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Güncel Pediatri

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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

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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.

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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).

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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.

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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.

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

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

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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.

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MANUSCRİPT ORGANİZATİON

A. Title Page

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

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- 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.

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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

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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.

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

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research on animals,

Retrospective studies by the personal data protection law,

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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.

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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.

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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.

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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.

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İçindekiler / *Contents*

Özgün Araştırmalar / Original Articles

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İçindekiler / *Contents*

ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Does Vitamin B12 Deficiency in Childhood Affect Hematological Parameters?

Çocukluk Çağında Görülen Vitamin B12 Eksikliğinin Hematolojik Parametrelere Etkisi Var mı?

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Abstract

Introduction: Vitamin B12 deficiency causes permanent neurological complications that can be resolved with early treatment. Studies have shown that changes in hematological parameters observed in the early period may contribute to early diagnosis.

Materials and Methods: A retrospective evaluation was made of the hematological parameters (hemoglobin, hematocrit, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, erythrocyte count, mean erythrocyte volume, erythrocyte distribution width, leukocyte count, platelet count and mean platelet volume) of 74 patients with vitamin B12 deficiency and 74 healthy controls with normal vitamin B12 levels, who presented to the pediatric neurology clinic with various complaints. Patients aged 0-18 years with normal ferritin and folic acid levels, with no infections or chronic disease were included. The patients with low vitamin level were divided into subgroups: Group 1 (<150 pg/mL), group 2 (150-200 pg/mL) and group 3 (200-250 pg/mL). The control group was assigned as group 4 (>250 pg/mL).

Results: The vitamin B12 deficient group and the control group were similar in terms of sex and age. Vitamin levels were significantly different between the groups, while the hemogram parameters did not differ significantly. Group 1 included 16.21%, group 2 included 54.05% and group 3 included 29.72% of the patients. The subgroups were similar in terms of sex and age, and hemogram parameters did not differ significantly.

Conclusion: Changes in hemogram parameters may not be observed even at very low vitamin B12 levels, so vitamin levels should be checked in patients with clinical findings and a history suggestive of deficiency.

Keywords
Vitamin B12 deficiency, effect, pediatric, hematological parameters

Anahtar kelimeler
Vitamin B12 eksikliği, etki, pediatrik, hematolojik parametreler

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Öz

Giriş: Vitamin B12 eksikliğinde, erken tedavi ile önlenebilen, kalıcı nörolojik komplikasyonlar görülebilir. Çalışmalar, erken dönemde gözlenen hematolojik parametre değişikliklerinin, erken tanıya katkı sağlayabileceğini göstermiştir.

Gereç ve Yöntem: Vitamin B12 eksikliği saptanan 74 hasta ile çocuk nörolojisi polikliniğine farklı yakınma ile başvuran, vitamin B12 düzeyi normal olan, sağlıklı 74 kontrol hastasının hematolojik parametreleri (hemoglobin, hematokrit, ortalama eritrosit hemoglobini, ortalama eritrosit hemoglobin konsantrasyonu, eritrosit sayısı, ortalama eritrosit hacmi, eritrosit dağılım genişliği, lökosit sayısı, trombosit sayısı, ortalama trombosit hacmi) retrospektif olarak değerlendirildi. Ferritin ve folik asit düzeyi normal olan, enfeksiyon ve kronik bir hastalığı olmayan, 0-18 yaş aralığında olan hastalar çalışmaya alındı. Vitamin B12 düzeyi düşük olan hasta grubu üç sınıfa ayrıldı: Grup 1 (<150 pg/mL), grup 2 (150-200 pg/mL), grup 3 (200-250 pg/mL); grup 4 (>250 pg/mL) kontrol grubu olarak belirlendi.

Bulgular: B12 vitamini eksikliği olan grup ile kontrol grubu cinsiyet ve yaş özellikleri açısından benzerdi. Gruplar arasında vitamin düzeyleri anlamlı farklılık gösterirken, hemogram parametreleri anlamlı farklılık göstermedi. Hastaların %16,21'ini grup 1, %54,05'ini grup 2 ve %29,72'sini grup 3 oluşturdu. Alt gruplar cinsiyet ve yaş açısından benzerdi ve hemogram parametreleri anlamlı farklılık göstermedi.

Sonuç: Hemogram parametrelerindeki değişiklikler, çok düşük vitamin B12 düzeylerinde dahi görülmeyebilir, bu nedenle klinik bulgusu olan ve öyküsü vitamin B12 eksikliğini düşündüren hastalarda mutlaka vitamin B12 düzeyi bakılmalıdır.

Introduction

Vitamin B12 deficiency is a global problem that is common in all age groups. Vitamin B12 participates in DNA synthesis and plays a role in cell division and proliferation, and deficiencies can lead to serious neurological and hematological signs and symptoms (1,2). Hematological abnormalities accompanying vitamin B12 deficiency vary, and may not correlate strongly with vitamin B12 levels until late periods of the disease. Hemogram parameters are not always sufficient to predict vitamin B12 deficiency (2,3).

There is a scarcity of literature on hemogram parameters in vitamin B12 deficiency, although some studies have shown that changes in hematological parameters may be observed in the early period and may contribute to early diagnosis (3-6). In the present study, we evaluated the relationship between the severity of vitamin B12 deficiency and hematological parameters and assessed the value of hemogram parameters for detecting vitamin B12 deficiency.

Materials and Methods

Following the granting of approval by the Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (approval number: 20/317, date: 05.11.2021), this retrospective study was launched with 74 patients with vitamin B12 deficiency and 74 age- and sex-matched healthy controls with normal vitamin B12 levels who presented to the Pediatric Neurology Outpatient Clinic of the Süleyman Demirel University Faculty of Medicine between January 2019 and January 2021, with various complaints. Included in the study were patients who were 0-18 years of age with normal ferritin and folic acid levels, and with no infections, chronic disease, or history of chronic drug use. Patients with ferritin and folic acid levels outside the normal range, or with any infections or chronic diseases that may affect hematological parameters, and those with a history of chronic drug use were excluded from the study. The patients' age, sex, symptoms on admission, vitamin B12 levels and the following hematological parameters were retrieved from the patient's records: hemoglobin (Hb), hematocrit (HTC), mean erythrocyte hemoglobin (MCH), mean erythrocyte hemoglobin concentration (MCHC), erythrocyte count (RBC), mean erythrocyte volume (MCV), erythrocyte distribution width (RDW), leukocyte count (WBC), platelet count (PLT) and mean platelet volume (MPV). A cut-off point of <250 pg/L was used to identify vitamin B12 deficiency. Anemia was defined as an Hb level of <11.5 g/dL, thrombocytopenia as a PLT of <150,000/mm^3 and leucopenia as a white blood cell count of <1500/mm^3. Patients with low vitamin B12 levels were divided into three subgroups as: Group 1 (<150 pg/mL), group 2 (150-200 pg/mL) and group 3 (200-250 pg/mL), while the control group was assigned to group 4 (>250 pg/mL).

Statistical Analysis

All statistical analyses for this study were performed using IBM SPSS Statistics (version 20.0. Armonk, NY: IBM Corp.). Descriptive measurements were presented as mean ± standard deviation (median; minimum-maximum) and frequency (percentage). The normality of continuous numerical data was analyzed with a Kolmogorov-Smirnov test, the results of which revealed a non-normal distribution ($p<0.05$), and thus, non-parametric tests were preferred for group comparisons. A One-Way Analysis of Variance was used for the comparison of the vitamin B12 groups, and a chi-square analysis was used to compare categorical data. For a type 1 error rate of 5%, a p-value of <0.05 was considered statistically significant.

Results

The study sample included 74 patients and 74 healthy controls, totaling 148 participants, in the 0-18 years of age group. The vitamin B12 deficient group and the control group had the same sex ratio

and a similar mean age. In both groups, 73% of the participants were female and the remainder were male. The mean age was 10.79±6.11 years in the vitamin B12 deficiency group and 10.93±5.92 years in the control group.

The mean vitamin B12 level was 181.95±36.90 pg/mL in the patient group and 275.13±21.46 pg/mL in the control group, indicating a significant difference (p<0.001), while hemogram parameters (Hb, HTC, RBC, MCH, MCHC, MCV, RDW, WBC, PLT and MPV) did not differ significantly (Table 1).

The group of patients with low vitamin B12 levels was divided into three subgroups, as group 1 with 12 patients (16.21%), group 2 with 40 patients (54.05%) and group 3 with 22 patients (29.72%), with corresponding vitamin B12 levels of <150 pg/mL, 150-200 pg/mL and 200-250 pg/mL, respectively. The control group was assigned to group 4 (>250 pg/mL). A comparison of the groups revealed no significant difference in the sex ratio (p=0.958), and there was also no significant difference in the mean ages of the groups (p=0.487). A comparison of the vitamin B12 levels of the groups revealed a significant difference (p<0.001). The hemogram parameters of the groups did not differ significantly according to vitamin B12 levels, and there was no significant correlation between the hemogram parameters and vitamin B12 levels (Table 2).

The evaluation of the vitamin B12 subgroups also revealed no significant difference in the Hb values, or leukocyte and PLTs (Table 3).

Among the most common symptoms of vitamin B12 deficient patients who applied to the pediatric neurology outpatient clinic were fatigue (14.9%), paresthesia (13.5%), headache (13.5%), dizziness (12.2%), breath-holding spells (8.1%) and personality changes (6.8%) (Table 4).

A statistically significant difference was determined in clinical findings according to the age. The age of the patients with hypotonia, breath-holding spells, and developmental delay was significantly lower than the age of the patients with other neurological symptoms (p<0.001) (Table 4).

We compared the neurological findings in terms of hematological parameters. The hemogram parameters did not vary significantly among the patients with different clinical findings (p=0.540), and there was no significant difference in the sex distribution of the patients (p=0.257).

Table 1. Characteristics and hematologic parameters of the study groups

	B12 deficient group (B12 <250) (n=74)	Control group (B12 >250) (n=74)	p
Female (n, %)	54 (73.0)	54 (73.0)	
Male (n, %)	20 (27.0)	20 (27.0)	
Age	10.79±6.11 (12; 1-18)	10.93±5.92 (13; 1-18)	0.892
Vit B12 (pg/mL)	181.95±36.90	275.13±21.46	<0.001*
Hb (g/dL)	13.48±1.42	13.52±1.64	0.869
HTC (%)	39.58±3.81	39.95±6.17	0.665
RBC/(mm^3)	4.88±0.36	4.91±0.39	0.627
MCV (fl)	79.83±11.40	80.96±6.39	0.572
MCH (pg)	27.64±2.61	27.55±2.67	0.842
MCHC (g/dL)	33.80±2.39	38.29±6.05	0.287
RDW (%)	13.93±1.43	14.04±1.60	0.662
WBC/(mm^3)	7787±2580	7954±1939	0.658
PLT/(mm^3)	307,283±107,105	297,635±71,798	0.521
MPV (fl)	8.22±0.95	8.24±0.83	0.920

*: Significant at the 0.05 level according to the Mann-Whitney U test. Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, HTC: Hematocrit, RBC: Erythrocyte count, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Erythrocyte distribution width, MPV: Mean platelet volume

Table 2. Distribution of patients according to the vitamin B12 levels and hematological values					
	Vitamin B12 subgroups				
	B12 <150 (n=12)	B12:150-200 (n=40)	B12:200-250 (n=22)	B12 >250 (control) (n=74)	p
Female (n,%)	8 (66.7)	31 (77.5)	15 (68.2)	54 (73.0)	0.958
Male (n,%)	4 (33.3)	9 (22.5)	7 (31.8)	20 (27.0)	
Age (year)	12.16±6.08 (15; 1-18)	9.80±6.21 (13; 1-18)	11.86±5.89 (14; 1-18)	10.93±5.92 (13; 1-18)	0.487
Vit B12 (pg/mL)	122.63±27.11	177.86±14.85	221.75±15.38	275.13±21.46	<0.001*
Hb (g/dL)	13.47±1.46	13.20±1.40	13.99±1.36	13.52±1.64	0.308
HTC (%)	39.15±3.72	38.96±3.70	40.96±3.86	39.95±6.17	0.295
RBC/(mm³)	4.78±0.43	4.87±0.35	4.94±0.35	4.91±0.39	0.626
MCV (fl)	82.32±8.68	78.77±11.62	80.14±13.08	80.96±6.39	0.171
MCH (pg)	28.27±3.34	27.06±2.65	28.35±1.87	27.55±2.67	0.074
MCHC (g/dL)	34.38±0.80	33.86±0.95	33.40±4.17	38.29±6.05	0.244
RDW (%)	14.19±1.84	14.00±1.48	13.67±1.07	14.04±1.60	0.877
WBC/(mm³)	7,908±2,303	7,865±2,835	7,581±2,315	7,954±1,939	0.674
PLT/(mm³)	317,833±78,775	324,225±124,525	270,727±76,281	297,635±71,798	0.137
MPV (fl)	8.05±0.94	8.14±0.87	8.47±1.08	8.24±0.83	0.714

*: Significant at the 0.05 level according to the Kruskal-Wallis test. Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, HTC: Hematocrit, RBC: Erythrocyte count, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Erythrocyte distribution width, MPV: Mean platelet volume

Table 3. Distribution of hematological parameters according to the vitamin B12 level subgroups						
		Vitamin B12 subgroups				
		<150 (n=12)	150-200 (n=40)	200-250 (n=22)	>250 (n=74)	p
Sex, n (%)	Female	8 (66.7)	31 (77.5)	15 (68.2)	54 (73.0)	0.958
	Male	4 (33.3)	9 (22.5)	7 (31.8)	20 (27.0)	
Hb (g/dL)	<11.5	1 (11.1%)	6 (66.7%)	2 (22.2%)	11 (14.9%)	0.705
	>11.5	11 (16.9%)	34 (52.3%)	20 (30.8%)	63 (85.1%)	
WBC/(mm³)	<4,500	0	1 (33.3%)	2 (66.7%)	1 (1.4%)	0.896
	>4,500	12 (16.9%)	39 (54.9%)	20 (28.2%)	73 (98.6%)	
PLT/(mm³)	<150,000	0	1 (50.0%)	1 (50.0%)	1 (1.4%)	0.910
	>150,000	12 (16.7%)	39 (54.2%)	21 (29.2%)	73 (98.6%)	

Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet

Discussion

Patients with vitamin B12 deficiency present with hematological findings that vary from anemia to pancytopenia. In cases of vitamin B12 deficiency, pancytopenia is caused by ineffective erythropoiesis, leukopoiesis and thrombopoiesis associated with programmed cell death in the absence of vitamin B12, and the reduced survival of precursors in peripheral blood that may occur in the later phases of the disease (7). Literature contains a few studies examining the frequency of hematological findings associated with vitamin B12 deficiency in children. A previous study reported 22.7% of patients with vitamin B12 deficiency had anemia, while none of the children had leukopenia or thrombocytopenia (8). Another study reported no significant difference in anemia or complete blood count parameters between cases with and without vitamin B12 deficiency (9). Emen et al. (10), on

Table 4. Clinical features of patients with vitamin B12 deficiency			
Clinical findings	n (%)	Age (mean ± SD)	p
Fatigue	11 (14.9)	10.27±5.69	
Headache	10 (13.5)	12.7±4.37	
Paresthesia	10 (13.5)	14.9±1.2	
Dizziness	9 (12.2)	14.78±2.44	
Breath-holding spells	6 (8.1)	1	
Personality changes	5 (6.8)	5.4±6.11	
Developmental delay	4 (5.4)	2.5±3	<0.001
Memory impairment	4 (5.4)	16.5±2.38	
Tremor	4 (5.4)	16.25±1.5	
Hypotonia	3 (4.1)	1	
Syncope	3 (4.1)	14.67±1.15	
Vision blurring	2 (2.7)	12	
Difficulty in concentration	1 (1.4)	6	
Muscle weakness	1 (1.4)	15	
Poor school performance	1 (1.4)	11	
SD: Standard deviation			

the other hand, reported no statistically significant association between vitamin B12 levels and complete blood count parameters, excluding PLTs. In the present study, anemia was detected in nine (12.1%), leucopenia in three (4.05%) and thrombocytopenia in two (2.7%) of the patients with vitamin B12 deficiency, while in the control group, eleven (14.9%) had anemia, one (1.4%) had leukopenia and one (1.4%) had thrombocytopenia. There was no statistically significant difference between the two groups in this regard. Although macrocytic anemia is expected in cases of vitamin B12 deficiency, the mean MCVs were 79.83 fl and 80.96 fl in the deficiency and control groups, respectively, with no statistically significant difference between them. A study of 1,100 individuals evaluating the correlation between vitamin B12 and MCV could establish no correlation, identifying a high MCV value in only 14.59% of patients, and concluded that MCV should not be the only criterion for diagnosis of vitamin B12 deficiency (11). An MCV value within the reference range may be misleading if used as a screening parameter.

There have been studies suggesting that MPV and RDW deterioration starts in the early period of vitamin B12 deficiency, prior to the development of cytopenia, leading the authors to question the usability of these parameters in early diagnosis. Aktas et al. (3) reported no significant difference in the Hb and HTC levels of cases with vitamin B12 below and above 250 pg/mL, but identified a significantly higher RDW in patients with vitamin B12 deficiency, concurring with the studies by Pongstaporn and Bhatia, which also reported an elevated RDW in cases of vitamin B12 deficiency (5,6). A study involving an adult age group reported higher MPV and RDW values in patients with vitamin B12 deficiency than in the control group, which suggested these parameters could be used as indicators during the early periods (4).

That finding, however, contrasts with the findings of the present study, in which vitamin B12 levels were significantly different between the vitamin B12 deficient and control groups, while the hemogram parameters did not differ significantly. In another study, involving 640 pediatric patients, no relationship could be identified between vitamin levels and complete blood count parameters in vitamin B12-deficient cases (12). In a study by Colak et al. (9). comparing the hemogram parameters of patients with normal vitamin B12 levels and those of patients with deficiency, it was established that hemogram parameters were not predictive, and vitamin B12 deficiency may not always be reflected in hemogram parameters.

Hematological findings may not always correlate with vitamin B12 levels, and thus vitamin B12 deficiency should not be dismissed purely based on a normal blood count. The findings of the present study are consistent with those of most studies.

Neurological symptoms can be observed in vitamin B12 deficiency such as hypotonia, dizziness, ataxia, tremor, paresthesia, fatigue, developmental delay/ regretion; neuropsychiatric abnormalities including mood changes, attention deficit, memory impairment, and behavioral abnormalities (13,14).

In a study, where 38 pediatric patients with vitamin B12 deficiency were evaluated, mean serum B12 level was found to be 137.18 (40-196) mg/dL and most common neurological symptoms included syncope, dizziness, hypotonia, convulsion, paresthesia, fatigue and concentration difficulty; only 23.6% of the patients were anemic (2). Similar results were obtained in our

vitamin B12- deficient group; there was no clinical correlation with hematological parameters.

These results showed that clinical findings in vitamin B12 deficiency are variable and non-specific and may not be associated with hematological abnormalities. Clinicians must consider vitamin B12 deficiency in children with unexplained neurological manifestations.

Conclusion

In vitamin B12 deficiency, changes in hemogram parameters may not be observed even at very low vitamin levels, and hematological parameters may not be associated with vitamin B12 levels and clinical findings. Since clinical manifestations are so variable, a high level of suspicion is required for early diagnosis of vitamin B12 deficiency to prevent irreversible neurological complications by means of early diagnosis and treatment.

Ethics

Ethics Committee Approval: This was approval by the Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (approval number: 20/317, date: 05.11.2021).

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Children and Adolescents Admitted to the Emergency Department with Complaints of Chest Pain

Acil Servise Göğüs Ağrısı Şikayeti ile Başvuran Çocuk ve Adölesanların Değerlendirilmesi

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Abstract

Introduction: Chest pain (CP) is a common reason for pediatric emergency department presentation. The possibility of heart originated pain frightens the family. There is no pathology in most of the cases. Here, we aimed to evaluate the etiological causes of children and adolescents who admitted to the pediatric emergency service with complaint of CP.

Materials and Methods: Two hundred ninety eight cases aged between 8 and 18 years who admitted to the emergency service with GA complaints between February 2018 and 2019 were included in the study. Demographic characteristics, physical examinations, laboratory findings and diagnoses of the patients were analyzed retrospectively.

Results: The most common causes of CP were determined as idiopathic (50.3%), musculoskeletal system (24.1%) and psychogenic (10.2%). Most of the patients were over 12 years old (n=169, 58.7%) and female (n=155, 53.8%). There was no significant difference in terms of age and gender (p=0.06, p=0.07).The cardiac causes was found to be 4.5% of the all causes. The most common cardiac causes were mitral valve prolapse and mitral insufficiency. Psychogenic causes were higher in females, and psychogenic causes were anxiety, panic attack and depression, respectively.

Conclusion: Most of CP in children is due to non-cardiac causes. Although the most common cause of GA is idiopathic, the incidence of psychogenic causes in CP etiology is gradually increasing in adolescents. As a result of detailed history, physical examination and laboratory tests, families should be informed and felt comforted about the diagnosis of the patients.

Keywords
Chest pain, adolescent, psychogenic

Anahtar kelimeler
Göğüs ağrısı, adölesan, psikojenik

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Öz

Giriş: Göğüs ağrısı (GA), çocuk acil servisine başvurunun yaygın bir nedenidir. Ağrının kalp kökenli olma ihtimali aileyi telaşlandırmaktadır. Olguların çoğunda herhangi bir patoloji saptanmamaktadır. Çalışmamızda çocuk acil servisine başvuran çocuk ve adölesanların GA nedenlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Şubat 2018-2019 tarihleri arasında GA şikayeti ile acil servise başvuran 8-18 yaş arası 298 olgu çalışmaya dahil edildi. Hastaların demografik özellikleri, fizik muayeneleri, laboratuvar bulguları ve tanıları retrospektif olarak incelendi.

Bulgular: GA'nın en sık nedenleri idiyopatik (%50,3), kas-iskelet sistemi (%24,1) ve psikojenik (%10,2) olarak belirlendi. Hastaların çoğu 12 yaşın üzerinde (n=169,

%58,7) ve kızdı (n=155, %53,8). Hastalar arasında yaş ve cinsiyet açısından anlamlı bir farklılık yoktu (p=0,06, p=0,07). Kardiyak nedenler tüm nedenlerin %4,5'iydi. En sık kardiyak nedenler mitral kapak prolapsusu ve mitral yetmezliktir. Kızlarda psikojenik nedenler daha fazlaydı, psikojenik nedenler sırasıyla anksiyete, panik atak ve depresyondu.
Sonuç: Çocuklarda GA'nın büyük çoğunluğu kalp dışı nedenlerden kaynaklanmaktadır. GA'nın en sık nedeni idiyopatik olmakla birlikte, psikojenik nedenlerin insidansı adölesan yaş grubunda giderek artmaktadır. Ayrıntılı anamnez, fizik muayene ve laboratuvar tetkikleri sonucunda hastaların tanıları konusunda ailelerin bilgilendirilmesi ve kendilerini rahat hissetmeleri sağlanmalıdır.

Introduction

Chest pain (CP) is one of the most common reasons for admission to the emergency department in children and especially in the adolescent age group. The most common causes of CP in children are idiopathic, musculoskeletal system, respiratory system and gastrointestinal system (GIS) pathologies, respectively. Cardiac causes are extremely rare and their frequency is usually around 5% (1). In adults CP is often associated with heart disease and sudden death. Although cardiac causes are rare, anxious parents who associate CP with heart disease often present to the pediatric emergency department (2). Many families perceive CP as heart disease, and the most frightening of the family is the possibility of children dying suddenly. After a detailed physical examination and anamnesis, most of the patients can be diagnosed without the need for further examinations. However, further investigations such as echocardiography, ECG, cardiac catheterization and angiography may be required in patients who are suspected of having CP due to cardiac causes, where organic causes cannot be excluded. Therefore, clinicians should know the possible causes and the symptoms indicating these reasons in children presenting with CP (3-5). In this study, we aimed to evaluate the adolescent children who presented to the pediatric emergency department with the complaint of CP in terms of diagnosis and to investigate the causes of pain.

Materials and Methods

In this study, the data of 298 adolescent patients who were admitted to pediatric emergency service between 01.02.2018 and 2019 with CP complaints were retrospectively evaluated. The age range of the patients was 8-18 years. Patients' age, gender, time of onset of pain, season, time of admission to hospital, consultations, laboratory and radiological evaluations were evaluated. The patients were divided into two groups as <12 and >12 years old. The cases considered psychogenic were consulted with the child psychiatrist, and the cases considered cardiological were consulted with the child cardiology. Physical examination, vital signs, 12-channel electrocardiography (ECG), and cardiac markers [troponin, creatine kinase (CK), and CK-MB] were evaluated in all patients. Patients with suspected pneumonia had bilateral chest radiographs. Before the study, Erciyes University Faculty of Medicine, Non-invasive Clinical Research Ethics Committee approval was obtained (approval number: 2018/222, date: 18.04.2018).

Statistical Analysis

SPSS for Windows 20 program was used to evaluate the data in the study. All data were calculated as mean and percentage (%) values. The difference between categorical variables was evaluated using the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

In our study, 155 (53.8%) of the patients were female and 133 (46.2%) were male. The age range of the patients was 8-18 years. 58.6% of the patients were over 12 years old and in the adolescent age group. There was no significant difference between patients in terms of age and gender (p=0.06, p=0.07). The duration of the patients' onset of CP and their presentation to the emergency department ranged from one to 30 days. Most of the patients (79.1%) admitted within the first 24 hours. The patients admitted to the emergency department in the spring, summer, autumn and winter seasons, respectively (Table 1).

Only one patient had a high troponin value and was diagnosed with myocarditis. Sixty-six patients had chest radiography and 7 patients were diagnosed with pneumonia. The most common causes of CP were idiopathic, musculoskeletal, psychogenic, respiratory, cardiac, and GIS pathologies, respectively

(Table 2). Forty-four patients were consulted to child psychiatrists and 162 patients to child cardiology.

Psychogenic pathologies were detected in 29 patients, and they were anxiety (44.8%), panic attack (34.4%) and depression (20.8%), respectively. Cardiac pathology was detected in 14 patients as a result of the evaluation of the pediatric cardiology. These pathologies were mitral valve prolapse (MVP), mitral insufficiency, atrial septal defect (ASD), wolf parkinson white (WPW), supraventricular tachycardia (SVT) and myocarditis, respectively (Table 3).

ECG evaluation revealed abnormal findings in five patients: SVT in two patients, delta wave in two patients and ST elevation in one patient. Musculoskeletal pathologies were myalgia 18.2%, costochondritis 5.9%, respiratory system pathologies pneumonia 2.4%, asthma 2.9%, GIS pathologies were 3.4% gastroesophageal reflux.

Discussion

In each child presenting with CP, a detailed history should be obtained and not only cardiovascular system examination but also comprehensive systemic examination should have to be performed. In studies on children, CP accounts for 0.7-5.2% of visits to pediatric emergency department (6). In our study, patients presented with CP comprised 0.9% of all presentations in agreement with literature. In pediatric population, CP is most commonly encountered at adolescent period and at ages of 12-14 years. In addition, it was reported that CP was more common at adolescent period and girls (7,8). In our study, CP was more common in adolescents and girls but the difference did not reach statistical significance.

In our study, no underlying pathology was identified in 48.1% of patients presented with CP; such patients were considered as idiopathic CP. Idiopathic CP is most common cause of CP children with incidence ranging from 12% to 85% in several studies (7,9). Before making diagnosis of idiopathic CP, the patient should be evaluated with detailed anamnesis and physical examination; studies such as

Table 1. General characteristics of the patients with chest pain

	n	%
Age (year)		
<12	119	41.4
>12	169	58.6
Gender		
Female	155	53.8
Male	133	46.2
Starting time		
0-1 day	228	79.1
1-7 day	48	14.5
7-30 day	12	6.4
Beginning		
With effort	44	15.3
Rest	179	62.1
Both	65	22.6
Season		
Autumn	57	19.8
Winter	60	20.8
Spring	92	31.9
Summer	79	27.5

Table 2. The causes of chest pain

Reasons	**%**	**n**
İdiopathic	50.3	145
Musculoskeletal system	24.1	69
Psychogenic	10.2	29
Respiratory system	5.3	16
Cardiak system	4.8	14
Gastrointestinal system	3.4	10
Others (trauma, tonsillitis)	1.9	5
Total	100	288

Table 3. Psychogenic and cardiac causes of chest pain

	%	**n**
Psychogenic reasons		
Anxiety	13	44.8
Panic attack	10	34.4
Depression	6	20.8
Cardiac causes		
Mitral valve prolapse	4	28.5
Mitral regurgitation	3	21.4
Atrial septal defect	2	14.3
Wolff parkinson white	2	14.3
Supraventricular tachycardi	2	14.3
Myocarditis	1	7.2

ECG and echocardiography should be performed when needed; and organic and psychogenic causes that may play role in the etiology should be ruled out (1,7). In a study on 3,700 patients with CP, idiopathic causes were detected in 52% of children (10). This group of patients is generally adolescents and describes a sudden pain lasting for a few seconds or minutes. The children limit their activities during attacks. The attacks can recur and physical examination is always normal. The causes are mostly normal and self-limiting. No treatment is required (11). In such cases, the patient and patient should be assured that the pain is not associated with heart.

Among chest with an identifiable cause, musculoskeletal pathologies are most common. Of children presented to emergency department with CP, musculoskeletal system pathology was detected in 28% (1). In a series including 3,700 children, it was found as 37% (10). In the study by Çiçek et al. (12) it was found that musculoskeletal conditions were second most common causes of CP following idiopathic causes. In our study, musculoskeletal pathologies were the most common cause of CP in agreement with literature. The factors which are helpful in diagnosis include worsening pain with breathing or activity, relief of pain with removal of triggering event and lack of abnormal finding in the physical examination (13-15). Costochondritis, exercise, overuse of chest muscles by cough, trauma, slipping rib syndrome, herpes zoster, pleurodynia, Tietze's syndrome and chest wall and vertebral anomalies can cause CP (10,16). CP secondary to costochondritis is a common condition in children. It is more common in adolescents and girls. In general, costochondral and costosternal joints over ribs 2-5 are tender and painful at palpation in unilateral manner. The pain is exacerbated by deep breath and exercise. In general, it is recurrent and lasts over a few seconds and minutes. It is typically self-limiting condition; thus, symptomatic treatment is employed and non-steroidal anti-inflammatory agents are given during acute period (17). In our patients, myalgia and costochondritis were most commonly detected musculoskeletal system pathologies and non-steroidal anti-inflammatory drugs were prescribed in these patients. GIS disorders can manifest as CP. Many causes such as gastroesophageal reflux disease (GERD), gastritis, peptic ulcer, esophagitis and foreign body in esophagus can cause GIS-related CP. Among these, GERD is common and can present as heartburn. It is seen that the pain is associated with meal while it is exacerbated when the patient lie down and it is generally localized at epigastric region. In a case series including 441 patients, Güvenç et al. (8) found GIS-related CP incidence as 1.4%. In our study, GIS-related CP incidence was 3.4% as GERD being most common cause.

Respiratory disorders such asthma, pneumonia, pleural effusion, pulmonary embolism and pneumothorax can cause CP (9,18). The presence of complaints such as cough and fever, pain worsening with breathing and pathological lung sound at physical examination suggests respiratory system disorders. The diagnosis can be made directed studies such as chest radiograph and appropriate treatment is prescribed. Asthma is most common respiratory CP in children. CP following exercise, wheezing and respiratory distress may be present (19,20). In a study by Sert et al. (3) it was reported that respiratory CP incidence was 6.6% among children, 28% of which were asthma. Öztürk et al. (13) reported that 5.1% of all CP cases originated from respiratory system, 58% of which were diagnosed as asthma. In our study, respiratory CP comprised 5.3% of all cases with CP; of these, 56.3% were asthma and 43.7% were pneumonia. In pneumonia, overuse of accessory breathing muscles due to cough and pleural or diaphragmatic irritation can result in CP. Again, pleural inflammation secondary to effusion may cause pain which exacerbates with deep inspiration (17,21).

In recent years, psychogenic CP with increasing incidence is another cause of CP in children. Age is an important factor in the etiology of CP in children. It is more common in adolescent girls (22). While psychogenic or stress-related CP is more common among adolescents while cardiorespiratory CP resulting from asthma, pneumonia or cardiac disorders is more common in younger children. In Turkey, psychogenic factors are reported in 3-10% of children presented with CP (3,13,23). In our study, CP frequency was 10.2% and was more common among adolescent girls. CP following stressful events, presence of multiple complaints such as headache and abdominal pain, sleep disorder, prolonged complaints, recurrent complaints, healthy appearance, normal physical examination and problems in school and at home should suggest psychogenic CP. Divorce, breaking up friends, loss of a beloved individuals,

disapproval by friends and academic failure are common conditions (1,22,24). In recent years, some studies emphasized that psychogenic causes are more common than organic causes of CP and anxiety, depression and suicidal thoughts were higher in adolescents when compared to controls (25,26). In our study, psychogenic CP was second most common cause of CP with identifiable cause and there was anxiety, panic disorder and depression in the patient. Thus, it will be appropriate to perform as psychogenic assessment when all evaluations for CP were normal in adolescent girls.

Although cardiac CP is rare in children, it can be an important, fatal condition. Thus, families are concerned due to likelihood of cardiac origin when they faced CP. In previous studies, cardiac CP frequency ranges from 0% to 6% (1,17,24). Çiçek et al. (12) reported cardiac CP frequency as 6.7%. In our study, rate of cardiac CP was found as 4.5% in agreement with literature. It is difficult to rule out cardiac disease definitely since children could not fully describe or localize pain (18,27,28). The patient should be evaluated for cardiac disorders in detail and must be assessed by a pediatric cardiologist if there is sudden onset, exercise-induced CP; if there is accompanying respiratory distress, palpitation, nausea, sweating, pallor, pre-syncope or syncope and if there is history of previous cardiovascular surgery and family history of premature death. Initial evaluation includes ECG and cardiac enzyme assays (troponin, CK). MVP, arrhythmias, aortic stenosis, pulmonary stenosis, cardiomyopathy, cardiac tumors, myocarditis, pericarditis and infective endocarditis can lead CP (3,8,21,29). The MVP is a common condition in general population, which generally has a benign course. Its prevalence is 2-5% at childhood, which increased by advancing age. In a last study the prevalance of MVP in 7,550 Turkish school children was found 1.2-1.6% (30). It is particularly seen in adolescent girls. In general, there is positive family history. It may cause a vague pain due to stretching of papillary muscle at apex. Although definitive cause of pain is unknown, it has been proposed that pain may be due to ischemia in papillary muscles, abnormal stretching or arrhythmias (22,31). The MVP was reported as most common cardiac pathology underlying CP (12). In our study, the most common cardiac cause of CP was MVP (28.5%); followed by mitral regurgitation (21.4%), ASD (14.3%), WPW (14.3%), SVT (14.3%) and myocarditis (7.2%). ASD and mitral regurgitation are rare causes of CP in children, and we think that these findings are coincidental. In children, CP can occur due to arrhythmias such as ventricular extra-systole, SVT or ventricular tachycardia. It is more commonly seen in prolonged tachycardia resulting in decreased cardiac output and diastolic blood flow, and myocardial ischemia. There may be concomitant palpitation, dizziness, pre-syncope or syncope. Hypertrophic or dilated cardiomyopathy can cause CP at rest or during exercise due to ischemia and dysrhythmia. Family history, pathological murmur or findings of congestive heart failure as well was electrocardiographic and telecardiographic abnormalities are supportive for diagnosis. Sharp, long-lasting pain which is exacerbated by supine position and relieved by sitting or anterior bending can be seen in patients with pericarditis (1,21,24).

Study Limitations

Our study had some limitations. The fact that the study was not multicenter was one of the limiting features. Other limiting factors were the retrospective planning of our study and the small number of cases.

Conclusion

Cardiac CP which leads panic and fear in the family is extremely rare in children. The further evaluations should be performed in patients suspected to have cardiac pathology and a consultation with pediatric cardiologist should be ordered. As there is a non-cardiac cause in majority of patients, informing and assuring family is the most important part of management in emergency department. The psychogenic CP with increasing incidence should be kept in mind in adolescents.

Ethics

Ethics Committee Approval: Ethical approval was obtained for this study from the Erciyes University Clinical Research Ethics Committee (approval number: 2018/222, date: 18.04.2018).

Conflict of Interest: The authors have no conflict of interest to declare.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Is Hyponatremia a Predictor for Perforated Appendicitis in Children?

Hiponatremi Çocuklarda Perfore Apandisit için Prediktör mü?

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Abstract

Introduction: Acute appendicitis (AA) is a leading cause morbidity and mortality in childhood. Unfortunately AA can be difficult to distinguish from other clinical conditions during the early course of the disease. Biomarkers are molecular indicators of a disease process, diagnosis, prognosis and can be used to monitor the effects of disease management. We aimed to determine which of the demographic, clinical or laboratory data is more predictive for complicated AA.

Materials and Methods: A hundred fourty five consecutive patients aged 1 month to 18 years diagnosed with AA were retrospectively analyzed. Age, gender, body temperature (°C), laboratory data and symptom duration (days) of the patients were recorded.

Results: A total of 145 children with AA, 38 in group 1 and 107 in group 2, were included in the study. Group 1 was perforated appendicitis and group 2 was non-perforated appendicitis. Plasma sodium value was lower in group 1 than group 2, and C-reactive protein (CRP) values were significantly lower in group 2 compared to group 1.

Conclusion: Laboratory values can guess complicated appendicitis in children with appendicitis. CRP level and presence of hyponatremia may be more predictive than white blood cell count for the the diagnosis of perforated appendicitis.

Keywords
Acute appendicitis, C-reactive protein, hyponatremia, perfore appendicitis

Öz

Giriş: Akut apandisit (AA) çocukluk çağında önde gelen morbidite ve mortalite nedenidir. Ne yazık ki, AA hastalığın erken seyri sırasında diğer klinik durumlardan ayırt edilmesi zor olabilir. Biyobelirteçler, bir hastalık sürecinin, teşhisinin, prognozunun moleküler göstergeleridir ve hastalık yönetiminin etkilerini izlemek için kullanılabilir. Komplike AA için demografik, klinik veya laboratuvar verilerinden hangisinin daha prediktif olduğunu belirlemeyi amaçladık.

Gereç ve Yöntem: AA tanısı alan 1 ay-18 yaş arası ardışık 145 hasta retrospektif olarak incelendi. Hastalara ait yaş, cinsiyet, vücut ısısı (°C), laboratuvar verileri ve semptomların süresi (günler) kaydedildi.

Bulgular: Grup 1'de 38, grup 2'de 107'si olmak üzere 145 AA tanısı alan çocuk çalışmaya dahil edildi. Grup 1 perfore apandisit ve grup 2 non-perfore apandisit idi. Plazma sodyum değeri grup 1'de grup 2'ye göre daha düşüktü ve C-reaktif protein (CRP) değerleri grup 2'de grup 1'e göre anlamlı derecede düşüktü.

Sonuç: Apandisitli çocuklarda laboratuvar değerleri komplike apandisitleri tahmin edebilir. CRP düzeyi ve hiponatreminin varlığı perfore apandisit tanısında lökosit sayısından daha belirleyici olabilir.

Anahtar kelimeler
Akut apandisit, C-reaktif protein, hiponatremi, perfore apandisit

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Introduction

Acute appendicitis (AA) is the most common reason for emergency surgery in children (1). Despite advances in diagnosis and treatment, it is associated with significant morbidity (10%) and mortality (1-5%) (2). Perforation is an important factor for morbidity in patients with AA and associated with increased frequency of postoperative complications (3). Delayed diagnosis and treatment increase the risk of perforation, abscess, peritonitis and partial bowel obstruction. Laboratory markers can be used to predict perforated appendicitis. C-reactive protein (CRP), white blood cell (WBC) and absolute neutrophil counts are markers that are commonly used to differentiate perforation of appendicitis (4). Recent studies have shown that hyponatremia is associated with inflammatory events such as pneumonia, acute respiratory distress syndrome, meningitis and necrotizing soft tissue infections. However, studies examining the relationship between hyponatremia and AA are limited (5,6).

Our primary objective was to investigate the clinical significance of preoperative hyponatremia and to assess as a predictor of the perforated AA. Another objective was to identify the differences regarding age, gender, duration of symptoms, WBC count and CRP levels among both groups.

Materials and Methods

Study population

In this retrospective single-center study, we evaluated all (n=145) patients under 18 years of age with intraoperative diagnosed appendicitis who underwent appendectomy at our institution between June 2018 and June 2019. The study was approved by our institutional review board and the ethical committee (approval number: E-20/12-50).

Demographic and clinical information were retrospectively obtained from all subjects with AA. Demographic information included patient's age and gender. Clinical data included body temperature (as measured in the pediatric emergency room), duration of symptoms, laboratory data (WBC count, CRP and sodium levels) and outcome. Exclusion criteria were missing laboratory values, concomitant chronic disease, history of secondary or elective appendectomy. The collected data were complied in an electronic database and mean values and standart deviation (SD) for numeric items were calculated. Patients were divided into two groups as perforated and non-perforated appendicitis according to their surgical reports and pathology results. Age, gender, serum sodium levels, WBC count and CRP were compared between the two groups.

Statistical Analysis

Clinicopathological characteristics were compared between the two groups using Student's t-test. Parametric data were mean ± SD, categorical data were expressed as frequency (n) and percentage (%). The sensitivity and specificity in the diagnosis of acute perforated appendicitis with WBC count, CRP and serum sodium levels were evaluated with receiver operating characteristic (ROC) analysis. ROC curve analysis was performed to assess the best cutoff for the prediction of perforated AA and values for area under the curve (AUC). Multivariate analysis was carried out by binomial logistic analyses, with adjustments for variables significant in univariate analysis. Statistical significance was defined as $p<0.05$.

Results

A total of 145 patients with appendicitis were included the study. The mean age of the patients was 11±3.6 (minimum: 3-maximum: 17.5) years, and 92 (64.3%) of the patients were male. The mean WBC was 14,400/lL (range: 4,600-36, 400/lL), mean CRP level was 68 (range: 0-342) mg/L and mean serum sodium level was 136 (range: 128-141) mEq/L. The demographic and laboratory data of the patients are shown in Table 1. All patients were hospitalized and none of them died.

Thirty-eight patients (26.2%) had perforated appendicitis. No difference was found between patients with perforated and non-perforated appendicitis in terms of gender, age and body temperature. However, the duration of symptoms was longer in patients with perforated appendicitis ($p<0.001$).

There was a significant difference between the perforated appendicitis group and the non-perforated appendicitis group in terms of CRP level and plasma sodium levels ($p<0.001$, $p<0.001$ respectively). No significant relationship was found between acute perforated appendicitis and WBC count ($p=0.74$).

Table 1. The demographic and laboratory data of the patients			
Demographic and laboratory data (mean ± SD)	Perforated group (n=38)	Non-perforated group (n=107)	p-value
Age (years)	10.8±3.9	11.1±3.6	0.70
Gender (male) n (%)	25 (65)	67 (62%)	0.33
Body temperature (°C)	36.7±0.8	36.6±0.6	0.23
Semptom duration(day)	2.8±2.6	1.5±1.8	<0.001
WBC (x10^9/L)	15.8±5.3	13.9±5.2	0.74
CRP (mg/L)	139±94	43±49	<0.001
Plasma sodium (mEq/L)	134.3±3.2	136.6±2.1	<0.001
SD: Standard deviation, WBC: White blood cell, CRP: C-reaktif protein			

Most sensitive association with acute perforated appendicitis in reciever ROC analysis was determined by CRP (AUC: 0.814) and serum sodium value (AUC: 0.716). Figure 1 shows CRP level as a pedictor of acute perforated appendicitis. Using the Youden index we established the following cutoff points: serum CRP of 89 mg/L, serum sodium value ≤135 mEq/L. CRP value above 89 mg/L had 71.0% sensitivity and 84.1% specificity. For sodium value ≤135 mEq/L, sensitivity was 57.9% and specificity was 71.0. The ROC for plasma sodium levels considered as a predictor for perforated AA is shown in Figure 2.

Plasma sodium levels were found significantly lower in patients with perforated appendicitis than non-perforated group. The median (IQR) value is 135 (132-138) mEq/L in the perforated group and 136 (133-139) mEq/L in the non-perforated group. Sodium values of the two groups are shown in Figure 3.

Discussion

In this study, 145 pediatric patients were evaluated diagnosed with AA. Sodium levels were significantly lower and the CRP levels were higher in patients diagnosed with perforated appendicitis. WBC count did not differ significantly between simple and perforated appendicitis.

Young children can not explain their pain symptoms like an adolescent or adult. Therefore a significant delay may occur in assessment, diagnosis and treatment. Perforation, abscess and peritonitis are still common in children with appendicitis. Diagnosing perforated appendicitis presents with some difficulties, as children often do not present with the classic presentation of appendicitis (7). In clinical studies investigating complications in children with appendicitis, the mean age in complicated appendicitis was found to be significantly lower than those with uncomplicated

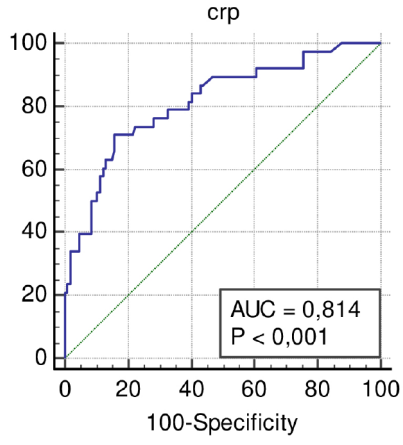

Figure 1. C-reactive protein as a predictor of perforated appendicitis. Area under the curve (AUC) is area under the curve; dashed line is the line of no predictive value, that is, AUC=0.5.

CRP: C-reactive protein

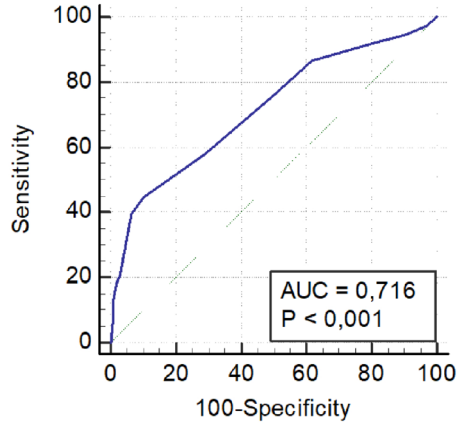

Figure 2. Receiver operating characteristic curve for plasma sodium concentration as a predictor of perforated AA. Area under the curve (AUC) is area under the curve; dashed line is the line of no predictive value, that is, AUC=0.5.

AA: Acute appendicitis

appendicitis (8-10). In our study, age of the patients was not found to be associated with perforation. This may be due to differences in the number of patients included in the study and differences in perforated non-perforated appendicitis rates.

Univariate analysis demonstrated that patients with perforated appendicitis had a longer duration of symptoms. However, there is no common consensus in the pediatric literature regarding for which time frame there is a significant increase in risk for perforated appendicitis (11-13).

We can interprete that objective laboratory parameters are needed for diagnosis. However, no parameter can show perforation in a satisfactory way. The importance of laboratory data in the diagnosis of acute perforated appendicitis is controversial. In a previous study, it was reported that WBC count did not differ in patients diagnosed with complicated and uncomplicated AA (9). Similarly, in our study, WBC count did not help distinguish the two groups. Although it is not an indicator alone, there is an increased number of WBC count in complicated appendicitis cases (14). CRP is an acute inflammatory protein and has been used as a marker of acute infections. In our study, increased CRP value was found to be sensitive in predicting perforated appendicitis, similar to some studies (11,15,16).

Hyponatremia is the most common electrolyte disorder in clinical medicine and may be seen in many inflammatory diseases such as Kawasaki disease, sigmoid diverticulitis and AA. In AA hiponatremia develops due to factors causing non-osmotic release of antidiuretic hormone such as, pain, hypovolemia, and nausea (17-19). Serradilla et al. (20) found that preoperative low serum sodium levels were associated with intraabdominal abscess in AA. In Sweden, a study in which 80 pediatric appendicitis patients were evaluated, serum sodium level was found to be significantly lower in patients with complicated appendicitis compared to simple appendicitis (21). Pogorelić et al. (22) evaluated 184 pediatric appendicitis patients and when the cut-off value for plasma sodium was 135, AUC to be 0.983 in predicting perforated appendicitis. In our study, serum sodium levels were significantly lower in patients with perforated appendicitis, and the best cut-off value for predicting perforated appendicitis was 135 mmol/L and AUC was 0.716. Our study was generally compatible with the literature.

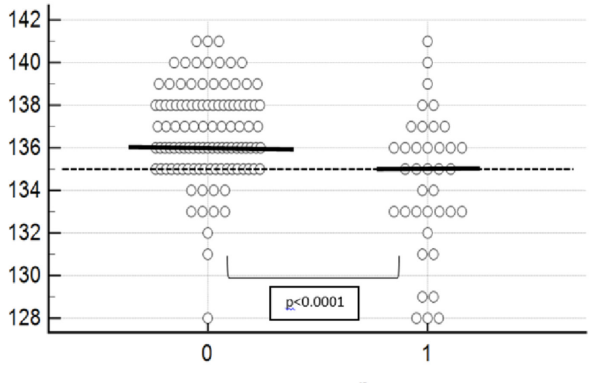

Figure 3. In the vertical column of the graph, serum sodium concentrations are indicated in mmol/L ar emergency admission. Plasma sodium levels of patients with perforated and non-perforated appendicitis (0: non-perforated appendicitis, 1: erforated appendicitis) straight line shows median value. Dashed line correponds to the chosen value for dichotomization of data. The groups were compared using the non-parametric Mann-Whitney U test.

Serum sodium level, which is routinely checked in patients with suspected appendicitis, is also low-cost, and can be a good predictor of perforated appendicitis cases. Early detection of hyponatremia at the time of presentation has been shown to be associated with complications, and in the light of this information, it has been emphasized that it can be an early predictor in terms of operation timing.

