribution rates of food ads by temporal properties

Variables	Unhealthy food (n=1732)		Healthy food (n=124)		Other (n=884)	
	n/h/c*	p	n/h/c	p	n/h/c	p
Day of the week						
Weekdays	6.93	**<0.001**	0.45	**<0.001**	3.33	**<0.001**
Weekend	6.70		0.58		3.93	
Time frame						
Prime time	5.60	**<0.001**	0.38	**<0.001**	3.31	**<0.001**
Off prime time	8.14		0.59		3.69	
Total	6.87	-	0.49	-	3.50	-

*The unit of measure used in delivery rate is the number of ads per hour and channel (n/h/c)

of food advertisements was higher. Similar to our findings, another study in China in 2012 was found that food advertisements were more widely showed during the time-periods when children were mostly watching the screen (6).

The majority of food advertisements are unhealthy foods; food ads such as fruits and vegetables that are beneficial for health were much less showed. Similar to the findings of our study, Gallus et al. (16) reported that fruit and vegetables were never advertised during children's programs, and that the majority of food advertisements consisted of snacks such as foods containing saturated fats, salt, and sugar. The use of media to explain the importance of healthy nutrition to child age groups in which food habits are gained to a great extent and behaviors that will determine the future health are developed can have beneficial effects. According to our research, if a child watches TV for only 2 hours a day, he/she is exposed to 76 food advertisements and 59 unhealthy food advertisements per week. In a study conducted by Kelly et al. (15) unlike our study, it was found that a child was exposed to 70 food advertisements and 56 unhealthy food advertisements within 2 hours. In the study which evaluated the TV channels broadcasting in China, these values were determined as 102 and 46, respectively (6).

After the date of this study, a regulation on broadcasting services was changed and the regulation regarding the publication of food advertisements was made. According to this regulation, it is decided that commercial communication of food and beverages containing food and substances which are not recommended to be over-consumed in general nutrition diets cannot be included with or within children's programs. In this context, food ads are categorized as red, orange, and green. Food advertisements on the red list are not allowed to be published in children's programs, and those on the orange list can be published if the criteria are met. During the publication of the program types other than children's programs (at the beginning, between, and at the end of the program), it is also possible to advertise food products that cannot be advertised in children's programs, provided that certain warnings are placed (20). In Chile, the Food Labeling and Advertising Law began to be implemented in 2016 to reduce the consumption of unhealthy foods. Correa et al. (21) examined the changes in food advertisements on television after the legislation and found that food advertisements containing high energy, saturated fat, sugar or sodium decreased from 41.9% before the regulation to 14.8% after the regulation. In Spain, a public health law aimed at protecting children against advertisements for unhealthy food was passed in 2011. Campos et al. (22) analyzed food advertising aimed at children on Spanish television in 2013 and 2018 to test the effect of law over time and they determined that the trends of nutritional profiles in food advertising on television are worsening over time and the prevalence of unhealthy food ads was higher in 2018 than in 2013. As a result, the necessity of improving laws and increasing compliance with them was emphasized.

The strengths of the research are the fact that the research sample covers all days of the week and PT and OPT periods, and the use of a standard advertising categorization form, which was created by the researchers by scanning the literature for data collection.

Study Limitations

The limitations of our study were that the sample did not include some hours when children were in front of the TV, especially in the morning hours, that the children's channels were not evaluated and that the effects of the convincing methods (music, animation, use of celebrities, promotion, etc.) used in advertising were not examined.

Conclusion

The prevalence of food advertising on national television channels is high. Obesity-promoting ads constitute the majority of food ads. The frequency of healthy food ads is low. The level of exposure to unhealthy food advertisements during a child's time in front of the TV is high. This study was conducted before the regulations on food advertisements and new studies are needed to examine the situation after the new regulation.

Ethics

Ethics Committee Approval: The study protocol was approved by Pamukkale University Ethics Committee (approval number: 60116787-020/81512, date: 05.12.2017).

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

Financial Disclosure: Pamukkale University Scientific Research Projects Coordination Unit (proje no: 2019 KRM004-050).

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Pathological Internet use Levels and Psychiatric Diagnoses in Adolescents Admitted to a Child Psychiatry Outpatient Clinic after Face-to-face Education Restriction Due to the Pandemic

Pandemi Nedeniyle Yüz Yüze Eğitim Kısıtlaması Sonrası Çocuk Psikiyatrisi Polikliniğine Başvuran Ergenlerde Patolojik İnternet Kullanım Düzeyleri ve Psikiyatrik Bozukluklar

Didem Ayyıldız* (0000-0001-9149-201X), Funda Gümüştaş (0000-0001-8104-9567)**

*Dörtçelik Children's Hospital, Clinic of Child and Adolescent Psychiatry, Bursa, Turkey
**Private Practice, Clinic of Child and Adolescent Psychiatry, İstanbul, Turkey

Abstract

Introduction: During the period of social restrictions against the pandemic, the screen time of individuals increased significantly, and youths' mental health was adversely affected due to the restriction of peer interactions and physical activities. The aim of this study was to evaluate the levels of internet overuse and psychiatric disorders in adolescents who applied to the child psychiatry outpatient clinic after the distance education period.

Materials and Methods: A semi-structured tool, "Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version" (K-SADS-PL) was used to assess psychiatric diagnoses and Young Internet Addiction Test (IAT) to determine excessive internet usage. A total of 141 adolescents aged 11-18 years were recruited for this study.

Results: The average score for IAT was statistically significantly higher in the youths with social anxiety disorder compared to those without (p=0.001) even after controlling for socioeconomic status (SES) (p=0.007). According to the hierarchical regression analyses, the girl gender (B=-6.899, p=0.029), younger age (B=-1.526, p=0.032) and co-morbidity of OCD (B=5.292, p=0.042) have statistically significantly predicted higher IAT scores in adolescents diagnosed with anxiety disorders.

Conclusion: Identifying the common psychiatric diagnoses related to pathological internet use in adolescents, who started face-to-face education after a long break would enable mental health professionals to plan appropriate interventions for problematic areas particularly in vulnerable population more quickly when similar outbreaks recur.

Keywords
Pathological internet use, psychiatric disorder, adolescent, pandemic

Anahtar kelimeler
Patolojik internet kullanımı, psikiyatrik bozukluk, ergen, pandemi

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Address for Correspondence/Yazışma Adresi: Didem Ayyıldız MD, Dörtçelik Children's Hospital, Clinic of Child and Adolescent Psychiatry, Bursa, Turkey
Phone: +90 507 256 25 39
E-mail: didemayyldz@gmail.com

Öz

Giriş: Pandemiye yönelik sosyal kısıtlamaların olduğu dönemde ergenlerin ekran başında kalma süreleri çok artmış, akran etkileşimlerinin ve fiziksel aktivitelerin kısıtlanması nedeniyle ruh sağlıkları olumsuz etkilenmiştir. Bu çalışmanın amacı, uzaktan eğitim döneminden sonra çocuk psikiyatrisi polikliniğine başvuran ergenlerde internet aşırı kullanımı ve psikiyatrik bozukluk düzeylerinin değerlendirilmesidir.

Gereç ve Yöntem: Psikiyatrik tanıların değerlendirilmesi amacıyla yarı yapılandırılmış bir araç olan "Okul Çağı Çocukları için Duygulanım Bozuklukları

ve Şizofreni Görüşme Çizelgesi- Şimdi ve Yaşam Boyu" (ÇDŞG-ŞY) ve internet aşırı kullanımını belirlemek üzere Young İnternet Bağımlılığı Testi (IAT) kullanılmıştır. Bu çalışmaya 11-18 yaş arası toplam 141 ergen dahil edilmiştir.
Bulgular: Sosyal anksiyete bozukluğu (SAB) olan gençlerde, IAT ortalama puanı SAB bulunmayanlara oranla istatistiksel olarak anlamlı derecede yüksekti (p=0,001). Sosyoekonomik durum (SED) kontrol edildikten sonra da (p=0,007) istatistiksel anlamlılık devam etmekteydi. Hiyerarşik regresyon analizlerinnin sonuçlarına göre kız cinsiyet (B=-6,899, p=0,029), küçük yaş (B=-1,526, p=0,032) ve OKB eş tanısı (B=5,292, p=0,042) anksiyete bozuklukları tanısı bulunan ergenlerde daha yüksek IAT puanlarını istatistiksel olarak anlamlı şekilde öngörmüştür.
Sonuç: Uzun bir aradan sonra yüz yüze eğitime başlayan ergenlerde patolojik internet kullanımı ile ilişkili yaygın gözlenen psikiyatrik tanıların belirlenmesi, benzer salgınlar tekrarlandığında ruh sağlığı profesyonellerinin özellikle risk altındaki bireylerde sorunlu alanlara uygun müdahaleleri daha hızlı planlamasına katkıda bulunacaktır.

Introduction

In the literature, "Pathological internet use" tends to be used to refer to use the internet excessively. As the internet/technology itself is not an object of addiction but can be a way to reach the addicted substances and situations, "internet addiction" isn't sufficient to define using internet in pathological levels. Throughout this paper we use the term "Pathological internet use" which has been suggested by Gönül (1). "Pathological internet use" has been included in the psychiatric diagnostic classifications with the mention of Online Gaming Disorder in the "conditions for further study" appendix in Diagnostic Statistical Manual-5 (DSM-5) (2). But it has not yet been established whether pathological internet usage is a separate psychiatric diagnosis since internet/technology abuse/dependence is co-occurred with a high rate of axis 1 psychiatric disorders (3). During the pandemic period, due to the restrictions, the length of time that adolescents are required to be online, including education, and therefore the risk of internet addiction has increased. Besides, decreased peer interaction and indirectly reduced stress regulation opportunities due to social isolation caused mental health of adolescents to be adversely affected. Worsening of interaction with parents whose mental health was deteriorated due to economic problems or anxiety related to the disease have contributed to this situation, and it has been known that adolescents with low socioeconomic status or who already have psychiatric problems have been more affected (4). At the same time, the appeal of adolescents with a psychiatric diagnosis and ongoing treatment to a doctor has been delayed due to the social restrictions regarding pandemic (5). Despite this interest, no one to the best of our knowledge has determined the psychiatric disorder diagnoses by structured interviews in adolescents brought to outpatient clinics after a long period of distance education. Additionally, what has been known about internet addiction and psychopathology is largely based on studies have tended to focus on adults and using self-report scales (6-9). In the present study, it was primarily aimed to determine internet excessive use levels and psychiatric diagnoses of the adolescents who were brought to a Child and adolescent psychiatry outpatient clinic after a long school restriction period, and secondly to evaluate the relationship between pathological internet use levels and current psychiatric diagnoses of the youths.

