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ANKARA BİLKENT ŞEHİR HASTANESİ
ÇOCUK HASTANESİ

Türkiye Çocuk Hastalıkları Dergisi
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ÇOCUK HASTANESİ

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Türkiye Çocuk Hastalıkları Dergisi'nde orijinal makale, derleme, olgu sunumu, editöryal, çalışma yöntemi, kısa rapor, kitap incelemeleri, biyografiler ve editöre mektup yayınlanmaktadır. Ayrıca pedatrik cerrahi, diş hekimliği, halk sağlığı, genetik, çocuk ve ergen psikiyatrisi ve hemşirelik konularında makaleler yayınlanabilir.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen yazılar çift kör hakemlik sürecinden geçecektir. Her bir yazı tarafsız bir değerlendirme süreci sağlamak için alanda uzman en az iki harici, bağımsız hakem tarafından incelenecektir. Baş editör, tüm başvurular için karar alma sürecindeki nihai otoritedir.

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Yazarlar Türkiye Çocuk Hastalıkları Dergisi'ne bir yazı gönderirken, yazıların telif haklarını Türkiye Çocuk Hastalıkları Dergisi'ne devretmiş olmayı kabul ederler. Yayınlanmamak üzere reddedilirse veya herhangi bir sebepten yazı geri çekilirse telif hakkı yazarlara geri verilir. Türk Türkiye Çocuk Hastalıkları Dergisi'ne ait Telif Hakkı Devri ve Yazarlık Formları (https://dergipark.org.tr/tr/pub/tchd adresinden indirilebilir). Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayınlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir.

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The publication language of Turkish Journal of Pediatric Disease is English. However, the journal welcomes manuscripts both in Turkish and English for the evaluation. The authors of articles who had manuscript in Turkish are required to provide an English version of their accepted article before the publication.

In the Turkish Journal of Pediatric Disease original articles, reviews, case reports, editorials, short reports, book reviews, biographies and letters to the editor are also published in the journal. Besides if related with pediatrics, articles on aspects of pedatric surgery, dentistry, public health, genetics, pshyciatrics and nursery could be published.

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Derginin yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (WAME)), Yayın Etiği Komitesi (Committee on Publication Ethics (COPE)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (ICMJE)), Bilim Editörleri Konseyi (Council of Science Editors (CSE)), Avrupa Bilim Editörleri Birliği (EASE) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO) (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice)) uygundur.

Yazıların yayına kabulü için en önemli kriterler özgünlük, yüksek bilimsel kalite ve atıf potansiyelidir. Değerlendirme için gönderilen yazılar daha önce elektronik veya basılı bir ortamda yayınlanmamış olmalıdır. Dergi, değerlendirilmek üzere başka bir dergiye gönderilen ve reddedilen yazılar hakkında bilgilendirilmelidir. Önceki inceleme raporlarının sunulması değerlendirme sürecini hızlandıracaktır. Kongre ve toplantılarda sunulan yazılarda yazının sunulduğu toplantının kongrenin adı, tarihi ve yeri de dahil olmak üzere ayrıntılı bilgi ile birlikte sunulmalıdır.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen yazılar çift kör hakemlik sürecinden geçecektir. Her bir yazı tarafsız bir değerlendirme süreci sağlamak için alanda uzman en az iki harici, bağımsız hakem tarafından incelenecektir. Baş editör, tüm başvurular için karar alma sürecindeki nihai otoritedir.

Yazarlardan deneysel, klinik ve ilaç çalışmaları ve bazı vaka raporları için gerekirse, etik kurul raporları veya eşdeğer bir resmi belge istenecektir. İnsanlar üzerinde yapılan deneysel araştırmalarla ilgili yazılar için, hasta ve gönüllülerin yazılı bilgilendirilmiş olurlarının alınabileceği prosedürlerin ayrıntılı bir açıklamasının ardından elde edildiğini gösteren bir ifade eklenmelidir. Hayvanlar üzerinde yapılan çalışmalarda, hayvanların acı ve ıstıraplarını önlemek için alınan önlemler açıkça belirtilmelidir. Hasta onamı, etik komite adı ve etik komite onay numarası hakkında bilgi de makalenin Materyal-Metod bölümünde belirtilmelidir. Hastaların anonimliklerini dikkatlice korumak yazarların sorumluluğundadır. Hastaların kimliğini ortaya çıkarabilecek fotoğraflar için, hasta veya yasal temsilcisi tarafından imzalanan bültenler eklenmelidir.