Conclusion

Perforated appendicitis is not uncommon in the childhood age group. Our study shows that plasma sodium levels and CRP at the time of admission may be useful in predicting perforated appendicitis. Hyponatremia and elevation of CRP may be more predictive in cases with perforated appendicitis than WBC count, age or body temperature.

Ethics

Ethics Committee Approval: The study was approved by our institutional review board and the ethical committee (approval number: E-20/12-50).

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

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

May HDL Cholesterol Level Have a Role in The Diagnosis of Kawasaki Disease?

HDL Kolesterol Düzeyinin Kawasaki Hastalığı Teşhisinde Olası Rolü

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Abstract

Introduction: Kawasaki disease (KD) is a multisystemic vasculitis that has no specific serum marker. The aim of our study is to evaluate whether the serum lipid profile, specifically HDL cholesterol (HDL-C) level, in KD differs from that in other febrile illnesses and if so, it can be used as a diagnostic tool in distinguishing KD from other febrile illnesses.

Materials and Methods: We examined prospectively 41 patients with KD (group 1) and 30 patients with febrile illness of viral or bacterial origin (group 2). The patients' demographic and clinical characteristics were analyzed. All blood samples were taken during the disease's acute phase. After fasting for four hours in infants and eight hours in young children, serum total cholesterol, HDL-C, triglyceride (TG), C-reactive protein (CRP), complete blood count, and other biochemical markers were determined. Group 1 was further divided into subgroups as incomplete vs complete cases and patients with vs without coronary artery involvement.

Results: Mean serum HDL-C level in KD group was significantly lower than in the febrile illness group (13.8±8.8 mg/dL vs 37.6±18.7 mg/dL, p <0.001). A statistically significant difference in TG levels was also present between both groups (group 1: 183±96 mg/dL vs group 2: 121±70 mg/dL, p=0.001). We detected a significant difference in terms of HDL-C levels, erythrocyte sedimentation rates, CRP, and TG levels between patients with febrile illness, complete KD, and incomplete KD (p <0.001; p=0.007, p <0.001, p=0.01, respectively). The most appropriate cut-off value of serum HDL-C level for affirming KD was ≤ 23 mg/dL. The area under the curve was 0.88 (95% confidence interval: 0.78-0.94, p <0.001).

Conclusion: The study showed that serum HDL-C level is lower in patients with KD than in those with acute febrile infectious disease. Presence of low serum HDL-C level (≤ 23mg\dL) may be helpful in establishing the diagnosis of incomplete KD.

Keywords
Kawasaki disease, coronary artery involvement, serum HDL-C level

Anahtar kelimeler
Kawasaki hastalığı, koroner arter tutulumu, serum HDL kolesterol

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Gereç ve Yöntem: KH tanısı alan 41 hasta (grup 1) ile viral veya bakteriyel kaynaklı ateşli hastalığı olan 30 hastanın (grup 2) değerlendirildiği prospektif bir çalışmadır. Çalışmaya dahil edilen hastaların demografik ve klinik özellikleri değerlendirildi. Tüm kan örnekleri hastalığın akut döneminde alındı. Bebekler için dört saat ve küçük çocuklar için sekiz saat aç kaldıktan sonra serum total kolesterol, HDL kolesterol (HDL-K), düşük yoğunluklu lipoprotein kolesterol (LDL-K), trigliserid (TG), C-reaktif protein (CRP), tam kan sayımı ve diğer biyokimyasal parametreler çalışıldı. Ayrıca KH ile takip edilen hastalar, inkomplet ve komplet vakalar ve koroner arter tutulumu olan ve olmayan hastalar olarak alt gruplara ayrılarak kendi içlerinde karşılaştırıldı.
Bulgular: KH grubunda ortalama serum HDL-K düzeyi ateşli hastalık grubundan anlamlı derecede düşük saptandı (13,8±8,8 mg/dL ve 37,6±18,7 mg/dL, p <0.001). Her iki grup arasındaTG düzeylerinde istatistiksel olarak anlamlı bir fark mevcuttu (grup1: 183±96 mg/dL ve grup 2: 121±70mg/dL, p=0,001). Ateşli hastalık, komplet KH ve inkomplet KH olan hastalar arasında HDL-K düzeyleri, eritrosit sedimantasyon hızları, CRP ve TG düzeyleri açısından anlamlı bir fark saptadık (p <0,001; p:=0,007, p <0,001, p <0,001, p <0,001, p=0,01, sırasıyla). KH tanısını doğrulamak için serum HDL-K düzeyinin en uygun eşik değeri ≤23 mg/dL idi. AUC 0.88 (%95 güven aralığı: 0,78-0,94, p <0,001) saptandı.
Sonuç: Çalışmamız, KH tanısı alan hastalarda, serum HDL-C seviyesinin akut ateşli enfeksiyon geçiren hastalara göre daha düşük olduğunu gösterdi. Düşük serum HDL-C düzeyinin (≤ 23mg\dL) varlığı, inkomplet KH tanısını koymada yardımcı olabilir.

Introduction

Kawasaki disease (KD), first defined in Japan, is now reported worldwide. It is an acute inflammatory multisystemic vasculitis of infants and young children. The disease is influenced by geographic and ethnic factors, and may recur (1). Even though its etiology is not fully determined, there are some clues to its infectious origin (2). The diagnosis of KD can be reached through laboratory-supported clinical findings (1). Although some laboratory findings can help establish the diagnosis, there is no specific serum marker for KD.

Clinical findings and the clinical course of KD may overlap with other febrile inflammatory diseases. The principal symptoms of KD may not be fully seen in incomplete cases, therefore the diagnosis continues to be challenging in incomplete cases (3,4). The diagnostic algorithm for evaluation of incomplete KD proposed in 2004 by the American Heart Association (AHA) had several limitations and was difficult to use in clinical practice (5). The 2017 guidelines have proposed a modified algorithm that is more meaningful and relatively easy to use (6). At the present time, the identification of serum or urine biomarkers of KD is an active area of research. Until a definitive diagnostic method exists, the best way for reducing diagnostic difficulties and enhancing diagnostic accuracy is to increase the number of supporting clinical and laboratory findings.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remain the most important supportive laboratory markers for vascultis in KD. Most other laboratory findings (anemia, thrombocytosis, leukocytosis, hypoalbuminemia, high alanine aminotransferase) also have supportive roles in the diagnosis. Recognizing the disease in the acute period and treating it with intravenous immunoglobulin reduce the rate of coronary artery involvement and aneurysm from 25% to 5% (7). The presence of incomplete cases seems to increase the probability of coronary artery involvement by causing delay in diagnosis (8). Therefore, a better laboratory marker is needed especially for diagnosing incomplete KD.

It has been known that lipoprotein levels change during acute inflammatory response in infectious or autoimmune-rheumatic diseases, and newer studies have further reported that change in serum lipoprotein levels correlate with the type and severity of the inflammation (9,10). Several studies have shown that serum HDL cholesterol levels in both the acute phase of KD and other febrile illnesses correlate with classical inflammatory markers (11-13). However, studies that compare serum HDL levels between KD and other febrile illnesses are still scarce. HDL-C level can be used as a supporting evidence in the diagnosis of KD by observing its decrease during the acute inflammatory response.

The aim of the study is to evaluate whether the serum lipid levels, especially HDL-C, in KD differ from that in acute febrile illnesses of infectious origin during the acute phase and to investigate whether there is a correlation between lipid levels and the type and severity of the disease.

Material and Methods

We conducted the study between December 2010 and November 2018. Forty-four patients diagnosed

with KD (group 1) and 30 febrile patients with viral or bacterial infection (group 2) were evaluated prospectively. Of the patients included in group 2, 16 were diagnosed with upper respiratory tract infection, four with urinary tract infection, three with acute gastroenteritis, three with pneumonia, three with meningitis and one patient with acute tonsillitis. Patients in group 1 were further divided into subgroups as incomplete *vs* complete cases and cases with *vs* without coronary involvement. These subgroups were evaluated within themselves. Patients who have a disorder affecting lipid metabolism such as obesity or endocrine-metabolic diseases were excluded from the study. The demographic and clinical features of the patients were also evaluated. All blood samples were taken during the acute phase of the disease. After four hours of fasting for infants and eight hours for young children, serum total cholesterol (TC), HDL-C, low density lipoprotein cholesterol (LDL-C), triglyceride (TG), CRP, full urine analysis, complete blood count and other biochemical parameters were assayed.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and MedCalc for Windows, version 19.2.0 (MedCalc Software, Ostend, Belgium). Shapiro-Wilk's test was used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean ± standard deviation or (in case of no normal distribution) median categorical variables were summarized as counts. Comparisons of continuous variables between groups were carried out using independent samples t-test/Mann-Whitney U test, whichever was appropriate. Associations between continuous variables were determined by Pearson and Spearman correlation analyses and the association between two categorical variables was examined by chi-square test. Receiver operating characteristic (ROC) analysis was used to determine area under the curve (AUC) and cut-off values. Associations between continuous variables were determined by Spearman correlation analysis and the association between two categorical variables was examined by chi-square test. All statistical analyses were carried out with 5% significance and a two-sided p-value <0.05 was considered as statistically significant.

Results

The average age of patients with KD (group 1) was 4.04±2.6 years, and the average age of patients with infectious disease (group 2) was 4.0±3.3 years. Regarding the age, there was no significant difference between two groups (p=0.76). Male/female ratio was 22/19 in group 1 and 13/17 in Group-2 (p=0.53). Of 41 patients diagnosed with KD, 33 (81%) were diagnosed as complete and 8 (19%) as incomplete KD. Conjunctivitis was present in 34 (82.9%) patients, oropharyngeal changes in 37 patients (90%), rash in 35 (85.3%), lymphadenopathy in 31 (75.6%) and peripheral extremity changes in 23 (56%). Eight patients (20%) diagnosed with KD had sterile pyuria and 9 (23%) had gallbladder hydrops. In the echocardiographic evaluation; although coronary artery aneurysm was not found in any of 41 patients with KD, coronary dilation was observed in 8 patients (19.5%), pericardial effusion in 3 (7.3%), and mitral regurgitation in 2 (4.8%), no cardiac pathology was observed in 28 patients (68.2%). Average fever on admission was similar in both groups (group 1: 38.03±0.9 °C *vs* group 2: 38.4±0.4 °C, p=0.08) while average fever duration was higher in group 1 (7.36±3.8 days vs 3.2±2.4 days, p <0.001) (Table 1).

When patients were evaluated in terms of laboratory findings, group 1 had significantly higher median leukocyte and platelet counts than group 2 (p=0.01; p=0.03, respectively). Serum sodium, albumin and hemoglobin levels were lower in group 1 than in group 2 (p=0.001; p<0.001; p <0.001, respectively). Average HDL-C value was significantly lower in group 1 than in group 2 (13.8±8.8 mg/dL *vs* 37.6±18.7 mg/dL, respectively, p<0.001) (Figure 1).

A statistically significant difference in TG levels was also present between both groups. The average TG value was 183±96 mg/dL in group 1 and 121±70 mg/dL in group 2 (p=0.001). There was no significant difference between the group 1 and 2 in terms of LDL-C and TC levels (p=0.907; p=0.51, respectively). Mean CRP value was 13.8±12.4 mg/L in group 1, 3.6±5.4 mg/L in group 2 (p<0.001). CRP levels exhibited a negative correlation with serum HDL-C level in patient with KD (r=-0.36; p=0.002). There was a positive correlation between serum HDL cholesterol level and the febrile period of disease in group 1 (r=0.24; p=0.04) (Figure 2).

Table 1. Demographic, clinical characteristics and laboratory findings of group 1 and group 2

	Group 1 (n=41) mean ± SD	**Group 2 (n=30)** mean ± SD	p-value
Age (year)	4.04±2.66	4.08±3.62	0.76
Gender (male/female)	22/19	13/17	0.53
The duration of fever (days)	7.29±3.71	3.20±2.42	<0.001
Fever on admission (°C)	38.03±0.96	38.42±0.47	0.08
Hemoglobin (gr\dL)	10.46±1.33	12.03±1.17	<0.001
WBC (mm^3)	13,800±5,800	10,600±6,100	0.01
PLT (mm^3)	328,000±134,000	265,000±113,000	0.03
Serum sodium (mEq\L)	135±3	137±2	0.001
Serum albumin (gr\dL)	3.37±0.58	3.92±0.53	<0.001
Total Cholesterol (mg\dL)	131 41	144±49	0,51
HDL-C (mg\dL)	13.8±8.8	37.6±18.7	0.000
LDL-C (mg\dL)	82.2±34.4	82.4±30.4	0.9
Triglyceride (mg\dL)	183±95	121±70	0.001
ESR (mm/hr)	43.8±4.4	26.2±5.2	0.003
CRP (mg\L)	13.7±12.5	3.6±5.4	<0.001

SD: Standard deviation, WBC: White blood cell, PLT: Platelet count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein-cholesterol

HDL-C, ESR, CRP and TG levels were significantly different between patients with febrile illness, complete KD, and incomplete KD (p=0.00; p=0.007, p=0.000, p=0.014, respectively). Duration of fever was significantly higher in patients with complete and incomplete KD than in those with febrile illness (p<0.001) (Table2). HDL-C and CRP levels in group 1 did not differ between patients with and without coronary artery involvement (Table 3). However, TG level was significantly higher in patients with coronary artery involvement (245.50±39.61 mg\dL, 164.1±15.06 mg\dL, respectively, p=0.03) (Table 3).

The ROC was performed to determine the predictive value of HDL-C level differentiation between KD and febrile illness of infectious origin. The most appropriate cutoff value of serum HDL-C level for affirming KD was ≤ 23 mg/dL. The AUC was 0.88 (95% confidence interval: 0.78-0.94, p<0.001). Sensitivity and specificity were 85.3% and 83.3%, respectively. The positive and negative predictive values of HDL-C at this cut-off level were 87.5% (95% confidence interval: 75.69-94.03) and 80.65% (95% confidence interval: 66.17-89.88). The ROC curve of HDL-C for diagnosing KD is displayed in Figure 3.

Discussion

KD is diagnosed through certain clinical findings, and does not yet have a specific-diagnostic biomarker. Studies on biochemical markers that can be used in the diagnosis of KD still continue (14). It can be challenging to establish the diagnosis of incomplete cases. Children with incomplete KD that remain undiagnosed and untreated for several days have a high risk for coronary artery involvement (8). While diagnosing KD in a patient with incomplete manifestation, one should consider additional laboratory and abnormal echocardiographic findings. Many clinical and laboratory signs not included in the principal diagnostic criteria have been used to support the diagnosis of KD (6). Perineal desquamation, sterile pyuria, hydrops of gall bladder, reactivation of the Bacillus Calmette-Guerin (BCG) injection site, peripheral arthritis, and myocarditis are other clinical findings. Anemia, thrombocytosis and hypoalbuminemia are the most accepted supporting laboratory findings in distinguishing KD (5). It is known that KD also affects the lipid profile. Studies on lipid profile in KD have focused on establishing the condition during the acute stage and evaluating the risks of cardiovascular morbidity in the chronic

Table 2. Demographic, clinical characteristics and laboratory findings of patient with Febrile illness, complete KD and Incomplete KD

	Febrile illness (n=30) mean ± SD	**Complete KD (n=33)** mean ± SD	**Incomplete KD (n=8)** mean ± SD	**p-value**
Age (year)	4.09±0.66	3.87±0.47	4,57±0.94	0.83
Gender (male/female)	13/17	19/14	3/5	0.53
The duration of fever (days)	3.20±0.44	7.18±0.65	7.75±1.47	<0.001
Fever on admission (°C)	38.4±0.8	38.0±0.1	38.1±0.3	0.16
Hemoglobin (gr\dL)	11.94±0.29	10.53±0.25	9.76±05	<0.001
WBC (mm^3)	10351±1.431	13,800±5,800	19,655±2,705	0.007
PLT (mm^3)	257,468±28,919	331,055±24,523	364,142±68,438	0.11
Serum sodium (mEq\L)	137±0.6	135±0.5	133±1.3	0.004
Serum albumin (gr\dL)	3.86±0.13	3.37±0.12	3.33±0.14	<0.001
Total cholesterol (mg\dL)	148±11	132±7	124±21	0.59
HDL-C (mg\dL)	36.5±4.1	16.4±5.3	14.7±1.8	<0.001
LDL-C (mg\dL)	85.5±7.5	84.8±6.3	73.6±18.9	0.61
Triglyceride (mg\dL)	131± 7	174±15	183.57±46.18	0.01
ESR (mm\h)	29.8±6.5	42.5±5.8	43.0±5.2	0.007
CRP (mg\L)	4.6±1.4	14.1±2.7	13.0±3.0	<0.001

SD: Standard deviation, KD: Kawasaki disease, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein - cholesterol

Table 3. Demographic, clinical characteristics and laboratory findings of Kawasaki disease patient with and without coronary artery involvement

	Patient with CAI (n=8) mean±SD	**Patient without CAI (n=33)** mean±SD	**p-value**
Age (year)	4.59±1.11	3.86±0.45	0.57
Gender (male/female)	7/1	15/18	0.46
The duration of fever (days)	8.38±2.06	7.09±0.57	0.64
Fever on admission (°C)	38.2±0.1	37.2±0.3	**0.008**
Hemoglobin (gr\dL)	10.04±0.65	11.10±0.20	0.74
WBC (mm^3)	9,898±1,980	14,926±988	**0.02**
PLT (mm^3)	338,925±51,973	325,303±24,045	0.98
Sodium (mEq\L)	134±1	136±0.4	0.23
Albumin (gr\dL)	3.39±0.20	3.38±0.09	0.56
Total cholesterol (mg\dL)	157±19	134±6	0.09
HDL-C (mg\dL)	15.2±4.04	14.7±1.6	0.88
LDL-C (mg\dL)	95.7±19.1	81.5±4.5	0.46
Triglyceride (mg\dL)	245±39	164±15	**0.03**
ESR (mm\h)	41.8±14.9	36.6±3.7	0.43
CRP (mg\L)	12.9±4.5	9.8±1.6	0.46

SD; Standard deviation, HDL-C; High Density Lipoprotein-Cholesterol, LDL-C; Low Density Lipoprotein - Cholesterol, TG: triglyceride, TC: total cholesterol, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Hgb: hemoglobin, WBC: White blood cell, PLT: platelet, CAI; Coronary artery involvement

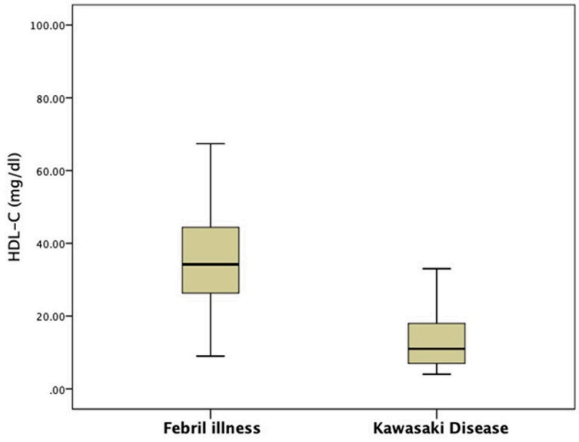

Figure 1. The box plot showing serum HDL-C level (mg/dL) in patient with Kawasaki disease and febrile illness.

stage. Research on the diagnostic ability of lipids has remained insufficient. In the present study we evaluated whether HDL-C has any diagnostic utility in KD, and whether it would be as reliable as classical supporting laboratory findings. Studies on lipid profile in recent years, and our own clinical experiences have suggested that serum HDL-C level, which is known to decrease during the acute inflammatory response, can be used to support the diagnosis of KD. No consensus exists regarding clinical usefulness of serum HDL-C level as a marker especially for patients with incomplete KD.

During the acute phase response, CRP can interact with various molecules, such as bacterial capsules, membrane phospholipids, complement proteins and lipoproteins (LDL-VLDL cholesterol) (15). Cytokine and interleukin induced-change of hepatic lipase activity in the liver and lipoprotein lipase activity in the peripheral tissue, use of LDL-C, VLDL-C as a ligand by CRP suggest that lipoproteins play an active role during the acute phase response. However, these changes do not fully explain the physiopathology of the alteration in the lipid profile. It is not clear whether change in lipid profile is a conservative response exhibited by the organism against inflammation or a secondary disorder that develops following inflammation.

A negative relationship between the changes in serum HDL and CRP levels has been reported in the acute period of KD and febrile infectious diseases. The study of Ou et al. (12) encompassing 119 patients with KD indicated that decrease in HDL-C level and increase in CRP level were more prominent in patients with coronary artery involvement than in those without. Connelly et al. (10) reported that decrease in HDL-C levels were more marked in KD patients than in those with acute infectious disease. Moreover, they reported that the decrease in HDL-C level was more prominent in patients with coronary artery involvement and it continued into the subacute phase of the disease. We found that HDL-C level was lower in patients with KD than in those with febrile infectious disease, which supports Connelly's study. But contrary to Connelly's study, we didn't find any differences in HDL-C levels between patients with and without coronary artery involvement. Interestingly, we determined that serum

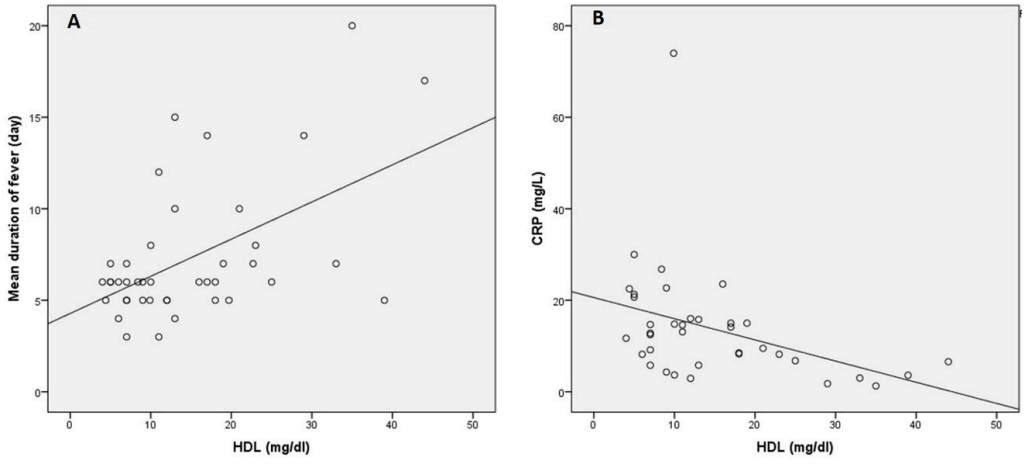

Figure 2. A. Positive correlation in patient with KD between HDL-C level and mean duration fever is shown in figure 2A. **2B.** Negative correlation in patient with KD between HDL-C and CRP level is shown in figure 2B.

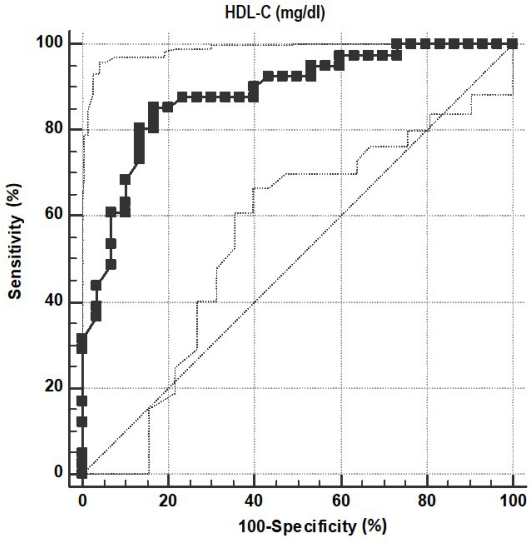

Figure 3. According to receiver operating characteristic curve, a HDL-C level of 23 mg/dL or less was the best cut-off value for predicting Kawasaki disease (AUC:0.88, p <0.001) with sensitivity 85.3%, specificity 83.3%.

TG level was significantly higher in KD patients than in those with febrile illness. Furthermore, mean TG level was significantly higher in patients with coronary artery involvement than in those without involvement. Some studies indicate that elevated TG level is associated with endothelial inflammation and dysfunction (16,17). These observations make one think that high TG levels in patients with KD can predispose to coronary involvement.

We found a negative correlation between HDL-C and CRP levels in both groups. The negative correlation between CRP and HDL-C detected in our study could suggest that decreased levels of HDL-C reflect the severity of inflammation. Additionally, in KD patients, HDL-C level was positively correlated with the duration of fever. Based on this observation, we think that the diagnostic value of HDL-C in KD patients decrease as the duration of fever gets longer. Therefore, the use of low HDL-C level as a diagnostic marker for KD may be feasible merely during the acute phase of the illness.

While HDL-C levels during the acute phase of inflammatory diseases have exhibited consistent and marked decrements in previous studies, LDL-C level exhibited decrement in one study and increment in another (18,19). We found no change in LDL-C level in both groups.

Studies regarding the lipid profile in KD have focused mostly on its prognostic value. However, there are few studies on its diagnostic value. A study of Newburger et al. (20) indicated that increased ratio of total cholesterol\HDL-C levels, in addition to decreased HDL-C level, was also meaningful in patients with KD but they did not determine a cut-off value. We propose that a HDL-C level cutoff value below 23mg\dL is feasible and acceptable in supporting KD with 85.37% sensitivity and 83.33% specificity. Our result suggests that serum HDL-C level can be used as a supportive finding in KD, just as other laboratory markers (ESR, CRP, thrombocytosis, and anemia etc.) recommended in the AHA guidelines.

Huang et al. (21) studied on another biochemical markers in patients with KD. They found a cutoff value of 2 using the ratio of haptoglobin\apolipoprotein A-1 for diagnosing KD with 89.7% sensitivity and 85.6% specificity. The study of Lin et al. (22) examined KD patients with regard to a relationship between altered lipid profile and further atherosclerosis. They did not find a long lasting effect on HDL-C profile in pediatric and adult patients who have KD.

Conclusion

The study showed that serum HDL-C level is lower in patients with KD than in those with acute infectious febrile disease. Serum HDL-C levels combined with clinical characteristic findings may help differentiate incomplete KD cases from other febrile illnesses of infectious origin. Our results showed that the cutoff value of 23 mg\dL HDL-C level has 85.37% sensitivity and 83.33% specificity for detection of KD. We did not detect a link between coronary artery involvement and HDL-C levels; therefore, the prognostic value of HDL-C level remains controversial. We also found that KD patients with coronary artery involvement have a higher TG levels than those without coronary involvement and those who had acute infectious disease. Further studies are needed to identify the prognostic value of higher TG levels in predicting the possibility of coronary artery involvement in KD.

Ethics

Ethics Committee Approval: Kocaeli University Non-Invasive Clinical Research Ethics Committee (approval number: KÜ GOKAEK 2018/7 date: 18.04.2018)

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

COVID-19 Pandemisi ve Kısıtlamalarının Tip 1 Diabetes Mellitus Hastalarında Glisemik Kontrol Üzerine Etkisi

The Effect of the COVID-19 Pandemic and its Restrictions on Glycemic Control in Patients with Type 1 Diabetes Mellitus

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Öz

Giriş: Şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonu tip 1 diabetes mellitus (DM) tanılı hastalarında karantina nedeni ile zorunlu hareketsiz yaşam, egzersiz programlarının aksamasına, fazla kalori alımına ve glisemik kontrolün kötüleşmesine neden olabilmektedir. Çalışmamızda kliniğimizde tip 1 DM tanısı ile izlenen olguların Koronavirüs hastalığı-2019 (COVID-19) pandemisi süresince glisemik kontrolü ve günlük insülin ihtiyaçlarındaki değişiklikleri değerlendirmeyi planlandık.

Gereç ve Yöntem: Çocuk endokrinoloji kliniğinde tip 1 DM tanısı ile izlenen olguların Türkiye'de ilk COVID-19 olgusunun görüldüğü Mart 2020 tarihinden önceki 1 yıllık ve sonrasındaki 1 yıllık izlem verileri incelendi. Takipte olan 350 olgunun verileri geriye dönük olarak incelendi. Çalışma kriterlerine uymayan hastalar çıkarıldıktan sonra geriye kalan 167 olgunun 36'sına bu dönemde insülin pompası takılması nedeni ile ayrıca değerlendirildi. Sonuç olarak 131 hastanın dosyaları, glikolize hemoglobin A1c (HbA1c) değerleri ve günlük insülin dozları değerlendirildi.

Bulgular: Olguların boy, boy standart deviasyon skoru (SDS), vücut ağırlığı, vücut ağırlığı SDS, vücut kitle indeksi (VKİ), ve VKİ SDS değerlerinde pandemi öncesine göre anlamlı farklılık saptanmadı. Glisemik kontrolde (HbA1c değerinde) kötüleşme saptanmadı (p=0,16). Pandemi öncesine göre olguların ortalama günlük insülin dozu anlamlı olarak artmıştı (p<0,001). On iki yaş altı ve üstü gruplarda glisemik kontrolde kötüleşme gözlenmezken günlük insülin dozlarında artış saptandı (sırasıyla; p=0,620/0,180; p=0,003/0,004).

Sonuç: Çalışmamızda olguların HbA1c düzeylerinde pandemi öncesine göre anlamlı artış saptanmamıştır. Bu hastalara tam kapanma döneminde dahi teletıp ile hizmet verilmesine bağlanmıştır. Ancak hastaların hareketsiz olmaları nedeni ile iyi glisemik kontrolü sağlayabilmek için insülin dozlarının artırılması gerekmiştir. Sonuç olarak, çalışmamız pandemi döneminde standart diyabet bakımının devamlılığının sağlanması halinde glisemik kontrolde bozulma olmayacağı gösterilmiştir.

Anahtar kelimeler
Glisemik kontrol, tip 1 DM, SARS-CoV-2

Keywords
Glycemic control, type 1 DM, SARS-CoV-2

Abstract

Introduction: Mandatory sedentary life due to quarantine, disruption of exercise programs, excessive caloric intake and worsening of glycemic control in patients diagnosed with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection type 1 diabetes mellitus (DM). In our study, we planned to evaluate the changes in glycemic control and daily insulin needs during the Coronavirus disease-19 (COVID-19) pandemic of the cases followed up with the diagnosis of type 1 DM in our clinic.

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Materials and Methods: The 1-year follow-up data of the cases followed up in the pediatric endocrinology clinic with the diagnosis of type 1 DM, before and after March 2020, when the first COVID-19 case in Turkey was seen, were analyzed. The data of 350 patients who were followed up were retrospectively analyzed. After the patients who did not meet the study criteria were excluded, 36 of the remaining 167 cases were evaluated separately because of the insertion of an insulin pump during this period. As a result, files of 131 patients, glycosylated hemoglobin A1c (HbA1c) values and daily insulin doses were evaluated.
Results: No significant difference was found in the subjects' height, standard deviation score (SDS), body weight, body weight SDS, body mass index (BMI), and BMI SDS values compared to the pre-pandemic period. There was no worsening in glycemic control (HbA1c value) (p=0.16). The mean daily insulin dose of the cases increased significantly compared to the pre-pandemic period (p<0.001). While no worsening was observed in glycemic control in the groups younger than 12 years of age and older, an increase was observed in daily insulin doses (respectively; p=0.620/0.180, p=0.003/0.004).
Conclusion: In our study, no significant increase was found in the HbA1c levels of the cases compared to the pre-pandemic period. This has been attributed to the provision of telemedicine services to these patients even during the full closure period. However, due to the inactivity of the patients, insulin doses had to be increased in order to achieve good glycemic control. In conclusion, our study has shown that glycemic control will not be impaired if standard diabetes care is maintained during the pandemic period.

Giriş

Tip 1 diabetes mellitus (DM), insülin üreten pankreas β-hücrelerinin selektif yıkımı ile ilişkili kronik bir otoimmün hastalık olup, çocukluk çağında en sık görülen DM tipidir (1). Pankreas hücrelerine yönelik otoantikorların (anti-glutamat dekarboksilaz, anti-adacık, anti-insülin) pozitif olması, serum C-peptit ve insülin düzeylerinin düşük olması DM sınıflamasında tip 1 DM'yi destekler (2).

2019 yılı sonuna doğru Çin'de ortaya çıkan şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonu kısa süre içerisinde dünya geneline yayılmıştır. Dünya Sağlık Örgütü tarafından pandemi kabul edilen SARS-CoV-2 enfeksiyonunun şu anda diyabetli çocuklarda sağlıklı çocuklara göre yüksek riskli olduğunu gösteren hiçbir kanıt yoktur. Ancak karantina nedeni ile zorunlu hareketsiz yaşam, egzersiz programlarının aksamasına, fazla kalori alımına ve glisemik kontrolün kötüleşmesine neden olmuştur. Bilindiği üzere sıkı metabolik kontrol kısa ve uzun vadeli komplikasyonları önlemek için zorunludur (3). Glikolize hemoglobin A1c (HbA1c), American Diabet Association ve Internatinal Society for Pediatric and Adolescent Diabetes'e (ISPAD) göre <%7 optimal, %7-9 arasında suboptimal ve >%9 kötü metabolik kontrol olarak sınıflandırılmıştır (4,5).

Türkiye'de ilk olgunun 11 Mart 2020'de görülmesinden sonra Türk Hükümeti tarafından üç aylık karantina uygulanmış ve bu esnada yüz yüze planlanan ziyaretler iptal edilmiştir. Tüm dünyada bu dönemde teletıp yöntemi, tip 1 DM hastalarına sağlık hizmeti vermek ve glisemik kontrolü sağlayabilmek için önerilmiştir (6).

Çalışmamızda, Akdeniz Üniversitesi, Çocuk Endokrinolojisi Kliniği'nde tip 1 DM tanısı ile izlenen hastaların COVID-19 pandemisi süresince glisemik kontrolündeki ve günlük insülin ihtiyaçlarındaki değişiklikleri geriye dönük olarak değerlendirmeyi planlandık.

Gereç ve Yöntem

Çalışma Dizaynı ve Veri Toplama

Akdeniz Üniversitesi, Çocuk Endokrinoloji Kliniği'nde tip 1 DM tanısı ile izlenen hastaların Türkiye'de ilk SARS-CoV-2 olgusunun görüldüğü Mart 2020 tarihinden önceki 1 yıl içindeki (Mart 2019-2020) ve üç aylık sokağa çıkma yasağı sonrasındaki bir yıl içindeki (Haziran 2020-2021) verileri incelendi.

Takipte olan 350 hastanın dosyası incelendi. Tip 1 DM dışındaki DM tanılı hastalar, Mart 2019 sonrasında tanı alan hastalar ve pandemi öncesi ve sonrasında en az bir poliklinik kontrolü olmayan hastalar çalışma dışında bırakıldı. Bu hastalar çalışma dışı bırakıldıktan sonra geriye kalan 167 hastanın 36'sı bu izlem döneminde insülin pompası takılması nedeni ile HbA1c değerlerini etkileyeceği düşünülerek ayrıca değerlendirildi. Sonuç olarak, toplam 131 çoklu doz insülin tedavisi alan ve 36 insülin pompası kullanan hastaların ayrı ayrı laboratuvar sonuçları incelendi. Hastaların günlük kan glukozu ve insülin dozları, diyete uyumları, egzersiz yapma durumları, karbonhidrat sayımı yapma durumları, SARS-CoV-2 enfeksiyonu geçirme durumları, diyabetik ketoasidoz (DKA) atağı geçirme durumları incelendi. Diyete

uyum ve egzersiz yapma durumları değerlendirilirken hasta beyanı esas alındı.

Pandemi döneminde ebeveynlerin evde kalması ile 12 yaş altı çocuklarda ve diyabet bakımını kendi yapan 12 yaş üstü çocuklarda glisemik kontrolde farklı değişiklik olabileceği düşünülerek iki grup oluşturuldu. Gruplar kendi içlerinde ayrıca değerlendirildi.

Tanımlama ve Teşhis Prosedürü

Hastalara tip 1 DM tanısı ISPAD 2018 kılavuzuna göre konuldu. Kandaki glukoz konsantrasyonu, C-peptit, HbA1c, venöz kan gazı pH ve bikarbonat değeri, tip 1 DM ile ilişkilendirilmiş otoantikor varlığı (en az bir pozitif sonucun varılığı) tanı için kullanıldı. Hastaların pandemi öncesi ve sonrası boy, boy standart deviasyon skoru (SDS), vücut ağırlığı, vücut ağırlığı SDS, vücut kitle indeksi (VKİ), VKİ SDS değerleri kaydedildi. VKİ, kilogram cinsinden ağırlığın metre cinsinden boyun karesine oranı (kg/m^2) olarak hesaplandı. Her antropometrik ölçümün SDS Türk çocukları standartlarına göre hesaplandı (7).

Etik

Olgularımız Helsinki Deklerasyon'u göz önünde bulundurularak değerlendirildi. Çalışma için Akdeniz Üniversitesi Etik Kurulu'ndan onay alındı (onay numarası: 70904504/890, tarih: 31.12.2021).

İstatistiksel Analiz

İstatistiksel analiz için SPSS 23.0 programı kullanıldı. Kategorik ölçümler sayı ve yüzde olarak, sürekli ölçümler ortalama ± SD veya ortanca çeyrekler arası aralık interquatil range olarak sunuldu. Çalışmadaki parametrelerin normal dağılım gösterip göstermediğini belirlemek için Shapiro-Wilk testi kullanıldı. Gruplar arası sürekli ölçümlerin karşılaştırmasında dağılımlar kontrol edildi ve normal dağılım göstermeyen parametreler için Wilcoxon testinde elde edilen $p<0,05$ değeri anlamlı kabul edildi.

Bulgular

Hastaların ortalama yaşı 12,84±3,61, ortalama diyabet süresi 5,95±3,37'di. Hastaların 64'ü (%49,2) kız, 66'sı (%50,8) erkekti. 43'ü (%32,8) diyetine uyuyor, 47'si (%35,9) ara sıra uyuyor, 41'i (%31,3) diyetine uymuyordu. 20'si (%15,3) düzenli egzersiz yapıyor, 47'si (%35,9) ara sıra egzersiz yapıyor, 64'ü (%48,9) hiç yapmıyordu. Hastaların 35'i (%26,7) karbonhidrat sayıyor, 96'sı (%73,3) karbonhidrat saymıyordu. Hastaların 4'ü (%3,1) izlem süresinde DKA tanısı ile yatırılarak izlenmişti, 7'si (%5,3) SARS-CoV-2 enfeksiyonu geçirmişti (Tablo 1).

Hastaların pandemi öncesi ve sonrası boy SDS, vücut ağırlığı SDS, VKİ SDS ve HbA1c değerlerinde anlamlı bir değişiklik izlenmedi. Ancak hastaların günlük insülin dozu pandemi öncesine göre anlamlı olarak artmıştı ($p<0,001$) (Tablo 2).

Diyabet bakımı ebeveynleri tarafından yapılan 12 yaş altı hastalar kendi içinde değerlendirildi. Bu hastaların pandemi öncesi ve sonrası boy SDS, vücut ağırlığı SDS, VKİ SDS ve HbA1c değerlerinde anlamlı bir değişiklik izlenmedi. Farklı olarak hastaların günlük insülin dozu pandemi öncesine göre anlamlı olarak artmıştı ($p=0,03$) (Tablo 3).

Tablo 1. Tip 1 DM tanılı hastaların genel özellikleri	
Yaş	12,84±3,61
Tanı yaşı	6,78±3,79
Diyabet yaşı	5,95±3,37
Cinsiyet	
Kız	64 (%49,2)
Erkek	66 (%50,8)
Diyet	
Diyete uyuyor	43 (%32,8)
Ara sıra uyuyor	47 (%35,9)
Diyete uymuyor	41 (%31,3)
Egzersiz	
Düzenli yapıyor	20 (%15,2)
Ara ara yapıyor	47 (%35,9)
Yapmıyor	64 (%48,9)
KH sayımı	
Yapıyor	35 (%26,7)
Yapmıyor	96 (%73,3)
DKA nedeni ile yatış	
Var	4 (%3,1)
Yok	127 (%96,9)
COVID	
Var	7 (%5,3)
Yok	124 (%94,7)

DM: Diabetes mellitus, KH: Karbonhidrat, DKA: Diyabetik ketoaidoz, COVID: Koronavirüs hastalığı

Tablo 2. Tip 1 DM hastalarının pandemi öncesi ve sonrası değerlerinin karşılaştırılması			
	PÖ	PS	p-değeri
Boy SDS	-0,06±1,31	-0,08±1,27	0,08
VA SDS	0,20 (0,95)	0,38 (1,40)	0,25
VKİ SDS	0,09 (1,37)	0,09 (1,68)	0,40
İnsülin dozu	0,83±0,23	0,91±0,29	0,00*
Ortalama HbA1c	9,48 (2,83)	9,18 (2,35)	0,16
DM: Diabetes mellitus, PÖ: Pandemi öncesi, PS: Pandemi sonrası, SDS: Standart deviasyon skoru, VA: Vücut ağırlığı, VKİ: Vücut kitle indeksi, HbA1c: Glikolize hemoglobin A1c			

Tablo 3. Yaş gruplarına göre tip 1 DM hastalarının pandemi öncesi ve sonrası değerlerinin karşılaştırılması						
	<12 yaş			>12 yaş		
	PÖ	PS	p-değeri	PÖ	PS	p-değeri
Boy SDS	0,32±1,09	0,27±0,99	0,420	-0,33±1,39	-0,33±1,38	0,090
VA SDS	0,40 (0,77)	0,15 (0,80)	0,430	0,10 (1,25)	0,10 (1,55)	0,380
VKİ SDS	0,16 (1,05)	0,12 (1,48)	0,400	0,08 (1,58)	0,33 (1,77)	0,080
İnsülin dozu	0,77±0,21	0,87±0,28	0,003*	0,88±0,24	0,94±0,29	0,004*
Ortalama HbA1c	8,57 (2,15)	8,68 (1,82)	0,620	9,21 (3,34)	8,90 (3,01)	0,180
DM: Diabetes mellitus, PÖ: Pandemi öncesi, PS: Pandemi sonrası, SDS: Standart deviasyon skoru, VA: Vücut ağırlığı, VKİ: Vücut kitle indeksi, HbA1c: Glikolize hemoglobin A1c						

Tablo 4. Tip 1 DM tanılı insülin pompası kullanan hastaların pandemi öncesi ve sonrası değerlerinin karşılaştırılması			
	PÖ	PS	p-değeri
Boy SDS	-0,08±0,93	-0,09±0,97	0,960
VA SDS	0,10 (1,20)	0,10 (2,00)	0,540
VKİ SDS	0,20 (1,48)	0,40 (2,40)	0,840
İnsülin dozu	0,89±0,31	0,94±0,28	0,160
Ortalama HbA1c	8,80 (1,59)	8,30 (1,53)	<0,001*
DM: Diabetes mellitus, PÖ: Pandemi öncesi, PS: Pandemi sonrası, SDS: Standart deviasyon skoru, VA: Vücut ağırlığı, VKİ: Vücut kitle indeksi, HbA1c: Glikolize hemoglobin A1c			

Diyabetini kendi yöneten ve düzensiz yaşamdan uzaklaşan 12 yaş üstü hastalar değerlendirildi. Bu grubun pandemi öncesi ve sonrası boy SDS, vücut ağırlığı SDS, VKİ SDS ve HbA1c değerlerinde de anlamlı bir değişiklik izlenmedi. Diğer grup ile benzer olarak günlük insülin dozu pandemi öncesine göre anlamlı olarak artmıştı (p=0,04) (Tablo 3).

İnsülin pompası kullanan hastaların pandemi öncesi ve sonrası boy SDS, vücut ağırlığı SDS, VKİ SDS ve günlük insülin dozu değerlerinde anlamlı bir değişiklik izlenmezken, farklı olarak hastaların ortanca HbA1c değeri pandemi sonrasında anlamlı olarak azalmıştı (p<0,001) (Tablo 4).

Tartışma

ISPAD pandemi sürecinde acile başvuru ve yatış ihtiyacını azaltmak için standart diyabet bakımının devamlılığının sağlanmasının gerekliliğini vurgulamıştır (8). Pandeminin erken döneminde Hindistan'dan yapılan retrospektif bir çalışmada pandemi sırasında karantinaya bağlı insülin ve glikostrip temin edememe, zayıf beslenme uyumu ve azalmış fiziksel aktiviteye bağlı olarak glisemik kontrolün bozulduğu ve HbA1c değerinin 8,8'den 10'a yükseldiği gösterilmiştir (9). Bu çalışmada ISPAD'nin önerilerini doğrular niteliktedir.

Turan ve ark.'nın (10) çalışmasında 100 tip 1 DM hastasının pandemi öncesine göre vücut ağırlıklarının

arttığı, fiziksel aktivite skorlarının anlamlı olarak düştüğü, yeme alışkanlıklarının bozulduğu ve buna bağlı olarak ortalama HbA1c değerlerinin arttığı ancak günlük insülin dozlarının değişmediği gösterilmiştir. Ruissen ve ark.'nın (11), 280'i tip 1 DM tanılı toplam 435 DM'li hastayı değerlendirdiği çalışmada ise hastalarda anlamlı kilo artışı saptanırken glisemik kontrolde kötüleşme saptanmamıştır. Bu da hastaların karantina döneminde daha düzenli bir hayat sürmelerine bağlanmıştır.

Bizim çalışmamızda hastaların HbA1c değerlerinde pandemi öncesine göre anlamlı artış saptanmamıştır. Bu durum, hastalara tam kapanma döneminde dahi teletıp ile hizmet verilmesine bağlanabilir. Ayrıca hastaların raporları Sosyal Güvenlik Kurumu tarafından otamatik olarak uzatılmıştır ve hastalar reçetesiz eczaneden ilaçlarını alabilmiştir. Hastalar pandemi döneminde insülin ve strip temininde bulunabilmiş ve sağlık hizmetine ulaşmada sıkıntı yaşamamışlardır. Pandemi döneminde yüz yüze görüşmelerin iptal olması ile beraber teletıp (e-posta, zoom, whatsapp, telefon) uygulamalarının hayata geçirilmesinin diyabet yönetiminde faydalarının vurgulandığı benzer makaleler mevcuttur (12).

Hastalarımızın hareketsiz olmaları nedeni ile iyi glisemik kontrolü sağlayabilmek için insülin dozlarının artırılması gerekmiştir. Buna rağmen hastaların vücut ağırlığı SDS ve VKİ SDS değerlerinde de anlamlı artış olmamıştır. Bu bize hastaların evde oldukları dönemde daha düzenli ve sağlıklı beslenmeye vakit ayırmış olabileceklerini düşündürmüştür.

Pandeminin başında İtalya'dan bir çalışmada 13 sürekli glukoz moniterizasyonu (SGM) kullanan tip 1 DM'li adölesanın iki haftalık verileri değerlendirilmiş ve beklenenin aksine hastaların hedef aralıktaki değerlerinin artığı ve glisemik değişkenliklerinin azaldığı gösterilmiştir. Adölesan grubu kapsayan bu çalışmada karantina döneminde düzenli beslenme, düzenli yaşam ve okul stresinin azalmasının hastaların daha iyi glisemik sonuçlar elde etmesini sağladığı düşünülmüştür (13). Benzer olarak 62 hastanın pandemi öncesi ve sonrası SGM verilerinin değerlendirildiği çalışmada, hastaların glisemik kontrollerinde iyileşme, hedef aralıktaki değerlerinde artış saptanırken günlük insülin dozlarında değişiklik gözlenmemiştir. Bu sonuçlar düzenli yaşam şekli, ailelerin daha çok evde olması ve teletıp uygulamalarının etkisi olarak yorumlanmıştır. Ancak bu çalışmanın kısıtlılığı SGM kullanan hastaların genelde iyi bakım sağlayan hastalar arasında oldukları olarak bildirilmiştir ve genelleme yapılamayacağına değinilmiştir (14).

Hastalarımızın 12 yaş altı olanlarının diyabet bakımını daha çok ebeveynleri tarafından karşılanmaktadır. Bu grubun ebeveynlerinin daha çok evde kalması ile glisemik kontrolde beklenildiği üzere bir iyileşme gözlemlemedik. Bu, hastaların zorunlu hareketsiz yaşamına bağlanabilir. On iki yaş üstü hastalar da daha çok evde kalmaları ile stresten ve düzensiz yaşam şeklinden uzak kalmışlardır. Bu hasta grubumuzda da glisemik kontrolde değişiklik izlenmezken, günlük insülin dozunda artış izlenmiştir. Bu da yine zorunlu hareketsiz yaşam ile açıklanabilir.

Ayrı bir grup olarak değerlendiğimiz 36 pompa hastamızın ortalama HbA1c düzeylerinde anlamlı azalma saptandı. Predieri ve ark.'nın (14) makalesinde vurguladığı gibi diyabet teknolojilerini kullanan hastalar zaten iyi bakım sağlayan hastalar arasındadır. Ayrıca hastalarımızın bir bölümüne pandemi sürecinde pompa takılması nedeniyle de HbA1c değerlerinin etkilenmiş olabileceği düşünüldü. Bu sebeple glisemik kontroldeki iyileşmenin sebebini net saptamak güçtür.

Çalışmanın Kısıtlılıkları

Çalışmamızın kısıtlılıkları şunlardır: 1) Hastaların günlük karbonhidrat tüketimi ve günlük aktive skorları çalışmaya dahil edilse daha kıymetli veriler elde edilebilirdi. 2) Pompa kullanan hastaların hepsi SGM kullanmadığı için, SGM verileri çalışmaya eklenememiş ve bu veriler değerlendirilememiştir.

Sonuç

Çalışmamız pandemi döneminde standart diyabet bakımının devamlılığının sağlanması, gerekirse teletıp yöntemlerine başvurulması, diyabet hastaları ile yakın iletişim halinde olunmasının önemine dikkat çekmiştir. Bu koşullar sağlanması halinde glisemik kontrolde bozulma olmayacağı gösterilmiştir.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Serum Mindin, Nephrin and Podocalyxin Levels in Patients with Type 1 Diabetes: Are These New Markers to Detect the Development of Nephropathy?

Tip 1 Diyabet Hastalarının Serum Mindin, Nephrin ve Podokaliksin Düzeyleri: Nefropati Gelişimini Saptamada Yeni Markerlar Olabilir mi?