Materials and Methods

Adolescents aged 11-18 years who applied to the child and adolescent psychiatry outpatient clinic in October 2021-February 2022 when the schools reopened after a 1.5-year break in face-to-face education due to the pandemic were included in the study. Patients, with autism spectrum disorder (n=2), psychotic disorder (n=1) and clinical impression/history of mental retardation (n=5), were not included in the study. The data of 5 participants who were detected to have diagnosis of special learning disorder (SLD) and a youth with hearing loss during the psychiatric examination were excluded from the analysis. A small number of patients with neurodevelopmental disorders, such as ASD and SLD were not included in the statistical analysis to investigate the predictors of the pathological internet use in a more homogeneous sample.

Necessary permissions for the study were obtained from Uludağ University, Faculty of Medicine Clinical Research Ethics Committee (date 06.10.2021 and number 2021-14/17).

"Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present

and Lifetime Version" (K-SADS-PL) was applied to the adolescents by a child psychiatrist in an attempt to determine the psychiatric diagnoses. A detailed information form prepared by the researcher in which the age, gender, parent's education and employment status, monthly family income, whether they had received psychiatric treatment before, and their internet usage areas was filled by the researcher herself out by asking the participants. The adolescents were also asked to fill out "Young Internet Addiction Test-short form" (IAT).

Schedule for Affective Disorders and Schizophrenia for School-age Children-present and Lifetime Version

K-SADS-PL was developed by Kaufman et al. (10) for the pschiatric diagnostic assessment and revised based on DSM-5 criteria in 2016. Turkish validity and reliability study was carried out by Unal et al. (11). Authors have stated that, the validity and reliability of this adaptation has been demonstrated for wide range of disorders. The scale, which enables to assess psychiatric disorders other than specific learning disorder and mental retardation, is made up of 3 parts. In our study, during the first phase, the information about child's demographic findings, complaints, and previous treatments were obtained from parents. When any positivity was found in the second part of the scale, in which about 200 specific psychiatric symptoms were checked, the diagnoses were clarified with additional symptom lists. As soon as these steps have been carried out, in the third part, the current functional level of the child was determined. Since it is a semi-structured interview tool, psychiatric diagnoses causing functional impairment were detected by the child and adolescent psychiatrist after interviews were carried out with the adolescent and his/her family. Rates of the participants with subthreshold symptoms of psychiatric disorders were also noted.

Young Internet Addiction Test (IAT)-short Form

The IAT-short form was developed by Pawlikowski et al. (12) in accordance with the scale which was created by Young (13) through adapting the diagnostic criteria of pathological gambling to internet addiction. Answers ranging from 1 to 5 are given to the questions of the IAT-short form, which consists of 12 items. Although the scale does not have a cut-off value, the high total score indicates the severity of excessive internet use. The IAT-short form was used in a study conducted with university students in our country (14). It was stated that Young IAT-short form Cronbach's alpha coefficient was found as 0.91 in university students and 0.86 in adolescents. Correlation coefficient for test-retest reliability was found as 0.93 in university students and 0.86 in adolescents. Authors have suggested the scale was a valid and reliable tool for Turkish population as well.

Statistical Analysis

The data were evaluated by using the Statistical Package for the Social Sciences (version 20) program. Descriptive statistics were shown as mean-standard deviation or percentages (%). A 95% confidence interval was used to assess the data. Although the educational level and working status of the parents were ordinal variables, they were accepted as dummy variables and calculated as continuous variables in our study. The sum of the scores was expressed as socioeconomic status (SES). The correlation between the SES and the IAT total score variables were tested by Spearman correlation analysis. The IAT scores were compared according to the presence of co-morbid psychiatric diagnoses of the youths by adjusting the SES variable using 1-way analysis of covariance. Finally, in order to obtain a more homogeneous sample, children and adolescents with anxiety disorder were grouped and regression analysis was performed. The independent variables that might influence IAT scores were age and gender in the first step and comorbidity with obsessive-compulsive disorder (OCD) in the second step. For all analyses statistical significance was set at $p<0.05$.

Results

The mean age was (M=14.68, SD=1.8) of the 141 participants recruited for this study. A hundred and three (73.0%) of the youths were girls; 38 (27.0%) of them were boys. On average we found values for the IAT of (M=30.82, SD=10.3). There was no statistically significant difference in the average IAT scores in terms of gender (139) (p=0.055). Seventy-three (67%) of the participants have applied to the psychiatry outpatient clinic for the first time, while 36 (33%) had been diagnosed before. There was no significant difference in the mean IAT total score between those diagnosed for the first time and those already followed (t=0.707, p=0.481). No statistically significant correlation was

observed between IAT total score and age (p=0.070) or SES levels (p=0.209). When the youths were divided into 3 groups according to the scores, they got from the IAT, it was revealed that 15 (11%) of them were in the highest range (45-60), 56 (41.2%) of moderate range (30-44) and 65 (47.8%) of them mild (12-29).

When the internet usage areas of youths were evaluated; it was determined that the mean IAT total score of the adolescents who stated that they used social media frequently (71) was statistically significantly higher than those who did not (20) (t=-3.125, p=0.002, 95% CI=-13.39-2.98). Nevertheless, it was found that the mean scores of the adolescents who stated that they frequently used the internet for research/study (71) were statistically significantly lower than those who did not (21) (t=2.914, p=.005, 95% CI=2.38-12.62). No significant difference was identified in terms of IAT score between those who said that they used internet frequently for gaming and those who did not (p=0.311).

Statistical analyses showed that 134 (95%) of the 141 participants had at least one psychiatric disorder while 87 (65.9%) of the participants had two or more psychiatric disorders. (Table 1 shows the distribution of present psychiatric diagnoses). Participants with multiple psychiatric diagnoses (two or more) (85, M=33.12, SD=10.05) had significantly higher IAT scores than those with a single psychiatric diagnosis (45, M=27.04, SD=10.08) (t=-3.286, p=0.001, 95% CI=-9.74-2.42). It's fundamental to note that there was a statistically significant increase in the IAT scores in the youths with social anxiety disorder (38) compared to those without (90) (t=-3.527, p=0.001, 95% CI=-10.8-3.04). No such difference was found for other psychiatric disorders. Even after controlling for SES, the higher IAT scores in the group with social anxiety disorder remained statistically significant (after adjusted for SES, p=0.007, F=5.317).

When the cases with at least one anxiety disorder diagnosis were considered as the study group and analyzed based on whether M. Depressive disorder/ dysthymia, OCD and ADHD diagnoses were accompanied or not; patients with OCD diagnosis in addition to the anxiety disorder diagnosis (25), had a significantly higher IAT score than those without (49) (t=-2.130, p=0.037). Further analyses were carried out to examine the factors predicting the mean IAT total scores in anxiety disorders group (74). The age and gender variables were entered as the first block and the results indicated that the model was significant, and 14.3% of the variance was explained by the model (F=5.358, p=0.007) in the hierarchical linear regression analysis. After entry of the co-morbidity of OCD variable at the second block, the model was still significant (F=5.191, p=0.003) and total variance explained by the model as a whole was 19.8% (R squared change=0.055). In the model 2; the co-morbidity of OCD significantly predicted higher IAT total scores in adolescents with anxiety disorders (B=5.292, p=0.042). The gender (B=-6.899, p=0.029) and age (B=-1.526, p=0.032) variables were still statistically significant (Table 2).

Table 1. Distribution of psychiatric diagnoses

	n	%
M. depression	68	50.7
Generalized anxiety disorder	44	32.8
Social anxiety disorder	39	29.1
Attention deficit hyperactivity disorder	33	24.6
Obsessive-compulsive disorder	29	21.6
Dysthymia	17	12.2
Specific phobia	14	10.4
Panic disorder	11	8.2
Separation anxiety disorder	7	5.2
Tic disorders	7	5
Enuresis	7	5
Trichotillomania	5	3.7
Eating disorder (including subthreshold)	4	2.9
Skin picking disorder	3	2.2
Bipolar disorder, unspecified (BD)	3	2.2
Kleptomania	2	1.5
Conduct disorder	2	1.5
Gender dysphoria	2	1.5
Oppositional defiant disorder	1	0.7
Post-traumatic stress disorder	1	0.7
Conversion disorder	1	0.7

Discussion

In the present study, internet addiction and psychopathology were examined in a clinical sample of adolescents when the schools reopened after a 1.5-year break in face-to-face education due to the pandemic.

Table 2. Hierarchical linear regression analysis findings for variables predicting IAT total value in anxiety disorders group				
	Unstandardized coefficients		Standardized coefficients beta	Sig.
	B	Std. Error		
Model 1				
Age	-1.648	0.711	-0.269	0.024
Gender	-6.733	3.156	-0.247	0.037
Model 2				
Age	-1.526	0.696	-0.249	0.032
Gender	-6.899	3.079	-0.254	0.029
Co-morbidity of OCD	5.292	2.551	0.235	0.042
OCD: Obsessive-compulsive disorder, IAT: Internet Addiction Test				

The majority of the subjects were girls (69.0%) in our study. The inclusion criteria of the study may be responsible for this. Firstly, adolescents in the 11-to-18 age group have been included in the study, and it has been known that diagnoses such as mood disorders and anxiety disorders, which are common in this age group, are more frequent in girls than boys. Secondly, youth with diagnoses of such as autism spectrum disorder or specific learning disorder, which are seen higher in boys than girls, have been excluded from the study, since K-SADS is not suitable for detecting these developmental disorders.

In a study conducted with middle and high school students in Canada, spending more than 2 hours a day on social media has been associated with higher levels of psychological distress, suicidal ideation, and self-rated mental health symptoms (15). In a study from Netherlands, it has been shown that the risk of internet addiction was increased in those who use social networking sites (16). According to our results, it was determined that the mean IAT total score of the adolescents who stated that they used social media frequently was statistically significantly higher than those who did not. However, co-existing psychiatric diagnoses didn't differ related to social media usage in the present study.