Tüm başvurular intihal araştırılması için yazılımsal olarak (iThenticate by CrossCheck) taranır.

İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu COPE yönergelerine uygun olarak hareket eder.

Yazar olarak listelenen her bireyin Uluslararası Tıp Dergisi Editörleri Komitesi (ICMJE - www.icmje.org) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. ICMJE yazarlığın aşağıdaki 4 kritere dayanmasını önerir:

1. Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması

2. Dergiye gönderilecek kopyanın hazırlanması veya bu kopyayının içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması

3. Yayınlanacak kopyanın son onayı.

4. Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir.

Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir.

Yazı gönderim aşamasında ilgili yazarların, yazarlık katkı formunun imzalı ve taranmış bir versiyonunu (https://dergipark.org.tr/en/pub/tchd adresinden indirilebilir) Türkiye Çocuk Hastalıkları Dergisi'ne göndermesini gerektirir. Yayın kurulu yazarlık şartarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir. Makalenin gönderilmesi aşamasında bir yazar makalenin gönderilmesi ve gözden geçirilmesi aşamalarında tüm sorumluluğu üstlenmeyi kabul ettiğini bildiren kısa bir açıklama göndermelidir.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Yayın Kuruluna bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, ICMJE Potansiyel Çıkar Çatışması Bildirim Formu, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Yayın Kurulu tarafından COPE ve ICMJE yönergeleri kapsamında çözümlenecektir.

Derginin Yayın Kurulu, tüm itiraz durumlarını COPE kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir.

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Yazıların sonuçlarının rapor edilemesi sırasında genellikle istatistiksel analizler gereklidir. İstatistiksel analizler uluslararası istatistik raporlama standartlarına uygun olarak yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Tıp dergilerine katkıda bulunanlar için istatistiksel yönergeler. Br Med J 1983: 7; 1489-93). İstatistiksel analizler hakkında bilgi, Materyal ve Metot bölümünde ayrı bir alt başlık ile açıklanmalı ve bu süreçte kullanılan istatistiksel yazılımlar mutlaka belirtilmelidir.

Türkiye Çocuk Hastalıkları Dergisi'nde yayınlanan yazılarda belitilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

YAZILARIN HAZIRLANMASI

Yazılar, Tıbbi Çalışmalarda Bilimsel Çalışmanın Yürütülmesi, Raporlanması, Düzenlenmesi ve Yayınlanması için Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (ICMJE)) Önerileri'ne uygun olarak hazırlanmalıdır (Mayıs 2022'de güncellenmiştir - https://www.icmje.org/recommendations). Bu liste aşağıda görülebilir.

CONSORT	Randominize kontrollü çalışma
STROBE	Gözlemsel epidemiyolojik çalışmalar
STARD	Tanı yöntemleri
PRISMA	Sistemetik derleme ve metaanaliz
ARRIVE	Deneysel hayvan çalışmaları
TREND	Randomize olmayan tutum ve davranış çalışmaları

Yazılar yalnızca derginin çevrimiçi (online) makale gönderme ve değerlendirme sistemi aracılığıyla gönderilebilir.

www.dergipark.org.tr/en/journal/2846/submission/step/manuscript/new. Başka herhangi bir araç aracılığıyla gönderilen yazılar değerlendirmeye alınmayacaktır.

Dergiye gönderilen yazılar öncelikle sekreterlik tarafından yazının derginin kurallarına uygun olarak hazırlanıp hazırlanmadığı yönünden teknik bir değerlendirme sürecinden geçecektir.