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Abstract

Introduction: Type 1 diabetes mellitus (DM) is a chronic disease that develops as a result of absolute insulin deficiency. DM is accompanied by chronic complications which are associated with a high risk of morbidity and mortality. In the present study, we aimed to understand whether serum mindin, nephrin (NPHS1) and podocalyxin (PODXL) are useful biomarkers in the determination of nephropathy in patients with type 1 DM and to understand any correlation between serum mindin, PODXL, nephrin levels and hemoglobin A1c (HbA1c) levels and 24 hour urinary albumin excretion of patients. We investigated serum PODXL, nephrin and mindin levels in pediatric patients with type 1 DM.

Materials and Methods: Forty patients with type 1 DM along with controls, all in the pubertal stage, were included in the study. Serum mindin, nephrin and PODXL levels were measured using commercial ELISA kits. In the DM group, the mean age, gender distribution, follow-up time, and HbA1c levels were evaluated.

Results: There was no significant difference in the serum mindin levels between the DM and control groups (p=0.053). When the serum nephrin levels were compared between the two groups, the nephrin levels were significantly lower in the DM group (p=0.016). The serum PODXL levels of the DM group were significantly lower when compared to the control group (p=0.014).

Conclusion: We found that the blood levels of nephrin, PODXL were decreased in the DM group. These markers can be excreted in urine and may be sensitive markers for DM. This is the first study in the literature to evaluate PODXL, mindin, nephrin biomarkers in pediatric patients with type 1 DM.

Keywords
Diabetes mellitus, mindin, podocalyxin, nephrin, diabetic nephropathy

Anahtar kelimeler
Diabetes mellitus, mindin, podokaliksin, nefrin, diyabetik nefropati

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Öz

Giriş: Tip 1 diabetes mellitus (DM) mutlak insülin eksikliği ile gelişen kronik bir hastalıktır. DM yüksek mortalite ve morbidite ile sonuçlanabilen kronik komplikasyonlarla seyreder. Bu çalışmada serum mindin nefrin (NPHS1) ve podokaliksin (PODXL) düzeylerinin tip 1 DM hastalarında nefropatinin erken dönemde saptanmasında yararlı bir biyobelirteç olup olamayacağını ve serum mindin, PODXL, nefrin düzeyleri ile serum hemoglobin A1c (HbA1c) düzeyleri ve 24 saatlik idrarda albümin atılım düzeyleri arasında bir ilişki olup olmadığını araştırmayı hedefledik.

Gereç ve Yöntem: Tip 1 DM tanısı almış hastaların serum mindin, PODXL, nefrin düzeylerini çalıştık. Hasta grubu olarak tip 1 DM tanısı almış pubertal evredeki 40

hasta; kontrol grubu olarak pubertal evredeki ek bilinen hastalığı olmayan 40 hasta çalışmaya dahil edildi. Serum mindin, PODXL, nefrin düzeyleri ELISA kitleri kullanılarak ölçüldü. DM grubunda yaş ortalaması, cinsiyet dağılımı, takip süresi ve HbA1c düzeyleri değerlendirildi.

Bulgular: Kontrol ve hasta grubunun serum mindin düzeyleri arasında anlamlı fark saptanmadı (p=0,053). Hasta grubunun serum nefrin ve PODXL düzeyleri kontrol grubuna göre anlamlı olarak düşük saptandı (p=0,016; p=0,014).

Sonuç: Serum nefrin ve PODXL düzeylerini hasta grubunda düşük olarak saptadık. Bu belirteçlerin idrarla atılıyor olmaları ve serum düzeylerinin düşük olması diyabetik nefropatinin gelişimi için ilerde sensitif belirteçler olabileceğini bize gösterebilir.

Introduction

Diabetes mellitus (DM) is the most common chronic disease occuring in childhood and is a condition where absolute insulin deficiency develops as a result of the destruction of pancreatic beta cells (1). Microvascular and macrovascular complications may develop in the long-term as a result of poor glycemic control in patients with DM (2-4). One significant long-term complication is diabetic nephropathy (DN), which can result in end-stage renal failure (2-4). Detection of microalbuminuria is the most widely used laboratory tool for DN, however it is known to be affected by various factors; such as fever, dehydration, urinary tract infection, hypertension and heavy exercise. In previous studies, approximately 30% of diabetics patients with renal dysfunction have normoalbuminuria, while renal morbidity is increased in the high normal range of urine albümin excretion (5). The presence of microalbumin in urine may provide clues about damage to all three components of the glomerular filtration barrier: the endothelium, glomerular basement membrane, and podocytes and it is not a reliable marker that structural damage might precede microalbumin excretion. However, the other podocyte-specific proteins indicate only damage to podocytes, independent of the other two components of the glomerular filtration barrier (6).

The 24 hour collection of urine can be difficult due to patient compliance and is also time consuming. For these reasons, diagnosis can be delayed and a workday can be lost. Furthermore pediatric patients experience problem with timed and correct collection of 24 hour urine. Estimation of albumin in spot urine is no longer regarded as a reliable test, as it only provides instant information and this is not as accurate as that which is provided in 24-hour collection of urine. Thus, there is ongoing research to identify cheaper and more sensitive markers to better detect the development of nephropathy.

Mindin, a member of the F-mindin family, is an extracellular matrix protein synthesized in the basal lamina. Mindin has many functions in cells and acts similarly to integrin, which plays a crucial role in podocyte damage (7). It has been found that cytokines, such as transforming growth factor-beta and vascular endothelial growth factor, hyperglycemia, integrins, and extracellular proteins cause an increase in glomerular expression of mindin, fibrosis in glomeruli, and nephropathy (7-9). Similarly, mindin levels may increase in hyperglycemic situations. In recent studies, it was found that mindin mRNA expression was increased in diabetic mice (10). In addition, urinary mindin levels were reported to have increased in patients with type 2 DM who had developed DN (10).

Nephrin is a transmembrane protein located on the lateral surface of the glomerular podocyte feet. Nephrin provides complete physical barrier and makes up the structure of the filtration diaphragm. It was found that the expression of nephrin mRNA and protein increased in kidneys of patients with proteinuric nephropathy (7,11).

Podocalyxin (PODXL) is an anionic transmembrane protein found in the apical membranes of glomerular podocytes. PODXL is an O-glycolyzed and sialyzed type 1 transmembrane protein normally secreted by kidney podocytes, hematopoietic precursor cells, vascular endothelium and neurons. PODXL is one of the important proteins of the charge barrier of the glomerular basement membrane and plays a critical role in regulating the permeability of the glomerular filtration barrier (12). In a group of patients with type 2 DM and overt proteinuria, the level of urinary PODXL levels was found to be higher than those of the healthy control group (13).

To the best of our knowledge, markers that indicate podocyte inflammation, such as mindin, nephrin, and PODXL have not been previously investigated in children and adolescents with type 1 DM. In this study, we aimed to understand whether serum mindin, nephrin and PODXL are a useful biomarker in the determination of nephropathy in patients with type 1

DM and to understand any correlation between serum mindin, PODXL, nephrin levels and hemoglobin A1c (HbA1c), urea, creatinine levels and 24-hour urinary albumin excretion of patients. We chose to study these biomarkers in a serum, considering that we can get faster and more accurate results than urine due to the difficulties associated with collecting 24-hour urine in pediatric patients.

Materials and Methods

Participants

This study was performed on 40 patients with type 1 DM who were followed up in the pediatric endocrinology outpatient clinic of Bursa Uludağ University Faculty of Medicine between January 2016 and December 2017. The control group consisted of 40 healthy children without any endocrinological or renal disease who attended the pediatric outpatient clinic of the same university during the same period. This study was carried out after obtaining permission from the parents of the patients and controls and approval from the Bursa Uludağ University Faculty of Medicine Ethics Committee with the (approval number: 2016-16/1, date: 19.08.2016).

Patients with type 1 DM aged 10-18 (pubertal period), who had been followed up for at least two years following diagnosis of DM, were included in the study. Patients were questioned about their diagnosis date, medications, and any complications. Type 1 DM patients with nephropathies, syndromic cases, patients that were in pubertal stage 1 and those with a diagnosis of DM for less than two years were excluded from the study. The blood pressures of all patients was measured and they were all found to be normal. The HbA1c levels were classified as good/moderate (<9%) or poor control (>9%). Patients were subdivided according to diabetes duration time as <5 years and >5 years.

The control group consisted of age-matched individuals who attended the outpatient clinic for growth and development monitoring or vaccination with no complaint or known disease.

Statistical Analysis

Blood samples were taken using 0.18x40 mm needles (Becton Dickinson, USA) to obtain serum from the antecubital vein (Vacutainer, Becton Dickinson, USA) following 8-10 hours of fasting. The samples were centrifuged at 3,000x rpm for 10 minutes (1200 NF Core, Turkey) and divided into portions. The portioned serum samples were stored at -80 °C until study. Mid stream urine was collected in the morning was used for microalbumin analysis.

HbA1c was analyzed using high-performance liquid chromatography-specifically, the Boronate affinity chromatography method on a Premier Hb9210 (Trinity Biotech, Ireland) device. The serum mindin levels were measured using the micro-ELISA method with a MyBioSource human SPONDIN-2 ELISA kit. The serum nephrin levels were measured using the micro-ELISA method with the Fine Test human NPHS1 ELISA kit. The serum PODXL levels were measured using the micro-ELISA method with the Fine test human PODXL ELISA kit. By dissolving the lyophilized standard present in the kit, different concentrations were obtained with the diluent. The absorbance of the samples studied in accordance with the kit procedure was measured at 450 nm on the FLASHScan® S12 (Analytik Jena, Germany) device. Using the formula obtained with the help of the standard curve graph, the concentrations in ng/mL corresponding to all absorbances were calculated (Mindin kit range: 0.05-38 ng/mL, sensitivity: <0.78 ng/mL) (Nephrin kit Range: 3.12-200 pg/mL, sensitivity: <1.875 pg/mL) (PODXL kit range: 0.156-10 ng/mL, sensitivity: <0.094 ng/mL).

The SPSS package program (version 11.5) was used for statistical analyses. The compliance of the data with the normal distribution curve was evaluated using the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation. For continuous variables, the Student's t-test was used for the normally distributed data and the Mann-Whitney U test for the data that did not meet the normality assumption. Categorical data were compared using the chi-square test. The Spearman correlation test was conducted to investigate whether there was a correlation between the data. Results with $p<0.05$ was considered statistically significant.

Results

Of the 80 subjects who constituted the DM and control groups, 43 (53.7%) were girls and 37 (46.2%) were boys. Of the patients with type 1 DM, 17 (42.5%) were girls and 23 (57.5%) were boys while the control

group comprised 26 (65%) girls and 14 (35%) boys. The mean age of the DM group was 14.5 years, and that of the control group was 13.3 years (p=0.11) (Table 1). All of the DM patients and controls were in the pubertal stage. The HbA1c value was <9% in 12 patients and ≥9% in 28. The mean HbA1c level of the patients was calculated as 9.94±1.92% (Table 1). In the DM group, the mean duration of the disease was 7.64±3.05 years. In this group, nine (22.5%) patients had been followed up for DM for less than five years and 31 (77.5%) had been followed up for DM for more than five years, and the mean ages of these subgroups were 14 and 14.6 years, respectively.

The median serum mindin level was 5.38 pg/mL (3.66-9.82 pg/mL) in the DM group and 6.34 pg/mL (4.76-9.89 pg/mL) in the control group. A difference was found in the serum mindin level between the two groups, but it was not statistically significant (p=0.053) (Figure 1). The median serum mindin value of the patients with an HbA1c of <9% was 5.38 pg/mL (3.66-8.59 pg/mL), and that of the patients with an HbA1c of ≥9% was 5.38 pg/mL (4.20-9.82 pg/mL), indicating no significant difference (p=0.34) (Table 2). The median serum mindin level of the patients with a DM duration of <5 years was 5.38 pg/mL (4.89-7.63 pg/mL), and that of the patients with a DM duration of ≥5 years was 5.3 pg/mL (3.66-9.82 pg/mL), revealing no significant difference (p=0.97) (Table 3).

The median serum PODXL values were 0.28 pg/mL (0.24-1.26 pg/mL) and 0.36 pg/mL (0.15-0.91 pg/mL) for the DM and control groups, respectively. When the serum PODXL levels were compared between the two groups, they were significantly lower in the DM group (p=0.014) (Figure 1). The median serum PODXL value of the patients with HbA1c of <9% was 0.28 pg/mL (0.16-0.63 pg/mL), which did not significantly differ from the value of the patients with HbA1c ≥9% [0.29 pg/mL (0.14-1.26 pg/mL)] (p=0.69) (Table 2). Concerning the evaluation according to disease duration, the median serum PODXL value was determined as 0.33 pg/mL (0.26-1.26 pg/mL) for the patients with a DM duration of <5 years and 0.28 pg/mL (0.14-0.86 pg/mL) for those suffering from DM for ≥5 years. There was no significant difference in the serum PODXL levels between these two subgroups (p=0.075) (Table 3). There was no significant correlation between the DM duration and the serum mindin, nephrin, and PODXL levels of the patient

Table 1. Characteristics of the cases

	Diabetes mellitus patients	Controls
Age (year)	14.5±2.08	13.3±1.02
Gender (famele/male)	17/23	26/14
HbA1c (%)	9.94±1.92	-

HbA1c: Hemoglobin A1c

Table 2. Comparison of the serum mindin, nephrin, podocalyxin levels of moderately and poorly controlled DM cases according to HbA1c value

HbA1c	(n)	Mindin (pg/mL)			Nephrin (ng/mL)			Podocalyxin (pg/mL)		
%	Total	Median	Min.	Max.	Median	Min.	Max.	Median	Min.	Max.
<9	12	5.38	3.66	9.82	1.89	1.18	43	0.28	0.16	0.63
≥9	28	5.38	4.20	9.82	1.85	0.42	13	0.29	0.14	1.26
p	-	0.34	-	-	0.59	-	-	0.69	-	-

HbA1c: Hemoglobin A1c, DM: Diabetes mellitus, Min: Minimum, Max: Maximum

Table 3. Comparison of the serum mindin, nephrin, podocalyxin levels of the DM cases with a disease duration of <5 years and ≥5 years

DM duration	(n)	Mindin (pg/mL)			Nephrin (ng/mL)			Podocalyxin (pg/mL)		
	Total	Median	Min.	Max.	Median	Min.	Max.	Median	Min.	Max.
<5	9	5.38	4.89	7.63	3.71	0.94	43	0.33	0.26	1.26
≥5	31	5.38	3.66	9.82	1.83	0.42	7.86	0.28	0.14	0.86
P		0.97			0.106			0.075		

DM: Diabetes mellitus, Min: Minimum, Max: Maximum

group (r=0.034, -0.116, and -0.055, respectively; p=0.834, 0.475, and 0.735, respectively) (Table 3).

The serum nephrin levels were found to be low in the DM group. Accordingly, a negative correlation was found between the HbA1c levels and the serum nephrin levels (p=0.041, r=-0.32) (Figure 2) while a correlation wasn't detected between the HbA1c levels and the serum PODXL (p=0.69, r=0.064) and mindin levels (p=0.93, r=0.014) (Figure 2). The serum PODXL and mindin levels were low in the DM group. As in nephrin, we expected negative correlations between HbA1c and the levels of mindin and PODXL but in contrast, HbA1c did not correlate with these two proteins. However, it is not possible to draw any definitive conclusion concerning these results due to the insufficient number of patients.

The urea, creatinine and 24-hour urine albumin levels of the patients were measured. There was a significant difference in serum urea level between the patient group (n=40, mean 25.3±7.24 mg/dL) and the control group (n=40, mean 21±4.45 mg/dL) (p=0.002). Serum urea level in the patient group was found to be significantly higher than the control group. There was a significant difference in serum creatinine level

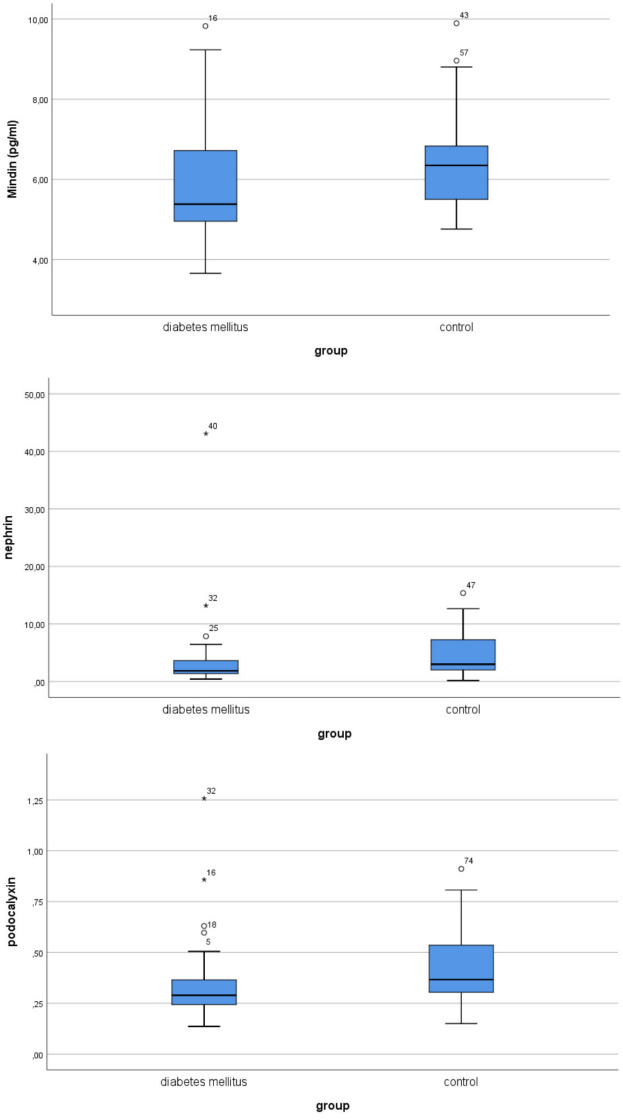

Figure 1. Serum mindin, nephrin, podocalyxin levels of the study groups (box-and-whisker diagram).

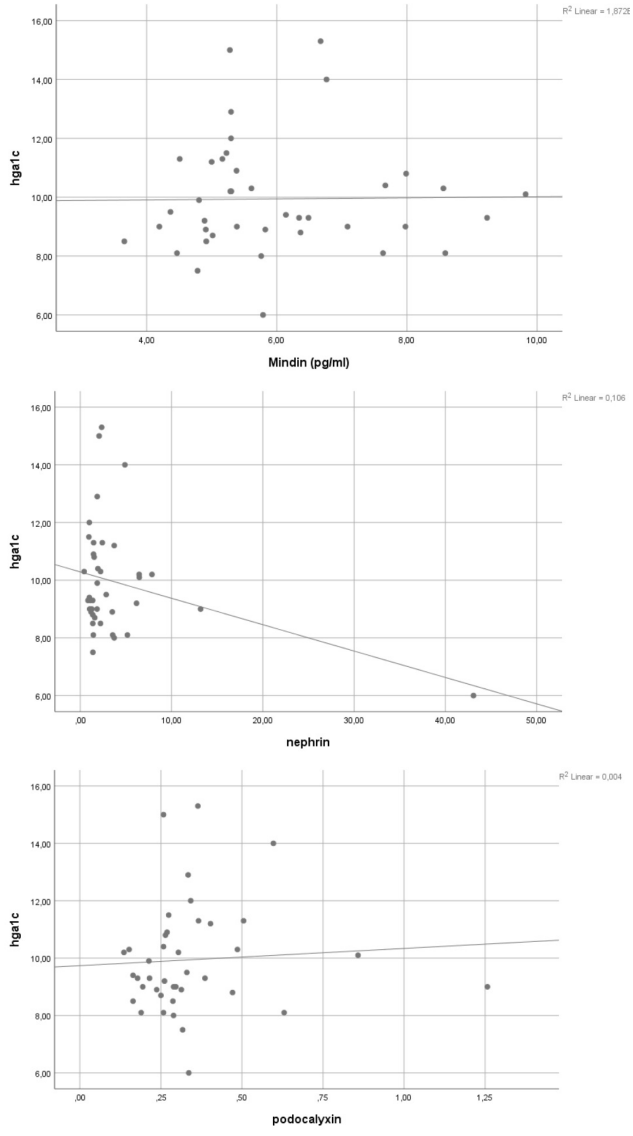

Figure 2. Correlation analysis with scatter plot HbA1c level and the serum mindin, nephrin and podocalyxin values.
HbA1c: Hemoglobin A1c

between the patient group (n=40, mean 0.70±0.082 mg/dL) and the control group (n=40, mean 0.61±0.86 mg/dL) (p<0.0001). Serum creatinine levels were found to be significantly higher in the patient group compared to the control group. Only 4 patients had microalbuminuria in a check of their last 24-hour urine albumin levels. When blood nephrine, PODXL and mindin levels of patients were correlated with albumin level in 24-hour urine, no significant difference was found (p=0.34, p=0.72, p=0.13).

Discussion

In the present study we found that serum PODXL and nephrin levels were significantly lower in type 1 DM patients (p=0.014 and p=0.016, respectively). Serum mindin levels were also lower with a significance of p=0.05. These results show that the serum levels of PODXL, nephrin, and mindin -which are extracellular matrix proteins known to have increased expression if the podocyte feet of the kidney are damaged- were lower. In our study serum nephrin, mindin and PODXL levels did not correlate with disease duration.

The fact that the patient group had no microalbuminuria yet their urea and creatinine values were found to be significantly higher compared to the control group, and that nephrin and PODXL levels were found to be significantly lower in the patient group compared to the control group made us think that nephrin and PODXL may be sensitive proteins in predicting renal damage before microalbuminuria develops.

Murakoshi et al. (10) showed that mindin mRNA expression increased in the glomeruli of mice with DM. Mindin is also excreted in the urine of patients with type 2 DM and DN in correlation with age. All the cases included in our study were in the pubertal stage, and no linear increase was observed in the serum mindin levels. Kahvecioglu et al. (14) found that serum mindin was high in the type 2 DM group. In the same study, it was demonstrated that the serum mindin levels in patients with type 2 DM had a close relationship with podocyte damage, although not as much as urine and tissue mindin levels Dogan et al. (15) showed in a study that serum mindin levels were significantly higher in patients undergoing hemodialysis treatment when compared to the population with normal renal functions.

Jim et al. (11) found that the synthesis of nephrin was significantly lower in the renal biopsy materials of the patients who developed DN compared to the control group. They also detected nephrinuria in 54% of the type 2 DM cases that were normoalbuminuric. Kostovska et al. (16) found urinary nephrin significantly higher in normoalbuminuric patients with type 2 DM compared to healthy subjects. These results led them to believe that damage in podocytes is present in patients before the appearance of microalbuminuria. Yang et al. (17) showed a downregulation of nephrin in the endocapillary proliferative lesion segment in children with Henoch-Schönlein purpura nephritis. They suggested that down-regulation of nephrin in the endocapillary proliferation segment is a potential molecular mechanism of nephrotic-range proteinuria. In our study, the serum nephrin levels of the DM patients were determined to be significantly lower compared to the control group (p=0.016) as shown in other studies. Urine nephrin excretion can increase due to renal loss; however, we were not able to confirm this in our study.

Kanno et al. (18) measured the urinary PODXL level in children with glomerular disease. The level of urine PODXL was significantly higher in the urine of the patients with glomerular disease compared to the controls. Wang et al. (19) found that patients with DN had a lower renal expression of PODXL and a higher urinary PODXL/urinary creatinine ratio than healthy subjects. The patients with DN in the low PODXL expression group had a longer diabetes disease course, lower plasma albumin and estimated glomerular filtration rate, higher HbA1c, 24 hour urinary protein, serum creatinine, and urinary PODXL/urinary creatinine ratio, and more severe glomerular, tubulointerstitial, and renal interstitial inflammation than patients in the high expression group. El-Ashmawy et al. (20) showed that serum PODXL levels were significantly higher in patients with type 2 DM and peripheral arterial disease compared with subjects with type 2 DM without any vascular complications. This study suggest that PODXL is released from an injured endothelium through a mechanism which may be similar to that of urinary PODXL release from injured podoctyes. In our study we found that serum PODXL levels were lower in the DM group and serum urea and creatinine levels were higher in the DM group whose serum PODXL levels were lower than

the control group. In our study, the low levels of serum PODXL in the DM group led us to consider that their urinary excretion might be high. However, since it was not possible to examine the levels of urinary PODXL in our study, we cannot make a definitive comment about this issue. This study was the first to investigate serum PODXL levels in pediatric patients with type 1 DM.

This was the first study to examine serum mindin, nephrin and PODXL levels in pediatric patients with DM. However, our study consisted of DM patients aged between 10 and 18 years, who had not yet developed nephropathy, a factor which could have affected our results. In addition, it would be better to examine the follow-up data of these patients. Further studies should be conducted to clarify the precise mechanism of these proteins.

Strengths of our study

The cases included in the study were in the pubertal period and this is the first study in type 1 DM patients in the pubertal period. In the literature, the levels of mindin, nephrin, and PODXL markers in the urine were previously examined, but there is no study in which the serum levels of these three parameters were analyzed at the same time. Our study is essential in terms of being the first to examine serum mindin, PODXL, and nephrin levels in type 1 DM patients aged 10-18 years. More significant results can be obtained by analyzing the serum and urine nephrin levels in the follow-up of these patients in 10 or 20 years.

Study Limitations

The limitations of this study include the small sample size, the low rate of developing DN among the DM patients aged 10-18 years, and the urine levels of mindin, PODXL, and nephrin not being simultaneously examined.

Conclusion

The results indicate that the low levels of serum mindin, nephrin, and PODXL may indicate podocyte damage in the early period of DM. However, this information needs to be confirmed by further studies analyzing the urine levels of these markers.

Ethics

Ethics Committee Approval: This study was carried out after obtaining permission from the parents of the patients and controls and approval from the Bursa Uludağ University Faculty of Medicine Ethics Committee with the (approval number: 2016-16/1, date: 19.08.2016).

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

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Aile Hekimlerinin Sağlam Çocuk İzlemleri Konusundaki Bilgi Düzey ve Tutumlarının Değerlendirilmesi

Evaluation of the Knowledge Level and Attitudes of Family Physicians on Follow-up of Healthy Children

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Öz

Giriş: Sağlam çocuk izlemleri birinci basamak koruyucu sağlık hizmetlerinin en önemli parçalarından birisidir. Sağlıklı bir toplum yetişebilmesi için sağlam çocuk izlemlerinin eksiksiz bir şekilde uygulanması hayati bir öneme sahiptir. Yaptığımız bu çalışma ile aile hekimlerinin bilgi düzeylerini, tutumlarını ve bunların sosyodemografik özellikleri ile ilişkisini saptamayı amaçladık.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel tipteki bu çalışma Türkiye'deki aile hekimleri üzerinde yapılmıştır. Örneklem büyüklüğü 380 olarak hesaplanmış olup çalışmaya 402 hekim dahil edilmiştir. Araştırmacı tarafından literatür ve kılavuzlardan faydalanılarak geliştirilen aile hekimlerinin sağlam çocuk izlemleri hakkındaki bilgilerini ve tutumlarını değerlendirmeyi amaçlayan 65 soruluk anket, gönüllü hekimlere yüz yüze ya da internet aracılığıyla uygulanmıştır. Verilerin analizi SPSS 21.0 paket programıyla yapılmıştır.

Bulgular: Çalışmaya katılan 402 hekimin %42'si (n=169) erkekti. Hekimlerin yaş ortalaması 34,75±9,51 yıl ve meslekteki ortalama çalışma süresi 9,90±9,56 yıl idi. Katılımcıların %46,5'i (n=187) aile hekimi, %35,3'ü (n=142) aile hekimliği araştırma görevlisi, %18,2'si (n=73) aile hekimliği uzmanıydı. Hekimlerin bilgi puan ortalaması 28,09±12,75'ti (minimum: 2, maksimum: 64). Cinsiyet, çalışılan kurum, izlemlere ayrılan süre, izlemler konusunda eğitim alma durumu, izlemleri yaparken bir algoritma/rehberden yararlanma durumları ile bilgi düzeyleri arasında istatistiksel olarak anlamlı fark saptandı. Tutum puan ortalaması 46,96±4,40'tı (minimum: 20, maksimum: 60). Tutum anketinin Cronbach's alfa değeri 0,663 bulundu.

Sonuç: Aile hekimlerinin sağlam çocuk izlemleri konusundaki bilgi düzeyleri ortalamanın altındadır ancak bu konudaki tutumlarının olumlu olması umut vericidir. Çalışmamızda doğru bilinme oranı %50'nin altında olan konular obezite, otizm spektrum bozukluğu, dikkat eksikliği hiperaktivite bozukluğu, gelişimsel kalça displazisi, inmemiş testis, görme keskinliği, kan basıncı konuları olup bu spesifik konular hakkında çalışmaların yapılmasına ihtiyaç olduğunu düşünmekteyiz. Ayrıca hekimlerin çoğu bu izlemlerin negatif performans ile değerlendirilmesini yanlış bulmaktaydı ve bu durum hekimleri teşvik edici yeni politikalar geliştirilmesi gerektiğini göstermektedir.

Anahtar kelimeler
Koruyucu hekimlik, çocuk sağlığı, birinci basamak sağlık hizmeti, aile hekimliği

Keywords
Preventive medicine, child health, primary health care, family practice

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Abstract

Introduction: Follow-up of healthy children is one of the most important parts of primary care preventive health services. It is of vital importance that healthy child follow-ups are fully implemented in order to raise a healthy society. In this study, we aimed to determine the knowledge levels and attitudes of family physicians and their relationship with their sociodemographic characteristics.

Materials and Methods: This descriptive and cross-sectional study was conducted on family physicians in Turkey. The sample size was calculated as 380 and 402 physicians were included in the study. The 65-question questionnaire, which aims to evaluate the knowledge and attitudes of family physicians about healthy child follow-up, was developed by the researcher using the literature and guidelines, and was administered to volunteer physicians either face-to-face or via the internet. Data analysis was done with SPSS 21.0 package program.

Results: Of the 402 physicians participating in the study, 42.0% (n=169) were male. The mean age of the physicians was 34.75±9.51 years and the mean working time in the profession was 9.90±9.56 years. Of the participants, 46.5% (n=187) were family physicians, 35.3% (n=142) were family medicine research assistants, and 18.2% (n=73) were family medicine specialists. The mean knowledge score of the physicians was 28.09±12.75 (minimum: 2, maximum: 64). A statistically significant difference was found between gender, institution of employment, time allotted to follow-ups, education about follow-ups, utilization of an algorithm/guide while making follow-ups, and knowledge levels. The mean score of attitude was 46.96±4.40 (minimum: 20, maximum: 60). The Cronbach's alpha value of the attitude questionnaire was found to be 0.663.

Conclusion: Level of knowledge of family physicians on healthy child follow-up is below the average, but it is hopeful that their attitudes on this issue are positive. In our study, the subjects with an accuracy rate of less than 50% are obesity, autism spectrum disorder, attention deficit hyperactivity disorder, developmental dysplasia of the hip, undescended testis, visual acuity, blood pressure, and we think that further studies are needed on these specific subjects. In addition, most of the physicians found it wrong to evaluate these follow-ups with negative performance, and this shows that new policies should be developed to encourage physicians.

Giriş

Sağlam çocuk, hastalık belirtileri göstermeyen, takvim yaşına uygun büyüme ve gelişme, ruhsal ve zeka gelişimi gösteren çocuk olarak tanımlanır. Birinci basamak çocuk sağlığı ve hastalıkları hizmetlerinin en önemli bölümünü sağlam çocuk izlemleri oluşturmaktadır. Sağlam çocuk izlemleri tüm çocuklara dünyaya geldikleri ilk günden itibaren verilmesi gereken bir hizmet olup, çocuğun fiziksel, ruhsal ve sosyal açıdan tam bir iyilik hali içinde olup olmadığı değerlendirilir (1).

Çocuğun sağlıklılığının desteklenmesi, hastalıkların erken dönemde fark edilerek önlenmesi, aşı hizmeti, ailelere sağlık danışmanlığının verilmesi gibi koruyucu hekimlik uygulamalarının yapılması sağlam çocuk izleminin temelini oluşturmaktadır. Sağlıklı bir toplum yetişebilmesi için sağlam çocuk izlemlerinin eksiksiz bir şekilde uygulanması hayati bir öneme sahiptir (2).

Sağlam çocuk izlemleri bebeklik, çocukluk ve ergenlik dönemini kapsayan düzenli sağlık kontrol ve muayenelerinin yapıldığı uzun soluklu bir takiptir. Bu izlemler aile hekimi, aile sağlığı elemanı ve ailelerle beraber iş birliği ile yürütülmektedir ve her çocuk yaşadığı çevre göz önünde bulundurularak değerlendirilmelidir (3). Ülkemizde sağlam çocuk izlemleri Sağlık Bakanlığı'nın yayınladığı "Bebek, Çocuk ve Ergen İzlem Protokolü" ne göre yapılmaktadır. Her bebek doğduğu andan itibaren kayıt altına alınmalı ve izlemleri başlatılmalıdır. Kaydedilen her çocuk doğumda, ilk 48 saat içinde, 15. günde, 41. günde, 2., 3., 4. aylarda ayda bir kez, 6., 9. ve 12. aylarda üç ayda bir kez, 1-3 yaş arası altı ayda bir kez, 3-6 yaş arası yılda bir kez, 6-9 yaş arasında yılda bir kez, 10-21 yaş arasında yılda bir kez olmak üzere izlemleri tamamlanmalı ve her izlem kayıt altına alınmalıdır (4).

Aile hekimlerinin ve ailelerin sağlam çocuk izlemlerine ilişkin bilgi, görüş ve tutumlarının araştırıldığı çalışmaların hala çok az sayıda olduğu görülmektedir. Yaptığımız bu çalışma ile birinci basamakta çalışan aile hekimlerinin, tıpta uzmanlık eğitimi almakta olan aile hekimliği asistanlarının ve çeşitli sağlık kuruluşlarında çalışmakta olan aile hekimliği uzmanlarının sağlam çocuk izlemleri konusundaki bilgi düzeylerini, tutumlarını ve sosyodemografik özellikleri ile ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem

Çalışma Tasarımı

Tanımlayıcı ve kesitsel tipte olan çalışmamız Ekim 2020-Ocak 2022 tarihleri arasında gerçekleşmiştir. Çalışmamızın evrenini Türkiye'deki 28.835 aile hekimi, aile hekimliği asistanı ve aile hekimliği uzmanı oluşturmaktadır. Örneklem büyüklüğü %5 hata payı, %95 güven aralığı ve prevalansın bilinmediği durumlar için 0,50 sıklık değeri ile 380 olarak hesaplanmıştır. Çeşitli nedenlerle olabilecek veri kaybı (%10) göz önüne alınarak 418 kişiye ulaşılması

hedeflenmiştir. Anketlere eksik veya geçersiz cevap verme gibi durumlar dışlandığında çalışmamıza 73 aile hekimi uzmanı, 142 aile hekimliği asistanı ve 187 aile hekimi olmak üzere toplam 402 hekim dahil edilmiştir. Katılımcılar çalışmaya dahil edilmeden önce bilgilendirilmiş ve katılım onamı verenler çalışmaya dahil edilmiştir. Çalışma için herhangi finans desteği alınmamıştır.

Veri Toplama Araçları

Araştırmacı tarafından literatür ve kılavuzlardan faydalanılarak geliştirilen aile hekimlerinin sağlam çocuk izlemleri hakkındaki bilgilerini ve tutumlarını değerlendirmeyi amaçlayan 65 soruluk anket, gönüllü hekimlere yüz yüze ya da internet aracılığıyla uygulanmıştır. Anket linkinin mail olarak paylaşılmasında Türkiye Aile Hekimleri Uzmanlık Derneği'nden destek alınmıştır. Çalışmamızda Sağlık Bakanlığı'nın hazırladığı "Bebek, Çocuk ve Ergen İzlem Rehberi" ve "Aile Hekimliği Uygulamasında Önerilen Periyodik Sağlık Muayeneleri ve Tarama Testleri" rehberlerinden ve literatürden yararlanılmıştır.

Sosyodemografik form: Anketin birinci bölümü olup kişilerin yaş, cinsiyet, medeni durum, çalışılan yer gibi sosyodemografik özelliklerinin yanında sağlam çocuk izlemleri konusunda eğitim alma durumları, sağlam çocuk izlemi yapma durumları, kendilerini sağlam çocuk izlemleri konusunda ne kadar yeterli buldukları ile ilgili 19 soru yer almaktadır.

Bilgi düzey anketi: Aile hekimlerinin sağlam çocuk izlemleri konusundaki bilgi düzeylerini ölçecek 27 soru yer almaktadır. Anketin bilgi puanı hesaplanırken her sorunun doğru şık yanıtı 1 puan olarak kabul edilmiştir. Birden çok seçeneğin işaretlenebileceği sorularda her doğru yanıtın seçilmesi 1 puan, yanlış yanıtların seçilmemesi 1 puan olacak şekilde puanlama yapılmıştır. Araştırmacı tarafından belirlenen bu puanlama kriterlerine göre bilgi düzeyi ile ilgili sorular için 0-65 aralığında bilgi puanı oluşturulmuştur.

Tutum anketi: Aile hekimlerinin sağlam çocuk izlemlerine yönelik tutumlarını belirlemeyi amaçlayan 20 ifadelik bir ankettir. Anket uygulanmadan önce bir pilot çalışma ile değerlendirilerek sorular tekrar düzenlenmiştir. Anketin Cronbach's alfa değeri 0,663 olarak bulunmuştur. Cronbach's alfa değeri 0,60 ile 0,80 arasında bulunması ankette kullanılan maddelerin "oldukça güvenilir" olduğunu göstermektir. Anket için 20-60 puan aralığında tutum puanı oluşturularak 40 puan ve altında alan hekimlerin tutumları olumsuz, 40 puanın üzerinde alanların tutumları ise olumlu olarak kabul edilmiştir.

İstatistiksel Analiz

Verilerin istatistiksel analizi SPSS 21.0 programı ile yapılmıştır. Verilerin analizinde kullanılan tanımlayıcı istatistikler ortalama (±), standart sapma, ortanca (minimum-maksimum), frekans dağılımı ve yüzde olarak sunulmuştur. Ölçüm ile elde edilen değişkenlerin normal dağılıma uygunluğu için Kolmogorov-Smirnov ve Shapiro-Wilk testleri uygulanmıştır. Normal dağılımlarda Student's t-testi ve One-Way ANOVA testleri kullanılmıştır. Normal olmayan dağılımlarda Mann-Whitney U testi ve Kruskal-Wallis testleri kullanılmıştır. Üç ve daha fazla bağımsız grup arasında saptanan anlamlı farkların kaynağını saptamaya yönelik post-hoc çoklu karşılaştırmalarda grupların varyanslarının homojenliğine göre Tukey veya Tamhane's T2 test sonuçları kullanılmıştır. Kategorik değişkenlerin karşılaştırılmasında Pearson ki-kare ve Fisher's exact testleri kullanılmıştır. Çalışmamızın tutum soruları Cronbach's alfa analizi yapılmıştır. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edilmiştir.

Etik Kurul Onayı

Çalışmanın etik kurul onayı Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır (onay numarası: 13, tarih: 14.10.2020).

Bulgular

Çalışmamıza katılan 402 aile hekiminin %58'i kadın, %75,4'ü evli olup yaş ortalaması 34,75±9,51'di. Hekimlerin %46,5'i aile hekimi, %35,3'ü aile hekimliği asistanı ve %18,2'si aile hekimliği uzmanıydı. Hekimlerin %78,1'i şehir merkezinde, %54,1'i aile sağlığı merkezinde (ASM) çalışmaktaydı. Hekimlerin %65,9'u sağlam çocuk izlemleri konusunda eğitim almış olup eğitim alan hekimlerin %49,1'i aldığı eğitimi yeterli bulmamıştı. Hekimlerin %65,4'ünün izlemler sırasında rehberlerden faydalandığı belirlendi. Katılımcıların detaylı sosyodemografik bilgileri Tablo 1'de yer almaktadır.

Tablo 1. Aile hekimlerinin sosyodemografik özelliklerinin dağılımı		
Sosyodemografik özellikler	n	%
Cinsiyet		
Erkek	169	42,0
Kadın	233	58,0
Medeni durum		
Evli	303	75,4
Bekar	99	24,6
Unvan		
Aile hekimi	187	46,5
Aile hekimliği asistanı	142	35,3
Aile hekimliği uzmanı	73	18,2
Çalışma yeri		
Şehir merkezi	314	78,1
İlçe	67	16,7
Köy-kasaba	21	5,2
Halen çalışılan kurum		
Aile sağlığı merkezi	218	54,2
Toplum sağlığı merkezi	9	2,2
Eğitim araştırma ve devlet hastanesi	71	17,7
Üniversite hastanesi	83	20,6
Diğer	21	5,2
Sağlam çocuk izlemleri konusunda eğitim alma durumu		
Evet	265	65,9
Hayır	137	34,1
Sağlam çocuk izlemleri konusunda nereden eğitim aldınız?		
Hizmet içi eğitimler	132	32,8
Lisans eğitiminde	128	31,8
Uzmanlık eğitiminde	138	34,3
Kongre veya toplantıda	78	19,4
Yüksek lisans	3	0,7
Diğer	16	4,0
Almış olduğunuz sağlam çocuk izlemi eğitimi sizce yeterli miydi?		
Evet	130	49,1
Hayır	135	50,9
Sağlam çocuk izlemleri konusunda herhangi bir algoritma/ rehberden faydalanıyor musunuz?		
Evet	263	65,4
Hayır	139	34,6

Tablo 1. Devamı		
Sosyodemografik özellikler	n	%
Türkiye için önerilen "Bebek, Çocuk, Ergen İzlem Protokolleri" hakkında bilgi sahibi misiniz?		
Evet	297	73,9
Hayır	105	26,1
Dünyada yayınlanıp uygulanan sağlam çocuk izlem protokolleri hakkında bilgi sahibi misiniz?		
Evet	60	14,9
Hayır	342	85,1

Çalıştığı sağlık kuruluşunda sağlam çocuk izlemi yapan hekimlerin oranı %65,7'ydi. Aile hekimliği asistanlığı yapan hekimlerin, asistanlıkta sağlam çocuk izlemi yapanların oranı ise %17,9'du. Hekimlerin %84,1'inin sağlam çocuk izlemlerinde her bir hastaya 15 dakikadan az vakit ayırdığı belirlendi (Tablo 1).

Katılımcılar kendilerini sağlam çocuk izlemleri konusunda 0-10 puan arasında puanladıklarında ortalama 5,90±2,15 puan aldıkları saptandı.

Hekimlerin sağlam çocuk izlemleri konusundaki bilgi düzey toplam puanları 2 ve 64 arasında değişmekte olup ortalama puan 28,09±12,75'ti. Tablo 2'de bilgi düzey sorularının unvan değişkenine göre doğru yanıt oranları sunulmuştur.

Bilgi düzey sorularından en yüksek puan ortalamasını 29,75±13,72 puan aile hekimliği uzmanları alırken en düşük ortalama puanı 27,20±13,88 ile pratisyen aile hekimleri almıştır ancak bu fark istatistiksel olarak anlamlı değildir (p=0,328). Bilgi düzey ortalama puanlarının unvana göre karşılaştırması Tablo 3'te yer almaktadır.

Bilgi düzey ortalama puanı ile cinsiyet, çalışılan kurum, her hastaya ayrılan muayene süresi, algoritma/rehberden faydalanma, sağlam çocuk izlem protokolünü okuma durumları arasında anlamlı düzeyde ilişki saptanmıştır (p<0,05). Unvan, medeni durum, çalışma yeri, asistanlıkta sağlam çocuk izlemi yapma ile bilgi düzeyleri arasında anlamlı bir ilişki saptanmamıştır (Tablo 4).

Cinsiyet ile bilgi düzey ortalama puanları arasında istatistiksel olarak anlamlı bir fark saptanmıştır (p<0,001). Erkeklerin bilgi düzey ortalamaları kadınlardan daha yüksektir (Tablo 4).

Hekimlerin sağlam çocuk izlemi sırasında hastalara ayırdıkları süre ile bilgi düzey ortalama puanlarını

Tablo 2. Aile hekimlerinin bilgi düzey sorularını doğru yanıtlama oranları

Bilgi düzey soruları	Unvan			Toplam	p*
	Aile hekimi	Aile hekimliği asistanı	Aile hekimliği uzmanı		
	n (%)	n (%)	n (%)	n (%)	
1) Sağlam çocuk takibi kaç yaş aralığını kapsar?	32 (17,1)	21 (14,8)	15 (20,5)	68 (16,9)	0,563
2) Bebek bir yaşına gelene kadar en az kaç kez izlem yapılması önerilmektedir?	71 (38,0)	27 (19,0)	13 (17,8)	111 (27,6)	<0,001
3) "GBP" kapsamında bebeklik ve çocukluk dönemi aşılama takviminde yer alan aşılar nelerdir?	125 (66,8)	84 (59,2)	49 (67,1)	258 (64,2)	0,299
4) İlk bir yaştaki izlemlerde yapılması gereken muayeneler nelerdir?	51 (27,3)	59 (41,5)	17 (23,3)	127 (31,6)	0,005
5) Sağlam çocuk izlemlerinde büyüme ve gelişmeyi değerlendirmek amacıyla hangileri kullanılır?	39 (20,9)	51 (35,9)	21 (28,8)	111 (27,6)	0,010
6) Yenidoğan topuk kanı ne zaman alınmalıdır?	138 (73,8)	106 (74,6)	57 (78,1)	301 (74,9)	0,772
7) Yenidoğan taramalarında hangi hastalıklar taranır?	88 (47,1)	60 (42,3)	38 (52,0)	186 (46,3)	0,377
8) Çocuklarda demir profilaksisine ne zaman başlanmalıdır?	136 (72,7)	108 (76,1)	55 (75,3)	299 (74,4)	0,774
9) Çocuklarda demir profilaksisine hangi dozlarda başlanmalıdır?	160 (85,6)	75 (52,8)	48 (65,8)	283 (70,4)	<0,001
10) Obezite taraması hangi yaşlar arasında yılda bir kez ağırlık, boy, BKİ ölçümleri ile yapılmalıdır?	117 (62,6)	72 (50,7)	52 (71,2)	241 (60,0)	0,009
11) Bebeklerde ilk hemoglobin değerine ne zaman bakılmalıdır?	122 (65,2)	81 (57,0)	54 (74,0)	257 (63,9)	0,44
12) Bebeklere D vitamini desteği ne zaman başlanmalıdır?	151 (80,7)	109 (76,8)	61 (83,6)	321 (79,9)	0,458
13) Yenidoğana D vitamini profilaksisi hangi dozda başlanmalıdır?	123 (65,8)	101 (71,1)	57 (78,1)	281 (69,9)	0,140
14) D vitamini ne kadar süre kullanılmalıdır?	146 (78,1)	71 (50,0)	55 (75,3)	272 (67,7)	<0,001
15) Büyüme eğrilerinde normalin alt ve üst sınırı hangi persentiller arasıdır?	124 (66,3)	103 (72,5)	51 (69,9)	278 (69,2)	0,475
16) Hangi persentilden (boya göre kilo persentili) sonra obezite tanısı konur?	49 (26,2)	39 (27,5)	30 (41,1)	118 (29,4)	0,050
17) GKD taraması hangi zaman diliminde yapılması aile hekimince zorunludur?	116 (62,0)	85 (59,9)	49 (67,1)	250 (62,2)	0,581
18) Aile hekimleri tarafından GKD hangisi ile taranır?	76 (40,6)	52 (36,6)	25 (34,2)	153 (38,1)	0,576
19) Hangi ay aralığındaki çocuklara en az 1 kez inmemiş testis muayenesi yapılmalıdır?	64 (34,2)	38 (26,8)	25 (34,2)	127 (31,6)	0,306
20) Sağlam çocuk takiplerinde görme keskinliği muayenesi kaç yaşından itibaren yılda 1 kez yapılmalıdır?	82 (43,9)	53 (37,3)	40 (54,8)	175 (43,5)	0,50
21) Prematüre retinopatisi muayenesi yapılması açısından hangi hafta ve ağırlıktaki bütün bebekler göz hastalıkları hekimine yönlendirilmelidir?	108 (57,8)	79 (55,6)	42 (57,5)	229 (57,0)	0,923
22) İşitme tarama testi ne zaman yapılmalıdır?	103 (55,1)	93 (65,5)	60 (82,2)	256 (63,7)	<0,001

Tablo 2. Devamı					
Bilgi düzey soruları	Unvan			Toplam	p*
	Aile hekimi	Aile hekimi araştırma görevlisi	Aile hekimi uzmanı		
	n (%)	n (%)	n (%)	n (%)	
23) Kan basıncı kaç yaşından itibaren yılda en az 1 kez ölçülmeye başlanmalıdır?	68 (36,4)	81 (57,0)	43 (58,9)	192 (47,8)	<0,001
24) Otizm hangi aylar arasında taranmalıdır?	63 (33,7)	36 (25,4)	43 (58,9)	142 (35,3)	<0,001
25) Hangisi otizm spektrum bozukluklarının erken tespitinde kullanılması önerilen gözlem maddelerinden biridir?	43 (23,0)	20 (14,1)	14 (19,2)	77 (19,2)	0,126
26) DEHB ile ÖÖG hangi aylarda en az bir kez değerlendirilmelidir?	35 (18,7)	35 (24,6)	28 (38,4)	98 (24,4)	0,004
27) Fiziksel istismarı düşündüren bulgular nelerdir?	58 (31,0)	68 (47,9)	33 (45,2)	159 (39,6)	0,005
p*: Pearson chi-square, BKİ: Beden kitle indeksi, GKD: Gelişimsel kalça displazisi, DEHB: Dikkat eksikliği hiperaktivite bozukluğu, ÖÖG: Özgül öğrenme güçlüğü					

karşılaştırdığımızda gruplar arasında anlamlı fark saptanmıştır (p=0,003). Hastalara 15 dakikadan çok vakit ayıranların puanları daha yüksektir (Tablo 4).