Our study revealed that the most common psychopathologies were m. depressive disorders, anxiety disorders, ADHD and OCD and participants with multiple psychiatric diagnoses had significantly higher IAT scores than those with a single diagnosis. It is crucial to note that over half of the youths had m. depressive disorder including sub threshold cases. When the association between higher IAT scores and each psychiatric diagnoses was investigated, statistically significant result was present only for social anxiety disorder. Milani et al. (17) have suggested that pathological internet use was associated with poor interpersonal relationships and avoidant coping behavior. As a result of a follow-up study conducted with 2293 high school students in Taiwan, it was determined that depression, attention deficit-hyperactivity disorder and social phobia predicted the occurrence of internet addiction in the follow-up (18). Kaur (19) indicated that adolescents' pathological internet use levels and perceived social self-efficacy were negatively correlated. It might have been possible that the avoidance behavior of youths with social anxiety was reinforced during the pandemic period, as well as the loss of the opportunity to develop their social skills, and the reinforcement of their negative beliefs about themselves.

In the literature on investigating the relationship between internet addiction and psychopathology, there are studies examining the psychopathology of individuals who have received a certain score from the self-report scales in terms of pathological internet use. In a review evaluating the relationship between pathological internet use and psychopathology, it was stated that there was a 75% association with depression, 57% with anxiety disorders, 100% with ADHD, and 60% with OCD. In the same paper, the fact that no study reported associations with social phobia and the heterogeneity of studies on the definition and diagnosis of pathological internet use were emphasized (20). Before the COVID pandemic, in two similar studies from Turkey (21,22), adolescents who were referred to child psychiatry outpatient clinics due to pathological internet use complaints and co-existing emotional-behavioral problems were examined.

Adolescents, with a Young Internet Addiction scale score above a certain value were screened with a semi-structured interview tool (K-SADS) in these studies. The most common psychiatric diagnoses detected in internet addicts according to both studies were m. depressive disorder, anxiety disorders, and ADHD in line with the previous results (23). Comparing our results with these studies, it should be taken into account that adolescents with varied levels of internet use were evaluated in our study. Additionally, the fact that our sample is predominantly female, and that neurodevelopmental disorders such as SLD and autism spectrum disorders excluded from the study might have caused not to find a relationship between pathological internet use and ADHD. Because, it has been known that ADHD is more common in males and is often seen together with other neurodevelopmental disorders. There's also a study that evaluated internet addiction with IAT in adolescents with a psychiatric diagnosis, who were followed up in an outpatient clinic of a children's hospital, similar to our study, but conducted before the pandemic. In that study, a significant positive relationship was found between IAT scores and mood disorders (24). Further, in a study conducted with medical students before the pandemic, those who scored 50 out of 100 in Young's internet addiction test were considered as internet addicts and psychopathology was investigated. Self-esteem, social anxiety, and depression were evaluated with self-report scales in that study. It has been shown that only 10.5% of the students got high scores indicating addiction and that depression and social anxiety were highly correlated with the IAT scores (25). This value correlates fairly well with our study finding which revealed that 10.9% of the adolescents' mean IAT scores were in the highest range.

Explanatory analyses have led us to conclude that although internet addiction scores in the initial sample did not differ in terms of age and gender, younger age and female gender predicted higher IAT scores in the anxiety disorders group. According to the results of a 2016 study that evaluated the relationship between internet addiction and depression in terms of gender, it was pointed out that depression leads to excessive use of the internet in boys, while internet overuse leads to depression in girls (26). Investigation of gender-specific co-morbid psychiatric conditions in cases with pathological internet use is important in terms of determining individual-specific interventions. Our results would also seem to suggest that co-morbidity with OCD were associated with higher IAT scores in adolescents with anxiety disorders. In a study conducted with students aged 16-18 in Greece, internet addiction scores were found to be associated with obsessive compulsive symptom levels (27). In an adult study conducted with female patients with eating disorders, a relationship was found between compulsive buying and internet excessive use levels (28). In another study, conducted in adult individuals with OCD, internet addiction scores were found to be higher compared to controls, and positively correlated with impulsivity (29). Our results are in line with previous studies, conducted to elucidate the nature of Internet addiction and reported that internet addiction was closely related to compulsion.

Finally, several weaknesses need to be considered. To begin with, the small sample size could have influenced the study results. The child psychiatry outpatient clinic of the state hospital where our study was conducted is a center with frequent referrals. Although the number of cases admitted within a 5-month period was quite high, the sample could have been increased by cooperating with different centers. In this way, participants from varied socio-cultural environments could also have been included in the study. Another limitation is that cases who applied to the polyclinic for the first time and were diagnosed before were evaluated together. However, it was observed that the majority of the youths who were diagnosed before did not receive treatment in the current situation. Further, the fact that the IAT-short form was used in order to identify pathological internet use could have affected the comparisons with similar studies in this area. Despite this, less time-consuming instrument represents a useful alternative to scales' long version especially when studying with adolescents.

Conclusion

The principal advantage of our study is that the psychiatric diagnoses have been determined using a semi-structured clinical interview by a child and adolescent psychiatrist. We hope that the current study adds to our understanding the association with pathological internet use and psychopathologies of adolescents based on data from clinical samples

during the pandemic period. Increasing findings on relationship between pathological internet use and psychiatric disorders has been important for a better understanding of the mechanism of internet addiction and the organization of appropriate/early interventions.

Ethics

Ethics Committee Approval: Necessary permissions for the study were obtained from Uludağ University, Faculty of Medicine Clinical Research Ethics Committee (date: 06.10.2021, decision no: 2021-14/17).

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

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Adölesanlarda Anormal Uterin Kanamaya Hematolog Gözüyle Yaklaşım

Hematolog Approach to Abnormal Uterine Bleeding in Adolescents

Özge Vural* (0000-0001-7523-7553), Hilal Susam Sen (0000-0002-1329-1287), İbrahim Eker** (0000-0002-1880-546X)**

*Gazi Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Hematoloji ve Onkoloji Bilim Dalı, Ankara, Türkiye
**Afyonkarahisar Sağlık Bilimleri Üniversitesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Pediatri Bilim Dalı, Afyonkarahisar, Türkiye

Öz

Giriş: Anormal uterin kanama (AUK), menstrüel kanama düzeni, süresi veya miktarındaki değişiklikler için kullanılan bir terimdir. Adölesan kızlarda hipotalamohipofiz-over aksın immatur olması kanama bozuklukları, enfeksiyonlar, endokrin bozukluklar, sistemik hastalıklar, vajina-serviks-uterus ve overi ilgilendiren sorunlar ve ilaçlar da etiyolojide sorumlu olabilir. Bu değerlendirmede farklı disiplinler arasında farklı yaklaşımlar olmaktadır. Çalışmamızda Afyon Sağlık Bilimleri Üniversitesi Çocuk Hematoloji Bilim Dalı'nda anormal uterin kanama tetkik ve tedavi edilen olguları retrospektif olarak değerlendirerek sonuçlarımızı paylaşmak ve bu olgulara hematolojik yaklaşıma katkı sağlamayı amaçladık.

Gereç ve Yöntem: Temmuz 2016-Eylül 2019 tarihleri arasında Afyonkarahisar Sağlık Bilimleri Üniversitesi Çocuk Hematoloji Polikliniği'ne başvuran 12 yaş üzeri kız hastalardan hemoglobin değeri <12 gram/dL ve normal menstrüel periyotta 60-80 mL üzerinde kanaması olanlar (3-6 ped/gün veya 10-15 ped/siklus), menstrüel siklusu 8 günden uzun sürenler ve menstrüel siklusu 21-28 günden daha sık tekrar edenler ve çalışmaya dahil edildi ve kayıtları retrospektif olarak incelendi. Hastaların demografik özellikleri, başvuru şikayetleri, başvuru esnasındaki tetkikleri ve hemostaz defekti varlığı açısından yapılan tetkikler, konsültasyonlar, uygulanan tedaviler ve sonuçları dokümante edilerek değerlendirildi.

Bulgular: Çalışmaya 39 kız hasta dahil edildi. Hastaların yaş ortalaması 16,2±1,5 (13,2-21,5), ilk adet yaşı 12,4±1,1 (8-14) idi. Hastaların %53,8'inde (n=21) hb<8 g/dL, %23'ünde (n=9) hb %8-10 g/dL ve % 23'ünde (n=9) %10-12 g/dL idi, 1 hastada von Willebrand Tip 1 saptandı.

Sonuç: Anormal uterin kanama adölesan kız çocuklarında aneminin önemli bir nedenidir. Hastaların öykülerinin dikkatle alınması özellikle etiyolojiye yönelik tetkiklerin yapılması, ayırıcı tanıda kanama diatezinin; özellikle von Willebrand hastalığının göz önünde bulundurulması, anormal uterin kanamalı olguların etkin sağaltımı için farklı disiplinlerin iletişim içinde olması ve diğer disiplinlerin konuya yaklaşım hakkında bilgi sahibi olmaları hastane başvurularının azalması ve tedavi başarısının artmasında önemli rol oynar.