Derginin yazım kurallarına uymayan yazılar, düzeltme talepleriyle birlikte gönderen yazara iade edilecektir.

Yazarların yazıları hazırlarken ve sisteme yüklerken aşağıdaki konulara dikkat etmesi gerekmektedir:

Telif Hakkı Devri ve Yazarlık Formunun Kabulü ve ICMJE tyarafından önerilen Potansiyel Çıkar Çatışması Bildirim Formu İlk başvuru sırasında (katkıda bulunan tüm yazarlar tarafından doldurulmalıdır) sisteme yüklenmelidir. Bu formları www.dergipark.org.tr/tr/pub/tchd adresinden indirebilirsiniz.

Kapak SayfasınınHazırlanması:

Kapak sayfası tüm yazılarla birlikte gönderilmeli ve bu sayfa şunları içermelidir:

Yazının kapak sayfasında yazının İngilizce başlığı bulunmalıdır. Kapak sayfası yazarların adlarını, akademik ünvanlarının, ORCID numaralarını, kurumsal/mesleki bağlantılarını, yazının kısa başlığını (en fazla 50 karakter), kısaltmaları, finansal açıklama bildirimini ve çıkar çatışması bildirimini içermelidir. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse yazılar için Türkçe bir başlık da gereklidir. Bir yazı birden fazla kurumdan yazar içeriyorsa, her yazarın adını, ayrı olarak listelenen kurumlarına karşılık gelen bir üst simge numarası izlemelidir. Tüm yazarlar için için isim soy isim, e-posta adresi, telefon ve faks numaraları dahili iletişim bilgileri verilmelidir. Ayrıca yazı ile ilgili olrak iletişim kurulacak sorumlu sorumlu yazarın kim olduğu belirtilmelidir.

Önemli Uyarı: Kapak sayfası ayrı bir belge olarak yüklenmelidir.

Derleme türü makalelerde özet tek paragraf olacak şekilde hazırlanmalı ve 300 kelime ile sınırlı olmalıdır. Bölümlendirilmiş özet hazırlanmasına gerek yoktur. Derlemeler 8000 kelime ve 60 kaynak ile sınırlandırılmaya çalışılmalıdır.

Anahtar kelimeler:

Özetin sonunda konu indeksleme için her gönderime en az üç en fazla altı anahtar kelime eklenmelidir. Anahtar kelimeler kısaltma olmadan tam olarak listelenmelidir. Anahtar kelimeler "National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html)" veritabanından seçilmelidir. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe anahtar kelimeler de gereklidir.

YAZI TÜRLERİ

Orijinal Araştırma Makalesi

Kelime sayısı: En çok 3500 kelime (Başlık, özet, anahtar kelimeler, kaynaklar, tablo ve figür yazıları hariç).

Ana metnin içereceği bölümler: Giriş, Yöntemler, Sonuçlar, Tartışma

Başlık: En çok 20 kelime

Yapısal özet: En çok 250 kelime. Bölümler: Amaç, Gereç ve Yöntem, Sonuçlar ve Tartışma

Anahtar kelimeler: En az 3 en fazla altı kelime, alfabetik olarak sıralanmıştır.

Şekiller ve tablolar: Sayı sınırı yok ancak tam olarak gerekçelendirilmeli ve açıklayıcı olmalıdır.

Kaynaklar: En çok 40.

Orijinal makale İngilizce ise, İngilizce başlık, İngilizce yapılandırılmış özet (yapılandırılmış, İngilizce anahtar kelimeler). Makale Türkçe ise, Türkçe başlık ve İngilizce başlık, Türkçe yapılandırılmış özet ve İngilizce özet (Amaç, Gereç ve Yöntem, Sonuç ve Tartışma olarak yapılandırılmıştır), Türkçe ve İngilizce anahtar kelimeler gereklidir.

Çoğu okuyucu ilk olarak başlık ve özeti okuduğu için bu bölümler kritik öneme sahiptir. Ayrıca, çeşitli elektronik veritabanları yazıların sadece özetlerini indekstedikleri için özette önemli bulgular sunulmalıdır.