Sağlam çocuk izlemleri konusunda eğitim alma durumu ile bilgi düzey ortalama puanları arasında anlamlı ilişki saptanmıştır (p<0,001). Eğitim alan hekimlerin puan ortalamaları almayanlardan daha yüksektir. Sağlam çocuk izlemleri konusundaki bilgi düzey ortalama puanları ile bu izlemler için herhangi bir algoritma/rehberden yararlanma durumu arasında anlamlı bir fark saptanmıştır (p<0,001). Herhangi bir algoritma/rehberden yararlanan hekimlerin ortalama puanlarının daha yüksek olduğu görülmektedir (Tablo 4).

Türkiye için önerilen "Bebek, Çocuk, Ergen İzlem Protokolleri" hakkında bilgi sahibi olma durumu ile bilgi düzey ortalama puanları arasında anlamlı ilişki saptanmıştır (p<0,001). Protokol hakkında bilgi sahibi olan hekimlerin ortalama puanları daha yüksektir (Tablo 4). Dünyada yayınlanıp uygulanan sağlam çocuk izlem protokolleri hakkında bilgi sahibi olma durumu ile bilgi düzey ortalama puanları arasında anlamlı fark saptanmıştır (p=0,008). Bu protokoller hakkında bilgi sahibi olmayan hekimlerin ortalama puanları daha yüksektir (Tablo 4).

Tablo 2'de aile hekimlerinin unvan ile bilgi düzey sorularını bilme durumları verilmiştir. Aile hekimlerinin en çok bildiği soru %85,6 ile demir profilaksisi başlama dozu olmuştur. Aile hekimliği asistanlarının ve uzmanlarının en çok doğru yanıtladığı soru ise sırayla %76,8 ve %83,6 oranları ile D vitamini başlama zamanı sorusudur. Ayrıca unvan değişkeni ile soruları doğru bilme durumlarının istatistiksel olarak anlamlı olduğu sorular; ilk bir yaştaki izlem sıklığı, ilk bir yaşta yapılması gereken muayeneler, büyüme ve gelişmeyi değerlendirmek için kullanılan parametreler,

Tablo 3. Unvan ile bilgi düzey ve tutum puanları arasındaki ilişki			
	n (%)	Bilgi düzey anketi (ortalama ± SS)	Tutum anketi (ortalama ± SS)
Aile hekimi	187 (46,5)	27,20±13,88	47,08±4,22
Aile hekimliği asistanı	142 (35,3)	28,40±10,46	47,19±0,27
Aile hekimliği uzmanı	73 (18,2)	29,75±13,72	46,20±6,34
Toplam	402 (100)	28,09±12,75	46,96±4,40
		p*=0,328	p**=0,900
SS: Standart sapma; p*: One-Way ANOVA testi; p**: Kruskal-Wallis testi			

Tablo 4. Aile hekimlerinin sosyodemografik özellikleri ile bilgi düzey ve tutum puanlarının karşılaştırması		
Özellikler	Bilgi düzey puanı (ortalama ± SS)	Tutum puanı (ortalama ± SS)
Cinsiyet		
Erkek	25,04±12,49	47,46±4,02
Kadın	30,30±12,51	46,60±4,63
p	p^a<0,001	p^c=0,026
Medeni durum		
Evli	27,93±12,35	47,22±3,59
Bekar	28,56±13,96	46,15±6,21
p	p^a=0,671	p^d=0,584
Çalışma yeri		
Şehir merkezi	28,10±12,60	47,02±3,94
İlçe	28,50±13,17	46,49±6,52
Köy-kasaba	26,57±14,19	47,57±1,96
p	p^b=0,832	p^d=0,216
Halen çalışılan kurum		
Aile sağlığı merkezi	28,09±12,94	46,94±4,47
Toplum sağlığı merkezi	35,55±08,63	48,33±2,64
Eğitim araştırma ve devlet hastanesi	28,69±14,18	45,80±5,68
Üniversite hastanesi	28,95±10,40	47,31±2,81
Diğer	19,42±12,91	49,04±3,49
p	p^b=0,009	p^d=0,027
Sağlam çocuk izlemlerinizde her bir hastaya ortalama ayrılan süre		
15 dakikadan az	27,75±12,23	46,99±4,48
15 dakikadan çok	35,28±16,86	46,32±3,61
p	p^a=0,003	p^c=0,016
Sağlam çocuk izlemleri konusunda algoritma/rehberden faydalanma		
Evet	30,79±12,76	46,82±4,52
Hayır	22,97±11,10	47,21±4,17
p	p^a<0,001	p^c=0,079
Türkiye için önerilen ‘‘Bebek, Çocuk, Ergen İzlem Protokolleri’’ hakkında bilgi sahibi olma		
Evet	30,72±12,41	46,88±4,41
Hayır	20,63±10,62	47,19±4,39
p	p^a<0,001	p^c=0,205
Dünyada yayınlanıp uygulanan sağlam çocuk izlem protokolleri hakkında bilgi sahibi olma		
Evet	24,05±13,16	46,13±6,89
Hayır	28,80±12,56	47,10±3,80
p	p^a=0,008	p^c=0,698
SS: standart sapma; p^a: Student t-testi; p^b: One-Way ANOVA testi; p^c: Mann-Whitney U testi; p^d: Kruskal-Wallis testi		

demir profilaksi dozu, D vitamini kullanım süresi, obezite tanısını koyduran persentil sınırları, işitme tarama zamanı, kan basıncı takibi, otizm taraması, dikkat eksikliği hiperaktivite bozukluğu (DEHB) ve özgül öğrenme güçlüğü taramaları, fiziksel istismar soruları olduğu saptanmıştır.

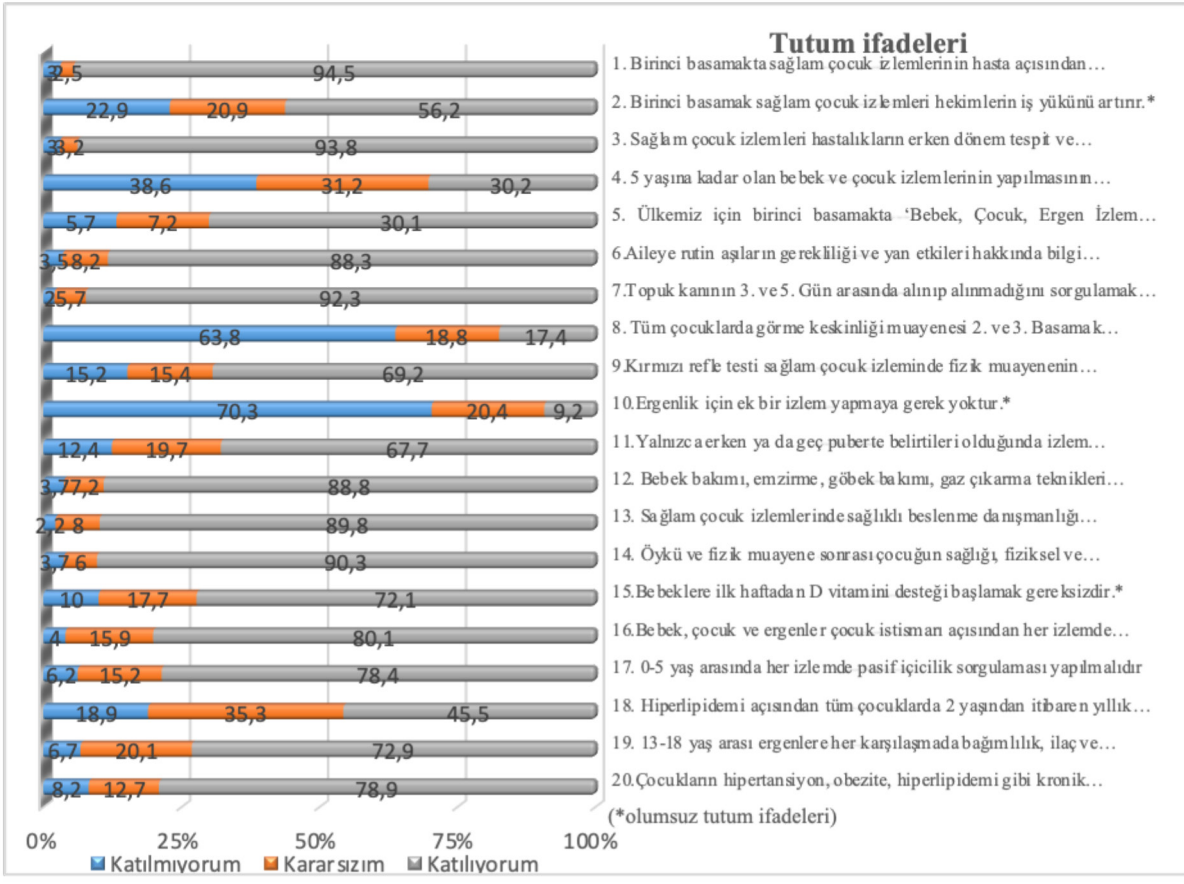
Hekimlerin sağlam çocuk izlemleri konusundaki genel tutum puanı 20 ve 60 arasında değişmekte olup ortalama puan 46,96±4,40'tır. Tutum sorularına verilen cevaplar Şekil 1'de sunulmuştur. Hekimlerin sağlam çocuk izlemleri konusundaki tutumları ile cinsiyet, çalışılan kurum, her hastaya ayrılan süre arasında anlamlı bir ilişki olduğu görülmüştür ($p<0,05$). Bununla beraber medeni durum, unvan, çalışma yeri, asistanlıkta sağlam çocuk izlemi yapma, algoritma/rehberden faydalanma, protokolü okuma arasında ilişki olmadığı görülmüştür (Tablo 4).

Sağlam çocuk izlemleri konusundaki tutumların unvana göre karşılaştırması Tablo 3'te verilmiştir. Aile hekimliği asistanları en olumlu tutuma sahip iken aile hekimliği uzmanları en olumsuz tutuma sahip olan gruptur. Ancak bununla beraber istatistiksel olarak unvan ile bilgi düzey toplam puanı arasında anlamlı bir ilişki saptanmamıştır ($p=0,900$).

Bilgi düzey toplam puanı ile tutum puanlarının arasındaki ilişki, araştırmamızın verileri normal dağılıma uymadığı için Spearman's rank korelasyon testi ile değerlendirilmiştir. Spearman's rank korelasyon katsayısı $r_s=-0,129$, $p=0,010$ olup değişkenler arasında negatif yönde ve düşük düzeyde anlamlı bir fark saptanmıştır.

Tartışma

Birinci basamak koruyucu sağlık hizmetlerinin en önemli parçalarından birisi olan sağlam çocuk izlemleri konusunda aile hekimlerinin bilgi düzey ve tutumlarını değerlendirmek amacıyla yaptığımız çalışmada hekimlerin bilgi düzey puanları ortalamanın altındaydı. Hekimlerin bilgi düzeyleri beklenenden düşüktü ancak bu konudaki tutumlarının olumlu olması umut verici bir sonuçtu.



Şekil 1. Tutum ifadelerine verilen cevaplar.

Hekimlerin yarıdan fazlası sağlam çocuk izlemleri konusunda eğitim aldığını belirtmişti. Bilgi edinilen kaynaklara bakıldığında en çok uzmanlık eğitiminde ve hizmet içi eğitimlerde eğitim aldıkları saptanmıştı. Bu sonuç tıp fakültesi lisans eğitimi sırasında sağlam çocuk izlemleri hakkında yeterli eğitimin verilemediği ve farkındalığın oluşturulamadığını düşündürmektedir. Hekimlerin büyük bölümünün daha önce aldığı eğitimi yeterli bulmadığı sonucundan yola çıkarak ülkemizde bu konuda verilen eğitimlerin değişmesi, güncellenmesi, dikkat çekici bir hale getirilmesi gerektiğini söyleyebiliriz.

Aile Hekimlerinin Bilgi Düzeyleri

Çalışmamızın bilgi düzey anketinden alınan ortalama puanlara bakıldığında beklenen düzeyden düşük olduğu görüldü. Benzer çalışmalarda da hekimlerin bilgi düzeyleri hedeflenen düzeylerden düşüktü (5,6). Çalışmamızda tam puan alan hekim yokken Yılmaz ve ark.'nın (5) çalışmasında 7 kişi tam puan almıştır. Yılmaz ve Şahin'in (6) çalışmasında ise benzer şekilde tam puan alan yoktur. Aile hekimlerinin bu konudaki farkındalığı artırılmalı ve bilgilerini güncellemeleri sağlanmalıdır.

Bilgi düzey anketinden en yüksek puanı aile hekimliği uzmanları, en düşük puanı ise pratisyen aile hekimleri almıştı. Ancak unvan ile bilgi düzey ortalama puanları arasında anlamlı bir fark saptanmadı (p=0,328). Bununla beraber aile hekimliği asistanlığı yapan hekimlerin eğitimleri sırasında sağlam çocuk izlemi yapma durumları ile bilgi düzeyleri arasında ilişki yoktu (p=0,275). Çalışmamıza benzer şekilde Ankara ilinde yapılan çalışmada unvan ile bilgi düzey arasında anlamlı fark saptanmamıştır (6). Tugay ve ark.'nın (7) çalışmasında ise hekimlerin bilgi düzeyleri ile unvanları arasındaki fark anlamlı saptanmış olup farkı oluşturan grup pratisyen aile hekimleriydi. Tüm bu sonuçlar aile hekimliği asistanlık eğitimlerinin sağlam çocuk izlemleri konusunda yeterli farkındalığı sağlayamadığı ve alınan eğitimin yetersiz kaldığını düşündürmektedir. Aynı zamanda bu eksiklik uzmanlık eğitimleri sırasında birinci basamaktan uzak kalınmasından kaynaklanıyor olabilir.

Kadın hekimlerin bilgi düzeyleri erkeklerden anlamlı düzeyde yüksekti (p<0,001). Literatürdeki benzer bir çalışmada da kadın hekimlerin bilgi düzeyi erkeklerinkine göre anlamlı düzeyde yüksek saptanmıştır (7). Bu konuya kadın hekimlerin annelik içgüdüsü ile erkeklerden daha fazla ilgi duyması böyle bir sonuca yol açmış olabilir.

Katılımcıların çalışma yerlerine göre bilgi düzeyleri arasında anlamlı bir fark yoktu (p=0,832). Ancak hekimlerin çalıştıkları kurum ile bilgi düzeyleri arasında anlamlı bir fark saptanmıştı (p=0,009). Çalıştığı kurumu "diğer" olarak belirten hekimlerin bilgi düzeylerinin daha düşük olması birinci basamak sağlık hizmetlerinden uzak kalmalarından ve mevcut şartlarda sağlam çocuk izlemi yapmamalarından kaynaklanıyor olabilir.

Sağlam çocuk muayenelerine 15 dakikadan çok vakit ayırabilen hekimlerin bilgi düzeyi anlamlı düzeyde daha yüksekti (p=0,011). İzlemlere gerekli önemi veren, vakit ayırmaya çalışan hekimlerin farkındalığının yüksek olması bu farkın oluşmasının sebebi olduğu düşünülebilir.

Sağlam çocuk izlemleri konusunda eğitim almış olan hekimlerin bilgi düzeyi, eğitim almayanlardan anlamlı düzeyde yüksekti (p<0,001). Ancak sağlam çocuk izlemleri konusunda alınan eğitimi yeterli bulma durumu ile bilgi düzeyleri arasında ilişki yoktu (p=0,537). Her ne kadar sağlam çocuk izlemleri konusunda eğitim alınmış olsa da yeterli farkındalığın oluşmaması, öğrenilen bilgiyi pratikte kullanamama gibi sebepler aile hekimlerinin bilgilerinin eksik kalmasına sebep olmaktadır.

Hekimlerin sağlam çocuk izlemleri konusunda kendilerine verdikleri puan arttıkça bilgi düzeylerinin de anlamlı düzeyde arttığı görüldü (p=0,021). Bu durum bilginin artmasının kendine olan güveni artırdığını göstermektedir.

Sağlam çocuk izlemleri konusunda rehberlerden faydalanan hekimlerin bilgi düzeyi anlamlı düzeyde yüksekti (p<0,001). Türkiye için önerilen "Bebek, Çocuk, Ergen İzlem Protokolleri" hakkında bilgi sahibi olan hekimlerin bilgi düzeyi de anlamlı düzeyde yüksekti (p<0,001). Benzer şekilde Ankara'daki çalışmada rehberlerin okunma durumu ve rehberleri okuma sıklıkları ile bilgi düzeyi arasında anlamlı bir ilişki olduğu saptanmıştır (5). Rourke ve ark. (8) sağlam çocuk takibi için rehber kullanan hekimlerin daha iyi sağlam çocuk takibi yaptıklarını ortaya koymuştur. Bu sonuçlar bizlere yeni rehberler üretmenin ve başucu kaynaklarının hazırlanmasının önemini göstermektedir.

Çalışmamızın bilgi düzey sorularına baktığımızda bebeklerin ilk bir yılda en az 9 kez izlenmesi gerektiğini

hekimlerin %27,6'sı bilmişti. Bu soruyu pratisyen aile hekimleri; uzman ve asistan aile hekimlerine göre anlamlı düzeyde daha doğru bilmişti (p<0,001). Bu konuya asistanlık eğitimlerinde yeterli düzeyde yer ayrılmadığı ve hekimlerin bu konuda eksik kaldıkları görülmektedir.

İlk bir yaştaki izlemlerde yapılması gereken muayeneleri hekimlerin %68'i yanlış yanıtlamıştı. Ayrıca bu soruyu aile hekimliği asistanları anlamlı düzeyde daha çok doğru bilmişti (p=0,005). Çalışmamıza benzer şekilde Yılmaz ve Şahin'in (6) çalışmasında da gerekli tüm muayeneleri bilen hekim sayısı oldukça azdır. Bu sonuç asistanların bu konudaki teorik bilgisinin güncel olmasından ancak uzman ve pratisyen hekimlerin hizmet içi eğitimlerden uzak kalması nedeniyle bilgilerinin güncelliğini yitirmesinden kaynaklanıyor olabilir.

Büyüme ve gelişmeyi değerlendirmek için kullanılan vücut tartısı, tartı alma hızı, persentil eğrileri, boy uzunluğu ve boy uzama hızı parametrelerini hekimlerin %27,6'sı bilmişti. Yılmaz ve Şahin'in (6) çalışmasında bu oran %26,2'dir. Ayıca bu soruyu aile hekimliği asistanları anlamlı düzeyde daha çok doğru yanıtlamıştı (p=0,010). Çocuklarda obezitenin 6-18 yaş aralığında tarandığını hekimlerin %60'ı ve obezite persentil sınırının %95 olduğunu hekimlerin %29,4'ü doğru bilmiştir. Yılmaz ve ark.'nın (5) çalışmasında ise bu oran %20,9'dur. Obezite konusunda aile hekimliği uzmanlarının bilgi düzeyi diğerlerinden anlamlı düzeyde yüksekti (p=0,050). Literatürdeki çalışmaya göre geçen süreçte hekimlerin obezite konusunda farkındalıklarının arttığını söyleyebiliriz. Hekimlerin çoğunun persentil sınırlarını tam olarak bilmese de obezite farkındalıklarının olması umut verici bir sonuçtur. Ayrıca asistan hekimlerin eğitimlerinin hali hazırda devam ediyor olması, pediatri rotasyon eğitimleri sırasında büyüme gelişme ve obezite konusunda farkındalıklarının artması diğer gruplara göre bilgi düzeyinin yüksek olmasını açıklayabilir.

Profilaktik demir tedavisinin 4. ayda başlanacağını hekimlerin %74,4'ü, 1 mg/kg/gün dozda başlanacağını %70,4'ü, kontrol hemoglobin değerine 9. ayda bakılması gerektiğini %63,9'u doğru bilmişti. Demir profilaksi dozunu pratisyen aile hekimleri diğer gruplardan anlamlı düzeyde daha çok doğru bilmekteydi (p<0,001). Yılmaz ve ark.'nın (5) çalışmasında profilaktik demir tedavisinin başlangıç zamanını hekimlerin %85,3'ü, kontrol hemoglobin değerine bakılma zamanını %83,2'si doğru bilmişti. Bu konunun yalnızca birinci basamakta yapılan benzer çalışmaya göre daha düşük oranlarda doğru bilinmesi çalışmamızın sahadan uzak kalan bir popülasyonu da kapsamasından kaynaklanıyor olabilir.

Bebeklerde profilaktik D vitamininin doğumun ilk haftasında başlanacağını hekimlerin %79,9'u, 400 IU dozda başlanacağını %69,9'u ve 12. aya kadar kullanılması gerektiğini %67,7'si doğru yanıtlamıştı. Asistan aile hekimlerinin D vitamini kullanım süresini bilme durumları diğerlerinden anlamlı düzeyde yüksekti (p<0,001). Yılmaz ve ark.'nın (5) çalışmasında D vitamininin başlama zamanını katılımcıların %9,4'ü, dozunu %76,9'u ve kullanım süresini %82,1'i doğru cevaplamıştır. Yılmaz ve Şahin'in (6) çalışmasında katılımcıların %43,4'ü D vitamini başlama zamanını doğru bilmiştir. Hekimlerin D vitamini profilaksisi konusundaki bilgi düzeyleri diğer benzer çalışmalardan daha yüksekti. Sağlık Bakanlığı'nın 0-12 ay arası tüm bebeklere ücretsiz D vitamin preparatları dağıtmaya başlaması bu konuda hekimlerin ve ailelerin farkındalıklarını artırmış olabilir (9). Ayrıca asistan hekimlerin bilgi düzeylerinin diğer gruplardan anlamlı düzeyde yüksek saptanması teorik bilgilerinin daha güncel olmasından kaynaklanıyor olabilir.

Yenidoğan işitme taramasının ilk 72 saatte yapılması gerektiğini hekimlerin %63,7'si bilmişti. Yılmaz ve ark.'nın (5) çalışmasında bu oran %38,7'ydi. Aile hekimliği uzmanlarının bu konudaki bilgi düzeyleri, diğer gruplardan anlamlı düzeyde yüksekti (p<0,001). Literatürdeki benzer bir çalışmada aile hekimlerinin bilgi seviyelerinin düşük olduğu saptanmış olup tarama zamanını hekimlerin %52'si bilmiştir (10). İşitme kaybı olan çocukların erken tespit edilmesi (ilk 3 ayda) ve cihazlandırılması çocukların bilişsel ve konuşma yeteneklerinin gelişimi için çok önemlidir. Aile hekimleri aileleri tarama yöntemleri konusunda bilgilendirmeli ve onların kaygılarını gidermelidir. Çalışmamızda tarama zamanını hekimlerin yarıdan fazlasının biliyor olması sevindiricidir.

Çocuklarda kan basıncı takibini hekimlerin %47,8'si doğru bilmiştir. Aynı zamanda pratisyen aile hekimleri diğerlerine göre anlamlı düzeyde daha doğru yanıtlamıştı (p<0,001). Duzova ve ark. (11) yaptığı çalışmada 5-18 yaş aralığında hipertansiyon sıklığı %6,1; Sarıkan ve Öngel (12) okul çağındaki çocuklarda yaptığı çalışmada ise %5,5 olarak

saptanmıştır. Bu oranlar azımsanmayacak düzeylerde olup 3 yaşından sonra düzenli kan basıncı takibi yapmanın önemini ortaya koymaktadır. Pratisyen aile hekimlerinin sahada olmaları ve hali hazırda sağlam çocuk izlemi yapmaları bilgi düzeylerinin yüksekliğini açıklayabilir.

Çocuklarda otizm spektrum bozukluğunun (OSB) 18-36. ayda ve DEHB'nin 48-60. ayda yapıldığını ve otizm gözlem maddelerini hekimlerin çoğu yanlış yanıtlamıştır. Sabuncuoğlu ve ark'nın (13) çalışmasında hekimlerin OSB ve DEHB hakkındaki bilgi düzeylerinin düşük olduğu belirlenmiştir. Erden ve ark. (14) yaptığı çalışmada 125 OSB tanılı çocuğun yalnızca %11,2'sinin çocuk hekimleri tarafından fark edilebildiği vurgulanmıştır. Bu konuda ülkemizdeki hekimlerin otizm belirti ve gözlem maddelerini fark edebilme ve yönlendirebilme konusunda bilgi eksikliklerinin olduğu görülmektedir.

Çalışmamızda ayrıca OSB ve DEHB sorusunu aile hekimliği uzmanları, diğerlerine göre anlamlı düzeyde daha çok doğru yanıtlamıştı (sırasıyla; OSB ve DEHB için; p<0,001; p=0,004). Gürbüz'ün (15) yaptığı çalışmada aile hekimliği asistanlarının OSB konusundaki bilgilerinin eksik olduğu, OSB konusunda eğitim almak ve OSB tanılı hasta takip etmiş olmanın bilgi düzeyi ile ilişkili olduğu belirlenmiştir. OSB ve DEHB gibi spesifik konulara lisans eğitimlerinde veya uzmanlık eğitimlerinde yeterli farkındalığın oluşturulması gereklidir. Aile hekimliği uzmanlık eğitimleri sırasında çocuk psikiyatri rotasyonlarında hasta görmüş olmak ve bu konuda eğitim almış olmak uzman aile hekimlerinin bilgi düzeylerinin diğer gruplardan yüksek olmasının sebebi olabilir.

Fiziksel istismarı düşündüren bulguları hekimlerin %39,6'sı bilmişti. Yılmaz ve Şahin'in (6) çalışmasında bu oran %42'dir. Aynı zamanda pratisyen aile hekimleri diğerlerine göre anlamlı düzeyde daha doğru yanıtlamıştır (p=0,005). Çalışmamızın bu konudaki doğru yanıt oranı literatürden daha düşüktür. Hekimlerin yasal sürece girmekten çekinmesi ve mevcut pandemi koşullarının taramaları aksatması bu sonuca sebep olmuş olabilir.

Aile Hekimlerinin Tutumları

Çalışmamızın tutum soruları bölümünden alınan ortalama puan 46,96±4,40 olarak bulundu. Bu sonuca göre çalışmaya katılan hekimlerin sağlam çocuk izlemleri konusundaki tutumlarının olumlu olduğunu söyleyebiliriz. Tugay ve ark.'nın (7) çalışmasında benzer şekilde aile hekimlerinin periyodik sağlık muayene rehberine yönelik tutumları olumludur.

Sağlam çocuk izlemleri konusunda aile hekimliği asistanları en olumlu, aile hekimliği uzmanları ise en olumsuz tutuma sahipti. Ancak unvan ile tutum arasında anlamlı bir ilişki saptanmamıştı (p=0,900). Pratisyen aile hekimlerinin tutumlarının daha olumlu olması sahada olmaları ve sağlam çocuk izlemlerini hali hazırda uyguluyor olmalarından, asistan ve uzman hekimlerin ise birinci basamaktan daha uzak kalmalarından kaynaklanıyor olabilir.

Erkek hekimlerin kadın hekimlerden anlamlı düzeyde daha olumlu tutuma sahip olduğu görüldü (p=0,026). Literatürde hekimlerin "Periyodik Sağlık Muayeneleri ve Tarama Rehberi"ne yönelik tutumları ile cinsiyet arasında anlamlı bir ilişki saptanmıştır (7). Negatif performansa bağlı izlemlerin olması ve her geçen gün istenen izlemlerin kapsamının genişlemesi taramalar için daha fazla zaman ve emek harcanmasını gerektirmektedir. Kadın hekimlerin tutumlarının daha olumsuz olmasının sebebi iş hayatı dışındaki sosyal hayatlarındaki sorumluluklarının daha fazla olması olabilir.

Hekimlerin çalıştıkları kurum ile tutumları arasında anlamlı bir fark saptanmıştı (p=0,027). Çalışılan kurumu "diğer" olarak belirten hekimlerin tutumları daha olumluydu. Bu grubun hali hazırda sağlam çocuk takipleri yapmamasından ve kendi iş yüklerini etkilememesinden kaynaklanıyor olabilir.

Sağlam çocuk izlemleri sırasında her bir çocuğa ayrılan muayene süresi 15 dakikadan çok olan hekimlerin tutumları anlamlı düzeyde daha olumsuzdu (p=0,004). Sağlam çocuk izlemlerinin öneminin ve sorumluluğunun farkında olan hekimlerin muayenelere gerekli zamanı ayırmaya çalışmaları ancak mevcut poliklinik şartlarına dahil etme konusunda zorlanmaları tutumlarının daha olumsuz olmasının sebebi olabilir. Bu izlemlerin titizlikle sürdürülebilmesi için mevcut muayene şartlarının iyileştirilmesi gerekmektedir.

Hekimlerin %94,5'i birinci basamakta sağlam çocuk izlemlerinin hasta açısından önemli olduğunu ve %93,8'i sağlam çocuk izlemlerinin hastalıkların erken döneminde tespit ve tedavisinde etkili olduğunu düşünmekteydi. Hekimlerin sağlam çocuk izlemlerine yönelik tutumlarının bu düzeyde olumlu olması sevindiricidir. Ancak hekimlerin %56'sı birinci basamak sağlam çocuk izlemlerinin hekimlerin iş

yükünü artırdığını düşünmekteydi. Hekimler her ne kadar sağlam çocuk izlemlerinin faydasına inansa da bu hizmetlerin sunumunda zorlanmakta ve pratikte iş yükü olarak görmektedir. Hekimlerin %61,4'ü, 5 yaşına kadar olan bebek ve çocuk izlemlerinin yapılmasının negatif performans olarak değerlendirilmesini faydalı bulmamıştı. Tugay ve ark.'nın (7) çalışmasında da benzer şekilde hekimler periyodik sağlık muayenelerinin pozitif veya negatif performans ile zorunlu hale getirilmesi görüşüne katılmamışlardır. Eksik yapılan her takibin maddi bir geri dönüşünün olması hekimlerin bu hizmete karşı olan tutumlarını olumsuz etkileyecektir. Koruyucu sağlık hizmetlerinin kapsamlı bir şekilde sürdürülebilmesi için teşvik edici yeni yöntemler geliştirilmelidir.

Çalışmanın Kısıtlılıkları

Çalışmamıza katılan aile hekimliği uzman sayısı diğer gruplardan daha az sayıdadır. Hekimlerin unvana göre eşit şekilde dağılamamış olması çalışmamızın sınırlılığıdır. Ancak aile hekimliği uzmanlarının oranının ASM'lerde de benzer oranda olması daha gerçekçi sonuçların çıkmasına katkı sağlamış olabilir. Diğer bir kısıtlılık, COVID-19 pandemi şartları nedeniyle hekimlerin büyük bölümüne yüz yüze değil internet aracılığıyla ulaşılmış olmasıdır.

Sonuç

Aile hekimlerinin sağlam çocuk izlemleri konusundaki bilgi düzeyleri hala istenilen seviyelerde değildir ancak bu konudaki tutumlarının olumlu olması sevindiricidir. Sağlam çocuk izlemlerinden her çocuğun eşit şekilde yararlanabilmesi için hekimleri teşvik edici politikalar geliştirilmeli, hekimlerin standardize edilmiş rehberler ve eğitimler eşliğinde bilgi eksikliklerini kapatması sağlanmalıdır. Kolay okunabilir, takip edilebilir ve yeni gelişmelerle güncellenen kaynakların geliştirilmesi ile düzenli ve eksiksiz bir sağlam çocuk takibi sağlanabilecektir.

Sağlam çocuk izlemleri hakkında yapılan çalışmalar sınırlı sayıdadır ve kapsamlı araştırılmalara ihtiyaç vardır. Özellikle bilgi eksikliğini tespit ettiğimiz hekimlerin yarıdan fazlasının yanlış yanıtladığı obezite, OSB, DEHB, GKD, inmemiş testis, görme keskinliği, kan basıncı takipleri konularının hakkında çalışmaların yapılmasına ihtiyaç olduğunu düşünmekteyiz. Ayrıca pandemi koşullarında sağlam çocuk izlemlerinin nasıl etkilendiği, eksik kalan hizmetlerin neler olduğu, kaçırılmış izlemler için neler yapılabileceği gibi konular üzerinde düşünülmeli ve araştırılmalar yapılmalıdır. Ayrıca ailelerin sağlam çocuk izlemleri konusundaki farkındalıkları, bilgileri ve tutumları da araştırılması gereken hususlar arasındadır.

Etik

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Is Intravenous Iron Treatment in Pediatric Patients Safe and Effective Enough?

Pediatrik Hastalarda İntravenöz Demir Tedavisi Yeterince Güvenli ve Etkili mi?

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Abstract

Introduction: Iron deficiency anemia (IDA) is the most common hematological disease among infants and children. Although most of the children with IDA are treated with oral iron preparations, intravenous (IV) iron is an alternative for children with severe IDA who have difficulty in adhering to or absorbing oral iron. In this study, the reasons of IDA in patients treated with IV iron and the effectivity and safety of iron sucrose preparations in pediatric patients were evaluated.

Materials and Methods: The medical records of children received IV iron sucrose at a pheripheral hospital between June 2014 and June 2017 were reviewed retrospectively. The IDA patients who are unresponsive to oral iron or whose hemoglobin (Hb) <7 g/dL and received IV iron treatment were evaluated for the reasons of anemia, the efficacy and safety of IV iron treatment. Before and after iron sucrose infusion laboratory results were compared. All records were reviewed for serious side effects and allergic reactions.

Results: A total of 33 patients, aged between 3-18 years were enrolled into the study. While 58% of the patients who received IV iron treatment had inadequate consumption of iron, 24% had malabsorption. In the initial evaluation Hb levels of the patients were 3.2-7.8 (6.54±1.06) g/dL, (mean corpuscular volume) MCV was 59.18±6.66 fL and ferritin was 1.87±1.34 μg/L, the mean post-treatment Hb was 11.39±1.51 g/dL, MCV was 76.06±7.59 fL and ferritin was 54.79±15.64 μg/L. No serious side effects were seen.

Conclusion: The use of IV iron sucrose in pediatric patients with IDA leads to significant increase in Hb and reduces erythrocyte suspension transfusion and is an effective and safe method for iron treatment.

Keywords
Iron deficiency anemia, intravenous treatment, effectivity, safety

Öz

Giriş: Demir eksikliği anemisi (DEA) çocukluk çağında en sık görülen hematolojik hastalıktır. DEA olan çoğu çocuk oral demir ile tedavi edilse de, tedavi uyumu olmayan, emilim bozukluğu olan ağır DEA'lı çocuklarda intravenöz (İV) demir uygulaması bir tedavi alternatifidir. Bu çalışmada İV demir tedavisi uygulanan çocukların anemi nedenleri, tedavi etkinliği ve güvenliği incelenmiştir.

Gereç ve Yöntem: Haziran 2014-Haziran 2017 yılları arasında anemi nedeni ile çocuk hekimi tarafından çocuk hematoloji polikliniğine yönlendirilen ve İV demir tedavisi uygulanan olguların dosyaları retrospektif olarak incelenmiştir. Oral demire yanıt vermeyen veya hemoglobini (Hb) <7 g/dL olan ve İV demir tedavisi uygulanan DEA hastalarının anemi nedenleri, İV demir tedavisinin etkinliği ve güvenliği açısından değerlendirildi. Demir sükroz infüzyonu öncesi ve sonrası laboratuvar sonuçları karşılaştırıldı. Tüm kayıtlar ciddi yan etkiler ve alerjik reaksiyonlar açısından gözden geçirildi.

Anahtar kelimeler
Demir eksikliği anemisi, intravenöz tedavi, etkinlik, güvenlilik

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Bulgular: Çalışmaya 3-18 yaş arası toplam 33 hasta alındı. İV demir tedavisi alan hastaların %58'inde yetersiz demir alımı varken, %24'ünde malabsorbsiyon vardı. İlk değerlendirmede hastaların Hb düzeyleri 3,2-7,8 (6,54±1,06) g/dL, ortalama korpüsküler hacim (MCV) 59,18±6,66 fL ve ferritin 1,87±1,34 μg/Ll iken, tedavi sonrası 4-6. haftada bakılan Hb 11,39±1,51g/dL, MCV 76,06±7,59 fL ve ferritin 54,79±15,64 μg/L idi. Ciddi bir yan etki görülmedi.
Sonuç: DEA'lı çocuklarda İV demir tedavisi Hb'de hızlı artışa yol açar ve eritrosit süspansiyonu transfüzyon ihtiyacını azaltır. Güvenli ve etkili bir tedavi yöntemidir.

Introduction

Iron deficiency anemia (IDA) is the most common hematological disease among infants and children. Especially in developing countries IDA is frequently seen. Although iron deficiency affects 9% of toddlers and up to 16% of adolescent girls and 3% of all pediatric patients in American studies (1,2), iron deficiency is estimated up to 30-78% and IDA is estimated to 5.6-12.5% in different age groups in comprehensive studies performed in Turkey (3,4).

Iron deficiency can be caused by multiple factors including insufficient iron intake, decreased iron absorption and gastrointestinal blood loss from inflammatory bowel disease or chronic use of nonsteroidal anti-inflammatory drugs. In addition, cow's milk, which is a poor source of iron, can cause occult blood loss and inhibit the absorption of iron from other food sources (5). Adolescent girls with menorrhagia are also at a high risk of IDA.

As inadequate consumption of iron causes neurodevelopmental consequences, the rapid and effective treatment of IDA is mandatory. Nearly all of the children with IDA are treated with oral iron preparations. After starting the oral iron therapy, the increase of reticulocyte count is seen as early as 3 days, while improvement of hemoglobin (Hb) concentration is detected later. Hb normalization is a slow process, taking up to 6 months after the start of therapy (6). Although oral iron therapy is cheap, safe, and effective at correcting IDA, it is not well tolerated by some patients and in a subset of patients, it is insufficient. Patients in whom the blood loss is more than the intestinal ability to absorb iron (e.g. intestinal angiodysplasia, malabsorption, von Willebrand's disease..) may develop IDA refractory to oral iron supplementation. These patients are the most challenging to manage and they may have required multiple and frequent blood transfusions and suffer end-organ damage as a result of their refractory anemia (7).

In this study, the reasons of IDA in patients treated with intravenous (IV) iron in a peripheral hospital and the effectivity and safety of iron sucrose preparations in pediatric patients were evaluated.

Materials and Methods

The medical records of 33 children who received IV iron sucrose at a single center between June 2014 and June 2017 were reviewed retrospectively. The patients who aged between 3-18 years, were referred to pediatric hematology department with oral iron unresponsive or Hb <7 g/dL IDA and received IV iron treatment were evaluated for the reasons of anemia, the efficacy and safety of IV iron treatment. Firstly, the patients were evaluated for the etiology of anemia. The patients who were diagnosed as IDA were included in the study. The unresponsiveness was considered as using oral iron formulations appropriately at least for three months, but neither Hb nor reticulocyte count increase was seen. The patients who had diagnosis of hemoglobinopathy, chronic renal insufficiency or anemia of chronic disease were excluded.

The hospital's electronical medical records were used to obtain laboratory results pre-IV and post-IV iron sucrose including markers of anemia such as Hb and mean corpuscular volume (MCV), serum iron, ferritin, total iron binding capacity, and percent of iron saturation, Vitamin B12, folate and the reasons of iron deficiency such as anti-gliadin IgA and G, anti-endomysium IgA and IgG and occult blood test in stool, macroscopic and microscopic evaluation of stool for parasitic infections. Mean (when normally distributed) or median values of laboratory parameters were recorded. The post-IV treatment evaluations were performed 4-5 weeks after the initiation of the treatment.

For IV iron sucrose, the following calculation was used to determine the total iron deficit for initial repletion: total cumulative dose (mg) = [target Hb (12 g/dL) - actual Hb] × weight (kg) × 0.24 + [15 × weight (kg)]. To prevent adverse reactions, the maximum

daily dose of iron sucrose was limited to 200 mg/day or 4 mg/kg/day. It was diluted in 100 mL of normal saline and administered for 1 hour on each day (8). IV iron treatment was applied 2 times a week in either outpatient or inpatient clinic until the total cumulative dose was replaced.

Before and after iron sucrose infusion laboratory results were compared. HPLC was performed to 4 suspected patients after IV iron treatment. Fifteen patients with hemorrhage history were also evaluated for hemorrhagic diathesis. Eight patients were referred to pediatric gastroenterology and endoscopy - colonoscopy was performed.

All records were also reviewed for serious side effects and allergic reactions.

The study protocol was approved by the Institutional Ethics Committee of Balıkesir University, approval number: 2017/148, date: 13.12.2017. Informed written consent was obtained before enrolling children into the study.

Statistical Analysis

The paired t-test is used to assess statistical significance for all parameters except ferritin. As the data for ferritin were not normally distributed, the Wilcoxon signed rank test and interquartile range is used.

Results

A total of 33 patients who had IV iron treatment between June 2014 and June 2017 at Balıkesir Ataturk Government Hospital were enrolled into the study. The patients were aged between 3-18 (11.09±4.67) years. Seventeen of the patients were girls. The demographic data are shown in Table 1. The baseline Hb levels was lower than 7g/dL in nineteen (58%) of the patients and severe anemia was developed due to inadequate consumption of iron (four patients had also Thalassemia trait, one patient had intolerance to oral iron preparations and two patients had Pica). Iron unresponsiveness was seen in fourteen patients. While eight (24%) of the patients had malabsorption (one patient had Crohn disease and seven patients had Celiac disease), four (12%) of the patients had abnormal uterine bleeding and one of the patient had Von Willebrand's disease. One patient had total gastrectomy due to perforation in childhood.

While 8 patients had both vitamin B12 and iron deficiency, 2 patients had folate and iron deficiency. None of the patients had the deficiency of all and the combined deficiency was not related to malabsorption ($p>0.05$). The B12 and folic acid treatments were given during and after IV iron treatment.

The initial evaluation Hb of the patients were 3.2-7.8 (6.54±1.06) g/dL, MCV was 59.18±6.66 (50-83) fL and ferritin was 1.87±1.34 (0-5) μg/L. The pre and post treatment laboratory tests were shown in Table 2. The control mean Hb elevation at the first week of treatment was 2.3±1.5 g/dL. The mean time period of taking pre and post-treatment laboratory tests was 30±3.4 days. The comparison of the pre and post-treatment Hb, MCV and ferritin were shown in Table 2. The mean post-treatment Hb was 11.39±1.51 g/dL, MCV was 76.06±7.59 fL and ferritin was 54.79±15.64 μg/L. The average number of IV iron doses received was 5.6.

Only one patient whose Hb was below 5 (3.2) g/dL, had received only one unite of packed red blood cell and IV iron treatment was started when his post-transfusion Hb was 5.7 g/dL. This patient's pre-transfusion ferritin level was below 1 μg/L and serum iron was 4 μg/L. Any other erythrocyte suspension was needed.

One patient had fever during iron infusion. By giving antipyretic and tapering the infusion rate of iron, no problem was seen. One patient had

Table 1. Demographic characteristics of the patients receiving parenteral iron therapy

Ages (years)	N (%)
3-5	5 (16)
6-10	9 (27)
11-15	10 (30)
16-18	9 (27)
Sex	
Girls	17 (51.5)
Boys	16 (48.5)
Diagnosis	
Inadequate consumption	19 (58)
Malabsorption	8 (24)
Total gastrectomy	1 (3)
Dysfunctional uterine bleeding	4 (12)
Von Willebrand's disease	1 (3)

Table 2. Laboratory characteristics of patients before and after parenteral iron therapy			
	Pre treatment	Post treatment	p
Hemoglobin (g/dL)	6.54±1.06 (3-7.8)	11.39±1.51 (8.2-13.3)	0.00
MCV (fL)	59.18±6.66 (50-83)	76.06±7.59 (58-93)	0.00
RDW (%)	20.63±6.62 (17-48)	12.32±5.75 (11-23)	0.00
Fe (μg/dL)	16.94±10.37 (4-32)	35.3±8.8 (24-55)	0.00
Transferrin saturation (%)	5.3 (0-13)	42.1 (25-55)	0.00
Ferritin (μg/L)	1.87±1.34 (0-5)	54.79±15.64 (22-95)	0.00
B12 (nmol/L)	390±203 (101-1099)	N/A	-
Folate (μg/L)	5.48±2.59 (1-11)	N/A	-
MCV: Mean corpuscular volume, RDW: Red cell distribution width, B12: Vitamin B12, Fe: Iron			

thrombophlebitis after the third day of iron infusion. Neither any other adverse effects, nor allergic reactions were seen.

Discussion

Iron deficiency is the most widespread nutritional disorder in the World. Traditionally, oral iron therapy in the form of ferrous salts, carbonyl iron, and ferric protein succinate or iron polysaccharide combinations is the recommended treatment for IDA (9-13). Whatever is chosen, oral iron therapy requires good patient compliance for several months in order to be effective. Moreover, the most widely used and cheaper oral iron products (14), are less well tolerated, and in situations where IDA is due to gastrointestinal bleeding and menorrhagia, iron loss may be greater than the oral iron supply. The same as the general approach oral iron preparations are the first choice in our center. As few patients needed IV iron treatment, the effectiveness of iron sucrose on iron studies in addition to describing Hb increase after infusion in children with severe IDA and/or unresponsive to oral iron preparations were planned to evaluate in this study.

IV iron is an infrequently used therapeutic alternative to oral iron for the treatment of IDA in children. By far, the most common pediatric indications for IV iron in everyday clinical practice are unresponsiveness, intolerance or incompliance to oral iron therapy, malabsorption, rapid need of anemia correction, heavy menstrual bleeding in adolescent females (15).

Although IV iron was given for a variety of reason in this study, the most common reason was inadequate iron consumption, followed by malabsorption. Also as the initial Hb level of our cohort was 6.54±1.06 (3.2-7.8) g/dL, IV iron was given for quick correction of anemia and reduction erythrocyte suspension transfusion. The IV iron preparations that are being used in Turkey are iron sucrose, sodium ferric gluconate and ferric carboxymaltose (not yet approved for pediatric use). These products are similar in terms of safety profile but differ in the content and frequency of the doses administered (16). While a typical therapeutic course of iron sucrose requires 5-10 injections of 100-200 mg doses of each and multiple infusions are required to replenish iron stores, iron carboxymaltose allows the administration of high doses of iron over a limited time (17). As iron sucrose was the only IV preparation in the hospital during the study period, iron sucrose was used in our study, similar to the majority of pediatric studies (18-20). Considering the negative effects on neurodevelopment associated with IDA, the repletion of the iron stores of these children safely and immediately is important. Hb increment effect of IV iron formulations was shown in few studies and 1.56 to 4.8 g/dL increase was reported in one to sixteen weeks (21-27). Similarly, in our study the evaluation which was performed after the first week of IV iron therapy initiation, there was 2.3±1.5 g/dL improvement in Hb levels. Although IV iron therapy is more expensive than oral iron, it might lead to faster iron repletion in patients with severe anemia allowing for fewer doctor visits, less frequent laboratory tests, less time out of school, decreased need for packed red blood cell transfusions, and potentially lower overall costs. The presence of a safe IV alternative preparation of iron is necessary because there are many pediatric patients who cannot tolerate or do not adhere to oral formulations.

Also as the weights of children are smaller than adults, the measurement of iron deficiency is lower and high dose therapy can cause hemosiderosis in children. The correct calculation of iron deficiency and close follow up is important.

Although the current pediatric experience with IV iron administration for children with IDA is limited, IV iron is both effective and safe in children (11-13,16-27). Few side effects were seen during IV iron infusions in our patients. In a review and meta-analysis performed by Avni A et al. (22) IV iron therapy is not associated with an increased risk of SAEs or infections. Infusion reactions are more pronounced with IV iron.

As it was a retrospective study, the patients were neither paid nor reported.

The effectivity and the safety of IV iron in severe IDA is pointed out in this study. Not only the Hb levels were significantly elevated, but only two minor adverse events were seen. While 8 patients with B12 deficiency were also given oral B12 preparations, 2 patients with folic acid deficiency were given oral folic acid preparations during and after IV treatment.

Study Limitations

Limitations of our study were being retrospective and the reticulocyte count during the study was not included. There is a scarcity of literature in support of IV iron versus oral iron in the medical management of severe anemia and details of administration (doses, interval, factors to assess when the next dose is needed, etc.) are lacking. The study was performed by hematologists and pediatricians because no gastroenterologist was present in the hospital during the follow up. The comparison of the long-term cost effectiveness of using oral iron or IV iron sucrose should be evaluated in more comprehensive studies in future.

Conclusion

The use of IV iron sucrose in pediatric patients with IDA is safe and leads to significant increase in Hb and reduces erythrocyte suspension transfusion.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of Balıkesir University, approval number: 2017/148, date: 13.12.2017.

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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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Final Height in GnRH Analogue Treatment in Girls Diagnosed with Early Puberty: Comparison with Untreated Controls

Erkence Puberte Tanılı Kızlarda GnRH Analog Tedavisinde Final Boy: Tedavi Edilmemiş Kontrollerle Karşılaştırma

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Abstract

Introduction: In this retrospective study, it was aimed to examine the effect of gonadotropin-releasing hormone (GnRH) analogue treatment on final height in girls diagnosed with early puberty (EP) between the ages of 8 and 10.

Materials and Methods: In the study, 87 girls who were diagnosed with EP and reached the final height were included. Two groups, those who received GnRH analogue treatment and those who did not, were formed. The average age, bone age, average height, height standard deviation score (SDS), body mass index SDS, target height, predicted adult height of the groups at the time of admission were calculated. The final height they reached and their menarche ages were noted.

Results: No difference was found between the groups in terms of average age, average height, height SDS, bone age, body mass index SDS at the time of admission. The target height, predicted adult height, final height and the SDS of these were similar in both groups. All cases in both groups reached the target height.

Conclusion: It was determined that the GnRH analogue treatment did not make a positive contribution to the final height in the EP group, who were between the ages of 8 and 10. Therefore, it can be recommended to use GnRHa treatment in EP patients with psychosocial problems and for delaying menarche.

Keywords
Early puberty, puberty, gonadotropin-releasing hormone analogue, final height

Öz

Giriş: Bu retrospektif çalışmada, 8-10 yaş arası erkence puberte (EP) tanısı konulan kız çocuklarında gonadotropin salgılatıcı hormon (GnRH) analog tedavisinin nihai boy üzerine etkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: EP tanısı alan ve final boya ulaşmış 87 kız olgu alındı. GnRH analog tedavisi alanlar ve almayanlar olmak üzere iki grup oluşturuldu. Grupların başvuru anındaki ortalama yaşı, kemik yaşı, ortalama boy, boy standart sapma skoru (SDS), vücut kitle indeksi SDS, hedef boy, tahmini erişkin boyu hesaplandı. Ulaştıkları son boy ve menarş yaşları not edildi.