Anahtar kelimeler
Anormal uterin kanama, anemi, von Willebrand hastalığı

Keywords
Abnormal uterine bleeding, anemia, von Willebrand disease

Abstract

Introduction: Abnormal uterine bleeding (AUK) is a term used for changes in menstrual bleeding pattern, duration, or amount. In adolescent girls, it is associated with the immature hypothalamo-pituitary-ovarian axis, bleeding disorders, infections, endocrine disorders, systemic diseases, vagina-cervix-uterus and problems related to the ovary and drugs. There are different approaches between different disciplines in this assessment. In our study, we aimed to share our results

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Yazışma Adresi/Address for Correspondence: Dr. Özge Vural, Gazi Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Hematoloji ve Onkoloji Bilim Dalı, Ankara, Türkiye
Tel.: +90 312 202 60 21
E-posta: drozgevural@yahoo.com

and contribute to the hematological approach to these cases by retrospectively evaluating the abnormal uterine bleeding examination and treated cases in Afyon Health Sciences University Department of Pediatric Hematology.
Materials and Methods: Between July 2016 and September 2019, patients over 12 years admitted to the Afyonkarahisar University of Health Sciences Department of Pediatric Hematology who had hemoglobin value <12 grams/dL and 60-80 mL bleeding in normal menstrual period (3-6 pads/day or 10-15 pads/cycle), menstrual cycle lasting longer than 8 days, and menstrual cycle repeated more than 21-28 days were included in the study and their records were analyzed retrospectively. The demographic features, admittion complaints, consultations, treatments applied and the results were documented and evaluated.
Results: A total of 39 subjects were enrolled in the study. The mean age of the patients was 16.2±1.5 (13.2-21.5), the mean age at menarche was 12.4±1.1 (8-14). Hb <8 g/dL in 53.8% (n=21) of patients, hb 8-10 g/dL in 23% (n=9) and 10-12 g/dL in 23% (n=9) and von Willebrand Type 1 was detected in one patient.
Conclusion: Abnormal uterine bleeding is an important cause of anemia in adolescent girls. It is necessary to conduct investigations for etiology and bleeding disorders especially von Willebrand disease, in differential diagnosis. The communication of different disciplines and the knowledge of other disciplines about the approach to the subject for effective treatment of abnormal uterine bleeding plays an important role in decreasing hospital admissions and increasing the success of treatment.

Giriş

Anormal uterin kanama (AUK) menstrüel siklusların süre, düzen, miktar veya zamanlamasındaki anormalliklere verilen isimdir. Yaşamları boyunca tüm kadınların yaklaşık üçte birinde görülür; hastaneye başvuran ergenlerin en sık görülen jinekolojik şikayetidir (1). Adölesan dönmede normal menstrüel siklus, 21-45 günde bir iki ile yedi gün arasında süren kanamalar şeklindedir. Menstrüel sikluslar adölesanların %60-80'inde menarştan sonraki iki yılda düzensizdir (2). Genellikle anormal uterin kanamalar menstrüel siklusta ciddi olmayan düzensizlik olarak karşımıza çıkmakla beraber, bazı hastalarda ciddi kanamaya ve eşlik eden anemiye neden olabilecek ve hastane yatışı gerektirecek şekilde karşımıza çıkabilir. Menstrüel sikluslardaki bozukluklar ve bazen ağrı ile birliktelik yaşam kalitesini bozabilir ve okula devam etmeyi etkileyebilir. Adet döngülerinin ergenlik döneminde sıklıkla düzensiz oluşu anormalliğin farkına varılmamasına sebep olur. Bu yüzden ergenlerde rutin çocuk doktoru ziyaretleri sırasında menstrüel siklus mutlaka sorgulanmalıdır. Adölesanlarda adet kanaması anemiye (Hb<12 g/dL) neden oluyorsa patolojik olarak kabul edilmeli ve etiyolojiye yönelik tetkikler yapılmalıdır. Ergenlerde AUK tedavisi, altta yatan etiyolojiye ve kanamanın şiddetine dayanır (3). Hemodinamik stabilitenin sağlanması, aneminin düzeltilmesi ve normal döngülerin sürdürülmesi AUK yönetiminde temel hedefleri oluşturmaktadır. Bu çalışmada Afyonkarahisar Sağlık Bilimleri Üniversitesi Çocuk Hematoloji Bölümü'ne başvuran ve anormal uterin kanama tanısı alan hastalar retrospektif olarak incelenerek demografik özelliklerinin, etiyolojilerinin ve tedavi yönetimlerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem

Çalışmamızda Temmuz 2016-Eylül 2019 tarihleri arasında AUK ile Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Çocuk Hematoloji-Onkoloji Polikliniği'ne başvuran 18 yaş altı hastaların dosyaları retrospektif olarak değerlendirildi. Normal menstrüel periyotta 60-80 mL üzerinde kanaması olanlar (3-6 ped/gün veya 10-15 ped/siklus), menstrüel siklusu 8 günden uzun sürenler ve menstrüel siklusu 21-28 günden daha sık tekrar edenler ve cinsel açıdan inaktif olan olgular çalışmaya dahil edildi. Öyküde ailede kanama bozukluğu, ilaç kullanım öyküsü ve ek hastalık varlığı not edildi. Laboratuvar tetkiklerinden hemoglobin, ferritin, B12, folat, aPTT, PT, INR, fibrinojen, vWF, FVIII/FIX/FXI, trombosit fonksiyon testi, FSH, LH, total/serbest testosteron, DHEA, PRL, TSH, sT4 kaydedildi. Başka patoloji saptanmadıysa, hastalara hipotalamik-hipofiz-yumurtalık ekseninin gelişimsel olgunlaşmamışlığı nedeniyle oluşan AUK tanısı kondu.

Etiyolojik değerlendirme sonrası olgular hemoglobin değerine göre şu şekilde sınıflandırıldı: Hemoglobin 10-12 gr/dL hafif anemi; hemoglobin 8-9,9 gr/dL orta anemi; hemoglobin <8 gr/dL ağır anemi. Abdominopelvik ultrasonografi ile kitle varlığı, yapısal anomaliler, diğer uterus ve over patolojileri değerlendirildi. Verilen tedaviler ve tedavi yanıtları kayıt altına alındı. AUK için ilk değerlendirmeden sonra hastalar en az altı ay takip edildi ve altıncı ay kontrolünde tedaviye yanıtları yeniden değerlendirildi. Tedavi öncesi hasta ve yakınlarından bilgilendirilmiş onam alındı. Kurumumuz etik kurulu çalışmayı onayladı.

İstatistiksel Analiz

Hastaların demografik verilerini, klinik verilerini ve tedavilerini belirlemek için tanımlayıcı istatistiksel analizler yapıldı. Kategorik değişkenler için ki-kare testi kullanıldı. Tüm istatistiksel testler SPSS sürüm 21.0 kullanılarak yapıldı.

Çalışma Afyonkarahisar Sağlık Bilimleri Üniversitesi Etik Kurulu tarafından onaylandı (karar no: 2020/197, tarih: 05.05.2020).

Bulgular

Çalışmaya 39 kız hasta dahil edildi. Hastaların yaş ortalaması 16,2±1,5 (13,2-21,5), ilk adet yaşı 12,4±1,1 (8-14) idi. Hastaların %53,8'inde (n=21) Hb<8 g/dL, %23'ünde (n=9) Hb %8-10 g/dL, %23'ünde (n=9) Hb %10-12 g/dL idi, bir hastada von Willebrand Tip 1 saptandı. AUK tanısıyla takipli hastalarımızın klinik ve laboratuvar özellikleri özetlenmiştir (Tablo 1).

Tedavide kanamayı azaltmaya yönelik 15 (%38,5) hastaya transamin, 17 (%43,6) hastaya kombine oral kontraseptif, demir eksikliği olanlara demir tedavisi, B12 vitamin eksikliği olan bir hastaya B12 vitamin desteği verildi. Tedavi öncesi ve sonrası günde ped sayısı, hemoglobin, ferritin ve B12 düzeylerindeki değişikliklerin karşılaştırılması Tablo 2'de gösterilmiştir. Hastaların tedavi öncesi ve sonrası günlük ped sayıları sırası ile ortalama 7,4±1,6 (range 6-15), 4,1±1,6 (range 2-6) (p<0,05). Hastaların tedavi öncesi ve sonrası Hb düzeyleri sırasıyla ortalama 8,1±2,2 (range 3,7-11,9), 11,3±1,5 (range 8-14,3) (p<0,05). Hastaların tedavi öncesi ve sonrası ferritin düzeyleri sırasıyla 9,5±9,0 (range 1,6-34,8), 27,8±12,6 (range 7,5-56,7) (p<0,05). Hastaların tedavi öncesi ve sonrası vitamin B12 düzeyleri sırasıyla 354,7±215,4 (range 94-1459), 359,8±142,9 (range 134-786) (p=0,558). Günde ped sayısı, hemoglobin ve ferritin düzeylerinde anlamlı fark saptanırken, B12 vitamini düzeyinde anlamlı fark saptanmamıştır.

Tartışma

Anormal uterin kanamalar her yaşta görülebilmekle birlikte özellikle 9-11 yaş arasındaki adölesanlarda sık görülmektedir. Bir adölesan anormal uterin kanama ile hastaneye başvurduğunda, jinekolojik öykü de dahil olmak üzere, meme gelişimi, aksiller pubik kıllanma menstrüel siklusun başlangıç zamanını da içeren ayrıntılı tıbbi öykü alınır. Menstrüel öyküde, adet düzenini belirlemek önemlidir (4). Uluslararası

Tablo 1. Hastaların klinik ve laboratuvar özellikleri

Parametre	n=39
	Ort ± SS (min-maks)
Yaş (yıl)	16,2±1,5 (13,2-21,5)
Menarş yaşı (yıl)	12,4±1,1 (8-14)
Ped veya tampon sayısı/gün	7,4±1,6 (6-15)
Kanama olan gün sayısı	8,2±5,6 (4-30)
Hemoglobin (g/dL)	8,1±2,2 (3,7-11,9)
Lökosit (10^3/mm^3)	6,7±2,2 (3,3-12,6)
Trombosit (10^3/mm^3)	282,3±87,6 (100-445)

SS: Standart sapma, min-maks: Minimum-maksimum, Ort: Ortalama

Tablo 2. Hastaların tedavi öncesi ve sonrası bulguları

	Tedavi öncesi (n=39)		Tedavi sonrası (n=39)		p
	Min-maks	Ort + SS	Min-maks	Ort + SS	
Günde ped sayısı	6-15	7,4±1,6	2-6	4,1±1,6	<0,005
Hemoglobin	3,7-11,9	8,1±2,2	8-14,3	11,3±1,5	<0,005
Ferritin	1,6-34,8	9,5±9,0	7,5-56,7	27,8±12,6	<0,005
B12	94-1459	354,7±215,4	134-786	359,8±142,9	0,558

SS: Standart sapma, Ort: Ortalama, Min-maks: Minimum-maksimum

Jinekoloji ve Obstetrik Federasyonu (FIGO) anormal uterin kanama ve menstrüel siklusları tanımlama ve sınıflamada kullanılan terminolojiyi standardize etmek için önerilerde bulunmuştur. FIGO'ya göre menstrüel döngüler 24-38 günde bir olmalı, <24 veya >38 gün anormal, süresi 8 günden fazla ise uzamış olarak tanımlanmaktadır (1).