Makalenin diğer bölümleri Giriş, Gereç ve Yöntemler, Sonuçlar, Tartışma, Teşekkür (gerekirse) ve Kaynaklar'dan oluşmalıdır. Makalelerin tüm bölümleri yeni bir sayfada başlamalıdır.

Derleme:

Kelime sayısı: En fazla 5000

Özet: En fazla 500 kelime

Anahtar kelimeler: En az üç en fazla altı kelime, alfabetik olarak sıralanmıştır.

Şekiller ve tablolar: Sayı sınır yok ancak tam olarak gerekçelendirilmeli ve açıklayıcı olmalıdır.

Kaynaklar: 80'e kadar

Derleme makaleleri, tıptaki belirli konuların kapsamlı olarak gözden geçirildiği, konunun tarihsel gelişimini, mevcut bilinenleri, araştırıma ihtiyacı olan alanları içeren yazılarır. Konu hakkında orijinal araştırmaları yazarlar tarafından yazılmalıdır. Tüm derleme yazıları kabulden önce diğer yazılara eşdeğer değerlendirme süreçlerine tabi tutulacaktır.

Derleme makaleleri şunları içermelidir; İngilizce başlık, İngilizce özet ve İngilizce anahtar kelimeler. Makale Türkçe ise, Türkçe başlık ve İngilizce başlık, Türkçe özet ve İngilizce özet, Türkçe ve İngilizce anahtar kelimeler gereklidir.

Olgu Sunumu:

Kelime Sayısı: En fazla 2000 kelime

Özet: En fazla 200 kelime

Anahtar Kelime: En az üç en fazla altı kelime

Tablo ve Şekil: Toplamda en fazla beş ile sınırlandırılmıştır.

Kaynaklar: En fazla 15

Dergiye sınırlı sayıda olgu sunumu kabul edilmektedir. Olgu sunumlarının tanı ve tedavide zorluk oluşturan, nadir, literatürde yer almayan yeni tedaviler sunan ilginç ve eğitici olguların seçilmesine dikkat edilmektedir. Olgu sunumu giriş, olgu sunumu ve tartışma içermelidir.

Olgu sunumları şunları içermelidir; İngilizce başlık, İngilizce özet ve İngilizce anahtar kelimeler. Makale Türkçe ise, Türkçe başlık ve İngilizce başlık, Türkçe özet ve İngilizce özet, Türkçe ve İngilizce anahtar kelimeler gereklidir.

Editöre mektup:

Kelime sayısı: En fazla 1500 kelime

Şekil ve tablolar: En fazla 3

Kaynaklar: En fazla 15

Editöre mektup daha önce yayınlanmış bir makalenin önemli bölümlerini, gözden kaçan yönlerini veya eksik bölümlerini tartışır. Dergi kapsamında okurların dikkatini çekebilecek konularda, özellikle eğitici vakalarda yer alan yazılarda editöre mektup şeklinde de gönderilebilir. Okuyucular ayrıca yayınlanan yazılar hakkındaki yorumlarını editöre mektup şeklinde sunabilirler. Bir özet ve Anahtar Kelimeler dahil edilmemelidir. Tablo, şekil, görüntü içerebilir. Metin alt başlıkları içermemelidir. Yorum yapılan makaleye bu yazının içinde uygun şekilde atıfta bulunulmalıdır.

Editöre mektuplar; İngilizce başlık. Türkiye'de bulunan bir merkez tarafından gönderilmişse editör mektubu için Türkçe bir başlık da gerekmektedir.

Çalışma Metodları:

Türkiye Çocuk Hastalıkları Dergisi araştırmanın şeffaflığını artırmak ve devam etmekte olan araştırmalar hakkında ilgili kişileri bilgilendirmek için çalışma metodları yayınlamaktadır. Çalışma metodlarının yayın kararı editör tarafından verilmektedir. Pilot çalışmaların veya fizibilite çalışmalarının metodları genellikle yayınlanmamaktadır.