Bulgular: Başvuru anında ortalama yaş, ortalama boy, boy SDS, kemik yaşı, vucut kitle indeksi SDS açısından gruplar arasında fark yoktu. Hedef boy, tahmini erişkin boy, final boy ve bunların SDS'leri her iki grupta benzerdi. Her iki gruptaki tüm olgular hedef boya ulaştı.

Sonuç: GnRH analog tedavisinin 8-10 yaş EP grubunda final boya olumlu bir katkı yapmadığı tespit edildi. Bu nedenle, GnRHa terapisinin EP'de psikososyal zorlukları olan olgulara ve menarşın geciktirilmesi için kullanılması önerilebilir.

Anahtar kelimeler
Erkence puberte, puberte, gonadotropin salgılatıcı hormon analoğu, final boy

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Introduction

Central precocious puberty is the early development of secondary sexual characteristics before the age of eight in girls and nine in boys, due to the early activation of the hypothalamic-pituitary gonadal (HPG) axis. This condition may lead to acceleration in the bone maturation and premature closure of growth plates, resulting in remaining short after reaching the final adult height (FH) (1,2). Early puberty (EP) is the presence of clinical and auxological findings of pubertal development in girls between the ages of 8 and 10. It manifests itself with the characteristics of precocious puberty. In girls, breast development, increased growth rate and advanced bone age (BA) occur. There is an increase in the basal and stimulated gonadotropins (3). Although various age ranges have been specified for EP (4-6), it is a term mostly used for puberty that starts between the ages of 8 and 10 (6-8).

Gonadotropin-releasing hormone analogues (GnRHa) have been used for many years in the treatment of precocious puberty. GnRHa treatment suppresses the HPG axis and reduces hormones to the prepubertal level. Thus, it is believed to improve the FH by slowing the maturation of BA (9-11). In the literature reviews, it has been stated that GnRHa treatment is beneficial for the FH, especially in cases whose pubertal findings start before the age of 6 (7,12).

It has been reported that different results have been obtained regarding GnRHa treatment in cases between the ages of six and eight (4,10,13,14).

However, it is stated that it does not contribute to the FH in cases who receive GnRHa treatment after the age of 8 (6,15). Although it has been accepted that it does not improve the FH after the age of eight, it has been reported that GnRHa treatment can still be used for the psychosocial problems due to adolescence (16,17).

In this study, it was aimed to retrospectively compare the final heights (FH) of the two groups, who received GnRHa treatment and who did not, in girls diagnosed with EP between the ages of 8 and 10.

Materials and Methods

In this study, 87 female cases diagnosed with EP between the ages of 8 and 10 and reached the FH, who were admitted to Dicle University Faculty of Medicine Pediatric Endocrinology Polyclinic between 2010 and 2020, were included. Patients with onset of puberty after the age of 8 were included in the study. Patients with breast development, increased growth rate, advanced BA, pubertal response to the basal luteinizing hormone (LH) or GnRH-stimulated LH, signs of precocious puberty and who reached the FH were included in the study (3).

The medical records of the cases were examined retrospectively. Those who received gonadotropin-releasing hormone analogue treatment were named group 1 (n=57), and those who did not receive GnRHa treatment were named group 2 (n=30). Cases with a chronic disease, history of prematurity, organic brain lesions, congenital adrenal hyperplasia or other endocrinological problems were excluded from the study.

The age at the time of admission, body weight (BW), BW standard deviation score (SDS), height, height SDS, body mass index (BMI) and the BMI SDS of all of the cases were recorded. The height, weight, BMI and SDS were calculated according to the national data and using the "Child Metrics" software (18,19). The BW was measured using the SECA 767 scale (Carson City, NV, USA) and height was measured using the Harpenden stadiometer. The BMI was calculated with the formula BMI = weight (kg) x height^2 (m^2).

The stage of puberty, target height (TH) and TH-SDS, BA, predicted adult height (PAH) and PAH-SDS of the cases at the time of admission were calculated. In addition, the FH they reached and the FH-SDS were noted. The puberty stages of the cases were evaluated according to the Tanner scale (20).

The TH and TH-SDS were calculated by measuring the heights of the parents. The TH was calculated using the formula: TH = mid-parental height - 6.5 cm (8). Radiography of the left hand wrist was performed on all patients. The BA (21) was calculated with the Greulich-Pyle atlas, and the PAH (22) was calculated with the Bayley-Pinneau method. The hand-wrist radiographs of all patients were evaluated by the same pediatric endocrinologist. The delta height SDS was obtained by calculating the difference between the FH-SDS, and the height SDS at the start of the treatment.

The follicle stimulating hormone (FSH), LH and estradiol (E2) levels of the patients included in the study were measured. The hormone measurements were evaluated by collecting venous blood samples

from the patients in the morning after an eight-hour fast. Immunochemiluminometric assay kits were used to measure the follicle stimulating hormone, LH and E2 (ARCHITECT System, Abbott Laboratory Diagnostics, USA) levels. The HPG axis was thought to be active in cases with a basal LH level of ≥0.3 IU/L (8,23).

GnRH stimulation test was performed by injecting gonadorelin acetate intravenously between 8.00-8.30 in the morning for the evaluation of EP in patients with a basal LH level of <0.3I U/L. The HPG axis was considered to be active in patients with a peak LH level of ≥5 IU/L (23,24).

All cases in group 1 received 3.75 mg depot leuprolide acetate treatment every 28 days. The cases in group 2 did not receive any treatment. The patients who received treatment were followed up in 3-month periods. In the group who received treatment, GnRHa-stimulated LH levels of <4 mIU/mL and regression of breast development were considered as responses to the treatment (25). The HPG axis was suppressed by treatment in patients in Group 1. None of the patients received an increase in the dose or were excluded from the study. The BA was calculated every 12 months. The treatment was discontinued when the chronological age was 11 and the BA was 12 (15). The menarche ages of all patients whose follow-up was continuing were recorded. Patients with a BA of 15 and bone growth of <1 cm/year were considered to have reached the FH (8,26,27).

The approval for this study was obtained from the Ethics Committee of Dicle University Faculty of Medicine (approval number: 2021/173 date: 25.03.2021).

Statistical Analysis

The statistical analysis of the obtained results was performed using the SPSS 21.0 (Statistical Package for the Social Sciences-IBM®, Chicago, IL, USA) statistical software package. Whether the variables were normally distributed or not was evaluated using the Shapiro-Wilk test. Descriptive statistics for continuous variables were presented as mean ± standard deviation, minimum and maximum values, while categorical variables were expressed as numbers and percentages. In the comparison of two independent groups, Student's t-test was used. In order to determine whether there was a relationship between two or more variables, and if there was, the degree of this relationship, a correlation analysis was performed. A p value of <0.05 was considered significant in the statistical evaluation.

Results

Of the 87 patients included in the study, 39 (44.8%) were diagnosed using the GnRH stimulation test, while 48 (55.2%) were diagnosed according to the basal LH levels. Of the 87 cases included in the study, 57 (65.5%) were included in group 1 and 30 (34.5%) were included in group 2. The anthropometric and demographic characteristics of the groups are summarized in Table 1.

In group 1, 27 (47.4%) of the cases had Tanner stage 2 breast development and 30 (52.6%) had Tanner stage 3 breast development at the time of admission. Pubarche was also present in 32 (56.1%) of the patients in group 1. Of the cases in group 2, 19 (63.3%) presented with Tanner stage 2 and 11 (36.7%) presented with Tanner stage 3. None of our patients presented with menarche. No statistically significant difference was found between the groups in terms of Tanner staging (p=0.156). The Tanner stage, age of menarche, FSH, LH, E2, peak LH and LH/FSH values of the groups were compared. No statistically significant difference was observed between the groups in terms of FSH, E2, peak LH, LH/FSH ratios and Tanner stages at the time of admission (p>0.05). There was a significant difference between the groups in terms of basal LH levels (p=0.033). In group 1, the basal LH levels were higher (Table 1).

The average age of the cases in Group 1 at the time of admission was 8.75±0.44 years, the average height was 133.46±5.96 cm and the average BA was 10.12±0.86 years. The average age of the cases in group 2 at the time of admission was 8.80±0.53 years, the average height was 133.35±6.84 cm, and the average BA was found to be 9.96±0.96 years. The average age, height, height SDS, BA, BMI-SDS, PAH, PAH-SDS at the time of admission were similar between the groups.

The average FH was 158.62±6.13 cm in group 1, while it was found to be 157.59±5.76 cm in group 2. There was no statistically significant difference between the groups in terms of FH (p=0.43). There

Table 1. Comparison of the demographic characteristics and anthropometric data of the study groups			
	Group 1 (n=57)	Group 2 (n=30)	p value
Age at presentation (year)	8.75±0.44	8.80±0.53	0.70[a]
Height at presentation (cm)	133.46±5.96	133.35±6.84	0.93[a]
Height presentation SDS	0.44±0.97	0.38±1.0	0.79[a]
Weight presentation SDS	0.35±1.04	0.24±1.00	0.63[a]
Presentation BMI SDS	0.199±1.00	0.120±0.908	0.71[a]
Bone Age at presentation (year)	10.12±0.86	9.96± 0.96	0.45
Menarche(years)	11.9±0.71	11.1±0.85	<0.01[a]
Basal LH	0.43 (0.13-1.28)	0.20 (0.1-0.64)	0.033[b]
Basal FSH	4.03 (2.39-5.02)	3.66 (2.18-4.57)	0.401[b]
Basal estradiol (E2)	13.46 (5-21.79)	10.97 (5-16.07)	0.539[b]
Pik LH	6.27 (0-10.37)	6.10 (0-8.33)	0.529[b]
LH/FSH	0.60 (0-0.97)	0.65 (0-0.81)	0.974[b]
Tanner stage 2/3	27/30	19/11	0.156[c]

[a]:Student's t-test, [b]:Mann-Whitney U test, [c]:Chi-square test parameters are given as mean ± standard deviation (SD) or median (25-75th percentile). BMI: Body mass index, SDS: Standard deviation score, LH: Luteinizing hormone, FSH: Follicle stimulating hormone

Table 2. The target height, predicted adult height and final height of the study groups			
	Group 1	Group 2	p value
Target height (cm)	158.29±3.87	157.68±5.06	0.56
Target height SDS	-0.81±0.66	-0.92±0.86	0.55
Predicted adult height (cm)	156.61±7.47	157.75±6.50	0.46
Predicted adult height SDS	-1.10±1.27	-0.90±1.10	0.45
Final height (cm)	158.62±6.13	157.59±5.76	0.43
Final height SDS	-0.16±0.96	-0.04±1.08	0.61

SDS: Standard deviation score

was no significant difference between the groups in terms of TH (p=0.56) (Table 2). All cases in both groups reached the TH.

No statistical difference was found between the FH and the TH and PAH in Group 1 (158.62±6.13 cm, 158.29±3.87 cm and 156.61±7.47 cm, respectively). In group 2, there was also no difference between the FH and the TH and PAH (157.59±5.76 cm, 157.68±5.06 cm and 157.75±6.50 cm, respectively). In Group 1, there was a difference of 1.68 cm between the PAH and the TH, and a difference of 0.33 cm between the FH and the TH. In group 2, a difference of 0.09 cm between the FH and the TH occurred. The average duration of treatment in group 1 was 2.22±0.58 years. Menarche occurred in the cases an average of 11.1 (range: 3-24) months after the discontinuation of treatment. In group 1, the mean age of menarche was 11.9±0.71 years, and in group 2, 11.1±0.85 years. There was a significant difference between the groups in terms of menarche age (p<0.01). In group 1, the lowest age of menarche was 10.5, and the highest age of menarche was 13.5 years. In group 2, the lowest age of menarche was 10, and the highest age of menarche was 12.5 years.

In the general population, there was a positive correlation between the heights of the cases at the time of admission and the FH (r=0.624, p=<0.01), and between the TH (r=0.56, p=<0.01) and the PAH (r=0.703, p=<0.01). No correlation was found between the other parameters (Table 3). The delta height SDS was calculated as -0.60±0.80 in group 1 and as -0.43±0.67 in group 2. The groups were similar in terms of delta height SDS (r=0.29, p=0.27).

Table 3. Correlation of the final heights of the cases with other parameters		
	r value	p value
Height at presentation	0.624	<0.01
Bone age	-0.026	0.81
Menarche	0.058	0.594
Target height	0.56	<0.01
Predicted adult height	0.703	<0.01

Discussion

In early puberty, Tanner stage 3 can be reached much earlier due to the acceleration of puberty. Rapid development of secondary sexual characteristics in children can lead to poor social adaptation, psychological stress, emotional disorders, and remaining short after reaching the FH (15,28,29). In the literature, there are studies evaluating the effectiveness of the GnRHa treatment in patients whose pubertal findings started between the ages of 8 and 10. However, for this age group, there are only a few studies that include a control group (6,8,15). We compared the two groups, those who received GnRHa treatment and those who did not receive GnRHa treatment, among the patients who were admitted between the ages of eight and ten and were thought to have EP. We determined that the FH of the groups reached the TH and there was no significant difference between the groups in terms of FH.

Since the start of the therapeutic use of gonadotropin-releasing hormone analogues, their effect on FH has aroused interest. Until today, many studies have examined the effect of GnRHa use on FH in different age groups (4,11,12,25,30). Kletter and Kelch reported that in patients above the age of 6 and had an onset of puberty, there was no significant difference in terms of FH between those who received treatment and those who did not (11). In their series of 115 cases, Lazar et al. (12) examined the height gain of the patients, and stated that the use of GnRHa, especially before the age of 6, had an effect on the height. It was determined that there was a partial height gain between the ages of 6 and 8, but the treatment had no effect on the FH in girls between the ages of 8 and 9. In studies conducted by Cassio et al. (4) and Savaş-Erdeve et al. (30) on cases between the ages of 7.5 and 8.5, and 7 and 8.5 respectively, the cases that received and did not receive GnRH treatment were observed until they reached the FH, and no difference was observed between the groups in terms of FH.

It was observed that similar results were obtained especially in studies including cases above the age of 8 (6,15,31). In a meta-analysis of six studies recently carried out by Franzini et al. (31), 332 female cases between the ages of 7 and 10 were examined. In this meta-analysis, it was stated that no difference was found between the FH of the patients who received and did not receive GnRHa treatment. In a similar study, two groups consisting of 63 patients and 63 controls between the ages of 8 and 9 were compared. In the study, it was found that the FH of the girls who received and did not receive GnRH treatment were similar (157.26±6.16 and 156.66±5.70 cm, respectively). In the study, it was stated that the similar height gain of the groups was not dependent on the duration of puberty and the rate of pubertal development. It was stated that pubertal growth potential and FH are probably determined at the beginning of pubertal development (15). In a study conducted by Bouvattier et al. (6), a patient and a control group were formed with cases above the age of 8, and it was found that there was only a 1.44 cm difference in terms of FH. In another study, it was reported that after the GnRHa treatment administered to 44 EP patients between the ages of 8 and 10, the patients reached the TH, therefore the treatment made a significant contribution of 4.13 cm to the FH (8). In our study, we found that there was a difference of approximately 1.03 cm between the FH of the two groups. However, this difference was not statistically significant. In addition, it was determined that the FHs of 57 patients who received GnRHa treatment reached the TH. In our study, no difference was found between the FH and TH in the group that received GnRH analogue treatment and in the group that did not receive treatment. Since the FH and the TH were almost the same, it was thought that the GnRH analogue treatment did not contribute to the height in patients between the ages of 8 and 10.

In previous studies conducted on precocious puberty, it was stated that the most important parameters affecting the FH were the height at the onset of puberty and the TH (30,32). In our study, there was a positive correlation between the FH and the TH and PAH. Therefore, the taller the case at the onset of puberty, the higher the FH will be.

In patients who receive gonadotropin-releasing hormone analogue treatment, after the treatment is discontinued, the gonadal functions are restored and menstrual cycles begin. Studies have reported that menarche occurs approximately 1-1.5 years after the discontinuation of treatment (6,15,32-34).

In our study, it was observed that in the cases who received GnRHa treatment, menarche occurred an average of 11.1 months after the discontinuation of treatment. In the group that received gonadotropin-releasing hormone analogue treatment, menarche occurred at a later age compared to the group that did not receive treatment. It was thought that GnRH analogue treatment caused a delay in the age of menarche in these patients. In studies in the literature, generally, no height gain has been observed following the GnRHa treatment after the age of 8. However, it has been reported that the treatment in this age group can delay the age of menarche and reduce the psychological effects.

Study Limitations

There were some limitations to our study: Our study was designed retrospectively. The sample size constituting the patient and control groups was not sufficient.

Conclusion

This study, it was observed that the GnRHa treatment did not make a positive contribution to the FH in cases who were between the ages of 8 and 10. No difference was found between the groups in terms of FHs. The FHs of the cases in both groups reached the TH. The GnRHa analogue treatment slowed the rate of pubertal development and delayed the age of menarche. Therefore, GnRHa treatment in EP can be used for psychosocial problems that may be caused by rapid pubertal development.

Ethics

Ethics Committee Approval: The approval for this study was obtained from the Ethics Committee of Dicle University Faculty of Medicine (approval number: 2021/173, date: 25.03.2021).

Conflict of Interest: The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Investigating the Association Between Internet Addiction, Depression, Social Phobia, Social Anxiety and Psychiatric Disorders Among Secondary Education Students in Turkey

Türkiye'de Ortaokul Öğrencilerinde İnternet Bağımlılığı, Depresyon, Sosyal Fobi, Sosyal Kaygı ve Psikiyatrik Bozukluklar Arasındaki İlişkinin İncelenmesi

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Abstract

Introduction: The purpose of the study is to identify the prevalence of Internet addiction (IA) among students and evaluate the association of IA with depression, social phobia, social anxiety and psychiatric disorders.

Materials and Methods: A total of 297 students aged 9-14 years and studying at a private school in Gölbaşı/Ankara province were included in the study. The study was conducted between November 2015 and May 2016. The student's depression inventory; social phobia scale for student and adolescents; social anxiety scale for student-revised and strength and difficulties questionnaire were used as data collection tools. According to the Internet dependency scale, student were classified into 4 groups as non-addicted group, threshold group, risk group and addicted group.

Results: According to the Internet dependency scale, the majority (258/86.9%) of the students were not Internet addicts. Twenty seven (9.1%) students were in the threshold group and 12 (4%) student were in the risk group. Compared with the depressed mood, the likelihood of having depression in the risk group was higher (p=0.001). The risk group and the threshold group had higher social phobia and social anxiety scores at a statistically significant level than the non-dependent group (p≤0.05).

Conclusion: Internet use is an indispensable element for the lives of generation-Z student. However Internet addiction, which is directly related to this condition, causes many psychological and social problems for student at an alarming level. These problems cannot be ignored and can be avoided by rational use of the internet.

Keywords
Internet addiction, depression, social phobia, social anxiety, psychiatric disorders, student

Anahtar kelimeler
İnternet bağımlılığı, depresyon, sosyal fobi, sosyal kaygı, psikiyatrik bozukluklar, öğrenci

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Öz

Giriş: Bu çalışmanın öncelikli amacı, ortaokul öğrencilerinde İnternet bağımlılığının (İB) hangi düzeyde olduğunu belirlemek ve İB'nin depresyon, sosyal fobi, sosyal anksiyete ve psikiyatrik bozukluklarla ilişkisini incelemektir.

Gereç ve Yöntem: Araştırma Gölbaşı/Ankara ilinde özel bir okulda öğrenim gören 9-14 yaş arası 297 öğrenci ile Kasım 2015-Mayıs 2016 tarihleri arasında

yürütülmüştür. Araştırmada veri toplama aracı olarak öğrenci depresyon envanteri; çocuk ve ergenler için sosyal fobi ölçeği; öğrenci-gözden geçirilmiş sosyal kaygı ölçeğinin gözden geçirilmiş versiyonu ile güçler ve güçlükler anketi kullanılmıştır. İnternet bağımlılığı ölçeği sonuçlarına göre öğrenciler bağımlı olmayan grup, eşik grup, risk grubu ve bağımlı grup olmak üzere 4 gruba ayrılmıştır.

Bulgular: İnternet bağımlılığı ölçeğine göre öğrencilerin önemli bir çoğunluğunun (258/%86,9) internet bağımlısı olmadığı tespit edilmiştir. Yirmi yedi (%9,1) öğrenci eşik grupta iken 12 (%4) öğrenci risk grubunda yer almaktaydı. Depresif duygu durum ile karşılaştırıldığında, risk grubunda depresyon olma olasılığının daha yüksek olduğu belirlendi (p=0,001). Risk grubu ve eşik grubunun bağımlı olmayan gruba göre istatistiksel olarak anlamlı düzeyde daha yüksek sosyal fobi ve sosyal kaygı puanlarına sahip olduğu belirlendi (p≤0.05).

Sonuç: Günümüzde İnternet kullanımı Z kuşağı öğrencileri için vazgeçilmez bir unsurdur. Bu gerçekle doğrudan ilişkili olarak ortaya çıkan internet bağımlılığı, öğrencilerde pek çok psikolojik ve sosyal sorunu beraberinde getirmektedir. Bu sorunların göz ardı edilmesi mümkün olmamakla birlikte akılcı internetin kullanımı ile söz konusu sorunların önlenmesi mümkün olabilir.

Introduction

The use of information technology, new technologies and undoubtedly the internet have a great role in changing the lives of individuals in the modern world. Today the internet has become the most effective and indispensable tool in almost all areas of life, including science, business, education, culture, commerce and politics (1). The new generation has benefited from the internet more than ever before (2). As a consequence, internet is used in various ways, especially by young people (3).

The internet itself is a harmless and even highly functional tool. However, excessive and misuse of the it brings the risk of addiction (4). internet addiction (IA) or problematic internet use is defined as a type of behavioral addiction (5). It causes the difficulty of controlling impulses and the incapacity of disconnecting from internet (6).

IA has become a serious public health problem worldwide, especially in Asia (7) due to the cheap, fast and widespread use it. The easy accessibility of the internet makes it very dangerous, especially for young users (8) and brings along many negative effects for them. Depression is the psychological disorder most commonly associated with IA. However, previous studies support a bilateral relationship between IA and psychiatric symptoms (9). It has been documented that IA has been associated with depression (10-16) and other physiological, social, physical and academic problems (17-22). In this study we aimed to identify the prevalence of IA among student and evaluate the association of IA with depression, social phobia, social anxiety and psychiatric disorders.

Materials and Methods

In total, 297 student aged 9 to 14 studying at a private school in Gölbaşı district of Ankara were included in the study. The study was conducted between November 2015 and May 2016. Personal information (age, gender, familial characteristics of student, internet usage time, tools used for accessing the internet, internet usage purposes, types of social media they used) of the students were recorded. Ethical committee approval for the study was obtained.

Data Collection Tools

Internet addiction scale; The student's depression inventory; social phobia scale for student and adolescents; social anxiety scale for student-revised and strength and difficulties questionnaire were used as data collection tools.

As a result of the validity and reliability analyses, it was concluded that the use of the IA scale, which was developed by Gününç and Kayri (23) (2010) and consisted of 35 items, was appropriate. The Cronbach's alpha coefficient of the scale was 0.94. The students were asked to complete this scale. The Likert type scale items were scored from 5 to 1 (1= definitely not agree, 2= disagree, 3= neutral, 4= agree, 5= completely agree). According to the IA scale, students were classified into 4 groups as non-addicted group, threshold group, risk group and addicted group. The assessment over the total score of the scale was made as follows:

- 35-91 points: Non-addicted
- 92-119 points: Threshold group
- 120-147 points: Risk group
- 148-175 points: Addicted group (24)

In the next phase of the study, the depression

inventory (27 items), social phobia scale consisting (25 items), social anxiety scale (18 items) and power and strength questionnaire (25 items) were applied. The student's depression inventory was developed by Kovacs (25) (1985) and the Turkish validity and reliability study of it was carried out by Öy (26) (1991). It was a triple Likert type scale and each item was scored as 0, 1 and 2 according to the severity of depression symptoms. The scores of the one-dimensional scale varied between 0-54. Higher scores indicated more severe depressive symptoms. The internal consistency coefficient of the scale was 0.80 [Yavuz et al. (27)].

Social phobia scale was developed by Demir et al. (28). The Cronbachs alpha coefficient was 0.83. In the validity and reliability study, it was determined that it was a valid and reliable scale. Social anxiety scale was developed by La Greca et al. (29) and revised in 1993 [La Greca and Stone (30)]. The Turkish Validity and Reliability study of the scale was conducted by Demir et al. (31). The Cronbach alpha of the scale was 0.81. As a result of the Turkish adaptation study, it was determined that this 5-point Likert type scale was valid and reliable. A minimum of 18 and a maximum of 90 points could be obtained from the scale.

Strength and weaknesses questionnaire was developed by Goodman et al. (32). The Turkish validity and reliability study was performed by Güvenir et al. (33). As a result of the Turkish adaptation study, it was determined that the scale was valid and reliable. The Cronbach's alpha of the Parent scale was 0.84 and the Cronbach's alpha of the Adolescent scale was 0.73.

According to the depression scale, the cut-off score was 19. The cut-off score for the social phobia scale was calculated as 67 points, corresponding to the 90th percentile. In the case of patients with 67 points or more, there was an increase in the likelihood of clinical problems as the score of social phobia increased. The social anxiety scale and the strength and difficulty questionnaire did not have a cut-off point, so the average score was considered and the score was assessed as increasing the susceptibility to clinical problems (25,28,31,33). The association of IA with depression, social phobia, social anxiety and psychiatric disorders were compared.

Statistical Analysis

The demographic data of the students were evaluated with The Statistical Package for the Social Science Program (SPSS) version 21 (IBM Corp., NY, 2012). Data were presented with frequency (%), mean ± standard deviation, median, minimum and maximum values. Pearson Chi-Square (χ^2), Kruskal-Wallis, Mann-Whitney U and Spearman correlation tests were used for the comparisons. A p value of ≤0.05 were considered statistically significant.

Results

The results of the demographic characteristics of the student were given in Table 1.

It was concluded that the percentage of student using the internet to prepare homework was 21.8%, for watching movies/music was 22.1%, for playing games was 20.5% and for using social networking sites was 20.1%. 54.9% of the student reported that they were supervised by their parents while using the internet. The internet usage history of the student was 5.58±2.60 years. Weekly internet usage time was 9.84±10.64 (minimum 0, maximum 110 hours) hours. The daily usage time of mobile phones was 104.05±85.64 minutes. A significant majority of students (85.5%) stated that they were doing activities collectively at home with their families.

As the weekly internet usage time increased, the scale scores increased. The students in the threshold and risk groups were found to use the internet for a longer period of time on a statistically significant level compared to the non-addicted student (p≤0.05).

The IA levels of the students were shown in Table 2.

A statistically significant relationship was found between the level of IA and depression (χ^2 (2) =37,826; p≤0.05) (Table 3).

When the threshold group was compared with the non-addicted group, the students in the threshold group had higher social phobia, social anxiety and power and difficulty questionnaire scores (p values: 0.006, 0.001 and 0.031, respectively). When the risk group was compared with the non-addicted group, it was concluded that the student in the risk group had higher social phobia and social anxiety scores (p values: 0.014 and 0.013, respectively).

Table 1. Demographic characteristics of the student		
Variables	n	%
Gender (Female)	161	54.2
Age (years)		
9	21	7.1
10	65	21.9
11	88	29.6
12	90	30.3
13	32	10.8
14	1	0.3
Handedness (right)	264	88.9
Living with parents	277	93.2
Mothers working	213	71.7
Fathers working	289	97.3
Single child	97	32.6
Has at least one sibling	202	68.0
Mothers' education level		
Illiterate	0	0
Literate	6	2.0
Primary education	0	0
Lower secondary education	2	0.7
Upper secondary education	32	10.9
Bachelor's degree	202	68.0
Graduate degree	55	18.8
Fathers' education level		
Illiterate	0	0
Literate	5	1.7
Primary education	0	0
Lower secondary education	2	0.7
Upper secondary education	27	9.2
Bachelor's degree	182	61.2
Graduate degree	81	27.6
Has own room	284	95.6
Mother has a physical illness	28	9.4
Mother has a mental disorder	3	1.0
Father has a physical illness	27	9.1
Father has a mental disorder	1	0.3
Has a cellphone	275	92.6

There was a moderate association between IA and total depression ($p \leq 0.05$; $r=0.447$), social phobia ($p \leq 0.05$; $r=0.375$) and social anxiety ($p \leq 0.05$; $r=0.431$). A positive and low level correlation was found between IA and strengths and weaknesses scores ($p \leq 0.05$; $r=0.173$).

Table 2. Internet addiction levels of the students		
Groups	n	%
Non-addicted group	258	86.9
Threshold group	27	9.1
Risk group	12	4
Total	297	100

It was determined that 261 (87.9%) student used WhatsApp, 189 (63.6%) students used Facebook and 56 (18.9%) students used Twitter. It was also found that those who used Twitter were statistically significantly more internet addicts ($p=0.014$) (Table 5).

Discussion

Extreme use of the internet/computer; which is seen quite frequently in the school age youth, negatively affects both the academic and personal development of the student and makes them addicted. In this context, it is important to define "addiction" and explain its reasons, symptoms and solution proposals (34).

In their study conducted in Hong Kong, Mo et al. (35) examined the relationship between IA, social support and emotional disturbances in middle school students. They concluded that IA and emotional disturbances were at lower rates in student with high social support. They also argued that the relationship between social support, emotional disturbance and IA may be stronger among female students. In our study, there was no statistically significant association between IA and gender, age, family characteristics (parent education, physical and mental illnesses, number of siblings, house conditions, parental supervision, etc.). We think that the fact that the students included in the study were educated in a private school is the reason why there is no difference in terms of socioeconomic aspects.

In the study mentioned above it was found that more than half (52.1%) of the students used internet more than 11 hours per week, 9% of them used more than 50 hours per week (35). In another study it was concluded that secondary school students spent a wide range of time (1 hour to 84 hours) weekly on the internet (36). In our study, the weekly internet usage time of students was similarly 9.84±10.64 (minimum 0, maximum 110 hours). It was determined that the IA scale score increased as the weekly internet usage

Table 3. The relation of internet addiction with state of depression						
Groups		Depression		X^2	df	Sig.(p)
		Not-depressed (%)	Depressed (%)			
Internet Addiction	Non-addicted	230 (89.1)	28 (10,9)	37.826	2	0.000
	Threshold	17 (%63)	10 (%37)			
	Risk	4 (%33.3)	8 (%66.7)			

Table 4. Internet addiction and scales' total scores								
Variables	Min	Max	Mean + SD	1	2	3	4	5
1. Internet Addiction	35	154	65.64±23.2	-	-	-	-	-
2. Social Anxiety	18	78	33.75±14.2	0.431*	-	-	-	-
3. Depression	,00	47	11.63±7.44	0.447*	0.421*	-	-	-
4. Social Phobia	25	95	49.56±15.59	0.375*	0.780*	0.443*	-	-
5. Strengths and weak.	32	63	47.51±4.54	0.173*	0.393*	0.302*	0.444*	-
*p≤0.05, SD: Standard deviation								

Table 5. The relation of internet addiction with state of twitter usage						
Groups		Twitter usage		X^2	df	Sig.(p)
		User (%)	Non-user (%)			
Internet addiction	Non-addicted	43 (16.7)	214 (83.3)	8.519	2	0.014
	Threshold	8 (27.5)	21 (72.5)			
	Risk	5 (50)	5 (50)			

time increased. The students in the threshold and risk groups used the internet for a longer period weekly at a statistically significant level compared to the non-addicted students.

Looking at the world as a whole, it seems that IA is one of the most important problems especially for Asian countries. Such that the rate of IA among young people is 2.4-13.5% in China, 1.6-20.3% in South Korea, 0.7-26% in the United States and 1%-18.3% in Europe (37). In a study conducted in Turkey, 352 students were found to have an IA rate of 11% and a student with IA potential of 12%. It is remarkable that these students were 7th and 8th grade students (34). In our study, the rate of IA students was 4%, which was lower than in Asia and the average of our country.

IA is most prevalent among adolescents aged 12-18 years. In a study conducted with 41 students aged 11 to 16 years, it was reported that 64.3% of the internet addicted students were between 11 and 13 years old and 35% of them were between 14 and 16 years old. There were no significant differences between the addicted group and the control group in terms of age, gender, class, economic status, mother and father age and educational status (38). In another study it was stated that IA is unrelated to gender (39). According to Syahputra et al. (40) (2019), there was no difference in IA between male and female university students. Similarly, there was no significant difference in demographic characteristics between the non-addicted group and the other groups in our study.

Addiction states and other psychiatric disorders can be seen together. One of them is the combination of IA and other psychiatric disorders (5). Attention deficit hyperactivity disorder, depression, impulse control disorder and anxiety have been shown to be associated with IA. Among these, the psychiatric disorder most associated with IA is depression (9). However, the causal relationship between IA and depression has not yet been proven (5). In a study, *5HTTLPR* gene polymorphism, which was associated with serotonin functions, was suggested to be associated with depression and IA (41). In another study conducted with 208 adolescents aged 15 to 19 years in Hong Kong showed that the majority of IA symptoms were

thought to be serious suicidal ideation and depression. In a study that included 1573 adolescents aged 15-16 years in Korea, it was reported that the levels of depression and suicidal ideation were higher in the addicted group than in the non-dependent and possibly addicted group (42,43). In different studies there were significant positive correlations among IA, depression, and suicidal ideation in adolescents (44-49). In our study, as the IA scale score increased depression, social phobia and social anxiety scores also increased. This result supports the association between IA and depression, social phobia and social anxiety, similar to previous studies.

Conclusion

IA in students, which causes both psychological and social problems, cannot be overlooked. However, more comprehensive and socioeconomically diverse studies are needed to further evaluate the association between IA and psychosocial problems. In addition, it is concluded that large-scale occurrence of psychosocial problems can be prevented by the conscious use of internet especially in adolescents and young adults. For this reason, it is thought that it is necessary to educate the schools about the conscious use of the internet.

Ethics

Ethics Committee Approval: Ethical approval no: 600-5053, date: 08.07.2015) was received from the Ankara Training and Research Hospital Ethics Committee.

Conflict of Interest: The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

The Correlation Between Adherence to Mediterranean Diet and HOMA-IR in Children and Adolescents

Çocuk ve Adölesanlarda Akdeniz Diyetine Uyum ile HOMA-IR Arasındaki İlişki

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Abstract

Introduction: Nowadays, children's exposure to the obesogenic environment can lead to obesity and insulin resistance in the early period. However, it is suggested that the risk of developing health problems such as obesity, insulin resistance, and type 2 diabetes may decrease with increasing adherence to the Mediterranean diet. This study was aimed to evaluate the relationship between insulin resistance and the Mediterranean Diet Quality Index (KIDMED) in children and adolescents.

Materials and Methods: A total of 174 children and adolescents (35.6% boys, 64.4% girls) with a mean age of 11.6±3.17 years were included in the study. The data were collected by a questionnaire containing individuals' socio-demographic information, anthropometric measurements, KIDMED, and 24-hour food consumption records. According to World Health Organization criteria, the body mass index z-scores of the participants were evaluated, and participants were divided into three groups as normal weight (29.9%), overweight (23.6%), and obesity (46.5%).

Results: This study's findings were: mean KIDMED score was 5.7±2.62 points in the normal weight group, 5.4±2.39 points in the overweight group, and 4.6±2.70 points in the obesity group which was significantly lower than the normal weight group ($p<0.05$). Additionally, the mean KIDMED score of children with insulin resistance (4.3±2.72) was lower than those without insulin resistance (5.4±2.57) ($p<0.05$). A negative, moderate, and significant correlation was found between the participants' KIDMED scores and the homeostatic model assessment of insulin resistance value ($r=-0.338$, $p<0.001$).

Conclusion: The low level of adherence to the Mediterranean diet was associated with the risk of developing insulin resistance.

Öz

Giriş: Günümüzde, çocukların obezojenik ortama maruz kalması erken dönemde obezite ve insülin direncine yol açabilmektedir. Ancak, Akdeniz diyetine uyumun artmasıyla obezite, insülin direnci ve tip 2 diyabet gibi sağlık sorunlarına yakalanma riskinin azalabileceği ileri sürülmektedir. Bu çalışma, çocuk ve adolesanlarda insülin direnci ile Akdeniz Diyet Kalite İndeksi (KIDMED) arasındaki ilişkiyi değerlendirmeyi amaçlanmıştır.

Gereç ve Yöntem: Yaş ortalamaları 11,6±3,17 yıl olan 174 çocuk ve adolesan (%35,6 erkek, %64,4 kız) çalışmaya dahil edilmiştir. Veriler, bireylerin sosyo-demografik bilgilerini, antropometrik ölçümlerini, KIDMED ve 24 saatlik besin tüketim kayıtlarını içeren anket formu ile toplanmıştır. Dünya Sağlık Örgütü kriterlerine göre katılımcıların beden kütle indeksi z-skorları değerlendirilmiş ve

katılımcılar normal ağırlıklı (%29,9), fazla kilolu (%23,6) ve obez (%46,5) olarak üç gruba ayrılmıştır.
Bulgular: Normal ağırlıklı bireylerin KIDMED puanı ortalaması 5,7±2,62 puan, fazla kilolu̇ların 5,4±2,39 puan, obezite grubunda 4,6±2,70 puandır ve obezite grubunun normal ağırlıklılara kıyasla KIDMED puan ortalaması anlamlı olarak daha düşüktür (p<0,05). Ayrıca, insülin direnci olanların ortalama KIDMED puanı (4,3±2,72), insülin direnci olmayanlardan (5,4±2,57) daha düşüktür (p<0,05). Katılımcıların KIDMED puanları ile insülin direncinin homeostatik modeli değerlendirmesi değeri arasında negatif yönlü, orta düzeyde, anlamlı ilişki saptanmıştır (r:-0,338; p<0,001).
Sonuç: Akdeniz diyetine uyum düzeyinin düşük olması insülin direnci gelişme riski ile ilişkilidir.

Introduction

The Mediterranean diet, a diet model, based on the consumption of traditional foods and beverages of the countries surrounding the Mediterranean, plays a significant role in protecting and improving health (1). The use of olive oil as the primary source of fat, increasing the consumption of whole grains, nuts, legumes, vegetables, and fruits are among the Mediterranean diet principles. Also, it is recommended to consume moderate amounts of dairy products, fish, chicken and eggs, and low amounts of red meat and meat products (1-3).

The studies show that the Mediterranean diet with healthy nutritional recommendations and its components have beneficial effects on weight loss, reducing the risk of developing insulin resistance, cardiovascular diseases, and type 2 diabetes (4-6). It has been reported that the prevalence of obesity is low in children who follow the Mediterranean diet (7). Additionally, a study in children with obesity was found that those with poor compliance with the Mediterranean diet had higher fasting insulin levels and homeostatic model assessment of insulin resistance (HOMA-IR) values, which is an indicator of insulin resistance (8). In children and adolescents with obesity, compliance with the Mediterranean diet for 16 weeks has been found to reduce body mass index (BMI), fat mass, fasting blood glucose, triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels (9). A study in children with high cholesterol levels was found that the Mediterranean diet intervention for 12 months improved lipid profile and decreased glucose levels and HOMA-IR values (10). The Mediterranean diet, rich in vitamins, minerals, polyphenols, and unsaturated fatty acids [mainly monounsaturated fatty acids (MUFAs)], results in anti-inflammatory, antioxidant, antimutagenic effects; therefore, it has a protective effect against many diseases. In particular, antioxidant compounds reduce oxidative stress associated with pancreatic β-cell dysfunction and insulin resistance. These findings can explain the low risk of developing type 2 diabetes with the Mediterranean diet (11).

Today, obesity, which develops from unhealthy eating habits and low physical activity levels, has become a significant public health problem. Besides, obesity causes behavioral and emotional difficulties in children; moreover, it is also associated with insulin resistance which is related to developing complex processes such as type 2 diabetes, hypertension, dyslipidemia, and inflammation. For these reasons, it is crucial to identify the factors that play a role in preventing the increase in childhood obesity and insulin resistance. In this context, this study was aimed to evaluate the relationship between insulin resistance and the Mediterranean Diet Quality Index (KIDMED), which is an indicator of compliance with the Mediterranean diet in children and adolescents. Also, it was aimed to determine the relationship between the nutrient intake in the daily diets of children and HOMA-IR values.

Materials and Methods

Participants

A total of 174 children and adolescents [62 boys (35.6%), 112 girls (64.4%)] aged 6-17 who applied to the pediatric endocrine department participated in the study. The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Ethics Committee. Before the data collection, the participants and their parents were informed about the research. Informed consent was obtained from the children and their parents. The study did not include those who regularly used any nutritional supplements, non-volunteers, with thinness, growth retardation, and chronic diseases.

Design

Data collection took place from August 2019 to December 2019. The data were collected by the

researchers using a face-to-face interview technique with the questionnaire prepared for this cross-sectional study.

Questionnaire

The questionnaire consists of individuals' socio-demographic information, anthropometric measurements, KIDMED, and 24-hour food consumption records.

The researchers took the height and body weight measurements of the participants by the procedure, and BMI was calculated using these values. BMI z-scores of the participants were evaluated using the World Health Organization AnthroPlus program. Accordingly, those with BMI z-score, -1SD≥BMI≤+1SD were categorized in the normal-weighted group, those with +1SD>BMI≤2SD were categorized in the overweight group, and those with BMI>2SD were categorized in the obesity group (12).

The biochemical parameters [fasting insulin (uIU/mL), fasting glucose (mg/dL)] were obtained from the patient folders. The insulin resistance status of the participants was determined by pediatric endocrinologists using the formula HOMA-IR=[fasting insulin (uIU/mL) × fasting glucose (mg/dL)/405] (13). HOMA-IR reference values for Turkish children and adolescents (5-18 years) were used: insulin resistance was defined as in the prepubertal period, ≥2.67 in boys and ≥2.22 in girls; and in the pubertal period, ≥5.22 in boys and ≥3.82 in girls (14).

KIDMED, which was developed by Serra-Majem et al. (15) (2004), consists of 16 questions and determines some principles related to the Mediterranean diet and evaluates the nutritional habits of children. Twelve questions of this index are positive, and four questions are negative. Those who answer "Yes" to positive questions get +1 points, and those who answer "Yes" to negative questions score -1. As a result of the sum of these points, scores ranging from 0-12 are obtained. A total score of ≥8 is considered to be the optimal Mediterranean diet adherence (good), between 4-7 scores are regarded as an improvement needs to Mediterranean diet adherence (average), and ≤3 points are also considered as poor Mediterranean diet adherence (low).

The participants' food consumption data were obtained with a 24-hour recall method using and "Photo Catalog of Foods and Nutrients: Measures and Amounts" (16) was used to determine portion sizes of consumed foods. The average intake of energy and nutrients in the daily diet was determined by the "Nutritional Information Systems Package Program" (17).

Statistical Analysis

SPSS 26.0 (statistics program for social sciences) package program for Windows was used to analyze the data. Descriptive statistics were shown as mean (M) ± standard deviation (SD) and minimum-maximum values. Nominal variables were expressed as the number of cases (n) and percentage (%). The chi-square test was used to evaluate the relationship between categorical variables. The chi-square test was used to assess the comparison of qualitative data. Whether the quantitative data were normally distributed was examined using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. The independent samples t-test was used to compare the means of two independent groups. When the number of groups was more than two, the one-way analysis of variance was used to evaluate whether there was a statistically significant difference between the quantitative variables. The Pearson correlation test was used to assess the correlation between two variables under the condition that normal distribution assumptions. However, when at least one of the variables did not meet the normal distribution conditions, the Spearman correlation test was used. Statistical significance was accepted at $p<0.05$.

Results

A total of 174 children and adolescents, 62 boys (35.6%) and 112 girls (64.4%), between the ages of 6-17 years, with a mean age of 11.6±3.17 years, participated in the study. Participants were divided into three groups according to their BMI z-scores; 29.9% were categorized in the normal weight group, 23.6% were categorized in the overweight group, and 46.5% were categorized in the obesity group.

No statistically significant difference was found between the groups according to the KIDMED classification ($p>0.05$). The mean KIDMED score was found 5.7±2.62 points in the normal weight group, 5.4±2.39 points in the overweight group, 4.6±2.70 points in the obesity group. The obesity group had a significantly lower mean KIDMED score compared to the normal weight group ($p<0.05$). However,

KIDMED score of BMI groups in the ANOVA test, partial eta squared was found as 0.036. A significant difference with a small effect size was found in the KIDMED score according to BMI groups (Table 1).

No statistically significant difference was found between children and adolescents with and without insulin resistance according to KIDMED classification (p>0.05). However, the mean KIDMED score of those with insulin resistance (4.3±2.72) was lower than those without insulin resistance (5.4±2.57) (p<0.05) (Table 2).

A negative, moderate, significant relationship was found between the HOMA-IR value and KIDMED scores of the children and adolescents (r:-0.338, p<0.001). A positive, weak, and significant relationship was found between the HOMA-IR and dietary intake of energy and protein (respectively r:0.216, p:0.004; r:0.164, p:0.030). A positive, moderate, significant relationship was found between the daily intake of carbohydrates and HOMA-IR values (r:0.264, p<0.001). There was no significant relationship between the HOMA-IR values of the participants and their intake of saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs), dietary fiber, soluble and insoluble dietary fiber (p>0.05). Additionally, no significant relationship was found between the vitamin and mineral (except iron) intakes and HOMA-IR values (p>0.05). A positive, weak, and significant relationship was found between dietary iron intake and HOMA-IR (r=0.157, p=0.039) (Table 3).

Discussion

This study was conducted to evaluate the relationship between KIDMED and insulin resistance in children and adolescents with normal-weight, overweight, and obesity. The participants with obesity had lower KIDMED scores than individuals with normal weight (p<0.05). However, in line with other studies of children and adolescents in Turkey (18-20), this study was determined that more than half of the participants (52.9%) should improve Mediterranean diet adherence (average) (Table 1). Also, similar

Table 1. Distribution of children and adolescents according to KIDMED scores

KIDMED classification	Normal Weight (n=52)		Overweight (n=41)		Obesity (n=81)		Total (n=174)		χ^2/F	p
	n	%	n	%	n	%	n	%		
Low	9	17.3	10	24.4	28	34.6	47	27.0	7.418	0.115[a]
Average	28	53.9	22	53.6	42	51.8	92	52.9		
Optimal	15	28.8	9	22.0	11	13.6	35	20.1		
KIDMED score										
Mean ± SD	5.7±2.62		5.4±2.39		4.6±2.70		5.1±2.64		3.169	0.045[b*1]
minimum-maximum	0-11		0-10		0-10		0-11			

[a]Pearson chi-square test [b]One-way analysis of variance *p<0.05 [1]The significance arises from the difference between obesity and normal-weight groups, KIDMED: Mediterranean diet quality index, SD: Standard deviation

Table 2. KIDMED scores according to insulin resistance (IR) status of children and adolescents

KIDMED classification	IR + (n=37)		IR - (n=137)		Total (n=174)		χ^2/t	p
	n	%	n	%	n	%		
Low	14	37.8	33	24.1	47	27.0	4.081	0.130[a]
Average	19	51.4	73	53.3	92	52.9		
Optimal	4	10.8	31	22.6	35	20.1		
KIDMED score								
Mean ± SD	4.3±2.72		5.4±2.57		5.1±2.64		-2.324	0.021[b*]
minimum-maximum	0-9		0-11		0-11			

[a]Pearson chi-square test [b]Student's t test *p<0.05, KIDMED: Mediterranean diet quality index, SD: Standard deviation

Table 3. Correlation of HOMA-IR Value and KIDMED scores, energy and nutrient intake of children and adolescents								
Energy, some nutrients, KIDMED Score	Normal weight (n=52)		Overweight (n=41)		Obesity (n=81)		Total (n=174)	
	r	p	r	p	r	p	r	P
KIDMED score	-0.273	0.050[b]	-0.415	0.007[b]*	-0.283	0.011[b]*	-0.338	<0.001[b]*
Energy (kcal)	0.095	0.505[a]	0.274	0.083[a]	0.288	0.009[b]*	0.216	0.004[a]*
Carbohydrates (g)	0.019	0.891[a]	0.260	0.100[b]	0.356	0.001[a]*	0.264	<0.001[b]*
Dietary fiber (g)	0.106	0.455[b]	-0.021	0.897[b]	0.139	0.215[a]	0.129	0.089[b]
Soluble fiber (g)	0.031	0.827[b]	0.031	0.848[a]	0.225	0.043[b]*	0.128	0.092[b]
Insoluble fiber (g)	0.152	0.281[a]	-0.062	0.701[a]	0.240	0.031[b]*	0.148	0.052[b]
Protein (g)	0.013	0.928[b]	0.088	0.584[a]	0.167	0.137[b]	0.164	0.030[b]*
Fat (g)	0.093	0.513[a]	0.084	0.604[a]	0.001	0.993[b]	0.033	0.663[a]
SFAs (g)	-0.135	0.341[b]	0.008	0.960[a]	0.029	0.799[a]	0.010	0.898[a]
MUFAs (g)	0.200	0.156[a]	0.073	0.652[a]	-0.014	0.898[a]	0.080	0.292[b]
PUFAs (g)	0.051	0.722[a]	0.075	0.639[a]	-0.113	0.317[b]	0.047	0.541[b]
Vitamin A (mcg)	0.024	0.867[b]	-0.275	0.081[a]	-0.115	0.308[b]	-0.096	0.207[b]
Vitamin E (mg)	0.164	0.245[a]	0.039	0.806[a]	-0.060	0.594[b]	0.092	0.228[b]
Thiamine (mg)	-0.032	0,820[a]	0.046	0.773[a]	0.086	0.445[b]	0.039	0.611[b]
Riboflavin (mg)	-0.105	0.458[b]	-0.203	0.202[a]	-0.006	0.957[a]	-0.023	0.768[b]
Niacin (mg)	-0.102	0.473[b]	0.078	0.626[a]	0.170	0.128[b]	0.147	0.053[b]
Vitamin B_6 (mg)	0.062	0.661[a]	0.191	0.232[a]	-0.102	0.363[a]	0.103	0.175[b]
Folate (mcg)	0.236	0.092[a]	-0.116	0.469[a]	0.058	0.604[b]	0.072	0.344[b]
Vitamin B_{12} (mcg)	0.009	0.950[b]	-0.203	0.204[a]	-0.074	0.510[b]	-0.111	0.145[b]
Vitamin C (mg)	-0.005	0.974[b]	0.070	0.665[a]	-0.088	0.432[b]	-0.016	0.832[b]
Sodium (mg)	0.029	0.838[a]	-0.030	0.852[a]	0.207	0.064[a]	0.129	0.089[a]
Potassium (mg)	-0.081	0.570[b]	0.060	0.709[a]	-0.129	0.251[a]	0.030	0.695[b]
Calcium (mg)	-0.214	0.127[a]	-0.161	0.315[a]	0.007	0.947[a]	-0.077	0.310[a]
Phosphorus (mg)	-0.050	0.641[a]	-0.084	0.600[a]	0.044	0.698[a]	0.049	0.518[a]
Magnesium (mg)	-0.066	0.727[a]	-0.033	0.840[a]	-0.037	0.746[a]	0.083	0.278[b]
Iron (mg)	0.241	0.085[b]	0.007	0.963[a]	0.066	0.560[b]	0.157	0.039[b]*
Zinc (mg)	0.183	0.194[a]	-0.007	0.965[a]	0.035	0.757[a]	0.051	0.501[b]

[a]Pearson correlation [b]Spearman correlation *p<0.05, SFAs: Saturated fatty acids, MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids, KIDMED: Mediterranean diet quality index, HOMA-IR: Homeostatic model assessment of insulin resistance

results were seen in other countries (Turkish Republic of Northern Cyprus, Greece, Italy) with a coast to the Mediterranean (21-23). In Sicily, the Mediterranean Adequacy Index scores of normal weight children were higher than those of overweight (24). Although the KIDMED score varies according to countries and age groups, it has been determined that adherence to the Mediterranean diet should be improved, and this result is supported by a systematic review published by Garcia Cabrera et al. (25). Improving compliance with the Mediterranean diet will be beneficial for health because the Mediterranean diet's effects on the prevention of obesity and other nutrition-related chronic diseases are well known (26,27).