Ayrıntılı bir cinsel öykü, hamileliği ve hatta cinsel istismarı belirlemek için önemlidir. Cinsel olarak aktif hastalar pelvik muayeneden geçmelidir. Kontrasepsiyon kullanımı ve cinsel yolla bulaşan enfeksiyon öyküsü de sorgulanmalıdır. Pelvik patolojileri dışlamak için abdominopelvik ultrasonografi yapılmalıdır (5). Anovulatuvar döngüler, olgunlaşmamış hipotalamik-hipofiz-over ekseni, hipotiroidizm, hiperprolaktinemi ve polikistik over sendromu gibi bozukluklar AUK nedenlerindendir.

İlk adet kanamasından itibaren olan ağır menstrüel kanama ciddi anemiye neden olabilir. Anemi adet gören kadınlarda dünya çapında yaklaşık %30 civarında görülürken bu oran Güney Asya ve Afrika'nın bazı bölgelerinde %60'a ulaşmaktadır (6). Ağır menstrüel kanama semptomu olan kadınların %25'inde demir eksikliği anemisi olduğu gösterilmiştir (7). Knol ve ark.'nın (8) yaptığı bir çalışmada AUK ile başvuran hastaların %46'sında anemi görüldüğü bildirilmiştir. Anemi gelişen adölesanlarda yorgunluk, halsizlik yaşam kalitesini etkilemektedir. Özellikle gelişmekte olan ülkelerde sosyo-ekonomik ve kültürel nedenlerle yeterli beslenemeyenlerde gelişen demir eksikliği anemisi anormal uterin kanamaya bağlı olan aneminin derinleşmesine neden olmaktadır (9). Anemi ile başvuran hastalarda altta yatan nedeni bulmak tedavinin başarısı için önemlidir. Anemi ile başvuran adölesan kız çocuklarında anormal uterin kanama göz önünde tutulması gereken bir durumdur (10). Bizim çalışmamızda anormal uterin kanama nedeniyle başvuran hastaların tümünde anemi görüldü. Çalışmanın Çocuk Hematoloji Polkliniği'ne gelen hastalar arasında yapılmış olması, anemisi olan AUK'lu adölesanların ileri tetkik amacıyla yönlendirilmiş olması da bu duruma neden olmakla birlikte anormal uterin kanaması olan kız çocuklarında anemi sıklığının fazla olduğu da daha önce bildirilmiştir. Hastaların %53,8'inde (n=21) ağır, %23'ünde (n=9) orta, % 23'ünde (n=9) ise hafif anemi saptandı. Çalışmamızda hastaların başlangıç hemoglobin ve ferritin düzeyleri uygun tedavi ile anlamlı olarak yükselmiştir. Hastanın annesinin veya kız kardeşinin adet öyküsü, ayrıntılı fizik muayene, ailede endokrinopati veya hematolojik bozukluklar (hipo-hipertiroidizm, polikistik over sendromu, vWD) öyküsü ve ameliyat sonrası kanama öyküsü de önemli ipuçları sağlar. Altta yatan hemostatik bozukluklar genel olarak kabul edilenden daha yaygın olabilir. Jinekolojik anormallikleri olmayan ağır menstrüel kanaması olan hastaların yaklaşık %5-20'sinde altta yatan bir kanama bozukluğu tespit edilmiştir (11). Ağır menstrüel kanaması olan premenopozal kadınlarda yapılan bir çalışmada hastaların % 29'unda altta yatan bir kanama bozukluğu saptandı. Bunlardan 6 hastada von Willebrand hastalığı, 4 hastada faktör XI eksikliği ve 1 hastada faktör VII eksikliği tanısı konduğu bildirilmiştir (8). Çok çeşitli hemostatik bozukluklar anormal uterin kanama ile ilişkilendirilebilmekle birlikte von Willebrand hastalığı (vWh) önemli bir neden ve katkıda bulunan faktör olarak kabul edilmiştir (12). Amerika Birleşik Devletleri'nde Hastalık Kontrol ve Önleme Merkezleri tarafından yapılan son olgu kontrol çalışmasında "menorajili" kadınların %10,7'sinde vWh tespit edildiği bildirilmiştir (13). Ülkemizden yapılan bir çalışmada Kanbur ve ark. (14) Hacettepe Üniversitesi İhsan Doğramacı Çocuk Hastanesi'ne Mayıs 1999'dan Nisan 2002'ye kadar menoraji nedeniyle başvuran 47 kızı inceledi. Bu çalışmada 47 hastanın 3'ünde (%6) primer pıhtılaşma bozukluğu saptandı (2 vWD, 1 faktör XI eksikliği) (14). Bu nedenle menarşta uzamış ve fazla kanaması olan kızlar hematolojik bozukluklar açısından araştırılmalıdır (15). Bizim çalışmamızda bir hastada (%2,5) von Willebrand hastalığı saptandı. Menoraji kanama bozukluklarının tek semptomu olabilir bu nedenle klinisyenler anormal uterin kanamanın nedeni olarak koagülopatinin farkında olmalıdır. Ayrıca, Amerikan Obstetrik ve Jinekoloji Birliği, anormal uterin kanama veya menoraji ile başvuran 18 yaşın altındaki kızlarda kanama bozukluklarının değerlendirilmesini önermektedir (16). Açıklanamayan menoraji, genellikle endometriyal ablasyon ve/veya histerektomi gibi cerrahi müdahaleleri tetikler. Altta yatan kanama bozukluğu varsa, bu girişim gereksiz olabilir ve aslında aşırı kanama ve gereksiz kan ürünlerinin kullanılması riski oluşturabilir bu nedenle etiyoloji iyi belirlenmelidir (17).

Adölesan dönemde düzensiz adet kanamalarının en sık görülen endokrinolojik nedeni PKOS'tur

(18). Kronik anovulasyon nedeniyle PKOS'ta düzensiz kanamalar görülebilir (19). Ayrıca tiroid hormonlarının ovarian reseptörlerini etkilediği ve dolayısıyla üreme fonksiyonlarını etkilediği bilinmektedir. Attia ve ark. (20) tiroid disfonksiyonu ile menstrüel bozukluklar arasında anlamlı bir ilişki bildirmiştir. Literatürde AUK'da hormonal tedavi ile diğer tedavi yöntemlerinin etkinliğini karşılaştıran az sayıda randomize çalışma bulunmaktadır. Fraser ve McCarron (21) 1991 yılında AUK'li hastalarda oral kontraseptif, mefenamik asit, düşük doz danazol ve naproksen üzerinde çalışmış ancak gruplar arasında anlamlı bir ilişki bulamamışlardır. Lethaby ve ark. (22) tarafından yapılan bir çalışmada orta düzeyde kanıtlar kombine oral kontraseptiflerin altı ay süre ile kullanımının AUK olan kadınlarda AUK'yi %12 ile %77 arasında (plasebo alan kadınlarda %3'e kıyasla) azalttığını göstermektedir. NSAID'ler veya uzun etkil progesteron ile kombine hormonal kontraseptiflerin karşılaştırmalı etkinliğini belirlemek için yeterli kanıt yoktu (22). Çalışmamızda Hb düzeyi 12 g/dL'nin altında olan hastaların tedavi öncesi ve sonrası Hb ve ferritin düzeyleri karşılaştırıldığında anlamlı fark görüldü. B12 düzeyleri karşılaştırıldığında anlamlı fark görülmedi. Çalışmamızda hormonal tedavi alan 17 (%43,6) hastada, tedavi öncesi ve sonrasında hemoglobin konsantrasyonlarında istatistiksel olarak anlamlı fark saptandı. Bu hastaların tedavi öncesi ve sonrası günde ped sayısı karşılaştırıldığında anlamlı fark görüldü. Aşırı adet kanaması olan adölesanlarda en sık görülen koagülopati vWh'dir ve popülasyonun %1'ini etkiler (16). Bir hastamıza vWH Tip 1 tanısı kondu; bu hastaya adet dönemlerinde traneksamik asit tedavisi uygulandı ve bu tedavi ile kanamaları kontrol altına alındı.

Sonuç

Adölesanlarda AUK tedavisi, altta yatan nedenin ve aneminin ciddiyetinin dikkatli bir şekilde değerlendirilmesine dayanır. Hemodinamik instabiliteyi kontrol etmek ve menstrüel kanamanın düzenlenmesi acil yönetim hedefleridir. Acil müdehalenin ardından kanamanın kaynağını bulmalı, organik nedenleri belirlemeli ve gerekiyorsa demir eksikliğini tedavi etmelidir. Menarş, çocukluktan ergenliğe geçiş yapan adölesanın hayatında dönüm noktasıdır. Aşırı ve uzun süreli kanama bu dönemde sadece jinekolojik değil sosyal bir problemdir. Aile ve adölesan bu durum hakkında bilgilendirilmeli ve hem tıbbi hem de psikolojik danışmanlık verilmelidir. Adölesanların menstrüel bozuklukları konusunda, sağlık personelinin eğitilmesi ve menorajinin ayırıcı tanısında koagülopatilerin düşünülmesi gerektiği bilincinin artırılması tanıda gecikmenin önlenmesine yardımcı olacaktır.

Etik

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CASE REPORT OLGU SUNUMU

A Novel PHEX Mutation in A Case Followed Up with A Diagnosis of X-linked Hypophosphatemic Rickets

X'e Bağlı Hipofosfatemik Raşitizm Tanısı ile Takip Edilen Bir Olguda Yeni Bir PHEX Mutasyonu

Özgecan Demirbaş* (0000-0002-6922-5203), Erdal Eren* (0000-0002-1684-1053), Yasemin Denkboy Öngen* (0000-0002-5657-4260), Şebnem Özemri Sağ (0000-0002-3948-8889), Hakan Gürkan*** (0000-0002-8967-6124), Şehime Gülsün Temel** (0000-0002-9802-0880)**

*Bursa Uludağ University University Faculty of Medicine, Department of Pediatric Endocrinology, Bursa, Turkey

**Bursa Uludağ University Faculty of Medicine, Department of Medical Genetics, Bursa, Turkey

***Trakya University Faculty of Medicine, Department of Medical Genetics, Edirne, Turkey

Abstract

Introduction: X-linked hypophosphatemic is a result of a mutation which leads to loss of function in the *phosphate-regulating endopeptidase homolog X-linked (PHEX)* gene. The case is here presented of a patient followed up for XLH rickets, with the formation of a stop code through frame-shifting mutation in the PHEX gene.