Çalışma metodları yazıları, çalışmanın hipotezi, gerekçesi ve metodolojisi hakkında ayrıntılı bir açıklama sunan SPIRIT yönergelerine uymalıdır. Tüm çalışmalar için etik kurul onayı alınmış olmalıdır. Klinik araştırmalar için tüm protokoller, araştırma kayıt numarasını ve kayıt tarihi verilmelidir.

Tablolar

Tablolar, referans listeden sonra ana belgeye dahil edilmelidir ana metin içine yarleştirilmemelidir. Ana metinde atıfta bulundukları sırayla numaralandırılmalıdır. Tabloların üzerine açıklayıcı bir başlık konulmalıdır. Tablolarda kullanılan kısaltmalar ana metinde tanımlansalar bile tabloların altında dipnotlarla tanımlanmalıdır. Tablolarda sunulan veriler, ana metinde sunulan verilerin tekrarı olmamalı, ancak ana metni desteklemelidir. Kısaltmalar için aşağıdaki semboller sırayla kullanılmalıdır: *, †, ‡, §, ||, ¶, **, †→, ‡‡.

Şekiller ve şekil alt yazıları

Şekiller, grafikler ve fotoğraflar, gönderim sistemi aracılığıyla ayrı dosyalar (TIFF veya JPEG formatında) olarak gönderilmelidir. Dosyalar bir Word belgesine veya ana metne yerleştirilmemlidir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturacak şekilde birleştirilmemeli, her alt birim, başvuru sistemi aracılığıyla ayrı ayrı yüklenmelidir. Resimlerin üzerine etiketleme (örneğin a,d,c,d gibi) yapılmamalıdır. Şekil altyazılarını desteklemek için görüntülerde kalın ve ince oklar, ok uçları, yıldızlar, yıldız işaretleri ve benzeri işaretler kullanılabilir. Görüntülerde bir bireyi veya kurumu gösterebilecek her türlü bilgi kör edilmelidir. Gönderilen her bir şeklin çözünürlüğü en az 300 DPI olmalıdır. Değerlendirme sürecinde gecikmeleri önlemek için, gönderilen tüm şekiller net ve büyük boyutlu olmalıdır (en küçük boyutlar: 100 × 100 mm). Şekil açıklamaları ana metnin sonunda metindeki sıraya göre ayrı ayrı listelenmelidir.

Makalede kullanılan tüm kısaltmalar ve akronimler, hem özet hem de ana metinde ilk kullanımda tanımlanmalıdır. Kısaltma, tanımın ardından parantez içinde verilmelidir.

Ana metinde bir ilaç, ürün, donanım veya yazılım programından bahsedildiğinde, ürünün adı, ürünün üreticisi ve şehri ve şirketin ülkesini (ABD'de ise eyalet dahil) içeren ürün bilgileri, parantez içinde aşağıdaki biçimde sağlanmalıdır: The skin prick tests were performed using a multi-prick test device (Quantitest, Panatrex Inc, Placentia, California, USA)

Tüm referanslar, tablolar ve şekiller ana metin içinde belirtilmeli ve ana metin içinde belirtildikleri sırayla numaralandırılmalıdır. Orijinal makalelerin kısıtlılıkları tartışma bölümü içinde sonuç paragrafından önce belirtilmelidir.

KAYNAKLAR

Yayınlara atıf yapılırken, en son ve en güncel yayınlar tercih edilmelidir. Yazarlar beş yıldan eski referansları kullanmaktan kaçınmalıdır. Yazılarda 5 yıldan eski tarihli referans sayısının toplam referans sayısının %20'sini geçmemesine dikkat edilmelidir. Elektronik olarak yayınlanmış ancak cilt ve sayfa numarası verilmemiş yazılar atfedilirken DOI numarası verilmelidir. Yazarlar kaynakların doğruluğundan sorumludur. Referans numaraları metindeki cümlelerin sonunda metinde kullanıldıkları sıra ile numaralandırılmalıdır. Dergi adları "Index

Medicus" veya "ULAKBIM/Turkish Medical Index" de listelendiği gibi kısaltılmalıdır. Mümkün olduğunca yerel referanslar kullanılmalıdır. Kaynaklar aşağıdaki örneklere uygun olarak yazılmalıdır.