Increasing compliance with the Mediterranean diet is an effective method in reducing the risk of developing chronic diseases (28,29). Additionally, the Mediterranean diet components positively affect body composition and metabolic health (30,31). It has been reported that individuals who comply with the Mediterranean diet in different populations have a low level of insulin resistance (8,10,32,33).

In this study, the mean KIDMED score of children and adolescents with insulin resistance (4.3±2.72) was found to be lower than those without insulin resistance (5.4±2.57) ($p<0.05$) (Table 2). Also, while the Mediterranean diet quality decreased, the HOMA-IR value was found to be increased ($p<0.05$) (Table 3). The Mediterranean diet, which is rich in components such as polyphenols, unsaturated fatty acids, and dietary fiber, has positive effects on insulin sensitivity (34-36). Among the foods recommended for daily consumption in the Mediterranean diet, vegetables, fruits, whole grains, legumes, nuts, olive oil, and tea are important sources of polyphenols (35,37). Polyphenols, which have antioxidant and anti-inflammatory properties, contribute to insulin resistance prevention through various mechanisms. These mechanisms include slowing carbohydrate digestion and glucose absorption, stimulation of insulin secretion, activation of insulin receptors, and glucose uptake in insulin-sensitive tissues (38). It has also been reported that polyphenols can activate and/or inhibit transcription factors, therefore affect gene expression, and contribute to glucose homeostasis by regulating different signaling pathways in muscle, liver, pancreatic β-cells, hypothalamus, and adipose tissue (35). MUFAs and PUFAs from olive oil and nuts can also have beneficial effects on insulin sensitivity by improving the inflammatory responses of adipose tissue (39,40). It was stated that MUFA, essentially oleic fatty acid, can prevent insulin resistance in the myotubes by the activation of PI3K and a mechanism dependent on amp-activated protein kinase (41). Proinflammatory cytokines and chemokines such as tumor necrosis factor-alpha, interleukin-6, and resistin, which are overproduced by dysfunctional adipose tissue in obesity, can trigger insulin resistance by activating intracellular pathways in insulin-target tissues. However, the anti-inflammatory potential of PUFAs may indirectly improve peripheral insulin response and reduce the risk of glyco-metabolic changes in patients with insulin resistance. Additionally, PUFAs can increase the secretion of glucagon-like peptide 1 (GLP-1) hormone from enteroendocrine L cells. With the consequences of increased glucose uptake from skeletal muscles by stimulating insulin release from pancreatic cells, increased GLP-1 levels can prevent postprandial hyperglycemia. Besides, GLP-1 can affect satiety at the central nervous system level, reducing the feeling of appetite (39). As compliance with the Mediterranean diet can lead to positive health outcomes such as preventing obesity, increasing insulin sensitivity, and reducing cardiovascular disease risk, healthy nutrition education should be made widespread to cover all age groups starting from childhood.

This study was found that the HOMA-IR value increased significantly as the energy, carbohydrate, protein, and iron intake of the participants increased ($p<0.05$) (Table 3). No significant relationship was found between the HOMA-IR value of the participants and their intake of dietary fiber, water-soluble fiber, water-insoluble fiber, fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, vitamins, and minerals (except iron) ($p>0.05$) (Table 3). The types and amounts of carbohydrates, which are the body's primary energy source, have substantial effects on metabolic health (42). Excessive consumption of carbohydrates triggers insulin resistance by increasing insulin secretion (43). Increased energy intake with a diet high in added sugar and fructose is associated with adverse health outcomes such as obesity, insulin resistance, high blood pressure, and dyslipidemia (44). On the other hand, dietary fiber affects the glycemic index of the food, delaying gastric emptying time and decreasing glucose absorption (45). For these reasons, in the prevention and treatment of insulin resistance, adequate energy intake should be provided with a diet plan containing healthy carbohydrate types by the individual's requirements. Additionally, the carbohydrate content of the diet should be composed of foods with a low glycemic index and load, such as whole grains, legumes, vegetables, and fruits, instead of foods with high glycemic index and load, such as sucrose and refined grains. Also, dietary protein and amino acids may affect insulin sensitivity and glucose metabolism. However, it is reported that the results of human studies are contradictory (46). Additionally, the results of studies on the effect of high protein diets on insulin resistance are also conflicting (47-50). For this reason, it is a critical necessity to evaluate the daily protein intake individually, taking into account the protein amounts of animal and plant origin in the diet. In order to discuss the effect of dietary fat on insulin resistance, the fat content and fatty acid pattern of the diet should be analyzed well. The excess amount of total fat intake with the diet, trans fatty acids, and

saturated fatty acids may be associated with insulin resistance. In contrast, the MUFAs and PUFAs may have positive effects on insulin sensitivity (51).

One of the findings of this study was the positive correlation between dietary iron and HOMA-IR (Table 3). It has been reported that excessive iron overload in the body is associated with insulin resistance in the liver and adipose tissue by increasing gluconeogenesis, pancreatic β-cell mass (increase in insulin release), and decreasing adiponectin levels (52). Considering that excessive iron increases may potentially play a role in the pathogenesis of insulin resistance, it may be beneficial to control serum iron levels and dietary iron intake of individuals with insulin resistance. Besides, dietary iron intake should be maintained at an optimal level to prevent both deficiency and excess. Iron supplements should only be used in a controlled manner when deemed necessary by the physician.

Study Limitations

A limitation of our study is that Tanner stage of puberty and sex hormones were not assessed in our subjects. In the study, the age range was 6-17 years. The overweight and normal weight sample could not be reached as much as the obesity sample during the research period. In future studies, it will be beneficial to increase the number of samples and reach the BMI groups in more similar numbers by children in the same age range.

Conclusion

This study determined that compliance with the Mediterranean diet should be improved in children and adolescents. Also, low compliance with the Mediterranean diet was associated with an increased risk of insulin resistance. Insulin resistance and obesity are among the preventable health problems with a healthy diet and lifestyle changes. For this reason, it is essential to acquire the correct nutritional habits in childhood. Gaining adequate and balanced dietary habits in the early period contributes to preventing nutrition-related health problems such as obesity and insulin resistance in childhood and adulthood.

Ethics

Ethics Committee Approval: The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (Decision no: İ2-32-19, date:).

Conflict of Interest: The authors declare that they have no conflict of interest.

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Malpraktis İddiaları ile Değerlendirilen Yenidoğan Hemorajik Hastalık Olguları

Neonatal Hemorrhagic Disease and Malpractice

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Öz

Giriş: Prenatal dönemde plesantal K vitamini geçişinin az olmasına bağlı olarak yenidoğanda Faktör II, VII, IX, X'un sentezinde meydana gelen azalma sonucu erken, klasik ve geç tip hemorajik hastalık gelişebilmektedir. Yenidoğan hemorajik hastalığı doğum sonrası uygulanan K vitamini proflaksisi ile önemli ölçüde önlenebilmektedir. Klinik prezentasyon değişkenlik göstermekle birlikte intrakranial kanama ve multiple sistem kanamaları görülebilmektedir. Çalışmada K vitamini proflaksisi yapılmamış ve medikolegal sürece yansımış olguların sosyodemografik, klinik, radyolojik ve laboratuvar özelliklerinin tartışılması amaçlandı.

Gereç ve Yöntem: Çalışma tanımlayıcı retrospektif bir çalışma olarak planlandı. Ocak 2017-Haziran 2021 tarihleri arasında Adli Tıp 7. İhtisas Kurulunda "Yenidoğan Hemorajik Hastalığı" tanısı ile medikolegal değerlendirme yapılmış olan 7 olgu çalışmaya dahil edildi. Olguların sosyodemografik, klinik, radyolojik ve laboratuvar özellikleri retrospektif olarak incelendi ve kaydedildi.

Bulgular: Beş (%71) erkek ve 2 (%28,5) kız olgunun yaş aralığı 15-49 gün (ortalama: 29 gün) saptandı. Tüm olgularda tıbbi uygulama hatası iddiası; K vitamini proflaksisi uygulanmadığı ve takipte tanılamanın yetersiz olduğu ile ilgili idi. Olguların tamamında yenidoğan döneminde K vitamini proflaksisi uygulanmadığı kayıtlıydı. Olgularımızın tamamı intrakranial kanama ile prezente olmuş ve nörolojik sekel ile iyileşmişti. Kurul değerlendirmesinde bakıldığında iki olguda malpraktis saptanırken 5 olguda tıbbi uygulama hatası saptanmadığı görüldü.

Sonuç: Yenidoğan hemorajik hastalığı morbidite ve mortalitesi yüksek önlenebilir bir durum olduğundan, K vitamini profilaksisi uygulanmasının yaygınlaştırılarak standart hale getirilmesi gerekmektedir.

Anahtar kelimeler
K vitamini proflaksisi, yenidoğan, malpraktis

Keywords
Vitamin K prophylaxis, neonatal, malpractice

Abstract

Introduction: Early, classical and late type hemorrhagic disease may develop as a result of the decrease in the synthesis of Factors II, VII, IX, and X in the newborn due to the low rate of transfer of vitamin K from the placenta in the prenatal period. Neonatal hemorrhagic disease can be significantly prevented with postnatal vitamin K prophylaxis. Although the clinical presentation varies, intracranial hemorrhage and multiple system hemorrhages can be seen. In the study, it was aimed to discuss the sociodemographic, clinical, radiological and laboratory characteristics of the cases that did not receive vitamin K prophylaxis and were reflected in the medicolegal process.

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Materials and Methods: The study was planned as a descriptive retrospective study. Between January 2017 and June 2021, 7 cases who underwent medicolegal evaluation with the diagnosis of "Neonatal Hemorrhagic Disease" in the 7th Specialization Board of Forensic Medicine were included in the study. Sociodemographic, clinical, radiological and laboratory features of the cases were retrospectively analyzed and recorded.
Results: The age range of 5 (71%) male and 2 (28.5%) female cases was 15-49 days (median: 29 days). Allegations of medical malpractice in all cases; It was related to the fact that vitamin K prophylaxis was not applied and the diagnosis was insufficient in the follow-up. It was recorded that all of the cases did not receive vitamin K prophylaxis in the neonatal period. All of our cases presented with intracranial hemorrhage and recovered with neurological sequelae. In the evaluation of the committee, malpractice was detected in two cases, and no medical malpractice was found in 5 cases.
Conclusion: Since neonatal hemorrhagic disease is a preventable condition with high morbidity and mortality, the application of vitamin K prophylaxis should be standardized by expanding it.

Giriş

Yenidoğan hemorajik hastalığı, K vitamini eksikliğine bağlı doğumdan sonraki ilk birkaç hafta içerisinde ortaya çıkan bir kanama bozukluğudur (1-3). K vitamini, esas olarak yetişkinlerde bağırsak bakterileri tarafından sentezlenen yağda çözünen bir vitamindir. Prenatal dönemde plesantal K vitamini geçişinin az olması ve buna bağlı olarak olarak K vitamini bağımlı faktör (Faktör II, VII, IX, X) sentezi yaşamın ilk birkaç gününde belirgin olarak azalır (1,3-5). Bununla birlikte fibrinojen (Faktör I), FV ve FVIII hayatın ilk günlerinde dahi normal düzeydedir (1-4). Yenidoğanlarda antikoagulan proteinler de (Antitrombin, protein C, protein S) düşük seviyededir. Pıhtılaşma faktör düzeyleri erişkin seviyesine altıncı aydan önce ulaşamaz (2-4). Bu durum yenidoğanların kanamaya eğilimini arttırır. K vitamini proflaksisi almayan yenidoğanlarda yenidoğan hemorajik hastalığı sıklığı %6-12 arasında değişkenlik göstermektedir. Rutin K vitamini proflaksisi başlanan Ülkelerde K vitamini eksikliğine bağlı kanama bozukluğu insidansı (%0,1) belirgin bir gerileme görülmektedir (2-5). Amerikan Pediatri Akademisi, K vitamini eksikliğine bağlı yendioğan hemorajik hastalığını önlemek için tüm yeni doğan bebeklere doğumda 0,5 ila 1 mg intramüsküler tek doz K vitamini yapılmasını önermektedir (5-9). Ülkemiz'de de Sağlık Bakanlığı ve Türk Neonatoloji Derneğinin önerisi ile doğum sonrası ilk 24 saatte inramusküler K vitamini proflaksisi uygulanmaktadır (8-10,11). Ülkemizde, yenidoğan hemorajik hastalığı sıklığına ilişkin epidemiyolojik bir çalışma bulunmazken K vitamini yapılmadığı için yenidoğan hemorajik hastalığı tanısı almış birçok olgu bildirilmiştir (12-15,16). Çalışmada medikolegal sürece yansıyan K vitamini proflaksisi yapılmamış olguların sosyodemografik, klinik, radyolojik ve laboratuvar özellikleri değerlendirilerek yendioğan hemorajik hastalığının önemi ve önlenebilir sonuçlarının tartışılması amaçlanmıştır.

Gereç ve Yöntem

Araştırma, tanımlayıcı bir çalışma olarak planlandı. Adli Tıp 7. İhtisas Kurulunda, Ocak 2018-Eylül 2021 tarihleri arasında düzenlenmiş raporlar retrospektif olarak incelendi. Adli Tıp Kurumu 7. Adli Tıp İhtisas Kurulu, ölümle sonuçlanmayan tıbbi uygulama hataları hususunda resmi bilirkişilik görevini yürütmektedir. Yenidoğan Hemorajik Hastalığı tanısı almış ve medikolegal değerlendirme yapılması istenen olgular çalışmaya dahil edildi (n=7). Kurul tarafından düzenlenen raporlarda kayıtlı olan, taraf ifadeleri, tıbbi belgeler, Kurul tarafından incelenmiş olan radyolojik tetkikler değerlendirildi. Medikolegal sürece konu olan iddialar, davalı olan sağlık personeli branşı, Kurula yönlendirilen adli merciler, olguların sosyodemografik verileri, klinik prezantasyonları, radyolojik bulguları ve laboratuvar sonuçları, medikolegal değerlendirme sonuçları kaydedildi.

Adli Tıp Kurumu 7. Adli Tıp İhtisas Kurulu ölümle sonuçlanmayan tıbbi uygulama hataları hususunda resmi bilirkişilik yapmakta olup multidisipliner bir yapılanmaya sahiptir. Çalışma izni Adli Tıp Kurumu Bilimsel Araştırma Komisyonundan 04.10.2021 tarih ve 21589509/2021/1131 sayılı izin ile alınmıştır.

Bulgular

Beş (%71) erkek ve 2 (%28,5) kız olgunun yaş aralığı 15-49 gün (median: 29 gün) saptandı. Altı (%85) olguda medikolegal sürece yansıyan iddialar; K vitamini proflaksisi uygulanmadığı ve takipte tanı konulmasının yetersiz olduğu iken, bir olguda ise tanı ve tedavide yetersiz kalındığı iddiası yer almaktaydı.

Dört olguda pediatri uzmanından, bir olguda hemşireden, bir olguda ise kadın doğum uzmanı ve pediatri uzmanından şikayetçi olunduğu kayıtlıydı.

Tıbbi belgelerde, 6 (%85,7) olguda yenidoğan döneminde K vitamini proflaksisi uygulanmadığı kayıtlı idi. Bir olgunun klinik özellikleri yenidoğan hemorajik hastalığı tablosuna uymakla birlikte yenidoğan döneminde K vitamini uygulanıp uygulanmadığı bilgisine ulaşılamadı. Ortalama tanı alma yaşı 34,7 gün (15 gün-49 gün) olarak hesaplandı. Olguların hepsi hastanede doğmuştu. Prenatal ve postnatal öykü hakkında kayıt bulunamadı.

Olguların konvülziyon, kusma, yenidoğan reflekslerinde azalma, hipotoni gibi klinik bulgular ile prezente olduğu görüldü (Tablo 1). Olguların tanı anında yapılan radyolojik görüntülemelerinde intrakranial kanama saptanmış olduğu görüldü. Olguların laboratuvar sonuçları da K vitamini eksikliğini desteklemekte idi (Tablo 1).

Olguların son durum muayeneleri değerlendirildiğinde; bir olguda serebral palsi, bir olguda motor gelişim geriliği, bir olguda hafif sol spastisite, üç olguda hemipleji, bir olguda epileptik nöbet saptandı ve tüm olgularda nörolojik sekeller kalmış olduğu görüldü.

K vitamini uygulanmama nedeni 4 olguda ülkemizde K vitamini tedarik aşamasında sorun olduğu bildirilmişti. Bu konu ile ilgili 2 olguda hekim ve idari merciler tarafından tutulan kayıt ve resmi bildirim saptandı.

Adli Tıp Kurumu 7. Adli Tıp İhtisas Kurulu tarafından verilen kanaatler değerlendirildiğinde bir olguda takip sürecinde tıbbi uygulama hatası saptanmadı. Kurul sonuçlarında, K vitamini proflaksisinin yenidoğan hemorajik hastalığını önlemek amacıyla kullanımının tıbben önerildiği ve proflaksi uygulansa dahi yatkın olan hastalarda yenidoğan hemorajik hastalığının azalmış olasılıkla görülebileceği kayıtlı idi. Bununla birlikte K vitamini temini ile ilgili sorun yaşandığı iddia edilen durumlarda, tıbbi kayıtlarda bu duruma ilişkin kayıtlar bulunduğu taktirde takip eden sağlık

Tablo 1. K vitamini eksikliği tanısı olup medikolegal değerlendirme yapılan olguların özellikleri

Olgu	Yaş	Doğum yılı	Cinsiyet	Tanı yaşı	Dava konusu sağlık personeli	Klinik prezentasyon	Radyolojik bulgular	Laboratuvar		
								Trombosit sayısı/mm3	INR/ aPTT	Hemogram
1.	2 ay 9 gün	2019	Kız	30 günlük	Hemşire	Kusma, strupor, nöbet	İntrakraniyal kanama	313.000	-/24,3	Normal
2.	1 ay	2019	Erkek	26 günlük	Kadın doğum uzmanı	Huzursuzluk, kusma, beslenme bozukluğu	İntrakraniyal kanama	239. 000	1,09/ 155,6	Normal
3.	2 ay 15 gün	2019	Kız	15 günlük	Çocuk sağlığı ve hastalıkları uzmanı	Huzursuzluk, fontonel bombeliği, kusma	İntrakraniyal kanama	532.000	0,97/ 40,8	Normal
4.	8 ay	2019	Erkek	45 günlük	Çocuk sağlığı ve hastalıkları uzmanı	Batan güneş manzarası, sarılık	İntrakraniyal kanama	864.000	>5/250	Normal
5.	4 ay 18 gün	2017	Erkek	49 günlük	Kadın doğum uzmanı	Solunum sıkıntısı	İntrakraniyal kanama	372.000	1,1/16,9	Normal
6.	9 ay	2019	Erkek	39 günlük	Çocuk sağlığı ve hastalıkları uzmanı	Beslenme bozukluğu, dalma, güç kaybı	İntrakraniyal kanama	-	/>120	Normal
7.	1 ay 17 gün	2019	Erkek	39 günlük	Çocuk sağlığı ve hastalıkları uzmanı	Huzursuzluk, kusma, ağlama	İntrakraniyal kanama	-	-	Normal

personeline tıbbi hata atfedilemeyeceği kayıtlı idi. Davalı Sağlık Kuruluşlarının İdari olarak medikolegal olarak değerlendirilmesinde de benzer şekilde temin sorunlarına ilişkin resmi belgelerin kayıtlı olması halinde idari açıdan tıbbi hata atfedilemeyeceği kayıtlı idi.

Tartışma

Yenidoğan hemorajik hastalığı K vitamini proflaksisi ile önlenebilen mortalite ve morbiditesi yüksek olan bir klinik tablodur (1-10,11). Yenidoğanlarda K vitamini uygulaması ülkeler arası değişkenlik göstermekle birlikte proflaksi uygulanmayan bölgelerde yenidoğan hemorajik hastalığı görülme sıklığının arttığı bilinmektedir (5, 13-15).

Ülkemizde ise Sağlık Bakanlığı'nın "Yenidoğanlarda K Vitamini Uygulamasına İlişkin 2010/17 Sayılı Genelge"sinde doğum yapılan merkezlerde yenidoğanlara K vitamini uygulanması ve usulleri yer almaktadır (10,11,20). Dolayısıyla K vitamini proflaksisi genel tıbbi uygulamalar arasında yer almaktadır.

Çalışmamızda değerlendirilen olgular 2019 yılında K vitamini temin sürecinde aksama yaşandığı bir dönemde tespit edilmiştir. Olguların medikolegal sürece yansıma nedenlerine bakıldığında özellikle aile ve hekim arasında konu ile ilgili iletişim sorunlarının yaşanmış olduğu görülmektedir. Bu dönemde K vitamini temini ile ulusal boyutta bir sorun yaşandığı görülmektedir. Medikolegal açıdan uygulanması tıbben gerekli olan bu ilacın uygulanmamış olması sorun teşkil ederken tedarik aşamasında yaşanan sorunların belgelenmiş olması hekimlere herhangi bir uygulama hatası atfedilmesini önlemiştir. Medikolegal değerlendirmede hekimin tedavide güncel standart uygulamaları yapmaması durumu, beceri noksanlığı yahut hastanın tedavisini vermemesiyle gelişen zarar malpraktis olarak tanımlanmaktadır. Dolayısıyla hekimin uygulayamadığı tedavinin gerekçesini kayıt altına alması ve idari mercileri durumdan haberdar etmesi, bu bilgiyi de aile ile paylaşması gerekmektedir. Olgular özelinde bakıldığında bir olguda da K vitamini proflaksisinin önerildiği ancak temini ile ilgili sorun yaşandığı kayıt altına alındığı görülmüştür. Diğer olgularda söz konusu durum ile ilgili tıbbi kayda ulaşılamamış; bu durumda malpraktis hususunda değerlendirme yapılamamış ve konu adli incelemeye bırakılmıştır. Medikolegal değerlendirme kayıtlı tıbbi belgeler ve adli belgeler üzerinden yapıldığından tıbbi değerlendirme dışındaki konuları adli mercilerin taktirine bırakmak gerekmektedir. Görüldüğü gibi hekimlerin talep ettikleri ya da ulaşamadıkları tedavi ya da proflaksi için elzem olan ilaç ya da hizmet ile ilgili yeterli kayıt tutmamaları ya da kaydı ilgili idari mercilere ulaştırmamaları durumunda medikolegal sorunlar doğmaktatadır.

Klinik tablo değişkenlik göstermekle birlikte özellikle intrakranial kanamalar mortalitede artışa neden olurken ciddi sekeller bırakabilir (13,17-20). Çalışmada incelenen olguların tamamında intrakranial kanama saptanırken güncel nörolojik muayenelerinde belirgin nörolojik sekel kaldığı saptanmıştır. Bu durum klinik tablonun ciddiyetini ortaya koymaktadır (19-22).

Amerikan Pediatri Akademisi (AAP), yenidoğan döneminde K vitamini eksikliğine bağlı kanamaları önlemek amacıyla doğumda profilaktik K vitamini (1 mg) önermektedir (2). Bununla birlikte im uygulanma sonrasında ortaya çıkabilecek komplikasyonlar nedeniyle (lokal travma, damar, sinir zedelenmesi, apse, osteomiyelit ve kanama) oral K vitamini uygulaması da gündeme gelmiştir (2,15,18). Oral uygulamada doğumda 2 mg, ikinci ve dördüncü haftalarda ek doz şeklinde önerilmektedir (2,15,18-22). Bununla birlikte oral K vitamini aile uyumu ve aile sağlık ile çalışanının iş birliğini gerektiren bir konu olduğundan K vitaminin özellikle ülkemiz koşullarında tek doz İM uygulamasının pratikte daha güvenilir ve etkin olduğu düşünülmektedir (2,19-25). Herhangi bir nedenle proflaksi uygulanamayan çocuklarda ailelerin K vitamini uygulamasının önemi, uygulanmadığı hallerde oluşabilecek riskler ve neden uygulanamadığı hususunda bilgilendirilmesi, bu bilgilendirmenin kayıt altına alınarak idari merciler ile paylaşılması birçok medikolegal sorunun oluşmadan önüne geçecektir. Kayıt tutulması ve hastanın bilgilendirilmesi yükümlülüğü esastır.

Sonuç

Sonuç olarak, yenidoğan döneminde uygulanan K vitamini profilaksisi yenidoğan hemorajik hastalığı gelişimini önlemede önem arz etmektedir. Özellikle intrakraniyal kanama ve buna bağlı gelişebilecek

hidrosefali, konvülziyon, ciddi psikomotor retardasyon ve serebral hasara bağlı sekeller gibi komplikasyonları büyük ölçüde azaltacak bir uygulamadır.

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Adölesan Obezitesinin Elektrokardiyografi ve Solunum Fonksiyon Testleri Üzerine Etkilerinin Değerlendirilmesi

Evaluation of the Effects of Adolescent Obesity on Electrocardiography and Pulmonary Function Tests

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Öz

Giriş: Ülkemizde ve tüm dünyada obezitenin sıklığı giderek artmaktadır. Obezite, özellikle kardiyovasküler sistem ve solunum sistemi gibi yaşamsal önemli sistemleri de etkileyerek, mortalite ve morbiditeyi artırabilmektedir. Bu anlamda obezitenin erken tanınması ve komplikasyonlarının önlenmesi hayati önem arz etmektedir. Çalışmamızda, adölesan dönemde obezitesi olan olguların elektrokardiyografi (EKG) ve solunum fonksiyon testlerinin (SFT) bulguları normal kiloda olan olgularla kıyaslanarak adölesan obezitesinin etkilerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmamıza polikliniğimize başvuran 10-18 yaş aralığında olan adölesan olgular dahil edildi. Olgular vücut kitle indekslerine göre üç gruba ayrıldı. Olguların EKG ve SFT ölçümleri alınarak çalışma verileri elde edildi. Elde edilen veriler SPSS paket programı ile değerlendirildi.

Bulgular: Çalışmamıza 156 olgu dahil edildi. Çalışmamızda değerlendirilen EKG parametrelerinden kalp hızı açısından gruplar arasında anlamlı fark saptanmadı (p=0,107). QT ve QTc açısından olgu grupları karşılaştırıldığında, istatistiki açıdan anlamlı fark saptandı (p<0,001). QT dispersiyonu ve QTc dispersiyonu açısından anlamlı fark saptanmadı (sırasıyla p=0,314, p=0,624). Tp-e açısından gruplar arasında anlamlı derecede fark saptandı (p<0,05). Tp-e/QT ve Tp-e/Qtc oranları açısından gruplar arasında anlamlı fark saptanmadı (sırayla p=0,054, p=0,058). Solunum fonksiyon testi sonuçlarından, FEV1, FEV1/FVC, PEF, FEF25-75 değerleri kıyaslandığında, tüm gruplar arasında istatistiki açıdan anlamlı fark saptandı (p<0,001).

Sonuç: Çalışmamızda, obezitenin adölesanlarda solunum ve kardiyovasküler sisteme olan etkilerinin EKG ve SFT ile önceden tespit edilerek olası komplikasyonların önlenebileceği sonucuna vardık.

Anahtar kelimeler
Obezite, adölesan, elektrokardiyografi, solunum fonksiyon testleri

Keywords
Obesity, adolescent, electrocardiography, pulmonary function tests

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Abstract

Introduction: The frequency of obesity is increasing in our country and all over the world. Obesity can also increase mortality and morbidity by affecting vital vital systems such as the cardiovascular system and the respiratory system. In this sense, early recognition of obesity and prevention of complications are of vital importance. In our study, we aimed to evaluate the effects of adolescent obesity on

patients with obesity and normal by compairing electrocardiography (ECG) and pulmonary function tests (PFT) findings.
Materials and Methods: Adolescent cases between 10 and 18 years of age were included in our study. Cases were divided into three groups according to body mass index. ECG and PFT measurements of the patients were obtained and study data were obtained. The data were evaluated with SPSS package.
Results: One hundred fifty six patients were included in our study. In our study, no significant difference was found between ECG parameters in terms of heart rate (p=0,107). When Qt and QTc groups were compared, a statistically significant difference was found (p<0.001). There was no significant difference in QT dispersion and QTc dispersion (p=0.314, p=0.624, respectively). There was a significant difference between the groups in terms of Tp-e (p<0.05). There was no significant difference between the groups in terms of Tp-e/QT ratio and Tp-e/QTc ratio (p=0.054 and p=0.058). When the values of FEV1, FEV1/FVC, PEF, FEF25-75 were compared, a statistically significant difference was found between all groups (p<0.001).
Conclusion: In our study, we concluded that the effects of obesity on respiratory and cardiovascular system in adolescents can be determined by ECG and PFT and possible complications can be prevented.

Giriş

Obezite, vücut kitle indeksi (VKİ) ≥30 kg/m^2 olan patolojik olarak artmış vücut yağ kütlesi olarak tanımlanırken, aşırı kilo ise VKİ 25-30 kg/m^2 arasında değişen bir ön evreyi tanımlar (1). Obezitenin görülme sıklığı tıpkı erişkinlerde olduğu gibi çocuklarda da hızla artmakta olup, ekonomik ve sosyal anlamda da ciddi problemlere yol açmaktadır. Dünya Sağlık Örgütü tarafından en riskli hastalıklardan birisi olarak kabul edilen obezite vücudun endokrin, metabolik, kardiyovasküler ve solunum sistemlerini etkileyerek çok çeşitli sorunlara sebep olabilen, multifaktöriyel, oldukça kompleks bir hastalıktır (2). Obezitenin; tip 2 diyabetes mellitus, yağlı karaciğer hastalığı, hipertansiyon, miyokard enfarktüsü, felç, demans, osteoartrit, obstrüktif uyku apnesi ve çeşitli kanserler gibi hastalıkların riskini önemli ölçüde artırdığı, yaşam kalitesini azaltmanın yanında yaşam beklentisinde de düşüşe sebep olduğu için önemli bir sağlık sorunudur (3). Erişkin yaşlarında gördüğümüz obezite komplikasyonlarının temeli çocukluk ve adölesan döneminde atılmaktadır. Çocukluk ve adölesan dönemindeki prevalans çalışmalarının ve özellikle obeziteye yönelik önleyici girişimlerin önemi hayati öneme sahiptir.

Obez bireylerde aritmi sıklığı, yapılan çalışmalarda artmış olarak bulunmuştur (4). Özellikle 12 derivasyonlu elektrokardiyografi (EKG)'den elde edilen P dalga dispersiyonu, QT aralığı, düzeltilmiş QT ("Corrected" QT-QTc), QT dispersiyonu ve düzeltilmiş QT dispersiyonu, miyokardın aritmilere duyarlılığını göstermektedir ve ani kardiyak ölüm riski ile ilişkili bulunmuştur (5,6). P dalga dispersiyonu, atrial aritmi gelişimini tahmin etme araçlarından biridir ve P dalga dispersiyonunun uzaması, atrial aritmi açısından riskin artmış olduğunu gösterir (7,8). Son yıllarda obezite ile astım birlikteliğindeki artış, obez bireylerde nefes darlığı ve öksürük gibi solunum sistemi problemlerine daha sık rastlanılması, obezite ile astım ve diğer solunum sistemi sorunları arasında bir ilişki olabileceği ihtimalini akla getirmektedir (9). Bu çalışmamızda, adölesan yaş grubunda obezite tanısı alan çocuklarda obezitenin EKG ve solunum fonksiyon testlerinin (SFT) üzerine etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem

Çalışma Popülasyonu

Çalışmamıza, Aralık 2018-Nisan 2019 tarihleri arasında, kurumumuz çocuk sağlığı ve hastalıkları polikliniklerine kilo alma şikayeti ile başvuran adölesanlar dahil edilmiştir. Dünya Sağlık Örgütü'nün tanımladığı şekilde, yaşları 10-18 olan adölesanlar çalışmaya alınmıştır (10). Araştırmamıza dahil edilen adölesanlar VKİ'ye göre obez (VKİ ≥30 kg/m^2), hafif kilolu (VKİ=25-30 kg/m^2), normal kilolu (VKİ=18-25 kg/m^2) olmak üzere üç gruba ayrıldı ve çalışmaya toplam 156 hasta dahil edildi.

Altta yatan diyabetes mellitus, hipotiroidi, cushing hastalığı, monogenik obezite gibi endokrin hastalığı olanlar, bilinen herhangi bir kronik hastalığı, doğuştan veya edinsel ritim bozukluğu, hipertansiyon gibi kardiyak bozukluğu olanlar, herhangi bir sebeple kalp ritmini veya solunum fonksiyonlarını bozacak ilaçlar ve kortikosteroid kullananlar, ailesel hiperlipidemi öyküsü olanlar, nöromüsküler hastalık, laringomalazi, kraniyofasiyal sendrom veya genetik hastalığı olanlar, solunum sistemine ait ventilasyon bozukluğu yapabilecek bronşektazi, bronşiyal astım gibi hastalığı olanlar, sigara kullanan adölesanlar, VKİ <18 kg/m^2

olanlar, mental retardasyonu olanlar, EKG ve SFT'ye uyum sağlayamayan hastalar, herhangi bir nedenle ailesi tarafından aydınlatılmış onamı imzalanmayan ve çalışmaya katılmayı reddeden hastalar, 10-18 yaş aralığı dışında kalan hastalar çalışmaya dahil edilmedi.

Bu çalışma için kurumumuz Etik Kurulu'ndan 05.10.2018 tarihli 2015-KAEK-86/12-120 sayılı etik kurul onayı alındı ve tüm aşamalar Helsinki Bildirgesi'ne uygun olarak yürütüldü.

Elektrokardiyografik Değerlendirme

Çalışmaya alınan adölesanların antropometrik ölçümleri alındı ve dijital ortama aktarılan standart 12 derivasyonlu EKG ile kalp hızı, QT ve QTc ölçümleri, QT dispersiyonu, QTc dispersiyonu, Tp-e, Tp-e/QT, Tp-e/QTc oranları manuel hesaplandı. Kalp hızı ölçümleri, DII derivasyonundan ardışık üç atımın ventrikül hızı hesaplanarak ortalamasının alınması ile elde edildi. EKG kaydı alınacak olan hastalara, 30 dakika öncesinde egzersiz yapmaması, kafein almaması, 20 dakika boyunca istirahat etmesi belirtilerek değerlendirilmeye alındı. Tüm EKG ölçümleri aynı hekim tarafından yapıldı. Uygun koşullar sağlandıktan sonra olgulardan sırtüstü pozisyonda standart derivasyon pozisyonları ile ProMedic PRMECG-12A 12 kanallı EKG cihazı ile 10 mm/mV amplitüt ve 25 mm/sn hızda EKG kaydı alınarak araştırma verileri elde edildi.

QT intervalleri; QRS kompleksinin başlangıcından başlayarak, TP taban çizgisine dönüşü olarak tanımlanan T dalgasının sonuna kadar alındı. QT dispersiyonu, farklı derivasyonlarda maksimum ve minimum QT aralığı arasındaki fark olarak belirlendi. QT mesafesi, kalp hızına göre değişkenlik gösterdiğinden, Bazett formülü ile düzeltilerek QTc hesaplandı. T dalgasının en yüksek amplitüde ulaştığı nokta ile T dalgasının bittiği yer arasındaki süre Tp-e intervali olarak hesaplandı.

Solunum Fonksiyonlarının Değerlendirilmesi

Solunum fonksiyon testleri için katılımcılara göğüs ve karın hareketlerini kısıtlayacak giysiler giymemesi, testten iki saat öncesine kadar yemek yememesi, testten 30 dakika önce ağır egzersiz yapmaması, kafein almaması belirtildi ve test öncesi 10 dakika istirahat etmeleri sağlandı. Tüm katılımcılara aynı hekim tarafından test uygulandı. Test öncesi hekim tarafından katılımcılara burnunun test esnasında klipsle kapatılacağı, akciğerler bütünüyle hava doluncaya kadar nefes alması, test cihazının ağızlığını hava kaçırmayacak şekilde dudaklarının arasında sıkıca kavraması, tüm gücüyle ve olabildiğince hızlı nefes vermesi gerektiği anlatılarak uygulamalı olarak gösterildi. Test pediyatrik uyumlu VYNTUS® IOS SPİROMETRY cihazı kullanılarak uygulandı ve FEV1, FEV1/FVC, PEF ve FEF25-75 parametre değerleri hesaplandı. Her katılımcı için test üç kez tekrarlanarak, elde edilen ideal üç kayıttan uygun olanı araştırma verilerini elde etmek için kullanıldı.

İstatistiksel Analiz

Araştırmamızda elde edilen veriler, SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 17.0 programında değerlendirildi. Tüm veriler için ortalama ve standart sapma değerleri hesaplandı. Verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov testi ile araştırıldı. Normal dağılıma uyan grupların karşılaştırılmasında t-testi ve One-Way ANOVA, normal dağılmayan gruplar arasındaki fark Pearson ki-kare, Kruskal-Wallis testleri ile değerlendirildi. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

Bulgular

Çalışmamıza dahil edilen adölesan yaş grubunda 156 olgunun; 74'ü erkek (%47,4), 82'si kız (%52,6), olguların yaş ortalaması 14,47±1,75 yıl idi. Olgular VKİ'lerine göre normal (n=59, %37,8), hafif kilolu (n=47, %30) ve obez (n=50, %32,2) olarak üç gruba ayrıldı. Normal kilolu olguların yaş ortalaması 14,71±1,64 yıl, hafif kilolu olguların yaş ortalaması 14,62±1,65 yıl, obez olguların yaş ortalaması ise 14,04±1,94 yıl olarak hesaplandı. Çalışmamızdaki olgular VKİ'ye göre karşılaştırıldığında, her grup içinde yaş ortalamaları ve cinsiyetler açısından istatiksel anlamlı fark saptanmadı ($p>0,05$).

Normal, hafif kilolu ve obez gruplarda çalışılan EKG parametrelerinin ortalama, standart sapma (SD), ortanca ve en yüksek-en düşük değerleri Tablo 1'de görülmektedir. Obez ve hafif kilolu olgu grupları ile normal kilolu grup, QT, QTc, QT dispersiyonu, QTc dispersiyonu, Tp-e ve Tp-e/QT oranı açısından karşılaştırıldı. QT değeri açısından normal grup, hafif kilolu ve obez grupla kıyaslandığında, istatistiksel olarak anlamlı derecede farklı bulundu ($p<0,001$). Benzer şekilde QTc değeri açısından normal grup, hafif kilolu ve obez grupla kıyaslandığında istatistiksel

Tablo 1. Adölesanların elektrokardiyografik değerleri									
	Ortalama ± SS			Ortanca			Minimum-maksimum		
EKG parametresi	Normal kilo	Hafif kilo	Obez	Normal	Hafif kilo	Obez	Normal	Hafif kilo	Obez
QT	349,41±33,53	353,05±28,76	370,18±28,01	351,0	351,5	373,0	280,0-420,0	292,0-440,0	288,0-464,0
QTc	407,12±32,27	423,0±36,1	439,42±30,79	404,5	427,0	440,5	324,0-504,0	335,0-517,0	379,0-526,0
QT dispersiyonu	19,14±11,79	21,87±11,99	22,24±11,0	16,0	20,0	18,0	4,0-48,0	2,0-48,0	8,0-56,0
QTc dispersiyonu	24,97±17,58	27,71±15,69	27,18±12,7	22,0	26,5	23,5	2,0-82,0	2,0-82,0	12,0-59,0
Tp-e	71,5±13,36	75,69±12,28	77,5±11,54	72	76	77,0	8,0-94,0	40,0-96,0	54,0-102,0
Tp-e/QT	0,22±0,04	0,21±0,03	0,22±0,03	0,23	0,21	0,22	0,16-0,29	0,15-0,29	0,12-0,32
Tp-e/QTc	0,20±0,03	0,19±0,03	0,19±0,04	0,20	0,19	0,19	0,12-0,26	0,12-0,27	0,12-0,26
SS: Standart sapma, EKG: Elektrokardiyografi									

olarak anlamlı farklılık saptandı (p<0,001). QT dispersiyonu ve QTc dispersiyonu açısından normal kilolu, hafif kilolu ve obez gruplar karşılaştırıldığında aralarında istatistiksel oalrak anlamlı derecede farklılık saptanmadı (sırasıyla p=0,314, p=0,624).

Çalışmamızda Tp-e değerleri normal grup ile hafif kilolu ve obez grupta karşılaştırıldığında istatistiki açıdan anlamlı derecede farklılık saptandı (p<0,05). Tp-e/QT oranı karşılaştırıldığında gruplarda istatistiksel olarak önemli farklılık saptanmadı (p=0,054) Tp-e/QTc oranı açısından da gruplar arasında istatistiksel anlamlı fark yoktu. (p=0,058). Kalp hızı ortalama ± SS değerleri; normal, hafif kilolu ve obez grupta sırasıyla 83,79±16,98, 84,94±13,63 ve 83,44±11,17 olarak bulundu. Normal kilolu grup ile hafif kilolu ve obez grup kalp hızı açısından kıyaslandığında istatistiksel olarak anlamlı fark saptanmadı (p=0,147). Çalışmamızda istatistiksel olarak anlamlı farklılık saptanan parametreler için post-hoc çoklu karşılaştırma testleri yapıldı. QT değeri, normal grup ile obez grup arasında anlamlı bulundu (p<0,05). QT değeri açısından etki değeri epsilon kare hesaplandığında e^2= 0,08 bulundu. Cohen kriterlerine göre orta-büyük etki düzeyine sahip bulundu. QTc değeri açısından ise normal grup ile obez grup arasında, hafif kilolu ve obez grup arasında, hem de normal grup ile hafif kilolu grup arasında istatistiki açıdan anlamlı fark bulundu (p<0,05). Etki değeri e^2= 0,14 bulundu ve büyük bir etki büyüklüğü değerine sahip olduğu saptandı. Tp-e değeri açısından, normal ile hafif kilolu, hafif kilolu ve obez, normal ve obez gruplar arasında istatistiki açıdan anlamlı fark saptandı (p<0,05). Etki değeri e^2=0,052 olarak hesaplandı ve orta etki değeri büyüklüğüne sahip olduğu saptandı.

Çalışmamızda yer alan olgu grupları, solunum fonksiyon testinde yer alan FEV1, FEV1/FVC, PEF ve FEF25-75 parametreleri açısından karşılaştırıldı (Tablo 2). Solunum fonksiyon testi sonucunda ölçülerek çalışmamızda değerlendirilen FEV1, FEV1/FVC, PEF ve FEF25-75 değerlerinin hepsi için normal, hafif kilolu ve obez bireyler arasında istatistiki açıdan anlamlı derecede fark bulundu (p<0,001). Solunum fonksiyon test parametreleri açısından gruplar arası istatistiki anlamlı fark bulunduğundan, farkın hangi gruplar arasında olduğunu saptamak için, post-hoc analizleri yapıldı. FEV1 değeri açısından normal grup ile hafif kilolu olgular arasında ve normal kilolu olgularla obez olgular arasında istatistiki açıdan

Tablo 2. Adölesanların solunum fonksiyon testi değerleri				
	Normal	Hafif kilolu	Obez	p
FEV1	97,35±13,12	88,65±13,83	86,48±9,65	<0,001
FEV1/FVC	87,77±9,44	84,12±7,39	81,88±7,0	<0,001
PEF	4,84±0,96	4,17±0,88	3,83±0,84	<0,001
FEF 25-75	98,04±21,47	98,88±17,11	94,07±13,01	<0,001

anlamlı fark saptandı (p<0,001). Hafif kilolu olgular ile obez olgular arasında ise istatistiki açıdan fark saptanmadı (p=0,769). Etki değeri e^2=0,134 olarak bulundu ve FEV1 açısından Cohen kriterlerine göre büyük etki düzeyine sahip olduğu görüldü. FEV1/FVC değeri açısından, normal olgularla hafif kilolu olgular arasında anlamlı fark saptanmazken (p=0,066), obez olgular normal olgulara göre anlamlı derecede farklı olarak bulundu (p<0,001). Etki değeri ise e^2=0,09 olarak hesaplandı ve orta-büyük etki değerine sahip olduğu saptandı. PEF değeri açısından normal olgular ile hafif kilolu olgular arasında istatistiksel olarak anlamlı fark saptanmazken (p=0,156), normal kilolu olgular ile obez olgular arasında ise istatistiksel olarak anlamlı fark vardı (p<0,001). Etki değeri e^2=0,29 olup büyük etki düzeyine sahip olduğu saptandı. FEF25-75 değeri açısından normal ve hafif kilolu olgular arasında istatistiksel anlamlı fark bulunmazken (p=0,416), normal ve obez olgular anlamlı derecede farklı bulundu (p<0,05). Etki değeri e^2=0,09 ile Cohen kriterlerine göre orta-büyük etki değerine sahip olduğu gözlendi.

Tartışma

Obezite, günümüzde gelişmiş ve gelişmekte olan ülkelerde sıklığı giderek artan en önemli halk sağlığı sorunlarından birisidir (3). Vücuttaki ağırlık artışından farklı olup, yağ dokusunun anormal ve sağlığı bozacak düzeyde artışı olarak tanımlanabilir. Erişkin çağda olduğu gibi çocukluk çağında da artan obezite sıklığı, sağlık açısından çeşitli riskler barındırmaktadır. Çocukluk döneminde obez olan bireylerin, erişkin dönemde de obezite açısından risk taşıdığı bilinmektedir (3,11). Çocukluk çağı obezitesinin bir diğer önemi de pek çok kronik hastalığa zemin hazırlamasından kaynaklanmaktadır. Obezite ve obeziteyle ilişkili mortalite riskini artıran başlıca durumlar arasında, hipertansiyon, koroner kalp hastalığı, kardiyak aritmiler ve ani kardiyak ölüm, astım gibi pek çok kronik hastalık sayılabilir (3,4,12). Bu nedenle obezitenin ve obeziteyle ilişkili komplikasyonların tedavisi ve önlenmesi önemlidir.

Obezitenin çeşitli EKG anormalliklerine sebep olabileceği bilinmektedir. Özellikle, EKG ile ilişkili bir takım anormalliklerin ani ölüm ile ilişkilendirildiği çeşitli çalışmalar mevcuttur. Obezitede beklenen başlıca EKG değişiklikleri P dalgası morfolojisinde değişiklik, QRS voltajında azalma, bazı derivasyonlarda T dalgasında düzleşme, QT ve QTc aralığında uzamadır (13,14). Kardiyak aritmi sıklığı da obez olgularda artmış bulunsa da, sol ventrikül hipertrofisi ve uyku apne sendromuyla da ilişkili olabilir (15). Ayrıca, ventriküler ve supraventriküler ektopik atımların, atriyoventriküler bloklarında görülebileceğini bildiren çalışmalar mevcuttur (16). Obezitede meydana gelen EKG değişiklikleri büyük oranda kilo kaybı sonrasında geri dönüşlüdür (15,16). Çalışmamızda ele alınan hasta grubuna ait EKG kayıtlarında herhangi bir ileti veya ritim bozukluğu saptanmadı.

Basit obezitesi olan çocuklarda, kalp hızının normal vücut ağırlığındaki çocuklara göre daha yüksek olabileceğini bildiren çalışmalar mevcuttur (6,14,17). Bunda artmış adipoz dokuya adaptasyonun etkili olabileceği düşünülmektedir (6). Çalışmamızda ise obez ve hafif kilolu çocuklar ile normal kilolu çocuklar arasında kalp hızı açısından istatistiksel olarak anlamlı bir değişiklik saptanmadı.