Case Report: An 18-month old male infant presented at our clinic with the complaint of curvature in the legs. In the physical examination of the infant, height was measured as 78 cm (-1.67 SDS) and weight was 12.5 kg (0.52 SDS). Deformity was present in the frontal protusion, the wrist widths and the legs. Laboratory test results were determined as phosphorus: 2.3 mg/dL (n=3.5-4.7), calcium: 9.8 mg/dL (n=8.5-10.5) , alkaline phosphatase (ALP) 707 IU/L (n=40-150), 25(OH) D vitamin:18 µg/L (n=18-40), PTH: 79 pg/mL (n=15-68), and tubular phosphorus reabsorption was low (71%). Visualisation on wrist radiographs of collapse in the metaphyseal sections of the radus and ulna and metaphyseal irregularity. Conventional treatment was started. Next generation sequence analysis of the proband revealed the presence of a hemizygous c.281_288delTTCCCGAA (p.lle94ArgfsTER14) frameshift variant in *PHEX* gene. This novel variant is pathogenic according to the ACMG criteria, and not reported in any database before. While full-fill clinical recovery was not achieved with conventional treatment and some complications occured, Burosumab treatment was started.

Conclusion: Here presented of a patient who was diagnosed with XLH, and was then determined with a novel mutation in the *PHEX* gene. The current treatment options directed at the basic pathology render genetic diagnosis more important in cases of hypophosphatemic rickets.

Keywords
Hypophosphatemic rickets, *PHEX* gene, X-linked

Anahtar kelimeler
Hipofosfatemik rikets, *PHEX* geni, X'e bağlı kalıtım

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Address for Correspondence/Yazışma Adresi: Özgecan Demirbaş MD, Bursa Uludağ University Faculty of Medicine, Department of Pediatric Endocrinology, Bursa, Turkey
Phone: +90 507 926 77 26
E-mail: o.dgny@hotmail.com

Öz

Giriş: X'e bağlı hipofosfatemik (XLH) rikets *fosfat düzenleyici endopeptidaz homolog X (PHEX)* geninde fonksiyon kaybına yol açan bir mutasyon sonucunda gelişmektedir. Burada, XLH tanısı ile izlenen ve PHEX geninde novel bir mutasyon saptanan olgu sunulmaktadır.

Olgu Sunumu: On sekiz aylık erkek bacaklarla eğrilik nedeniyle başvurdu. Fizik muayenesinde boyu 78 cm (-1,67 SDS) ve ağırlığı 12,5 kg (0,52 SDS) olarak ölçüldü. Frontal bölgede belirginleşme, bilekte genişleme ve bacaklarda o bind deformitesi mevcuttu. Laboratuvar incelemesinde fosfor: 2,3 mg/dL (n=3,5-4,7), kalsiyum: 9,8 mg/dL (n=8,5-10,5), alkalen fosfataz 707 IU/L (n=40-150)

idi. 25(OH) D vitamini: 18 µg/L (n=18-40), parathormonu 79 pg/mL (n=15-68) ve tübüler fosfor geri emilimi düşüktü (%71). Bilek grafisinde radius ve ulnanın metafiz bölümlerinde düzensizlik ve çanaklaşma vardı. Olguya hipofosfatemik rikets tanısı ile konvansiyonel tedavi başlandı. Yeni nesil dizi analizi ile *PHEX* geninde çerçeve kayması mutasyonuna yol açan hemizigot c.281_288delTTCCCGAA (p.lle94ArgfsTER14) varyantı tespit edildi. Bu yeni varyant, ACMG kriterlerine göre patojenik ve daha önce herhangi bir veri tabanında rapor edilmemiştir. Konvansiyonel tedavi ile tam klinik düzelme sağlanamayınca ve tedavi ile ilişkili komplikasyonlar oluşması üzerine olguya Burosumab tedavisi başlandı.

Sonuç: Burada *PHEX* geninde yeni bir mutasyon saptanan bir olgu sunulmuştur. Burosumab gibi temel patolojiye yönelik mevcut tedavi seçenekleri, hipofosfatemik raşitizm olgularında genetik tanıyı daha önemli hale getirmektedir.

Introduction

As XLH causes the loss of phosphorus from the kidneys, it is the most frequently seen form of rickets characterised by hypophosphatemia, with a frequency of 1/20,000. The disease forms as a result of mutation in the *PHEX* gene localised on XP22.1 (1). The *PHEX* gene encodes a protein named phosphate-regulating neutral endopeptidase (2). This protein suppresses serum levels of the phosphatonin, fibroblast growth factor 23 (FGF-23). Inactivating mutations in *PHEX* result in an upregulation of FGF-23 expression. Elevated levels of serum FGF-23 downregulates renal sodium-phosphate transporters and increase urinary phosphorus excretion. It also reduces the absorption of phosphorus from the intestine by restricting the synthesis of active vitamin D (3). While phosphate salts and active vitamin D metabolites have been used in treatment for many years, it is currently known that differentiation of XLH from other hypophosphatemic rickets types can change the treatment approach (4).

The case is here presented of a patient who presented at the rickets clinic, was diagnosed with XLH, and was then determined with a novel mutation in the *PHEX* gene.

Genomic DNA was isolated from peripheral blood nucleated cells. The amino acid coding regions of the relevant genes were amplified with the Osteo-GeneSGKit DensidadOsea-CE 57 Genes kit and sequenced in the Illumina MiSeQ system. The Genomized Database was used in the analysis of the data, and the IGV_2.3.6 program was used in the visual evaluation of the data.

Case Report

An 18-month old male infant presented at our clinic with the complaint of curvature in the legs. There had been no previous complaints in the patient history, and the curvature in the legs had been noticed as the infant started to walk. There was no parental consanguinity and the infant had been born at term as the first pregnancy. The mother was short in height, with curvature in the legs (Patient's pedigree is shown in Figure 1). In the physical examination of the infant, height was measured as 78 cm (-1.67 SDS) and weight was 12.5 kg (0.52 SDS). Deformity was present in the frontal protusion, the wrist widths and the legs. Laboratory test results were determined as phosphorus: 2.3 mg/dL (n=3.5-4.7), calcium: 9.8 mg/dL (n=8.5-10.5), alkaline phosphatase (ALP) 707 IU/L (n=40-150), 25(OH) D vitamin: 18 µg/L (n=18-40), PTH: 79 pg/mL (n=15-68) and tubular phosphorus reabsorption was low (71%). The diagnosis of hypophosphatemic rickets was made from the visualisation on wrist radiographs of collapse in the metaphyseal sections of the radius and ulna and metaphyseal irregularity.

Conventional treatment was started for the patient at the recommended doses of 30 mg/kg/day phosphate and 20 ng/kg/day calcitriol. In the 6th month of treatment, ALP and PTH levels returned to normal. In the second year of treatment, nephrocalcinosis developed. At the age of 5 years, the height of the patient was SDS -1.87 and rachitic findings continued, more evidently in the lower extremity bones. Next generation sequence analysis of the proband revealed the presence of a hemizygous c.281_288delTTCCCGAA

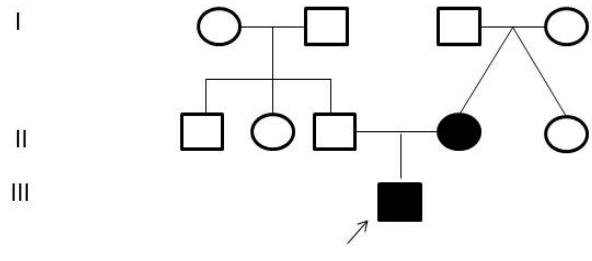

Figure 1. Pedigree of patient.

(p.Ile94ArgfsTER14) frameshift variant in *PHEX* gene (Figure 2). Sanger sequencing confirmed this variant in heterozygous manner in his mother demonstrating true hemizgosity. This novel variant is pathogenic according to the ACMG criteria and not reported in any database before. While full-fill clinical recovery was not achieved with conventional treatment and some complications occured, Burosumab was planned to use as a treatment option.

Discussion

The genetic basis of XLH disease is a mutation in the PHEX gene leading to function loss (1). Mutation result in increased synthesis and secretion of fibroblast growth factor 23 (FGF-23) (5). By leading to reduced gene expression of sodium-phosphate co-transporters (NaPi-IIa and NaPi-IIc) in the apical surface of proximal renal tubule cells, increased FGF-23 impairs proximal renal tubular re-absorption of phosphate (6). In addition, increased FGF-23 activates CYP24A1 enzyme by inhibiting CYP27B1 enzyme and decreases the level of 1.25-dihydroxyvitamin D (1.25(OH)2D), which is the active metabolite of vitamin D in the circulation (7).