Obezitede ventriküler aritmilere eğilimin arttığını gösteren çalışmalar mevcuttur (14,18). Ventriküler aritmiler, EKG parametrelerinden QT, QTc, QT dispersiyonu ve QTc dispersiyonudur. QT ve QTc uzaması ventrikül repolarizasyonunun uzadığını, QT dispersiyonu ve QTc dispersiyonu artışı ise repolarizasyonun homojen olmadığını ve aritmilere karşı duyarlılık artışı olduğunu gösterir (18). Altmış obez çocuk üzerinde yapılan bir çalışmada, QT dispersiyonu değerinin kontrol grubuna göre anlamlı düzeyde arttığı belirtilmiştir (19). Serum insülin düzeyindeki artış ile birlikte ventrikül repolarizasyonunun akut olarak uzayabildiği ve QT dispersiyonu değerinin artığı saptanmıştır (20,21). Pek çok çalışmada, obezlerde QT ve QTc intervalinin uzadığı, ancak bu durumun kilo kaybı sonrası geri dönüşlü bir değişiklik olduğu belirtilmiştir (16,22). Ancak bu durumun geri dönüşlü olmadığını da savunan çalışmalar mevcuttur (23,24). Ayrıca bazı çalışmalarda obezite ile QTc intervali arasında bir ilişki bulunmadığı da savunulmaktadır (25). Çalışmamızda ele alınan normal kilolu, hafif kilolu ve obez gruplar QT, QTc, QT dispersiyonu ve QTc dispersiyonu değerleri açısından karşılaştırıldı. QT değeri, obez grupta normal kilolu gruba göre istatistiksel olarak anlamlı derecede artmış bulundu. QTc değeri ise, normal kilolu ile hafif kilolu grup arasında, normal kilolu ile obez grup arasında ve hafif kilolu ile obez grup arasında istatistiksel olarak anlamlı derecede artmış

bulundu. Çalışmamızda kardiyak repolarizasyon göstergelerinden birisi olan QT dispersiyonu ve QTc dispersiyonu da değerlendirilmiş ancak gruplar arasında istatistiksel anlamlı fark saptanamamıştır. Bunun olası nedenleri, obezitenin QT dispersiyonu ve QTc dispersiyonu değerlerini etkilememesi olabileceği gibi, çalışmamızda ele alınan hasta grubunun henüz adölesan dönemde olmalarına bağlı kardiyovasküler sistemin henüz etkilenmemiş olmasıdır.

Kardiyak repolarizasyonu gösteren bir diğer EKG parametresi olan Tp-e intervali, ventrikül repolarizasyon dispersiyonunda artış gösterir ve bu parametrenin artışı ile ventriküler aritmi riskinin arttığı söylenebilir. QTc intervali normal olan hastalarda bile ventriküler aritmileri ve ani ölümü öngören Tp-e intervalinin obezlerde ventriküler aritmiler için invaziv olmayan EKG tarama yöntemi olarak kullanılabileceğini belirten çalışmalar mevcuttur (26). Tp-e/QT oranının da ventriküler aritmi ve ani ölüm riski açısından kullanılan bir diğer duyarlı parametre olabileceği bildirilmiştir (26,27). Çocukluk çağında, Tp-e intervalini ani ölüm riskiyle ilişkili olarak değerlendiren, kardiyak mortalite üzerine etkilerini net olarak açıklayan bir çalışmaya tarafımızca rastlanmamıştır. EKG'de rutin ölçülen bir parametre olmadığından, Tp-e intervali açısından yaşa göre normal değerleri de bilinmemektedir. Çalışmamızda olgular arasında Tp-e/QT oranı ve Tp-e/QTc oranı açısından istatistiki açıdan anlamlı fark saptanmazken, Tp-e intervali hafif kilolu ve obez gruplar ile normal kilolu grup arasında karşılaştırıldığında, istatistiksel olarak anlamlı derecede artış olduğu saptandı. Bu artış, kardiyak etkilenme veya mortalitede artış açısından bir risk faktörü olarak değerlendirilebilir.

Obezitenin sistemik komplikasyonlarından birisi de solunum sistemini ilgilendiren komplikasyonlarıdır. Obezitede görülen solunum sistemi semptomlarının mortalite ve morbiditeyi artırdığına yönelik çalışmalar mevcuttur (9,28,29). Solunum sistemindeki bu semptomlar, akciğerler sağlıklı olsa da toraks ve diyafragmaya olan etki ile de meydana gelebilmektedir (29). Bu bireylerde özellikle FEV1'deki azalmanın, mortalite ve morbiditeyi artırdığı belirtilmiştir (30). Yine bir başka çalışmada obez kadınlarda, normal kilolu bireylere göre FEV1, FEV1/FVC, FEF25-75 değerlerinin anlamlı derecede düşük olduğu, hem erkek hem de kadınlarda kilo kaybı ile FEF25-75 değerinin arttığı ve nefes darlığı semptomlarının kaybolduğu bildirilmiştir (31). Solunum fonksiyon testlerindeki parametrelerden özellikle FEV1 ve PEF santral hava yolları ve ekspiratuar kas gücü ile alakalı iken, FEF25-75 küçük hava yolu direncini gösteren bir parametredir. Çalışmamızda incelenen olgu gruplarında, FEV1 değeri açısından normal olgulara göre hem hafif kilolu hem de obez grupta istatistiksel olarak anlamlı derecede düşük olduğu saptandı. PEF değeri açısından da, normal kilolu olgularla kıyaslandığında, obez grupta anlamlı derecede düşük olduğu gözlendi. FEV1/FVC oranı da, restriktif akciğer hastalıklarında artarken, obstrüktif hastalıklarda ve hava yolu darlığı durumlarında azalır. Çalışmamızda normal kilolu gruba göre, hafif kilolu grup ve obez grupta da anlamlı düzeyde azaldığı gösterilmiştir. Bu sonuçlarla, obez bireylerde astım bulguları gelişiminin VKİ'deki artış ile paralellik gösterdiği söylenebilir.

Bu çalışmada bazı sınırlamalar mevcuttur. İlk olarak çalışmamız uzun süreli planlanmış bir prospektif çalışma olmadığından, obez ve hafif kilolu olgular açısından bulguların geri dönüşlü olup olmadığı değerlendirilemedi. İkinci olarak, elde edilen bulguların uzun dönemdeki anlamlılığı açısından bir bulgu vermemektedir. Üçüncü olarak, örneklem sayısı düşük olduğundan ve tek merkezli bir çalışma olduğundan, elde edilen verilerin geniş katılımlı ve çok merkezli çalışmalarla doğrulanması gereklidir. Tüm bunlara rağmen, çalışmamız çocukluk çağında obez hastalarda Tp-e intervali, Tp-e/QT oranı ve Tp-e/QTc oranı ile ani ölüm riskini değerlendiren sınırlı sayıdaki çalışmadan biri olması ile bu alanda yapılacak çalışmalara yol gösterici olma niteliği taşımaktadır.

Sonuç

Bu çalışmada, obezitenin kardiyovasküler ve solunum sistemi üzerine morbidite ve mortaliteyi artırıcı etkilerinin, invaziv olmayan EKG ve SFT ile önceden belirlenerek, önlemlerin daha erken alınabileceği ve ölümcül sonuçların önlenebileceği sonucuna vardık. Sonuçlarımızı doğrulamak için uzun süreli takip ve geniş ölçekli prospektif çalışmalara ihtiyaç vardır.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Why to Use Intraluminal Impedance in the Evaluation of Children with Repaired Esophageal Atresia

Onarılmış Özofagus Atrezisi Olan Çocukların Değerlendirilmesinde Neden İntraluminal İmpedans Kullanılmalı

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Abstract

Introduction: Gastroesophageal reflux disease (GERD) and esophageal dysmotility are frequent in esophageal atresia (EA) patients. The aim of this study was to assess the role of intraluminal impedance (MII-pH) in the evaluation of GERD in children with repaired EA.

Materials and Methods: The medical records of 13 pediatric patients with repaired Gross type C EA were reviewed retrospectively. The MII-pH recordings were analyzed by software automatically and the results were then reviewed manually. The results of barium studies including upper gastrointestinal tract series and videofluoroscopic swallowing studies were also reviewed to evaluate dysmotility.

Results: The most common extra-esophageal and esophageal complaints were recurrent pulmonary infections (92%) and dysphagia (77%). pH measurements showed a median reflux index (RI) of 3.8% (0.1-35.4) with 38% (n=5) of patients having pathologic RI (RI >5%). In impedance analyses, 70% of the reflux episodes were non-acidic (4≤ pH). Percent of patients having non-acidic retrograde bolus movements (RBM) above 95th percentile of normal values was 38% (n=5). Five of the 8 patients with normal pH monitoring results had pathological non-acid RBM in impedance analyses. Esophageal motility problem was a common finding (n=10, 77%) followed by pharyngeal phase problems (n=5, 38.5%) in contrast studies.

Conclusion: Majority of the RBM in repaired EA patients were non-acidic which would have gone undetected with standard pH monitoring. Half of the patients with pathologic reflux indices could only be detected by impedance monitoring. MII-pH monitoring should be preferred over conventional pH monitoring in the surveillance of EA patients.

Keywords
Dysmotility, esophageal atresia, gastroesophageal reflux, non-acidic reflux, pH-impedance

Anahtar kelimeler
Dismotilite, özofagus atrezisi, gastroözofageal reflü, asidik olmayan reflü, pH-impedans

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Öz

Giriş: Gastroözofageal reflü hastalığı (GÖRH) ve özofageal dismotilite özofagus atrezisi (ÖA) hastalarında sık görülür. Bu çalışmanın amacı, onarılmış ÖA'lı çocuklarda GÖRH'nin değerlendirilmesinde intraluminal impedansın (MII-pH) rolünü değerlendirmektir.

Gereç ve Yöntem: Onarılmış Gross tip C ÖA'lı 13 pediyatrik hastanın tıbbi kayıtları retrospektif olarak incelendi. MII-pH kayıtlarının yazılım tarafından otomatik olarak analiz edilmesiyle elde edilen sonuçlar manuel olarak tekrar gözden geçirildi. Dismotiliteyi değerlendirmek için, üst gastrointestinal sistem

kontrastlı çalışmalarını ve videofloroskopik yutma çalışmalarını içeren baryumlu tetkiklerin sonuçları gözden geçirildi.
Bulgular: En sık görülen ekstra-özofageal ve özofageal yakınmalar sırasıyla tekrarlayan akciğer enfeksiyonları (%92) ve disfajiydi (%77). pH ölçümlerinde ortanca reflü indeksi (RI) %3,8 (0,1-35,4) olarak saptanırken hastaların %38'i (n=5) patolojik RI (RI >%5) değerlerine sahipti. İmpedans ölçümlerinin analizinde, reflü epizodlarının %70'i non-asidik karakterdeydi (4≤ pH). Non-asidik retrograd bolus hareketlerinin (RBH) sayısı, normal değerlerin 95. persentilinin üzerinde olan hastaların oranı %38 (n=5) idi. pH monitörizasyonu sonuçları normal olan 8 hastanın 5'inin impedans analizinde patolojik non-asidik RBH saptandı. Özofageal motilite sorunu kontrastlı çalışmalarda en sık görülen bulguyken (n=10, %77), bunu faringeal faz sorunları (n=5, %38,5) izlemekteydi.
Sonuç: Onarılmış ÖA hastalarında görülen RBH'nin çoğunluğu non-asidik karakterdeydi ve standart pH monitörizasyonu kullanılsaydı saptanamayacaktı. Patolojik reflü indekslerine sahip hastaların yarısı ancak impedans monitorizasyonu ile tespit edilebildi. ÖA hastalarının sürveyansında MII-pH monitörizasyonu konvansiyonel pH monitörizasyonuna tercih edilmelidir.

Introduction

Esophageal atresia (EA), with or without a tracheoesophageal fistula (TEF), is the most common congenital anomaly of the esophagus with a prevalence of 2.4 per 10,000 births (1). Advances in pre- and postoperative care and surgical techniques have led to a better prognosis with reported survival rates of over 90% (2). This excellent survival outcome has shifted current focus from mortality to management of long-term complications in patients with repaired EA. Gastrointestinal and respiratory problems are not only common in the long-term follow-up but also related with significant post-surgical morbidity in these patients (3,4).

Gastroesophageal reflux (GER) and esophageal dysmotility occur frequently following surgical repair of EA (5). Gastroesophageal reflux disease (GERD) which is defined as GER leads to troublesome symptoms that affect daily functioning and/or complications is common after surgical repair of EA in children with a reported prevalence of 20% to 63% in different studies (6). Given the high prevalence and related complications, it is vital to appropriately monitor and treat GERD in this population (5). Combined multichannel intraluminal impedance and pH monitoring (MII-pH) is a sensitive tool in the objective evaluation of pediatric GERD (7). Detecting both acidic and non-acidic refluxate, differentiating intraesophageal content state (liquid or gas), determining the height of the reflux, distinguishing between swallow and reflux and making possible to establish a temporal association between symptoms recorded during the test and both non-acid and acid refluxate are the main advantages of MII-pH monitoring over conventional pH monitoring (8,9). Multiple studies have reported that GER in children with EA is mostly non-acid or weakly acid which can be missed with conventional pH monitoring (6).

The aim of this study was to assess the role of MII-pH monitoring in the evaluation of pediatric patients with repaired EA who had esophageal and/or extra-esophageal symptoms suggestive for GERD and to determine the reflux characteristics.

Materials and Methods

Study Design and Patients

This was a retrospective chart review study. Pediatric patients with repaired EA who underwent MII-pH monitoring between May 2016 and May 2018 were enrolled in the study. Patients who underwent MII-pH monitoring for the evaluation of symptoms suggestive of GERD (esophageal complaints like dysphagia, persistent vomiting and extra-esophageal complaints like recurrent pulmonary infections, chronic coughing, asthma/wheezing) were included in the study. Isolated TEF, esophageal replacement therapy and tube feeding were exclusion criteria. All available medical records of eligible patients were included in further data analysis. Demographic data (gender, birth weight, gestational age, age at primer repair, age at MII-pH monitoring), medication history at the time of impedance procedure, type of EA and performed surgical procedure, symptomatology necessitating MII-pH monitoring and swallowing characteristics of patients were collected from medical records. The reports of upper gastrointestinal tract (UGT) series were also reviewed when available. Recurrent pulmonary infections were defined as two or more pneumonia episodes in a 1-year period (10). Non-interventional Clinical Research Ethics Board of the hospital approved the study (GO 21/107, 2021/02-38). The study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

MII-pH Monitoring Protocol

MII-pH monitoring was performed over a 24-hour period with age-appropriate MII-pH catheters. Catheter replacement was performed on an outpatient setting in the pediatric gastroenterology clinic. We used age-appropriate Greenfield (Dover, USA) single use pH-MII catheters (6.4 French, 6 impedance channels, 1 pH antimony channel) to perform 24-hour MII-pH studies. At the beginning of the procedure pH electrode was calibrated using pH 4.0 and 7.0 buffer solutions. The catheter was introduced nasally, and the approximate position of the probe was calculated according to Strobel's formula (11). The position of pH probe was confirmed with a chest X-ray and corrected if necessary. All acid suppressive and prokinetic therapies or drugs affecting lower esophageal sphincter function were discontinued at least 7 days before the procedure. Symptoms, body position (upright or recumbent), food/beverage intake, sleep periods and daily activities were asked to be recorded by parents during MII-pH monitoring.

The MII-pH recordings were analyzed by software (MMS, version 9.1w, Enschade, the Netherlands) automatically following an initial manual review to delete artifacts (acid/alkaline limits: pH 4.0 and 7.0; minimum reflux duration: 5 seconds; air threshold: 5,000Ω). Finally, all reflux events identified by software were reviewed manually for any misinterpretation. Parameters analyzed in this study were as follows: number of pH changes to <4; reflux index [(RI); percent time with esophageal pH <4]; number of long (>5 minutes) acid exposures; longest acid exposure (minutes); number of retrograde bolus movements (RBM); number of acidic (pH <4), weak acidic (4≤ pH <7) and weak alkaline (pH ≥7) RBM; number of liquid/mixed RBM; and number of proximal RBM (RBM reaching at least the second uppermost impedance channel); symptom index (SI) for reflux; and symptom association probability [(SAP); window of 2 minutes before and after a reflux event]. An RI >5% was considered to be abnormal (12). SI ≥50% and SAP ≥95% were considered positive.

Videofluoroscopic Swallowing Study

The swallowing functions of all patients were imaged and recorded during a videofluoroscopic swallowing study (VFSS) by a swallowing therapist and a radiologist as reported from our center before (13). Oral phase dysfunction, laryngeal penetration, aspiration, abnormal esophageal body function, and reflux were identified based on the previously proposed definitions (14). The results were reviewed particularly for aspiration and abnormal esophageal body function.

Data Analysis

All data were summarized in a descriptive fashion. No statistical testing was performed. Data were presented using descriptive statistics [mean ± SD, and median with range (minimum-maximum)] for continuous variables, and frequencies (n, %) for categorical variables].

Data Availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

There were 13 patients (5 females and 8 males) with repaired EA who underwent MII-pH monitoring for symptoms suggestive of GER. Patient demographics were summarized in Table 1. None of the patients had long gap EA. All the patients were Gross type C (EA with distal TEF). Repeated bougie dilations were performed in 3 patients (23%) due to post operative anastomotic strictures and 2 patients (15%) had a history of esophageal food impaction. The most common extra-esophageal and esophageal complaints among patients necessitating a MII-pH monitoring and VFSS were recurrent pulmonary infections (92%) and dysphagia (77%), respectively (Table 1). Refusal of feeding, history of food impaction, swallowing difficulties, coughing/chocking during meal and sensation of food stuck in the chest were accepted as signs of clinical dysphagia.

MII-pH Monitoring

The results of MII-pH monitoring are summarized in Table 2. pH measurements showed a median RI of 3.8% (0.1-35.4) with 38% (n=5) of patients having RI >5%. The total and median numbers of reflux episodes (pH <4) were 618 and 30 (3-233), respectively. Fifty-three episodes (8.6%) were pH-only reflux events which were defined as a decrease in pH to <4 in the absence of reflux detected by impedance monitoring.

Table 1. Demographic characteristics of study patients	
Number	13
Gender (female/male)	5/8
Age at MII-pH monitoring, years, median (minimum-maximum)	6.5 (1.3-13.5)
Age at primer repair, days, median (minimum-maximum)	2 (1-74)
Birth weight, grams, mean ± SD	2594 ± 1083
Gestational age, weeks, median (minimum-maximum)	38 (30-42)
*Acid suppressive therapy at the time of MII-pH monitoring	7 (54%)
Bronchodilator therapy at the time of MII-pH monitoring	11 (84.6%)
Symptoms, n (%)	
Dysphagia	10 (77%)
Persistent vomiting	2 (15%)
Recurrent pulmonary infections	12 (92%)
Asthma/wheezing	11 (85%)
Chronic coughing	6 (46%)

*Acid suppressive therapy was stopped in all patients one week before the procedure.
GERD: Gastroesophageal reflux disease, MII-pH: Combined multichannel intraluminal impedance and pH monitoring, SD: Standard deviation.

Table 2. Results of pH-impedance monitoring	
Recording duration, minutes, median (minimum-maximum)	1,453 (1,068-1,501)
pH monitoring results	
Total number of reflux episodes with pH <4	618
Reflux episodes, median (minimum-maximum)	30 (3-233)
Reflux episodes >5 minutes, n (%)	46/618 (13%)
Reflux index, median (minimum-maximum)	3.8 (0.1-35.4)
Reflux index >5%, n (%)	5 (38%)
Impedance results	
Total number of RBM	565
RBM, median (minimum-maximum)	43 (3-96)
Acidic RBM, median (minimum-maximum)	14 (0-38)
Non-acidic RBM, median (minimum-maximum)	31 (1-67)
Liquid RBM, median (minimum-maximum)	15 (0-39)
Mixed RBM, median (minimum-maximum)	24 (2-76)
*Total number of proximal RBM, n (%)	240 (42)

*RBM reaching at least the second uppermost impedance channel.
RBM: Retrograde bolus movements

In impedance analyses, a total of 565 RBM were detected of which 34% were liquid and 66% were mixed episodes. Forty-two percent (n=240) of the RBM were proximal reflux episodes reaching at least the second uppermost recording sensor while nearly one-fourth (n=136, 23%) reaching the uppermost impedance channel. Thirty percent of the reflux episodes were acidic (pH <4), 47.5% were weakly acidic (4≤ pH <7) and 22.5% were weakly alkaline (pH ≥7) episodes. Characteristics of RBM regarding reflux type, acidity and extent were shown in Figure 1. When normal values for children older than 1 year (15) were applied to our study group, percent of patients having non-acidic RBM above 95th percentile of normal values was 38% (n=5). Five of the 8 patients with normal pH monitoring results had pathological non-acid RBM in impedance analyses. Only 2 of the patients (15.4%) with esophageal symptoms had SI >50% and SAP >95%.

Videofluoroscopic Swallowing Study and Upper Gastrointestinal Tract Series

Radiographic findings of study patients including VFSS and UGT series were summarized in Table 3. The oral phase revealed normal findings in all but one of the patients. VFSS revealed aspiration in 5 patients (38.5%) all of whom also had a significant delay in swallowing response. Esophageal phase was impaired in most of the patients (n=10, 77%). The most common problem was varying degrees of esophageal motility problem which was particularly severe below the anastomosis. UGT series results were available in 12 patients (92%). Decreased peristalsis and slow passage of contrast below the anastomosis (n=8, 67%) were the most common findings followed by narrowing of the lumen at the site of anastomosis (n=3, 25%), mucosal irregularity (n=3, 25%) and gastric organo-axial malrotation (n=2, 16%). GER was detected only in 2 patients (16%) in UGT series.

Among those without clinical dysphagia (patients # 2, 3 and 9), all had radiologic findings suggestive of

Table 3. Radiographic and pH-impedance monitoring findings of study patients

Patient no:	Acid suppressive therapy at the time of procedure	Clinical dysphagia*	Extra-esophageal symptoms	UGT series	VFSS	MII-pH monitoring (pathologic reflux)	
						Acidic (RI >5%)	Non-acidic**
1	-	+	RPI, chronic coughing	Normal findings	Aspiration with both liquids and solids, delay in swallowing response	-	-
2	-	-	RPI, asthma, chronic coughing	Mucosal irregularity at the site of anastomosis, decreased peristalsis and slow passage of contrast below the anastomosis, GER	Impaired esophageal motility	-	-
3	+	-	RPI	Decreased peristalsis and slow passage of contrast below the anastomosis, narrowing of the distal esophageal lumen	Severely impaired esophageal motility	+	-
4	+	+	RPI, asthma	Decreased peristalsis and slow passage of contrast below the anastomosis, GER	Aspiration with liquids, impaired esophageal motility	-	-
5	+	+	Asthma, wheezing	Mucosal irregularity, narrowing of the lumen at the site of anastomosis	Mild delay in swallowing response, severely impaired esophageal motility	-	+
6	+	+	RPI, wheezing	Normal findings	Aspiration with liquids, delay in swallowing response, normal esophageal motility	+	-
7	+	+	RPI, wheezing	n/a	Aspiration with liquids	+	-
8	-	+	RPI, wheezing, chronic coughing	Slow passage of contrast below the anastomosis	Aspiration with liquids, delay in swallowing response, impaired esophageal motility	-	+
9	-	-	RPI, asthma, chronic coughing	Decreased peristalsis and slow passage of contrast distal 2/3 of esophagus	Impaired esophageal motility	-	+
10	+	+	RPI, asthma	Decreased peristalsis and slow passage of contrast below the anastomosis	Severely impaired esophageal motility and GER	+	-
11	+	+	RPI, wheezing, chronic coughing	Gastric organo-axial malrotation, decreased peristalsis below the anastomosis	Aspiration with liquids, delay in swallowing response, mildly impaired esophageal motility	-	+
12	-	+	RPI, asthma, chronic coughing	Decreased peristalsis below the anastomosis, narrowing of the distal esophageal lumen	Severely impaired esophageal motility and GER	+	-
13	-	+	RPI, asthma	Mucosal irregularity at the site of anastomosis, gastric organo-axial malrotation	Impaired esophageal motility	-	+

MII-pH: Combined multichannel intraluminal impedance and pH, EA: Esophageal atresia, VFSS: videofluoroscopic Swallowing Study, UGT: Upper gastrointestinal tract, RPI: Recurrent pulmonary infections, RI: Reflux index, GER: Gastroesophageal reflux, n/a: not available

*Including refusal of feeding, history of food impaction, swallowing difficulties, coughing/chocking during meal, sensation of food stuck in the chest

**Reference values for impedance parameters per 24 h in healthy children older than 1 year were used [Mousa et al.(15)].

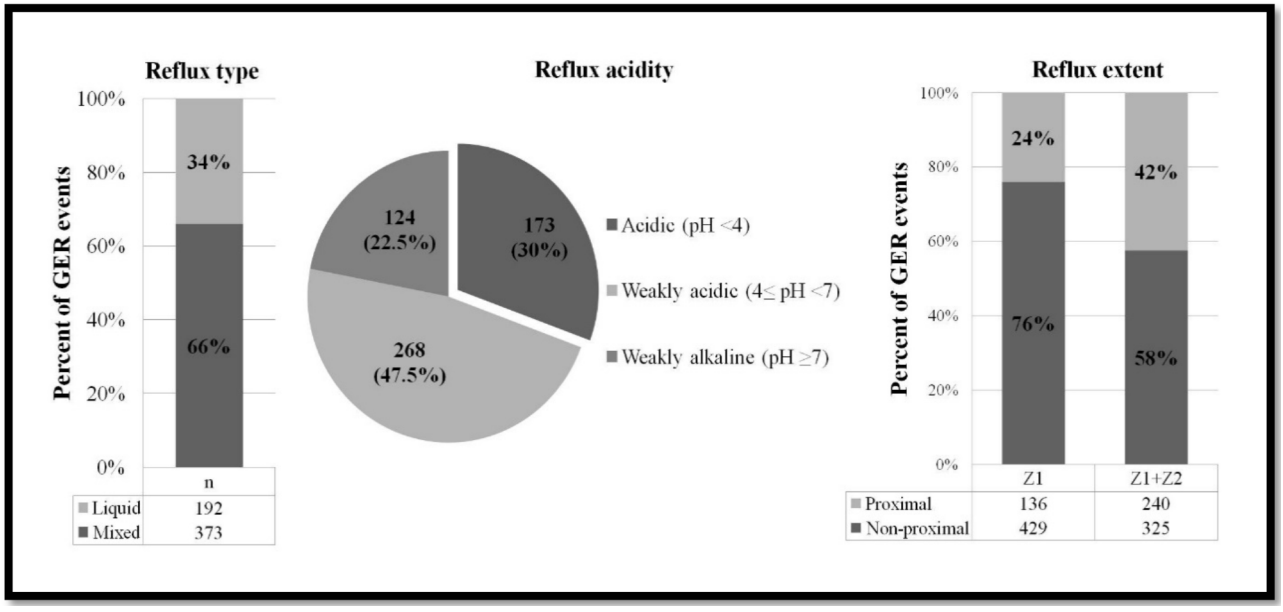

Figure 1. Characteristics of retrograde bolus movements regarding reflux type, acidity, and extent. Z1: Reflux episodes reaching the uppermost impedance channel, Z1+Z2: Reflux episodes reaching at least the second uppermost impedance channel, GER: Gastroesophageal reflux

esophageal dysmotility in both UGT series and VFSS (Table 3). Two of the 5 patients with acidic reflux (patients # 6 and 7) had aspiration with liquids without any sign of esophageal motility problem in radiologic evaluation while other 3 (patients #3, 10 and 12) had severely impaired esophageal motility and decreased peristalsis below the anastomosis. All but one patient with non-acidic reflux (patients # 5, 8, 9, 11 and 13) had clinical dysphagia. The common finding in VFSS of these patients was impaired esophageal motility. Two of these patients (patients # 11 and 13) also had gastric organo-axial malrotation detected in contrast series.

Anti-Reflux and Dietary Management of Patients

Seven patients (54%) were already on acid suppressive therapy with a proton pump inhibitor before MII-pH monitoring (Table 1). Anti-reflux treatment was continued in six as they had pathologic acidic (n=4) or non-acidic (n=2) reflux and discontinued in one with normal MII-pH monitoring. Proton pump inhibitor was started in one patient with pathologic RI and in 3 patients with pathologic non-acidic reflux. Two patients with clinical dysphagia and relatively normal esophageal motility were started domperidon as a prokinetic agent. Patients with oropharyngeal dysphagia (n=5) were included in a swallowing rehabilitation program. Beside rehabilitation, a diet modification including thickening of liquids was done in patients having aspiration with liquids. One patient aspirating both liquids and solid foods in VFSS was started to be fed through a nasogastric tube.

Discussion

Children with corrected EA continue to have significant morbidity related to GERD (16). In this study, we evaluated GER characteristics of 13 children with repaired EA using MII-pH monitoring. We also reviewed the results of contrast studies including VFSS and UGT series to evaluate swallowing and esophageal motility. Majority of RBM were non-acid (70%) and more than half of the patients with normal pH monitoring findings (5 out of 8 patients) had pathologic number of non-acid RBM in impedance analysis. Findings suggestive of esophageal dysmotility were common (approximately 70%) in both swallowing evaluation and UGT series.

GERD is one of the most frequent complications of repaired EA. The results of a long-term follow-up study reported a progressive increase in the incidence of GER during early childhood and concluded that spontaneous resolution is rare in this population (17).

The first study evaluating GER in EA patients with MII-pH monitoring revealed that EA patients with few or no symptoms may still have underlying severe GER and half of the GER events can be detected only by impedance analyses (18). In that study, 532 of 911 (58%) RBM in 24 patients with repaired EA were reported to be weakly acidic (18). Following studies have also reported similar findings (Table 4). Catalano et al. (19) reported that reflux episodes were mainly non-acidic (76.4% of total refluxes) in children with EA. They reported a pathologic bolus exposure index with normal pH RI in all patients younger than 1 year and concluded that the incidence of GER in children younger than 1 year would have been underestimated with conventional pH-meter (19). In a study where impedance results were interpreted in 10 infants and 10 adults with repaired EA, the percent of acidic reflux was only 20.6% in the infant group (20). Pedersen et al. (21) reported a similar median number of acidic and non-acidic reflux episodes in EA patients with a median age of 10.2 years. A higher incidence of non-acidic reflux (1,249 of the 1,457 episodes, 85.7%) was reported in 35 EA patients with a median age of 53 months which was probably related to more patients being on acid suppressive treatment at the time of procedure (22). In a more recent study, observed RBM were mainly non-acidic boluses (>60% of RBM) in 57 children with EA (23). In two other studies, although acidic reflux was observed more than non-acidic reflux in pediatric patients with EA by means of median number of refluxate or mean time of esophageal acid/non-acid exposure, there was still non-negligible amount or time of non-acidic reflux (24,25). In parallel to these literature findings, we also found that 70% of the reflux episodes were non-acidic, 47.5% being weak acidic and 22.5% being weakly alkaline. Anti-acid medication was not a contributing factor for high incidence of non-acidic reflux in our study as the use of acid suppressive treatment was stopped one week before the procedure. These results point a clear benefit of MII-pH monitoring in determining non-acidic reflux that cannot be evaluated with conventional pH-meter. It is of critical importance in EA patients as non-acidic reflux was reported to be associated with symptoms in these patients especially under 1 year of age (8,18,19).

In our study cohort median RI was 3.8% (0.1-35.4). Although it is comparable with the results of similar studies evaluating GER with MII-pH monitoring in repaired EA, median RI was reported in a wide range changing from 0.1 to 8.3% (Table 4) (18-25). Differences in pH-meter results were most likely due to differences in patient characteristics (age of patients, being symptomatic or asymptomatic) and study protocols (performing procedure under acid suppressive treatment). Feeding characteristics of infants younger than 1 year of age (more frequent feeding and milk feeding) and use of anti-acid treatments can be held responsible for the high incidence of non-acidic refluxes through buffering of gastric acid (19,22,26,27). However, our study cohort did not include infants younger than 16 months and the median age was 6.5 years (1.3-13.5). We discontinued acid suppressive treatment temporarily in our patients to eliminate the possible effect of treatment on reflux characteristics. We found a pathological RI in only 38% of the patients confirming the diagnosis of GERD which was much lower than we expected considering the clinical features of our patients and previously reported high incidence of GERD in children with repaired EA. However, 5 of 8 patients with normal pH recording results were found to have pathologic number of non-acidic reflux episodes in our study cohort. These non-acidic reflux events would be missed on sole pH monitoring which means half of the patients with pathologic GER episodes in our study cohort would have gone unrecognized. One important issue is that pediatric reference values of MII-pH monitoring are still an area of further research with only a few studies reporting normative data for pediatric population (15,28,29).

Correlation of persistent troublesome symptoms with GER events is one of the indications of MII-pH monitoring in the evaluation of GERD (8). In EA patients, respiratory complications related to GER are not rare (25). MII-pH monitoring allows symptom correlations between reflux episodes and respiratory symptoms including apnea, nocturnal/chronic coughing, wheezing, desaturation, asthma, and recurrent lower respiratory tract infections (30-33). Two different groups showed that more than half of the coughing episodes in children with repaired EA were associated with RBM (18,19). Respiratory symptoms were more prevalent than gastrointestinal symptoms

in our study cohort with all the patients having at least one respiratory complaint including having recurrent lower respiratory tract infections, asthma/wheezing and chronic coughing. However, only 2 of them (15%) had SI >50% and SAP >95% regarding coughing and wheezing. This finding was thought to be associated with inappropriate recording of symptom diaries as only a small number of symptoms were recorded in contrast to clinical complaints necessitating an impedance testing. Insufficient symptom recording has been reported previously (23,34). Among 12 EA patients with spontaneously reported symptoms before MII-pH monitoring, symptoms were absent during impedance testing in 83% of the patients making a symptom association analysis impossible (23). In another study, only half of the coughing episodes were recorded with a mean time lag of 11 seconds between the cough and the recording in the log (34). Proximal RBM were also reported to be associated with respiratory symptoms in children with persistent respiratory symptoms (30). However, another study from the same group did not find a significant association between cough production and the height of the refluxate (34). Percent of proximal RBM we found in our patients (23% reaching Z1 and 40% reaching Z1 and Z2) were comparable to literature findings. Frohlich et al. (18) reported that 37% of all reflux events ascended to the 2 most proximal channels without any correlation with respiratory symptoms. Catalano et al. (19) reported higher incidence up to 72.9% without any information regarding the relation between "high" refluxes and symptoms.

Esophageal dysmotility is considered as the main pathophysiological factor leading to significant digestive and respiratory morbidity via GER, aspiration, feeding disorders, and dysphagia in patients operated for EA. Studies have reported that dysphagia occurs in 21-84% of patients with EA at all ages after surgical repair (35). Food aversion, food impaction, difficulty in swallowing, odynophagia, choking, cough, pneumonia, alteration in eating habits, vomiting, and malnutrition were suggested as red flags for underlying dysphagia in children with EA (9). Our study cohort was evaluated for dysphagia with VFSS and UGT series as suggested by ESPGHAN/NASPGHAN guideline (9). Abnormal esophageal motility particularly distal to the anastomosis (77%) was the most frequent finding followed by aspiration (38.5%). In a previous study from our center, we evaluated deglutition in 32 EA patients by videofluoroscopy and found that 87.5% of the patients had moderate to severe esophageal phase problems (36). Higher frequencies for oral and pharyngeal phase problems were also reported. Forty seven percent of children with EA had aspiration or penetration during videofluoroscopic evaluation of deglutition (37). Coppens et al. (38) found oral phase abnormalities in 36% and pharyngeal phase abnormalities in 75% of patients. We could not find any specific correlation between radiologic findings and impedance results. Although esophageal dysmotility is present in 100% and 60% of patients with non-acidic and acidic reflux, respectively, the study cohort was too small to make a conclusion regarding the association of dysmotility with reflux acidity. Even patients without clinical dysphagia or with normal MII-pH monitoring had motility problems in VFSS or UGT series. Despite the high frequency of both GER and dysphagia in EA patients, MII-pH monitoring studies in children revealed that dysphagia is not consistently associated with reflux events (18,21,22). Treatment modalities for non-acidic GER and esophageal dysmotility in children are very limited and there are no specific recommendations in recent guidelines on this subject (8,23,35).

Study Limitations

There are some limitations of our study. Firstly, the retrospective nature of the study and small sample size were the main limitations. However, considering the limited number of studies regarding the use of MII-pH monitoring in the evaluation of children with repaired EA, our results contribute to the literature by confirming the high incidence of non-acidic reflux in repaired EA patients with GERD symptoms. Secondly, we only evaluated patients who were symptomatic, so the results regarding the characteristics of reflux episodes might be biased and cannot be generalized to whole EA patients. Thirdly, failure of appropriate symptom recording by the parents/patients made it impossible to make a symptom reflux correlation in our study.

Table 4. Studies using MII-pH in the evaluation of patients with repaired EA

Author	Study population	pH-meter results	Impedance results	Main findings
Frohlich et al. (18)	24 patients Median age 3.5 years (4 months-23 years) off anti-acid treatment	Median RI 2.5% (0%-42.3%) 33% had pathologic RI (>5%)	Median BI 1.7% (0.4 -12.2%). 67% had abnormal BI (according to adult reference data). Non-acidic RBM 58%. High reflux 36.8% (Z1+Z2). Impaired bolus transit in impedance swallowing test	A higher tendency of non-acidic refluxes to be related to symptoms. Half of the reflux episodes only detected by impedance
Catalano et al. (19)	22 patients Median age 15 months (3-40 months) off anti-acid treatment	Median RI 6.1% (1.3% – 13.8%) •<1 y; 2.6% •>1 y; 8.1% 45.5% had pathologic RI (>4.2% for >1 y and >10% for ≤1 y) •All >1 y	Median BEI 7.2% (2.5-13.7%) •≤1 y; 6.1% •>1 y; 7.9% 100% had abnormal BEI (according to adult reference data) Non-acidic RBM 76.4% •≤1 y; 89.2% •>1 y; 70.4% High reflux 72.9% (Z1+Z2) EA vs. non-EA • Higher median BEI in EA • Longer MACT and MBCT in EA Symptomatic vs. asymptomatic • Longer MACT and MBCT in symptomatic	MII-pH monitoring detects more reflux episodes than pH-metry Underestimation of GER in children ≤1 y with pH-metry alone. A pathological bolus transit in children with EA
Di Pace et al. (39)	15 patients Mean age 7.5 years (5-10 years) Anti-acid treatment status n/a Patients with non-acidic reflux were excluded	RI >6% in all An average of 26.9 episodes were detected by pH probe alone	An average of 72.1 RBM were detected by impedance High reflux 95.6% (Z1+Z2) MACT 552.9±121.6 s MBCT 59.9±11.3 s EA vs. control (patients referred for suspicion of GERD) •Longer median BPT, median TBTT and median STT in EA	Significant GER with impaired bolus transit in EA patients compared to controls
Pedersen et al. (21)	59 patients Median age 10.2 years (7.1 – 13.3 years) off anti-acid treatment	Median RI 8.3% (4.8-14.9%) 55.2% had pathologic RI (>7%)	Median number of acidic and non-acidic episodes were similar in EA patients EA vs. control (patients referred for suspicion of GERD) •Higher number of acidic episodes in control •Lower baseline impedance in EA	More than half of the children with EA suffer from GERD and all have impaired peristalsis
van Wijk et al. (20)	10 infants and 10 adults Median age 0.67 years (0.23-3.42 years) in infants and 24.5 years (18.1-31.3 years) in adults off anti-acid treatment	n/a	In overall •Non-acidic RBM 68.3% •High reflux 18.6% (Z1) In infants •Non-acidic RBM 79.4% •High reflux 25.5% (Z1)	TLESR is the main mechanism underlying GER episodes in EA patients Impaired esophageal motility, delayed bolus clearance and delayed gastric emptying are present in majority of the study cohort

Table 4. Continued

Author	Study population	pH-meter results	Impedance results	Main findings
Tong et al. (22)	35 patients Median age 53 months (3-207 months) 30 patients were on anti-acid treatment	Median RI 0.1% (0 - 4.4%)	Non-acidic RBM 85.7% MACT 53 s (0-1386) MBCT 17 s (5-71) EA vs. control (patients referred for suspicion of GERD) •Lower acidic RBM in EA •Higher NARI in EA •Lower DBI in EA •Similar total number of RBM and proximal events •Similar MACT and MBCT 28% of reported symptoms associated with RBM Similar reflux parameters •Long gap vs. no long gap •Fundoplication vs. no fundoplication	Increased detection of non-acidic reflux events with MII-pH monitoring Significant universal dysmotility in EA patients
Tambucci et al. (24)	18 patients Median age 5.5 years (2.2-12 years) off anti-acid treatment	Mean AET 4.5±6 %	EA vs. GERD vs. control (patients with normal endoscopy and MII-pH monitoring results) •Greater percentage of AET and higher number of both long-lasting reflux and AR in GERD group •Median number of Wac and Walk episodes were similar •Lower values in both proximal and distal baseline impedance in EA	Strong relation of proximal and distal basal impedance with esophageal motor abnormalities and excessive acid reflux Possible role of baseline impedance assessment in deciding which patients would benefit from further investigations
Iwanczak et al. (25)	22 patients (19 had complete MII-pH procedure) Mean age 47.3 months (16-79 months) off anti-acid treatment	Mean RI 5.8±3.7	BEI 4.7±2.9 MACT 161.1±117.5 s MBCT 14.8±5.1 s GERD was diagnosed in 52.6% (pathological acid reflux in 9 and a non-acid reflux in one) Higher total number of reflux episodes, reflux index, bolus exposure index, esophageal exposure, esophageal acid exposure and acid clearance time in EA patients with GERD	High frequency of GERD in children with corrected EA
Vergouwe et al. (23)	57 patients Median age 0.6 years (0.2-1.5 years) in infants ≤18 months and 8.2 years (8-9 years) in school age children off anti-acid treatment	Median RI •Infants; 2.6% (0.1-28.5) •Older children; 0.3% (0-14.4) Abnormal pH results in •10% of infants •12.5% of older children	Non-acidic RBM •Infants; 62% •Older children; 64% Median number of RBM •Infants; 61 (0-134) •Older children; 21 (0-54) Four infants had >100 RBM/24 hours None of the older children had >70 RBM/24 hours 39% of all RBM were manually deleted (52% of all non-acidic and 8% of all acidic RBM)	Normal RI but significant number of nonacid RBM in most children with EA off medication Over-detection of reflux events in EA patients by automated analyses

RI: Reflux index, BI: Bolus index, BEI: Bolus exposure index, MACT: Mean acid clearing time, MBCT: Mean bolus clearing time, RBM: Retrograde bolus movements, EA: Esophagus atresia, GER: Gastroesophageal reflux, GERD: Gastroesophageal reflux disease, BPT: Bolus presence time, TBTT: Total bolus transit time, STT: Segmental transit time, Z1: Most proximal impedance channel, Z2: Second most proximal impedance channel, HREM: High resolution esophageal manometry, TLESR: Transient lower esophageal sphincter relaxation, NARI: Non-acid reflux index, DBI: Distal baseline impedance, AET: Acid exposure time, Wac: Weakly acidic, Walk: Weakly alkaline

Conclusions

Majority of the RBM was non-acidic in repaired EA patients with dysphagia or airway symptoms. MII-pH monitoring allowed the detection of pathologic non-acidic reflux events which would have gone undetected with standard pH monitoring. Half of the patients with pathologic reflux indices could only be detected by impedance monitoring. Appropriate and accurate recording of symptoms during impedance testing is of critical importance to evaluate symptom-reflux correlation. Esophageal motility disorder is a major problem among EA patients and can be documented with contrast studies including VFSS and UGT series. MII-pH monitoring should be preferred over conventional pH monitoring in the surveillance of EA patients. Further studies are warranted regarding the use and interpretation of MII-pH monitoring and the treatment of non-acidic GER and esophageal dysmotility in EA patients.

Ethics

Ethics Committee Approval: Non-interventional Clinical Research Ethics Board of the hospital approved the study (GO 21/107, 2021/02-38).

Conflicts of Interest: The authors declare no conflict of interest.

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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Aşırı Prematüre Bebeklerde Mortalite Öngörüsünde Umbilikal Kord Kan Gazı Parametrelerinin Değerlendirilmesi

Evaluation of Umbilical Cord Blood Gas Parameters in the Prediction of Mortality in Extremely Premature Infants

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Öz

Giriş: Doğumda umbilikal kord kan gazı değerleri yenidoğanın asit-baz dengesini gösteren en iyi yöntemdir. Term ve geç preterm bebeklerde kan gazı değerleri yenidoğanın klinik sonuçları hakkında bilgi verirken aşırı prematürelerde bu değerlerin kullanımı açık değildir. Bu çalışmada <29 gebelik haftasında (GH) doğan preterm bebeklerde umbilikal kord kan gazı değerlerinin mortalite ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya GH <29 hafta olan bebekler dahil edilmiştir. Çalışmamız retrospektif olarak gerçekleştirilmiştir. Çalışmaya dahil edilen hastalarda kaybedilen ve yaşayan gruplarda umbilikal kord gazı (pH: potansiyel hidrojen, pCO_2: parsiyel karbondioksit basıncı, HCO_3: bikarbonat, BE: baz fazlası) değerleri, demografik özellikler ve klinik sonuçlar karşılaştırıldı.

Bulgular: Kaybedilen 54 ve yaşayan 292 hasta olmak üzere çalışmaya toplam 346 hasta dahil edildi. Sonuçlarımıza göre <29 GH olan prematürelerde mortalite oranı %15,6 (54/346) olarak tespit edildi. Yaşamını kaybeden grupta yaşayanlara göre GH ve doğum ağırlığı daha düşük bulundu (sırasıyla, p<0,001, p<0,001). Aynı zamanda yaşayanlara göre pH, HCO_3 ve BE değerleri de kaybedilenler grubunda daha düşüktü (sırasıyla; p<0,001, p<0,001, p<0,001). Gruplar arasında pCO_2 değerleri açısından sonuçlar benzer bulundu (p=0,270). Mortalite için eşik pH değeri ≤7,18 [area under curve (AUC): 0,627], eşik HCO_3 değeri ≤19,3 mmol/L (AUC: 0,950) ve eşik BE değeri ≤-8,1 mmol/L (AUC: 0,969) olarak tespit edildi.

Sonuç: GH <29 doğan prematüre bebeklerde umbilikal kord kan gazında mortalite göstergesi için en değerli parametreler HCO_3 ve BE'dir.

Anahtar kelimeler
Prematüre, mortalite, umbilikal kan gazı, pH, asidoz

Abstract

Introduction: Umbilical cord blood gas values at birth are the best method to show the acid-base balance of the newborn. While gas values in term and late preterm infants provide information about the clinical results of the newborn, the use of these values in premature infants is not clear. In this study, it was aimed to evaluate the relationship between umbilical cord blood gas values and mortality in preterm babies born at <29 weeks of gestation.

Materials and Methods: Babies with a gestational age of <29 weeks were included in the study. Our study was carried out retrospectively. Umbilical cord gas (pH: power of hydrogen, pCO_2: partial pressure of carbon dioxide, HCO3: bicarbonate, BE: base excess) values, demographic characteristics and clinical results were compared in the groups with and without mortality in the patients included in the study.

Keywords
Premature, mortality, umbilical blood gas, pH, acidosis

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Results: A total of 346 patients were included in the study, with 54 patients with mortality and 292 patients without mortality. According to our results, the mortality rate was 15.6% (54/346) in preterms with <29 weeks of gestation. Gestational week and birth weight were found to be lower in the group with mortality compared to the group without mortality (p<0.001, p<0.001, respectively). pH, HCO_3 and BE were lower in patients with mortality compared to patients without mortality (p<0.001, p<0.001, p<0.001, respectively). Results were similar between the groups in terms of pCO_2 values (p=0.270). Threshold pH value for mortality ≤7.18 [area under curve (AUC): 0.627], threshold HCO_3 value ≤19.3 mmol/L (AUC: 0.950), and threshold BE value ≤-8.1 mmol/L (AUC: 0.969) was detected.
Conclusion: HCO_3 and BE are the most valuable parameters for mortality in umbilical cord blood gas in premature babies born with a gestational week <29.

Giriş

Umbilikal kord kan gazı analizi doğumdan hemen sonra yenidoğanın asit-baz dengesini değerlendirmek için gerçekleştirilir. Anneden bebeğe giden umbilikal venden alınan oksijenlenmiş kan, annenin asit-baz durumu ve plasental fonksiyonları yansıtır. Oksijeni azalmış umbilikal arterden alınan kan ise fetusun asit-baz ve metabolik durumunu yansıtır. Kan gaz parametrelerindeki değişim doğumdan hemen önceki anne, fetüs ve plasental durumu gösterebilir (1).

Anne ya da fetustaki gaz değişimindeki bozulma metabolik asidoza neden olur. Bu metabolik asidoz ise düşük Apgar skoru, hipoksik iskemik ensefalopati, intrakranial kanama, nekrotizan enterokolit, sepsis, solunum sıkıntısı, nöbet, serebral palsi, nörogelişimsel gelişimde bozulma ve ölümle ilişkilidir (1-4). Kritik yenidoğan bebeklerde yaygın olarak kullanılan kan gazındaki parametreler, hipotermi tedavisi kararını vermede ve hastanın prognozunu belirlemede klinisyene değerli bilgiler vermektedir (5).

Term olarak doğan yenidoğan bebeklerde umbilikal arterdeki düşük pH ve baz fazlası (BE) ve daha yüksek parsiyel arteriyel karbondioksit basıncı (pCO_2) değerlerinin hipoksik iskemik ensefalopati, kardiyopulmoner resusitasyon ve nöbet sıklığında artış ile ilişkili olduğu gösterilmiştir (2,6). Umbilikal ven ya da arter pH değerinin <7,00 olmasının mortalite ile ilişkili olduğu rapor edilmiştir (7). Ayrıca term bebeklerde pH <7,00 ve BE ≤-12 mmol/L olmasının serebral palsi sıklığını artırdığı gösterilmiştir (8). Pretermlerde ise pH değerinin <7,0 olmasının erken başlangıçlı nöbetlerle ilişkili olduğu belirtilmiştir (9). Ancak prematüre bebeklerde umbilikal kord kan gazı değerleri ile klinik sonuçlar arasındaki ilişki halen belirsizdir (1). Çünkü prematürenin gelişmekte olan beyin ve diğer organ sistemlerinde fetal asidozun etkisi term bebeklerden farklı olabilir. Dolayısıyla preterm bebeğin umbilikal kord kan gazı parametrelerini değerlendirirken, term bebekten farklı olabilecek yanlarını bilmek gereklidir. Literatürde bu konuda yeterli veri bulunmamaktadır.