Chronic hypophosphatemia leads to reduced bone mineral density and the weighting of clinical symptoms varies in each case. Patients most frequently present with the complaint of curvature in the legs, as in the current case. In growing children, the main skeletal findings are progressive bowing in the extremities, anteromedial torsion in the tibia and short height. These findings improve with medical treatment but the majority are not completely eliminated. The main finding of rickets on radiographs is metaphyseal irregularity. Typical laboratory findings are hypophosphatemia and low/normal 1.25 (OH)2D vitamin level. The serum alkaline phosphatase level increases and serum calcium and 25 OH D vitamin levels usually are normal (8). Conventional XLH treatment consists of phosphate salts and active vitamin D preparates (9). Higher treatment doses are associated with nefrocalsinozis and could improve bone deformities (10). In recent years, a treatment option has come to the fore which targets the main pathogenesis of XLH rickets. Excessive action of FGF-23 is causing XLH, therefore the inhibition of FGF-23 activities to be new candidate for treatment (11,12). Burosumab is a recombinant human IgG1 monoclonal

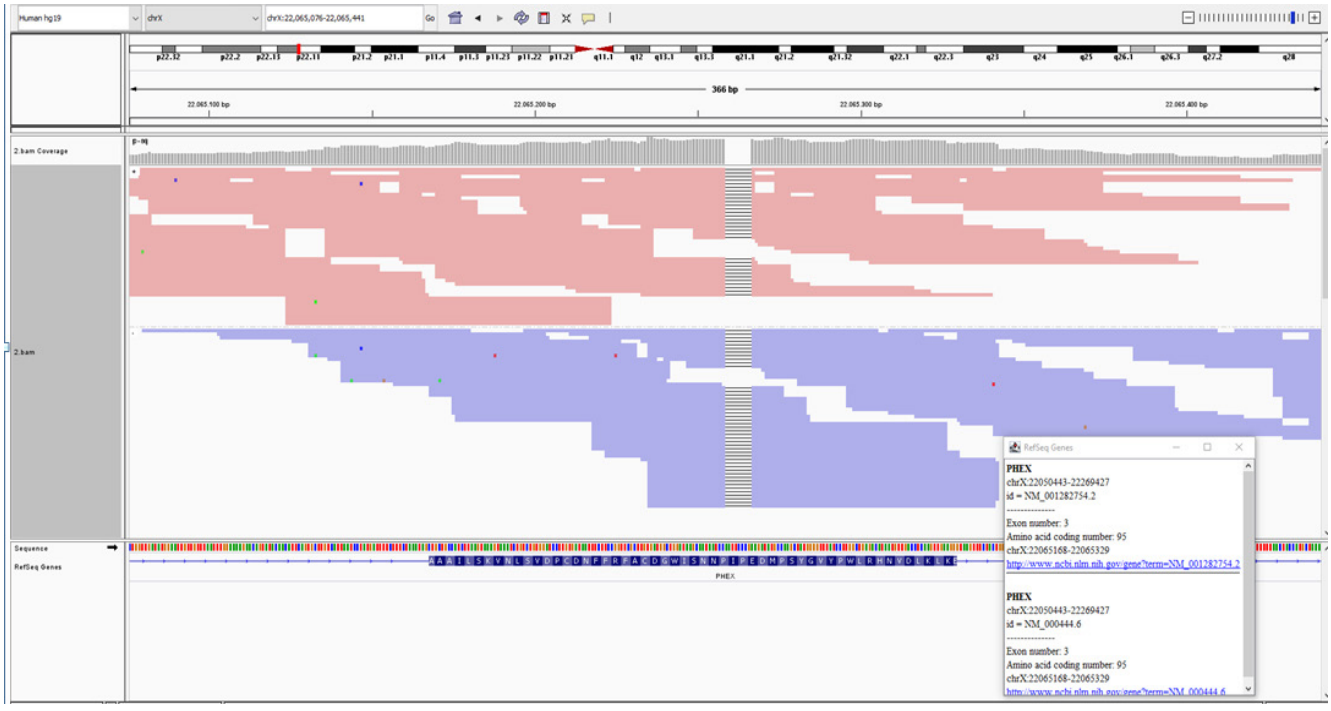

Figure 2. Integrative genomic view of c.281_288delTTCCCGAA (p.Ile94ArgfsTER14) hemizygous change in *PHEX* gene in exon 3.

antibody that inhibits FGF-23 activity. In phase 1 and phase 2 studies including adults diagnosed with XLH, treatment with Burosumab has been shown to correct phosphate re-absorption and thus normal levels of serum phosphorus and 1.25 $(OH)_2D$ are recovered (13). In a phase 2 study of children, Burosumab was shown to improve phosphorus metabolism and reduce the severity of rickets (4,14).

Burosumab treatment is superior to conventional management of the condition in both adults and children and has been transformative for the treatment of XLH (15). The current treatment options directed at the basic pathology render genetic diagnosis more important in cases of hypophosphatemic rickets. The case has been presented here of a patient determined with a novel mutation in the PHEX gene.

Ethics

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

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

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CASE REPORT OLGU SUNUMU

An Adolescent Girl with the Recurrent Attacks of Different Type of Thromboses

Farklı Tiplerde ve Tekrarlayıcı Trombozları Olan Adölesan Kız

Şenay Zırhlı Selçuk* (0000-0002-7886-2984), Yurday Öncül (0000-0003-2701-7980), Hanım Durmuş*** (0000-0003-1607-8040), Betül Sözeri**** (0000-0002-5079-5644), Yılmaz Tabel* (0000-0001-7359-4944)**

*İnönü University Faculty of Medicine, Department of Pediatric Nephrology, Malatya, Turkey
**İnönü University Faculty of Medicine, Department of Pediatric Hematology, Malatya, Turkey
***İnönü University Faculty of Medicine, Department of Pediatrics, Malatya, Turkey
****University of Health Science Turkey, Ümraniye Training and Research Hospital, Clinic of Pediatric Rheumatology, İstanbul, Turkey

Abstract

Introduction: Thrombosis is less common in childhood compared to adults and is usually acquired. Here, we present a patient who had recurrent thrombosis in different organs and was diagnosed with lupus secondary antiphospholipid syndrome (APS) when the lupus anticoagulant test was positive in the follow-up, which we treated quickly and effectively considering possible catastrophic prognosis due to kidney involvement in the same week.
Case Report: Fifteen-year-old girl who presented to the emergency department with complaints of sensitivity, pain, and swelling in her left leg. Her medical history revealed recurrent thrombosis attacks and development of mental retardation after a seizure at around the age of three, and no underlying disease had been identified to date. Her family history revealed that her aunt had complained of hand swelling after cold exposure. No significant finding was detected in her thrombophilia panel. A thrombophilia panel was conducted, but no significant findings were detected. Due to a positive lupus anticoagulant test, the patient was diagnosed with APS. The diagnosis of systemic lupus erythematosus was also considered secondary to APS after positive results for anti-nuclear antibody (ANA) and dsDNA tests. Due to the recurrent thrombosis attacks and kidney involvement, a possible catastrophic outcome was considered. In addition to the on going heparin, warfarin, and aspirin therapy, high-dose steroids, cyclophosphamide, intravenous immunoglobulin, and 5 sessions of plasmapheresis were administered, and all treatments were met with a positive response.
Conclusion: In this case presentation, we wanted to emphasize that despite the difficulties in the differential diagnosis of thrombosis in children and especially the diagnosis of catastrophic antiphospholipid syndrome (CAPS), prompt and effective treatment can be life-saving.

Keywords
Antiphospholipid antibodies, antiphospholipid syndrome, catastrophic antiphospholipid syndrome, child, thrombosis

Anahtar kelimeler
Antifosfolipid antikor, antifosfolipid sendrom, katastrofik antifosfolipit sendrom, çocuk, tromboz

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Address for Correspondence/Yazışma Adresi: Şenay Zırhlı Selçuk MD, İnönü University Faculty of Medicine, Department of Pediatric Nephrology, Malatya, Turkey
Phone: +90 422 341 06 60 (5311)
E-mail: senaydr@yahoo.com

Öz

Giriş: Tromboz çocukluk döneminde erişkine kıyasla daha nadir görülmekte olup genellikle edinsel nedenlidir. Burada farklı organlarda tekrarlayan tromboza sahip ve aynı hafta içinde böbrek tutulumunun da olması nedeniyle olası katastrofik gidiş düşünerek hızlı ve etkin bir şekilde tedavi ettiğimiz, izleminde de lupus antikoagülan testi pozitif saptanarak lupusa sekonder antifosfolipit sendromu (APS) tanısı alan hastamızı sunuyoruz.
Olgu Sunumu: On beş yaşında kız hasta acil servise sol bacakta hassasiyet, ağrı ve şişlik yakınmalarıyla başvurdu. Öyküsünden tekrarlayan tromboz atakları ve yaklaşık üç yaşlarında geçirilen konvülziyon sonrası mental retardasyon geliştiği

ve günümüze kadar etiyolojiye yönelik herhangi bir hastalık tespit edilmediği öğrenildi. Soygeçmişinde halasında soğukla temas sonrası ellerde morarma şikayeti haricinde başka özellik yoktu. Trombofili panelinde anlamlı bulgu saptanmadı. Lupus antikoagülan test pozitifliği olması nedeniyle APS tanısı alan hastada anti nükleer antikor (ANA) ve dsDNA testleri pozitif saptanarak sistemik lupus eritamatozus tanısına sekonder APS düşünüldü. Hastanın tekrarlayan tromboz ataklarının olması ve böbrek tutulumunun da tespit edilmesi nedeniyle olası katastrofik gidiş düşünüldü. Başlanmış olan heparin, warfarin ve aspirin tedavisine ek olarak yüksek doz steroid, siklofosfamid, intravenöz immünoglobulin ve 5 seans plazmaferez uygulandı ve tüm bu tedavilere olumlu yanıt alındı. **Sonuç:** Bu olgu sunumumuzda çocuklarda trombozun ayırıcı tanı ve özellikle katastrofik antifosfolipid sendrom (CAPS) tanısındaki zorluklara rağmen, zaman kaybetmeden etkin bir tedavinin hayat kurtarıcı olduğunu vurgulamak istedik.

Introduction

Thrombosis is a rare condition in childhood compared to adults, and changes in blood flow, vessel wall and blood levels of coagulation factors play a role in its formation (1,2). It has been shown that acquired factors cause thrombosis more frequently than inherited factors in childhood thrombosis (3). Although antiphospholipid syndrome (APS) is rare in childhood and adolescence, it is one of the main acquired causes of symptomatic thromboembolism in the pediatric population (4). Catastrophic antiphospholipid syndrome (CAPS) is a disease that causes rapid development of thrombosis in various organs, leading to dysfunction and failure in the presence of antiphospholipid antibodies (aPL) (5). CAPS is a life-threatening condition that needs to be treated early (6). Anticoagulation, antiplatelet agents, corticosteroids, intravenous immunoglobulins (IVIG) and plasmapheresis are treatments with proven efficacy in CAPS (7). We present our patient, who was diagnosed with a possible CAPS, whose treatment was started quickly and effectively, and thrombosis was taken under control with plasmapheresis.