Çalışmamızın primer amacı, preterm bebeklerin umbilikal kord kan gazı değerlerinin mortalite üzerine etkisinin değerlendirilmesidir. Çalışmamızın sekonder amacı ise yaşayan ve kaybedilen hastalarda prematüre morbiditelerinin sıklığının araştırılmasıdır.

Gereç ve Yöntem

Araştırmanın Planı

Araştırmamız 1 Haziran 2021 ile 30 Kasım 2021 arasında yenidoğan yoğun bakım ünitemize yatan prematüre bebekler üzerinde gerçekleştirilmiştir. Çalışmaya <29 gebelik haftasında (GH) doğan prematüre bebekler dahil edilmiştir. Gebelik yaşı ≥29 haftanın üzerinde olan veya majör konjenital anomalisi olan yenidoğanlar çalışmaya dahil edilmemiştir. Hastalara ait veriler hasta dosyalarından retrospektif olarak elde edilmiştir. Çalışmaya başlamadan önce yerel etik kuruldan etik onam alınmıştır.

Demografik ve Klinik Özellikler

Çalışmaya alınan hastaların anne yaşları, annede preeklampsi ya da gestasyonel diyabet varlığı, antenatal steroid uygulanması, GH, doğum ağırlığı (DA), doğum şekli (sezaryen/normal vajinal yol), Apgar skorları (1. ve 5. dakika), cinsiyeti, mekanik ventilasyon (MV) süresi, erken neonatal sepsis (ENS), geç neonatal sepsis (GNS), respiratuvar distres sendromu (RDS), intraventiküler kanama (İVK), hemodinamik anlamlı patent duktus arteriozus (PDA), prematüre retinopatisi (ROP), orta/ciddi bronkopulmoner displazi (BPD), nekrotizan enterokolit (NEK) ve mortalite durumu dosya verilerinden alınarak kayıt edildi. Umbilikal arterden alınan kan gazında pH, pCO_2, HCO_3 ve BE değerleri kayıt edildi.

Umbilikal Kan Gazı Analizi

Ünitemiz protokolü gereği prematüre bebeklerden doğumdan hemen sonra umbilikal arter kan gazı örnekleri alınmaktadır. Kan örnekleri heparinli enjektöre alınarak 15 dakika içinde çalışılmıştır. Kan gazı örnekleri kan gazı cihazı (Siemens RAPIDLabVR 1200 Systems, Almanya) ile analiz edildi. Analiz sırasında pH değerleri sıcaklığa göre düzeltildi ve ayrıca pCO_2, HCO_3 ve BE değerleri elde edildi.

Prematüre Morbiditelerinin Tanımı

Yenidoğan bebek eğer postnatal ilk 72 saat içinde sepsis tanısı alırsa ENS ve 72 saatten sonra sepsis tanısı alırsa GNS olarak tanımlandı (10). Doğum sonrası kranial ultrasonografik değerlendirmelerde ileri evre (evre ≥3) İVK varsa kayıt edildi (11). Ekokardiyografik ve klinik değerlendirme ile hemodinamik anlamlı PDA tespit edilip tedavi edilenler kayıt edildi (12). Uzman göz doktoru tarafından gerçekleştirilen retinal muayene sonrası ROP tespit edilip lazer tedavisi olanlar kayıt edildi (13). Prematüre bebek düzeltilmiş yaşı 36. haftaya geldiğinde ya da taburculuk esnasında oksijen desteği <%30 ise orta BPD, oksijen gereksinimi ≥%30 ise ya da pozitif basınçlı ventilasyon desteği alıyorsa ağır BPD olarak tanımlandı ve orta/ağır BPD olanlar kayıt edildi (14). Eğer kanıtlanmış ya da ciddi (evre >2) NEK bulgusu varsa kaydedildi (15). Prematüre bebeğin solunum sıkıntısı olması ve solunum sıkıntısı tedavisi için endotrakeal surfaktan verilmişse RDS olarak tanımlandı (16). Tüm demografik ve klinik özellikler ile kan gazı sonuçlarına ait veriler dosya kayıtlarından geriye dönük olarak elde edilmiştir.

Elde edilen veriler ile mortalite saptanan ve yaşayan gruplar arasında demografik ve klinik özelliklere ek olarak umbilikal kord kan gazı parametreleri karşılaştırıldı. Ayrıca mortalite tahmininde istatistiksel olarak önemli parametreler için eşik değer, eğri altında kalan alan (AUC), duyarlılık ve özgüllükler analiz edildi.

İstatistiksel Analiz

Hastaların verileri SPSS 20 (Statistical Package for Social Sciences) (IBM, Armonk,N.Y.,USA) istatistik programına girildikten sonra analiz edildi. Değişkenlerin normal dağılıma uygunluğu açısından değerlendirilmesi için görsel (olasılık grafikleri ve histogram) ve analitik yöntemler (Kolmogorov-Smirnov/Shapiro-Wilk testi) kullanıldı. Kategorik değişkenlerin değerlendirmesi için Fisher's Exact test ya da Pearson's chi-square test uygulandı. Sürekli değişkenler için bir t-testi ya da Mann-Whitney U testi uygulandı. Normal dağılım gösteren devamlı değişkenler ortalamaz ± standart sapma, normal dağılım göstermeyen değişkenler ortanca (minimum-maksimum) ve kategorik değişkenler ise sıklık olarak sunuldu. Olasılık oranı (OO) ve %95 güven aralığı (GA) hesaplamak için çok değişkenli lojistik regresyon kullanıldı. Doğum ağırlığı, GH olası karıştırıcı faktörler olarak kabul edildi ve lojistik regresyonla düzeltildi. Prematüre bebeklerde mortaliteyi saptarken parametrelerin duyarlılığını ve özgüllüğünü göstermek için receiver operating characteristic (ROC) analizi yapıldı. ROC analizi sonrası AUC değeri, duyarlılık, özgüllük ve mortalite için eşik değerler elde edildi. İstatistiksel olarak elde edilen p değeri <0,05 ise anlamlı olarak değerlendirildi.

Bulgular

Dahil edilme kriterlerine göre mortalite saptanan 54 ve yaşayan 292 olmak üzere toplam 346 prematüre bebek çalışmaya alındı. Sonuçlarımıza göre gebelik yaşı <29 olanlarda mortalite oranı %15,6 (54/346) olarak tespit edildi. Kaybedilen hastaların ortanca ölüm günü 4 gün (1-62 gün, minimum-maksimum) olarak tespit edildi. Ölen 54 hastanın 11'inin (%20,3) ilk 24 saatte, 33'ünün (%61,1) ilk 7 günde, 50'sinin ise (%92,5) ilk 30 günde öldüğü bulundu (Şekil 1). Ölen grupta GH, DA, 1. ve 5. dakika Apgar skoru, yaşayan gruba göre istatistiksel olarak anlamlı düşük bulundu (sırasıyla; p<0,001, p<0,001, p<0,001, p<0,001) (Tablo 1).

Ölen grupta MV süresi, ENS, RDS, İVK ve PDA sıklığı yaşayan gruba göre anlamlı olarak yüksek bulundu (sırasıyla, p=0,035, p<0,001, p=0,001, p=0,021, p=0,010) (Tablo 2).

Diğer demografik ve klinik özellikler gruplar arasında benzer olarak bulundu (p>0,05) (Tablo 1,2). Kan gazı sonuçları açısından ölen hastalarda yaşayanlara göre pH, HCO_3 ve BE değerleri de daha düşüktü (sırasıyla, p<0,001, p<0,001, p<0,001). Gruplar arasında pCO_2 değerleri açısından anlamlı fark tespit edilmedi (p=0,270) (Tablo 3, Şekil 2).

Regresyon analizinden sonra pH [OO: 2,1 (%95 GA 1,4-3,1), p=0,013], HCO_3 [OO:9,0 (%95 GA 2,5-30,2), p=0,001] ve BE [OO: -0,25 (%95 GA-0,47-0,04), p=0,001] düzeyleri mortalite ile ilişkili bulundu.

Tablo 1. Ölenler ve yaşayanlara göre demografik özellikler			
Değişkenler	Ölenler n=54	Yaşayanlar n=292	p
Anne yaşı (yıl),[a]	29,7±7,1	28,3±6,5	0,136
Annede preeklampsi,[b]	12 (22,2)	73 (25)	0,658
Annede gestasyonel diyabet,[b]	1 (1,8)	10 (3,4)	0,464
Antenatal steroid,[b]	30 (55,5)	205 (70,2)	0,020
Gebelik haftası (hafta),[a]	27,5±1,07	28,2±1,2	<0,001*
Doğum ağırlığı (g),[a]	918±214	1.073±208	<0,001*
Sezaryen,[b]	43 (79,6)	250 (85,6)	0,263
Apgar skoru, 1. dakika,[c]	4 (1-7)	5 (1-7)	<0,001*
Apgar skoru, 5. dakika[c]	6 (3-9)	8 (3-9)	<0,001*
Erkek cinsiyet,[b]	31 (57,4)	147 (50,3)	0,097

[a]ortalama ± standart sapma, [b]n (%), [c]ortanca (minimum-maksimum), *p<0,05 ise istatistiksel olarak anlamlı kabul edildi
BPD: Bronkopulmoner displazi, ENS: Erken neonatal sepsis, GNS: Geç neonatal sepsis, İVK: İntraventriküler kanama, MV: Mekanik ventilasyon, NEK: Nekrotizan eterokolit, PDA: Patent duktus arteriozus, RDS: Respiratuvar distres sendromu, ROP: Prematüre retinopatisi

Tablo 2. Ölenler ve yaşayanlara göre klinik sonuçlar			
Değişkenler	Ölenler n=54	Yaşayanlar n=292	p
MV süresi, gün[a]	5,6±3,6	3,9±2,6	0,035*
ENS[b]	8 (14,8)	4 (1,4)	<0,001
GNS[b]	13 (24)	68 (23,2)	0,810
RDS[b]	46 (85,1)	180 (61,6)	0,001*
İVK (evre ≥3)[b]	11 (20,3)	24 (8,2)	0,021*
PDA[b]	33 (61,1)	122 (41,7)	0,010*
ROP[b]	3 (5,5)	34 (11,6)	0,087
BPD (orta/ciddi)[b]	6 (11,1)	50 (17,1)	0,103
NEK, (evre ≥2)[b]	3 (5,5)	7 (2,4)	0,194

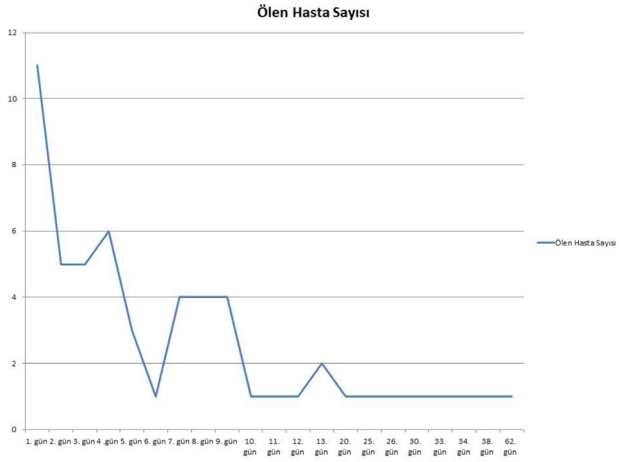
[a]ortalama ± standart sapma, [b]n (%), *p<0,05 ise istatistiksel olarak anlamlı kabul edildi. BPD: Bronkopulmoner displazi, ENS: Erken neonatal sepsis, GNS: Geç neonatal sepsis, İVK: İntraventriküler kanama, MV: Mekanik ventilasyon, NEK: Nekrotizan eterokolit, PDA: Patent duktus arteriozus, RDS: Respiratuvar distres sendromu, ROP: Prematüre retinopatisi

Prematüre bebeklerin mortalitesinin öngörülmesinde pH, HCO_3 ve BE için ROC analizi yapıldı. GH <29 hafta olan bebeklerde mortalite için eşik pH değeri ≤7,18 (AUC: 0,627), eşik HCO_3 değeri ≤19,3 mmol/L (AUC:0,950 ve eşik BE değeri ≤-8,1 mmol/L (AUC: 0,969) olarak tespit edildi. ROC analizi sonucu elde edilen AUC, eşik, duyarlılık, özgüllük değerleri ve grafikleri Şekil 3'te sunulmuştur.

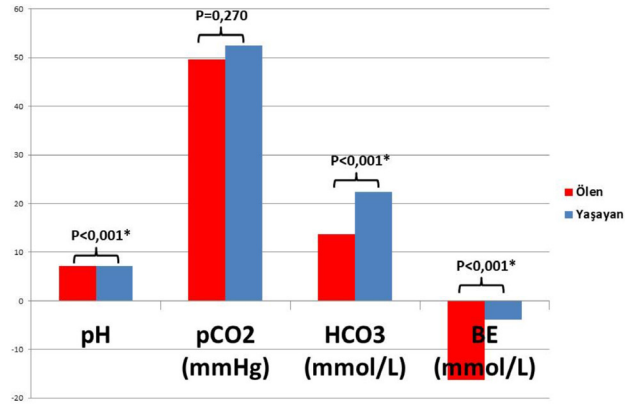
Tartışma

Çalışmamızın birincil sonucu olarak kaybedilen hastalarda yaşayanlara göre pH, HCO_3 ve BE değerleri anlamlı şekilde düşük bulundu. Umbilikal arter kan gazında pCO_2 değeri mortalite ile ilişkili bulunmadı. Bu çalışmada mortaliteyi ön görmede en değerli parametre BE olup, en yüksek AUC değeri (0,969), duyarlılık ve özgüllüğe sahip olduğu görüldü. Kan gazında mortalite tahmini için ikinci en değerli parametre HCO_3 (AUC: 0,950) ve son olarak pH (AUC: 0,627) olarak bulundu. Regresyon analizi sonrası yine pH, HCO_3 ve BE'nin mortalite ile ilişkili olduğu saptandı. İkincil sonuçlarımızda ölen grupta ENS, RDS, İVK ve PDA sıklığı daha yüksek, GH ve DA daha düşük bulundu.

Prematüre bebeklerde morbiditeleri ve mortaliteyi belirleyen en önemli faktör GH ve DA'dır. GH ve DA azaldıkça morbiditeler ve mortalite artmaktadır. Dolayısıyla prematüre mortalitesini azaltmanın en iyi yolu fetüsün iyilik halini yakından takip ederek gebeliği terme ya da terme yakın GH'lerine ulaştırmaktır. Ancak bu durum sağlanamaz ise ve bebek prematüre doğarsa mortalite ve morbiditeler de artacaktır (17,18). Çalışmamızın sonuçlarında olduğu gibi ölen grupta özellikle ilk bir hafta gibi erken dönemde görülen MV süresi, ENS, RDS, İVK ve PDA sıklığı artmaktadır. Daha sonraki haftalarda görülen GNS, ROP, BPD ve NEK gibi prematüre morbiditeleri, ölen ve yaşayan gruplarda benzer bulunmuştur. Ayrıca ölen grupta GH ile DA daha düşük bulunmuştur. Ölen grupta daha düşük GH ve DA'na bağlı olarak GNS, ROP, BPD ve NEK gibi orta vadede görülen morbiditelerin daha yüksek olması beklenir. Ancak ölen gruptaki



Şekil 1. Günlere göre ölen hastaların sayıları



Şekil 2. Ölen ve yaşayanlarda kan gazı parametreleri

*p<0,05 istatisksel olarak anlamlı kabul edildi.
pCO2: Parsiyel karbondioksit basıncı, HCO3: Bikarbonat, BE: Baz fazlası

hastaların kord kan gazındaki ağır asidozla ilişkili olarak ilk haftada mortalite hem de morbiditeleri de artmıştır. Dolayısıyla ölen gruptaki hastaların ilk hafta içinde çoğunun kaybedilmesi geç dönemde tanı konulan GNS, ROP, BPD ve NEK gibi morbiditeleri yaşamadan kaybedilmesi anlamına gelmektedir. Ayrıca sonuçlarımıza göre asidozu daha derin olan prematürlerin özellikle ilk hafta morbiditeleri açısından daha yüksek riske sahip oldukları söylenebilir. Ek olarak, sonuçlarımıza göre gebelik yaşı <29 hafta olan doğan prematürelerin mortalite oranı %15,6 olup bu oran dünya genelindeki morbidite oranlarına benzerdir. Çünkü ülkemizde yenidoğan alanında prematüre takibi için hazırlanan kılavuzlar, uluslararası kılavuzlar takip edilerek ortak fikir birliği ve bilimsel kanıt düzeyine göre düzenlenmekte ve bu da prematüre bebeklerin klinik sonuçlarını gelişmiş ülkeler düzeyine çıkarmaktadır (19).

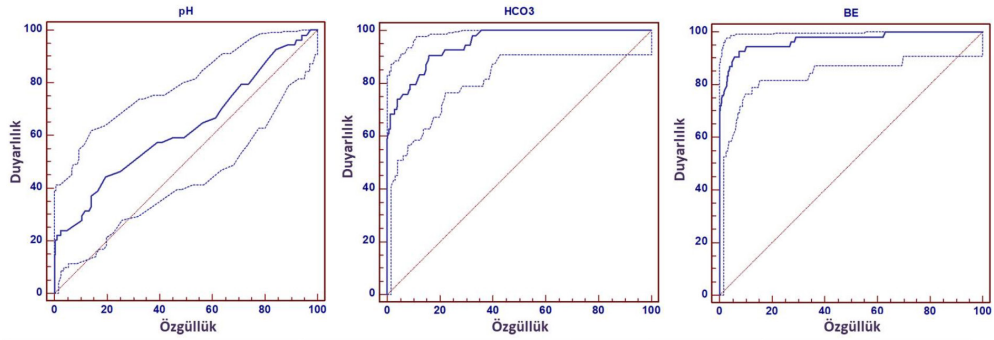
Doğumdan hemen sonra yenidoğan sonuçlarını tahmin etmek için çeşitli klinik ve laboratuvar değişkenlerine ilave olarak puanlama sistemleri de kullanılmaktadır. Apgar skorları, erken yenidoğan durumunu değerlendirmek için rutin olarak kullanılır. Ancak gelişimsel immatürite nedeniyle prematüre yenidoğanlarda kullanımı sınırlıdır. Sonuçlarımız daha düşük DA ve GH'ye sahip olan ölen grubunda Apgar skorlarının daha düşük olduğunu göstermektedir. Bu düşüklüğün kaybedilen hastaların daha kötü ya da daha immatür doğmasına mı bağlı olduğu açık değildir. Dolayısıyla prematüre bebekler için klinik risk indeksi (CRIB: Clinical risk index for babies) skoru ve neonatal akut fizyoloji skoru gibi skorlar doğumdan sonraki ilk 12 saat içinde hastalığın ciddiyetini değerlendirmek için kullanılabilir ve prognoz tahmininde yardımcı olabilir (1,20). Ancak verilerimizde bu iki skor bilgisi olmadığı için değerlendirilememiştir.

Çalışmamızın birincil sonucuna göre gebelik yaşı <29 hafta olan prematürelerin umbilikal kan gazında mortalite belirleyicisi olarak en önemli parametre BE, ardından sırasıyla HCO_3 ve pH olarak bulundu. Literatürde özellikle çalışmamızdaki gibi çok küçük prematüre bebeklerin kord kanında pH, pCO_2,

Tablo 3. Ölüm ve kan gazı parametreleri ilişkisi

Kan gazı parametreleri	Ölenler n=54	Yaşayanlar n=292	p
pH[a]	7,08±0,08	7,13±0,23	<0,001*
pCO_2, mmHg[a]	49,64±17,54	52,44±13,36	0,270
HCO_3, mmol/L[a]	13,66±4,45	22,45±3,22	<0,001*
BE, mmol/L[a]	-16,34±6,25	-3,85±3,19	<0,001*

[a]ortalama ± standart sapma
*p<0,05 ise istatistiksel olarak anlamlı kabul edildi.
pCO_2: Parsiyel karbondioksit basıncı, HCO_3: Bikarbonat, BE: Baz fazlası



Değişkenler	AUC	% 95 Güven aralığı	P değeri	Eşik değer	Duyarlılık (%)	Özgüllük (%)
pH	0,627	0,574-0,678	0,001	≤7,18	44	80
HCO3, mmol/L	0,950	0,921-0,970	<0,001	≤19,3	91	84
BE, mmol/L	0,969	0,945-0,985	<0,001	≥-8,1	91	92

AUC: eğri altında kalan alan (area under the curve), BE: baz fazlası, HCO3: bikarbonat, ROC: alıcı işletim karakteristiği (receiver operating characteristic)

Şekil 3. Prematürelerde mortalite tahmininde pH, HCO_3 ve BE için ROC eğrileri

HCO_3 ve BE parametrelerini beraber değerlendiren, mortalite ile ilişkisi ve tahminindeki değerini araştıran çalışma olmaması çalışmamızın gücünü artırmaktadır. Çalışmalarda sıklıkla yalnızca pH ya da pH ile beraber BE incelenmiş ve bu değerlerin prematüre morbiditesi ve mortalitesi ile ilişkisi değerlendirilmiştir (1,7,20,21).

Malin ve ark. (7), kord kan gazında pH <7,0 olmasını mortalite ile ilişkilendirmiştir (7). Çok geniş olgu serisi ile Yeh ve ark.'ın (22) yaptığı çalışmada da pH değerinin 7,0'ın altında olması, olumsuz nörolojik sonuçlar için eşik değer olarak belirlenmiştir. Randolph ve ark.'ın (23) ≤1.000 g doğan prematüre bebeklerde yaptıkları bir çalışmada, kord kan gazında p<7,0 ve BE <-12 olmasının mortalite ve 18-22 aydaki kötü nörogelişim ile ilişkili olduğu rapor edilmiştir. Ancak bu çalışmada umbilikal kord kan gazında mortalite için eşik değerler verilmemiştir. Umbilikal kordda hem pH hem de BE tüm GH'lerinda değerlendiren geniş serili retrospektif bir çalışmada, pH <7,00 ve BE <-16 olmasının mortalite ile ilişkili olduğu belirtilmiştir. Ancak bu eşik değerlerin serebral palsi ile ilişkisi gösterilememiştir (24). Zaigham ve ark. (25) ise, 22 ile 26 haftalar bebeklerde kord kan gazında düşük pH değerinin ne mortalite ne de 6,5 yaşında bozulmuş nörogelişimsel sonuçlarla ilişkisini gösterememiştir. Kord kan gazında sadece pH değeri değerlendirilerek daha ileriki çocukluk yaş grubu için prognostik faktörler belirlenememektedir. Çünkü hipoksinin ne kadar sürdüğü, asidozun sadece solunumsal mı yoksa metabolik mi olduğu çok önemlidir. Dolayısıyla tek başına pH değerini yorumlamak yerine tüm kan gazı parametrelerini beraber değerlendirmek mortalite ve uzun dönem sonuçları belirlemek için gereklidir (21).

Dört kan gazı parametresini term bebeklerde inceleyen çalışmanın sonucunda (5), sonuçlarımızda olduğu gibi mortalite grubunda daha düşük pH, HCO_3 ve BE değerleri elde edilmiştir. Bu çalışmada kaybedilen hastalardaki pH ve HCO_3 değerleri bizim kaybedilen hastalardan daha yüksekken, pCO_2 ve BE değerlerinin daha düşük olması dikkati çekmektedir. Çalışmamızla yukarıdaki çalışmanın sonuçları arasındaki bu farkın temel nedeni; bizim hastalarımızın çok prematüre bebeklerden, diğer çalışmadaki hastaların ise term bebeklerden oluşmasından kaynaklanıyor olabilir (5). Dolayısıyla kord kan gazı sonuçlarının mortalite ve diğer klinik sonuçlara etkisini değerlendirirken GH dikkate alınarak yorumlanması gerektiği sonucuna varılabilir. Ayrıca yukarıdaki çalışmada term bebeklerde mortalite tahmini için eşik kord kan gazı değerleri hesaplanmamıştır. Sonuçlarımızda ise <29 GH'de doğan prematürelerde mortalite öngörücüsü olarak eşik pH değerinin ≤7,18, HCO_3 ≤19,3 mmol/L ve BE ≤-8,1 mmol/L olduğu tespit edildi. Sonuçlarımız kendi merkezimizde yatan gebelik yaşı <29 hafta olan bebekler için geçerlidir. Ayrıca kan gazı parametreleri GH'den etkilenmesine ek olarak, klinik sonuçlar ile kan gazı parametreleri arasında güçlü bir ilişki olduğu hem sonuçlarımıza hem de literatür çalışmalarına göre söylenebilir. Dolayısıyla, çok merkezli ve

tüm GH'lerini içeren kord kan gazı değerlendirme çalışmaları ile mortalite tahmini için her GH'ye ait eşik kan gazı parametreleri belirlenmelidir (1,25,26).

Kan gazı parametrelerinin klinik sonuçlar ile ilişkisinde parametrelerin gücü konusunda veriler yeterli değildir. Kord kan gazı ve klinik sonuçlarının ilişkisini değerlendiren Victory ve ark.'ı (20), İVK için eşik pH değerini 7,25 (AUC: 0,800), RDS için eşik pH değerini 7,09 (AUC: 0,570) ve MV gereksinimi için eşik pH değerini 7,19 (AUC: 0,600) olarak bulmuştur. Ancak mortalite için eşik kan gazı değeri değerlendirilmemiştir. Sonuçlarımızda ise mortaliteyi değerlendirmek için en güçlü kan gazı parametresinin BE olduğu bulunmuştur. Hastaların klinik sonuçlarını öngörmede BE'nin tek başına kullanılması yerine, pH ile beraber kullanılması klinik anlamlılık değerini artırmaktadır (24). Ancak kan gazı parametreleri bir bütün olduğundan tüm parametreleri beraber değerlendirmek klinik sonuçlar hakkında fikir sahibi olmak için daha anlamlı olabilir (5).

Çalışmamız amacı ve yöntemi açısından ülkemizde yapılan ilk çalışmadır. Literatürde de <29 GH prematüre bebeklerin dört kan gazı parametresinin mortalite üzerine etkisini inceleyen yeterince çalışma bulunmamaktadır. Bu yönüyle de çalışmamızın sonuçları literatüre önemli katkı sağlayabilir. Buna rağmen çalışmamızın bazı kısıtlılıkları vardır. İlki çalışmamızın retrospektif olması ve hasta sayısının az olmasıdır. İkincisi ise tek merkez verisinden elde edilen sonuçlar olduğu için sonuçlarımız genelleştirilememektedir. Üçüncüsü kan gazı parametresi olarak laktat düzeyi değerlendirilememiştir. Dördüncüsü, çalışmamız kısa dönem sonuçlara odaklandığı için uzun dönem nörogelişimsel sonuçlar değerlendirilememiştir.

Sonuç olarak çalışmamızda çok küçük prematüre bebeklerin mortalite tahmini için kan gazı parametrelerinden en önemlisinin BE ve sonrasında sırasıyla HCO_3 ve pH olduğu bulundu. Mortalite için bulduğumuz eşik değerler sadece <29 GH doğan kendi hasta popülasyonumuz için geçerlidir. Literatürde çalışma hastalarının GH'lerinin farklı olmasından dolayı mortalite ve kan gazı parametreleri ilişkine dair sonuçlar birbiriyle çelişmektedir. Dolayısıyla ileride planlanacak prospektif çalışmalarda her GH'deki bebekler ayrı ayrı kan gazı parametreleri ile mortalite ve morbidite ilişkisine göre değerlendirilmelidir.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Swallowing Dysfunction in Children with Recurrent Respiratory Symptoms

Tekrarlayan Solunum Sistemi Semptomları Olan Çocuklarda Yutma Disfonksiyonun Değerlendirilmesi

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Abstract

Introduction: This study aims to determine the role of swallowing disorders in the etiology of recurrent lower respiratory tract infections (LTRIs) and persistent respiratory symptoms in children.

Materials and Methods: The records of 32 patients aged 0-18 years who applied to the outpatient clinic of the pediatric pulmonology department between November 2016-June 2019 with LTRIs or persistent respiratory symptoms and diagnosed as swallowing dysfunction were evaluated retrospectively. The swallowing function of the patients were imaged and recorded by videofluoroscopic swallowing study (VFSS), and parents were surveyed for with pediatric eating assessment tool-10.

Results: Median age of the patients was 14 (7.25-32.25) months, 81.3% were male. It was noted that 50% of the patient population had metabolic and/or neurologic disease, and half of the remaining 16 patients had risk factors for swallowing dysfunction, while the other half did not. Aspiration of thin liquids was found in 90.6% of patients, of which 68.8% were silent, 56.3% had oral phase dysfunction and 40.6% had a delayed swallowing reflex. Oral phase dysfunction and delayed swallowing reflex for thin and thick liquids were more frequent in 16 (50%) patients with metabolic and/or neurological disease on VFSS compared to those without metabolic and/or neurological disease ($p<0.05$). There was reduction in the annual number of LTRIs reported following implementation of swallowing therapy ($p=0.01$).

Conclusion: Swallowing dysfunction is an important diagnosis to consider when approaching patients with history of recurrent respiratory symptoms, regardless of their comorbidities and risk factors. Early diagnosis and treatment is crucial to avoid subsequent complications associated with it.

Keywords
Swallowing dysfunction, pediatric, dysphagia, respiratory symptoms

Anahtar kelimeler
Yutma disfonksiyonu, pediatrik, disfaj, solunum sistemi semptomları

Öz

Giriş: Bu çalışmanın amacı çocuklardaki tekrarlayan alt solunum yolu enfeksiyonu (ASYE) ve persistan solunum sistemi semptomlarının etiyolojisinde yutma disfonksiyonun rolünü belirlemektir.

Gereç ve Yöntem: Kasım 2016-Haziran 2019 tarihleri arasında çocuk göğüs hastalıkları polikliniğine ASYE veya persistan solunum sistemi semptomlar ile başvuran ve yutma disfonksiyonu tanısı alan 0-18 yaş arası 32 hastanın kayıtları geriye dönük olarak kaydedildi. Hastaların yutma fonksiyonu videofloroskopik yutma çalışması (VFSS) ve pediyatrik yeme değerlendirme aracı-10 ile değerlendirildi.

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Bulgular: Hastaların medyan yaşı 14 (7.25-32.25) aydı, %81.3'ü erkekti. Hastaların %50'sinin metabolik ve/veya nörolojik hastalığı vardı, %25'inin yutma disfonksiyonu için risk faktörlerine sahipti ve %25'inin herhangi bir risk faktörü veya altta yatan bir hastalığı yoktu. Hastaların %90.6'sında ince sıvıların aspirasyonu bulundu, bunların %68.8'i sessiz, %56.3'ünde oral faz disfonksiyonu ve %40.6'sında gecikmiş yutma refleksi vardı. VFSS'de metabolik ve/veya nörolojik hastalığı olan 16 (%50) hastada metabolik ve/veya nörolojik hastalığı olmayanlara kıyasla ince ve puding kıvamlı sıvılar için oral faz disfonksiyonu ve gecikmiş yutma refleksi daha sıktı ($p<0.05$). Yutma terapisi alan takipli hastalarda yıllık ASYE sayısında azalma saptandı ($p=0.01$).
Sonuç: Yutma disfonksiyonu, tekrarlayan solunum sistemi semptomları öyküsü olan hastaları değerlendirirken eşlik eden hastalıkları ve risk faktörleri ne olursa olsun etiyolojide düşünülmesi gereken önemli bir tanıdır. Erken tanı ve tedavi, yutma disfonksiyonu ile ilişkili komplikasyonları önlemek için çok önemlidir.

Introduction

The mechanics of respiration and swallowing have common neuromuscular structures and work in coordination with each other. This coordination is vital for airway protection and prevention of aspiration. Swallowing is a complex process and is divided into three consecutive phases: oral, pharyngeal and esophageal. It is influenced by multiple neurophysiological, anatomic, environmental and social factors. If any component is affected, it can lead to dysphagia, which is defined as abnormal swallowing due to incoordination, obstruction or weakness affecting swallowing biomechanics and can occur at any stage of swallowing. There are multiple causes of dysphagia including prematurity, gastroesophageal reflux, congenital malformations (cleft lip/palate, Moebius syndrome, Down syndrome, etc.), neurologic and metabolic disease (1). It can also be present in children without underlying risk factors (2,3).

Approximately 1% of children in the general population experience swallowing difficulties (2). This percentage is higher in patients with known comorbidities, such as cerebral palsy, traumatic brain injury, and airway malformations (4).

Children with dysphagia may not manifest with symptoms and may be clinically silent. Others present with vomiting, coughing, wheezing, recurrent respiratory tract infections, and/or choking (1,4,5). Aspiration is defined as food or liquid entering the airway below the level of the vocal cords (1). Silent aspiration is defined as the absence of coughing, despite aspiration before, during, or after swallowing (1). Although coughing is a mechanism that protects the airway against penetration and/or aspiration, most infants do not cough following aspiration (6). Therefore, recurrent pulmonary infections may be indicative of ongoing aspiration.

This study aims to determine the role of swallowing disorders in the etiology of recurrent lower respiratory tract infections (LRTIs) and persistent respiratory symptoms in children referred to the pediatric pulmonology department and whether there is a decrease in the number of LRTIs after treatment.

Materials and Methods

In the study, patients aged 0-18 years with recurrent LRTIs or persistent respiratory symptoms who were admitted to the outpatient clinic of the pediatric pulmonology department, between November 2016 and June 2019 were evaluated retrospectively through electronic medical reports. Patients with known swallowing dysfunction at admission were excluded from the study. Thirty-two patients were included in the study. The demographic characteristics of the patients, their symptoms and signs, whether they had any complaints while feeding, whether they were exposed to cigarette smoke, chest X-ray findings, the number of LRTIs before and after swallowing therapy, and whether they had known persistent diseases were noted (Table 1).

Patients who present to the pediatric pulmonology department with LRTIs or persistent respiratory symptoms and those with suspected swallowing dysfunction based on history, physical examination, and chest X-ray are routinely referred to the swallowing disorders unit. In this center, swallowing functions of the patients are imaged and recorded by videofluoroscopic swallowing study (VFSS). VFSS is a method that evaluates the oral, pharyngeal, and oesophageal phases of swallowing with liquid and viscous barium. Loss or delay in oropharyngeal reflexes, laryngeal penetration, reflux, residuals, and aspiration can be detected by VFSS. As described earlier, aspiration occurs when food or liquid enters the airway below the level of the vocal cords. On the other

hand, penetration is defined as the entry of food or liquid into the larynx without passing the vocal cords (1). The penetration aspiration scale (PAS) is an 8-point scale determined by the depth of the material passing through the airway and whether the material entering the airway can be expelled during videofluoroscopy (5). During their visits, parents are surveyed using the pediatric eating assessment tool-10 (PEAT-10). This PEAT-10 is effective in predicting the aspiration risks of patients and in monitoring the severity of initial symptoms and treatment effectiveness. The family is asked to score between 0 and 4 for 10 questions. A PEAT-10 score higher than 3 is predictive for airway aspiration (7).

The Gazi University Non-Interventional Clinical Research Ethics Committee approved the study (protocol number: 916100558, date: 04.01.02).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 18 was used for statistical analysis. The normal distribution of variables was tested with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean (standard deviation); non-normal distribution variables were reported as median (interquartile range). Categorical variables were shown as numbers and percentages. The Mann-Whitney U test and Student's test were used, respectively, to compare two groups of variables not normally distributed and normally distributed. The Pearson chi-square or Fisher's Exact test were used to evaluate categorical data. Correlations were analyzed using Spearman's test and Pearson's correlation analysis. A value of $p<0.05$ was considered as statistically significant.

Results

In the 3 years of the study period, a total of 2,666 patients were admitted to the outpatient clinic of the pediatric pulmonology department due to LRTIs or persistent respiratory symptoms. Seven patients had known swallowing dysfunction, were already followed up at the swallowing disorders unit, and were excluded from the study. Swallowing studies were performed in 73 patients due to complaints during swallowing or LRTI/persistent respiratory symptoms of unknown cause. Swallowing dysfunction was found in 32 of 73 patients (43.8%).

The median age of the 32 patients with swallowing dysfunction was 14 (7.25-32.25) months. The demographic and clinical characteristics of the patients are shown in Table 1. Of the patients, 16 (50%) had metabolic and/or neurologic disease and eight (25%) had risk factors for swallowing dysfunction (prematurity, congenital heart disease, laryngomalacia, and cleft lip and palate). Swallowing dysfunction was detected in eight patients (25%) without any underlying diseases or conditions that might affect swallowing. Of these eight patients, four patients had a chronic cough, three patients had recurrent LRTI and one patient had wheezing. On VFSS, among these eight patients, laryngeal aspiration was found in six children with thin liquids and in one child with both thin and thick liquids. Silent aspiration was detected in four of eight patients (50%). Half of these eight patients were exposed to cigarette smoke.

During admission, 26 patients (81.3%) had oral feeding, five patients (19.2%) had liquid modified feeding, and one patient (3.8%) had non-oral feeding. After VFSS, oral feeding was recommended for two patients (6.2%), liquid modified feeding for 22 patients (68,8%), and non-oral feeding for eight patients (25%). The results of the VFSS of the patients are shown in Table 2. The most common VFSS finding was a silent aspiration in 22 patients (68.8%). The mean of the PEAT-10 score of the patients was 14.4±11, and the median PAS score for thin liquids was 8 (7-8). Aspiration of thick liquids was detected in only six patients (18.8%), and all were silent aspirations.

No statistical difference was found in the PAS (thin-thick liquid) score according to gender of patients, birth weight-week, and underlying disease or risk factors. A significant difference was found between parental smoking and the PEAT-10 score of the patients ($p=0.046$). The PAS score of the patients exposed to cigarette smoke was higher, but the difference was not statistically significant ($p=0.081$). While no correlation was found between the number of LRTIs in one year and the PAS, a positive correlation was found with the PEAT-10 score ($p=0.008$, $r=0.781$). A comparison of the VFSS results of patients with and without metabolic and/or neurologic disease is shown in Table 3. On VFSS, 16 patients with metabolic and/or neurologic disease had oral phase dysfunction and a delayed swallowing reflex was more common in both thin and thick fluids than in those without metabolic

Table 1. Demographic and clinical characteristics of patients with swallowing dysfunction (n=32)	
	N (%)
Gender	
Male	26 (81.3)
Female	6 (18.8)
Age (months)	14 (7.2-32.2)*
Weight	
>(-2) SD**	14 (43.8)
<(-2) SD	18 (56.3)
Gestational age, week	
Term	23 (71.9)
Preterm	9 (28.1)
Symptoms	
Recurrent LRTI#	18 (56.3)
Persistent cough	9 (28.1)
Wheezing	5 (15.6)
Number of LRTI	
Total	5 (3-7)*
Annual (previous year)	3 (2-4)*
Symptoms while feeding	
Cough	14 (43.8)
Vomiting	9 (28.1)
Choking-growling	7 (21.9)
None	2 (6.3)
Chronic disease	
Yes	24 (75)
No	8 (25)
Neurometabolic disease	
Yes	16 (50)
No	16 (50)
Pulmonary infiltration	
Right	16 (50)
Bilateral	12 (37.5)
Left	2 (6.3)
Normal	2 (6.3)
Exposure to cigarette smoke	
Yes	20 (62.5)
No	12 (37.5)

#LRTI: Lower respiratory tract infection. *Median (interquartile range), SD: Standart deviation

Table 2. Evaluation of videofluoroscopic results of patients at admission and after swallowing therapy		
	At admission n=32 (%)	After swallowing therapies n=14 (%)
Penetration aspiration scale (thin liquid)		
None	2 (6.2)	8 (57.1)
Penetration	1 (3.1)	-
Aspiration despite patient's response	7 (21.9)	3 (21.4)
Aspiration absent patient's response	22 (68.8)	3 (21.4)
Penetration aspiration scale (thick liquid)		
None	26 (81.3)	1 (3.1)
Penetration	-	13 (40.6)
Aspiration despite patient's response	-	-
Aspiration absent patient's response	6 (18.7)	-
Oral phase dysfunction (thin liquid)		
Yes	18 (56.25)	1 (7.2)
No	14 (43.75)	13 (92.8)
Delayed swallowing reflex (thin liquid)		
Yes	13 (40.6)	4 (28.6)
No	19 (59.4)	10 (71.4)
Nasal regurgitation (thin liquid)		
Yes	3 (9.4)	1 (7.2)
No	29 (90.6)	13 (92.8)
Aspiration (thin liquid)		
Yes	29 (90.6)	6 (42.8)
No	3 (9.4)	8 (57.1)
Coughing (thin liquid)		
Yes	7 (21.9)	3 (21.4)
No	25 (78.1)	11 (78.6)
Oral phase dysfunction (thick liquid)		
Yes	17 (53.1)	1 (7.2)
No	15 (46.9)	13 (92.8)
Delayed swallowing reflex (thick liquid)		
Yes	10 (31.3)	2 (14.3)
No	22 (68.8)	12 (85.7)

Table 2. Continued		
	At admission n=32 (%)	After swallowing therapies n=14 (%)
Nasal regurgitation (thick liquid)		
Yes	2 (6.25)	-
No	30 (93,75)	14 (100)
Aspiration (thick liquid)		
Yes	6 (18.7)	-
No	26 (81.3)	14 (100)
Coughing (thick liquid)		
No	32 (100)	14 (100)

and/or neurologic disease, and it was statistically significant (p=0.037 and p=0.003 for thin liquids and p=0.004 and p=0.006 for thick liquids, respectively). Of the patients with metabolic and/or neurologic disease, 12 (75%) had growth retardation (weight is below 2 standard deviations according to his/her gender and peers). The weight Z-scores for the age of patients with metabolic and/or neurologic disease was lower than those without metabolic and/or neurologic disease (p=0.037).

In 20 patients (12 of 32 patients lost the follow-up in the pediatric pulmonology department), the median number of LRTIs per year before swallowing therapy was 3 (2-4), while the annual number of LRTIs after therapy was 1 (1-2.75). A reduction in the annual number of LRTIs of patients after swallowing therapy was statistically significant (p=0.010). The annual number of LRTIs was higher in patients with chronic disease or risk factors (p=0.035). There was no statistical difference between the annual number of LRTIs and the type of swallowing dysfunction.

Discussion

Children with swallowing dysfunction may present with recurrent LRTIs and persistent respiratory symptoms (1,3). Swallowing dysfunction should be suspected in children with persistent respiratory symptoms. In our study, swallowing dysfunction was found in eight children with normal neuromotor development without any underlying risk factors. The decrease in the symptoms of our patients with swallowing dysfunction after changing diets shows the importance of swallowing therapy in the management of children with recurrent LRTIs and persistent respiratory symptoms.

In our study, 1.2% of patients with recurrent LRTIs and persistent respiratory symptoms were diagnosed with swallowing dysfunction. Eight of these patients had no chronic disease or risk factor for swallowing dysfunction. Studies have shown varying degrees of swallowing dysfunction in children without risk factors (2,8-10). Silent aspiration is common among infants and young children with swallowing dysfunction (2-4,6). In a retrospective study, swallowing dysfunction was detected in 19 patients (19/517) who had no risk factors for dysphagia and had unexplained respiratory symptoms, and they detected silent aspiration in 57.9% of these patients (3). In our study, silent aspiration was found in half of the patients without risk factors and in 75% of the patients with risk factors.

In our study, patients with swallowing dysfunction presented mostly with recurrent LRTIs. Respiratory tract symptoms in patients with swallowing dysfunction vary in the literature (2-4,9). About half of our patients had a cough, while feeding and silent aspirations were detected in eight of these patients. The cough is one of the mechanisms that protects the respiratory tract (1). Silent aspiration was observed on VFSS even in patients who coughed while feeding, suggesting that coughing during feeding does not guarantee safe swallowing and does not protect airways completely, especially in children with persistent respiratory symptoms. One of the reasons for the high frequency of silent aspiration in children with dysphagia is thought to be incomplete maturation of airway clearance mechanisms (11). The absence of primary airway protection responses in recurrent aspirations may impair lung maturation, especially in 2-year-old children (12,13).

The position of the patient during aspiration determines the segment of the lung where aspiration is most likely to occur. If patients aspirate while in the supine position, the superior segment of the lower lobe of the right lung and the posterior segment of the upper lobe of the right lung are usually involved. Patients who aspirated in the upright position may have involvement of the basal segments of the bilateral lower lobes (14). In our study, most of our patients had infiltration in the right lung segments on chest X-rays. Suspicion of aspiration should be considered in children with recurrent LRTIs, especially with involvement of the right lung.

Table 3. A comparison of videofluoroscopic results of patients with and without neurometabolic disease				
		Neurometabolic disease		p-value
		Yes n=16 (%)	No n=16 (%)	
Thin Liquid	Oral phase dysfunction			
	Yes	12 (75)	6 (37.5)	0.037*
	No	4 (25)	10 (62.5)	-
	Delayed swallowing reflex			
	Yes	11 (68.8)	2 (12.5)	0.003
	No	5 (31.3)	14 (87.5)	-
	Nasal regurgitation			
	Yes	2 (12.5)	1 (6.3)	0.544
	No	14 (87.5)	15 (93.8)	-
	Aspiration			
	Yes	16 (100)	13 (81.3)	0.226
	No	-	3 (18.8)	-
	Coughing			
	Yes	3 (18.8)	4 (25)	1,000
	No	13 (81.3)	12 (75)	-
	Penetration aspiration scale			
	None	-	2 (12.5)	-
	Penetration	-	1 (6.3)	0.276
	Aspiration despite patient's response	3 (18.8)	4 (25)	-
	Aspiration absent patient's response	13 (81.2)	9 (56.3)	-
Thick Liquid	Oral phase dysfunction			
	Yes	13 (81.3)	4 (25)	0.004
	No	3 (18.8)	12 (75)	-
	Delayed swallowing reflex			
	Yes	9 (56.2)	2 (12.5)	0.006
	No	7 (43.8)	14 (87.5)	-
	Nasal regurgitation			
	Yes	2 (12.5)	-	0.484
	No	14 (87.5)	16 (100)	-
	Aspiration			
	Yes	5 (31.3)	1 (6.3)	0.333
	No	11 (68.8)	15 (93.8)	-
	Penetration aspiration scale			
	None	11 (68.8)	15 (93.8)	-
	Penetration	-	-	-
	Aspiration despite patient's response	-	-	0.172
	Aspiration absent patient's response	5 (31.3)	1 (6.3)	

Half of the patients without risk factors were exposed to cigarette smoke. Studies have shown that smoking is one of the etiologies of dysphagia in adults (15,16). Although this has not been observed in studies involving the pediatric population, the higher scores on the PEAT-10 and PAS of the patients exposed to cigarette smoke in our study suggest that smoking exposure may play a role. Although smoking has not yet been shown as an etiology of dysphagia in studies conducted in children, the higher scores on the PEAT-10 and PAS of the patients exposed to smoking in our study suggest that smoking exposure may also be involved in the etiology of swallowing dysfunction in children. Since smoking is also a risk factor for recurrent respiratory tract symptoms, suggestions to avoid smoking in the management of children with swallowing dysfunction may also be beneficial in the management of patients with persistent respiratory tract symptoms (17).

After changing the diet of the patients with swallowing dysfunction, the frequency of admission to the hospital due to LRTIs decreased. This shows the importance of swallowing therapies and nutritional recommendations in the management of patients with recurrent respiratory tract symptoms. Since multiple factors, such as other treatments received by the patients and environmental factors affecting the patients, could not be evaluated in our study, the decrease in the number of LRTIs cannot be attributed solely to changing the diet.

In patients with metabolic and/or neurologic disease, oral phase dysfunction and delay in the swallowing reflex were more common. Oral motor dysfunction is common in children with delayed neuromotor development. In these patients, problems such as sucking, chewing, swallowing, drooling, and persistent tongue thrust are frequently encountered (18,19). Oral motor dysfunction is seen in 90% of children diagnosed with cerebral palsy (20). Especially in patients with neurological disease, untreated nutritional problems can cause growth retardation, which may increase morbidity and mortality (18,21). Similarly, in our study, the weight of patients with metabolic and/or neurologic disease was lower compared to other patients and their age, and respiratory tract infections were more common. Many of these children with metabolic and/or neurologic diseases would benefit from a regular nutritional assessment and management as part of their overall care. In addition, patients without risk factors but with isolated swallowing dysfunction should be followed up for neurological diseases that may develop in the future. Swallowing dysfunction in infancy may be the first sign of associated neurological diseases or syndromes (9).

Management of pediatric dysphagia includes nutritional recommendations, medical and surgical interventions, positioning guidelines, and oral-motor/swallowing exercises. Underlying disease, neuromotor and behavioral development of children, and social and environmental factors affect the treatment recommendations of children (1,4). A multidisciplinary approach to the management of dysphagia in pediatric populations is required, involving physiotherapists, otolaryngologists, pediatric gastroenterologists, and pediatric pulmonologists (1). In addition to respiratory system symptoms, swallowing dysfunction can cause malnutrition, which can negatively affect cognitive and behavioral development in children (1,22). Successful management of swallowing disorders improves nutritional status and significantly reduces morbidity (23). The prognosis of patients with isolated swallowing dysfunction is very good in long-term follow-up (9). In our study, after the appropriate nutritional recommendations for our patients, there was a decrease in the number of lung infections and, accordingly, a decrease in the morbidity of the patients.

The retrospective design of the study and the small number of patients are the limitations of our study. There is a need for multicentre prospective studies with larger patient groups.

Conclusion

Swallowing dysfunction may cause recurrent respiratory tract symptoms in children. Patients with underlying risk factors should be evaluated for swallowing dysfunction. Swallowing dysfunction should be kept in mind in the differential diagnosis of patients with recurrent respiratory symptoms but without any risk factors for dysphagia. Early diagnosis of swallowing dysfunction and initiation of appropriate treatment is important and can reduce the morbidities associated with dysphagia.

Ethics

Ethics Committee Approval: The Gazi University Non-Interventional Clinical Research Ethics

Committee approved the study (protocol number 916100558-604.01.02).

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