Case Presentation

Fifteen-year-old girl initially presented to the emergency department with complaints of tenderness, pain and swelling in the left leg. The patient with mental retardation had discomfort and fever for the last few days. She had pain in her left leg and had no history of trauma. On physical examination, there was redness, tenderness, limitation of movement in the left thigh, and edema of the leg. Her fever was 37.8 °C, heart rate was 96/min, and blood pressure was 126/78 mmHg. In her past history, it was learned that she had convulsions at the age of three, and then the patient regressed mentally. No cranial radiological imaging was performed at that time. All neurometabolic tests were performed in this application for mental retardation in the patient and were found negative. The patient, who had no convulsions for ten years, was not using anticonvulsive drugs. In the family history, there were no other features except for her aunt; who experienced cyanosis in her hands after contact with the cold. The patient had no history of COVID-19 contact and COVID-19 PCR was negative. In laboratory examinations of the patient, the platelet value was 114,000/mm^3 and the erythrocyte sedimentation rate was 44 mm/hour. Of the coagulation tests, prothrombin time and activated partial thromboplastin time were found to be mildly elevated. In the thrombophilia panel; protein C 42 (55-111) and protein S 39.6 (52-92) levels were low, and antithrombin level 98.2 (79.4-112) was normal. The low levels of protein C and S detected in our patient were probably due to consumption during the acute thrombosis period and control examination was planned during the remission period of the disease. No mutation of factor V-Leiden and Prothrombin G20210A was detected. Homocysteine level, lipoprotein (a) level, factor VIII, IX, X, XI activities was normal. In the examinations made during this period MTHFR C677T heterozygous and MTHFR A1298C heterozygous mutations were detected. There was no evidence of hemolysis in the peripheral smear of our patient. Direct Coombs test was negative and reticulocyte count, LDH and haptoglobulin were normal. Kidney ultrasonography was normal. Low molecular weight heparin (100 IU/kg/dose) treatment was started for the patient who was hospitalized. Warfarin (0.1 mg/kg) treatment was started in the follow-up of this treatment. The patient, whose deep vein thrombosis improved in the follow-up, was admitted to our hospital again in the second week due to cyanosis, pallor and coldness on the fingertips of both hands while under antithrombotic treatment. On examination, the patient's general condition was good and vital signs were normal. The capillary filling time was very prolonged on the fingertips of both hands, the

skin was cold, and there was cyanosis, especially on the distal phalanges of the 4th fingers (Figure 1). Pulses were detected in both upper and lower extremities, and the flows were normal in the upper extremity Doppler examination. Having a family history of Raynaud's phenomenon, mental retardation and previous seizures [lupus with possible central nervous system (CNS) involvemen], mild hematuria and proteinuria (lupus with possible kidney involvement) in our patient suggested the diagnosis of antiphospholipid antibody syndrome (APS). When hematuria and proteinuria were detected, Doppler US performed to the patient revealed no pathology in the renal arteries and veins. To confirm the diagnosis of APS, lupus anticoagulant and anti cardiolipin antibodies tests were performed (about 12. week) and found positive. All laboratory tests performed on the patient are given in Table 1.

In our patient, a probable diagnosis of CAPS was considered because of the presence of aPL, the development of clinical findings within one week, venous thrombosis in the leg, arterial thrombosis in the fingertips of both hands and kidney involvement (8). In addition to antithrombotic and hydroxychloroquine treatments, two doses of IVIG 1 g/kg, three doses of pulse methyl prednisolone every other day, and one dose of pulse cyclophosphamide (750 mg/m^2) were administered, and the thrombosis in the fingertips improved. However, despite all these treatments, a very dramatic response was obtained with five sessions of plasmapheresis treatment applied to the patient due to the recurrence of her findings in the follow-up (Figure 2).

Figure 1. Cyanosis seen especially in the 4th distal phalanx.

Table 1. Blood and urine analysis values of patient

	Value (reference)
Blood	
Hb (g/dL)	10.7 (13.6-17.2)
Htc (%)	33.5 (38-44.1)
White blood cell count (mm^3)	9.8 (4.3-10.3)
Platelet count (mm^3)	114 (156-373)
Erythrocyte sedimentation rate (mm/h)	44 (1-20)
Blood urea nitrogen (mg/dL)	17 (5.1-16.8)
Creatinine (mg/dL)	0.5 (0.57-1.25)
C3 (mg/dL)	111 (83-193)
C4 (mg/dL)	13 (15-57)
Cardiolipin IgM (MPL U/m)-basaline and 12. week	18.3-18.4 (0-18)
Cardiolipin IgG (GPLU/mL)-basaline and 12. week	6.7-<3 (0-18)
Antinuclear antibody	2.6 (0-1.2)
Antibody to ds-DNA	127 (0-20)
Anti-beta 2 glycoprotein 1 IGM	2.3 (>18 Positive)
Anti-beta 2 glycoprotein 1 IGG	5.4 (>18 Positive)
Lupus anticoagulant-basaline and 12. week	1.91-2.14 (0-1.2)
Lupus anticoagulant confirmatory test-basaline and 12. week	55.3-41.0 (30-38)
Prothrombin time-	12.6 (10-14)
Prothrombin time-International normalized ratio (PTZ-INR)	1.1 (0.8-1.2)
Activated partial thromboplastin time (APTT)	35.4 (23-35)
Protein C (%)	42 (55-111)
Protein S (%)	39.6 (52-92)
Antithrombin-%	98.2 (79.4-112)
Fibrinogen (mg/dL)	204.53 (150-350)
D-Dimer (mg/dL)	0.37 (0-0.55)
Dipstick urine analysis	
Specific gravity	1.015
pH	6
Blood	+2
Protein	+1
Protein/creatinine (mg/mg)	1

Discussion

In this case report, we are highlighting that thrombotic diseases, which occur less frequently in children than in adults, can be severe and potentially fatal. They also mention that different mechanisms are involved in the development of venous and arterial thrombosis, with factors such as endothelial damage and platelet function being more important in the case of arterial thrombosis, while stasis and disorders in the coagulation-fibrinolytic system are more relevant in venous thrombosis (1,2). Our patient experienced both venous and arterial thrombosis at separate occasions.

It has been shown that acquired factors cause thrombosis more frequently than inherited factors in childhood thrombosis (3). The most common cause of thrombophilia among genetic disorders is the Factor V Leiden mutation (8). Factor V Leiden mutation was not detected in our patient. The prothrombin gene mutation is the second most common genetic change, and this mutation was not detected in our patient (9). In our patient, protein C and S levels were low. Considering that these values may be low at the time of acute thrombosis and during heparin and warfarin treatment, it is planned to repeat these tests at the end of the treatment and/or when the patient is in complete remission.

The patient without a family history of thrombosis was assessed for the presence of APS common cause of acquired thrombophilia, and APS was also considered because the lupus anticoagulant test and antiphospholipid antibodies were positive. Childhood APS is a rare, acquired multisystem autoimmune condition with venous and arterial thromboembolic events (10). It may occur secondary to an autoimmune disease such as systemic lupus erythematosus (SLE) or as a primary clinical syndrome. Although APS is rare in childhood and adolescence, it is one of the main acquired causes of symptomatic thromboembolism in the pediatric population (4). Our patient's ANA and dsDNA test results were positive and had borderline CNS and kidney involvement, it was considered to be APS secondary to SLE. At the same time, convulsion at the age of 3 years old was evaluated as CNS involvement of lupus. Thrombosis is a well-known clinical entity in SLE, and it is multifactorial. The most important risk factor is the presence of APL antibody. However, approximately 40% of adults with SLE who are negative for APL antibody are diagnosed with thrombosis, indicating the importance of other risk factors such as inflammation and disease activity (11).

Figure 2. Post-treatment image.

For the clinical and laboratory diagnosis of APS, one or more anti-phospholipid antibodies [lupus anticoagulant (LA), anti-cardiolipin (aCL) IgG/IgM, anti-ß2 glycoprotein I (anti-ß2 GPI) IgG/IgM] should be positive twice with an interval of at least 12 weeks at medium or high titer (12). aPL and LA values of our patient were planned to be checked after 12 weeks and acute treatment was started.

In European pediatric APS registries, the rate of venous thrombosis is 60%, arterial thrombosis is 30%, mostly in small vessels, and both arterial and vein involvement is reported at an even lower rate (13). Arterial involvement was observed in our patient after venous involvement. Hematological findings are seen in 30-50% of non-thrombotic involvements in APS. Among these, there are conditions such as Evans syndrome, autoimmune hemolytic anemia, and immune thrombocytopenia. Livedo reticularis and Raynaud's phenomenon may also occur (13). Our patient had only the findings of Raynaud's phenomenon among these findings.

CAPS is a disease that causes rapid development of thrombosis in various organs, leading to dysfunction and failure in the presence of aPL (5). CAPS is a rare condition seen in 1% of patients with APS (7). Classification criteria for CAPS were established in 2002 and validated in 2005 (5,14). However, these

criteria were created for classification, not diagnosis. CAPS criteria; it is defined as clinical involvement of at least three organ systems and/or tissues with histopathological evidence of small vessel occlusion and laboratory confirmation of the presence of aPL antibody (11). According to the updated Sapporo criteria, at least one clinical and one laboratory criteria are required for the definitive diagnosis of APS (15). In our patient, a possible diagnosis of CAPS was considered because of the presence of aPL antibodies, the development of clinical findings within one week, venous thrombosis in the leg, arterial thrombosis in the fingertips of both hands and kidney involvement. Hematuria and proteinuria were evaluated as renal involvement even though the Doppler was normal and biopsy could not be performed. Anticoagulation, antiplatelet agents, corticosteroids, IVIG and plasmapheresis are treatments with proven efficacy in CAPS (7). It is stated in the literature that rituximab can be used in patients who do not respond to all of these treatments.

In conclusion, we present a possible CAPS case who received high-dose steroids, cyclophosphamide, IVIG and five sessions of plasmapheresis in addition to heparin, warfarin and aspirin treatment and received a positive response from these treatments. It is aimed to emphasize that tombophilia tests in the acute phase of the disease may be misleading in children with recurrent thrombosis and there may be more serious underlying acquired conditions.

Ethics

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

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