Kaynak dergi ise;

Yazar(lar)ın soyadı adının başharf(ler)i (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan makaleler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi) kullanılmalıdır. Makalenin başlığı. Derginin Index Medicus'a uygun kısaltılmış ismi

(http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog) Yıl;Cilt:İlk ve son sayfa numarası.

Örnek: Benson M, Reinholdt J, Cardell LO. Allergen-reactive antibodies are found in nasal fluids from patients with birch polen-induced intermittent allergic rhinitis, but not in healthy controls. Allergy 2003;58:386-93.

Kaynak dergi eki ise;

Yazar(lar)ın soyadı adının başharf(ler)i. Makalenin başlığı. Derginin Index Medicus'a uygun

kısaltılmış ismi (http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog) Yıl;Cilt

(Suppl. Ek sayısı):İlk sayfa numarası-Son sayfa numarası.

Örnek: Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994; (102 Suppl 1):275–82.

Kaynak kitap ise;

Yazar(lar)ın soyadı, adının başharf(ler)i. Kitabın adı. Kaçıncı baskı olduğu. Basım yeri: Basımevi, Basım Yılı.

Örnek: Ringsven MK, Bond N. Gerontology and leadership skills for nurses. 2nd ed. Albany, NY: Delmar Publishers, 1996.

Kaynak kitaptan bölüm ise;

Bölüm yazar(lar)ının soyadı adının başharf(ler)i. Bölüm başlığı. In: Editör(ler)in soyadı, adının başharf(ler)i (ed) veya (eds). Kitabın adı. Kaçıncı baskı olduğu. Basım yeri: Yayınevi,

Baskı yılı:Bölümün ilk ve son sayfa numarası.

Örnek: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM (eds). Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York: Raven P, 1995:466–78.

Kaynak toplantıda sunulan bildiri ise;

Yazar(lar)ın soyadı adının başharf(ler)i. (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan bildiriler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi kullanılmalıdır).Bildirinin başlığı. Varsa In: Editör(ler)in soyadı adının başharf(ler)i (ed) veya (eds). Kitabın adı. Toplantının adı; Tarihi; Toplantının yapıldığı şehrin adı, Toplantının yapıldığı ülkenin adı. Yayınevi; Yıl. Sayfa numaraları.

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

Kaynak elektronik dergi ise;

Yazar(lar)ın soyadı adının başharf(ler)i. (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan makaleler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi kullanılmalıdır). Makalenin başlığı. Derginin Index Medicus'a uygun kısaltılmış ismi Yıl; Cilt (Sayı). Available from: URL adresi. Erişim tarihi: Gün.Ay.Yıl.

Örnek: Arrami M, Garner H. A tale of two citations. Nature 2008;451(7177): 397-9. Available from: URL:www.nature.com/nature/journal/v451/n7177/full/451397a.html. Aaccessed 20 January 2008.

Kaynak web sitesi ise:

Web sitesinin adı. Erişim tarihi. Available from: Web sitesinin adresi.

Örnek: Centers for Disease Control and Prevention (CDC). Erişim tarihi: 12 Mart 2013. Available from: http://www.cdc.gov/

Kaynak tez ise:

Yazarın soyadı adının baş harfi. Tezin başlığı (tez). Tezin yapıldığı şehir adı: Üniversite adı (üniversite ise); Yılı.

Örnek: Özdemir O. Fibrillin-1 gen polimorfizmi ve mitral kapak hastalığı riski. (Tez). Ankara: Gazi Üniversitesi, 2006."

Düzeltme istenmesi aşaması:

Bir makalenin hakemler tarafından istenen değişiklikler yapılmış kopyası gönderilirken yazar, hakemler tarafından istenen her açıklama/düzeltmeye cevap vermekle yükümlüdür. Yazarlar hakemlerin düzeltme/açıklama isteklerini her isteğin ardından olacak şekilde madde madde açıklmalı, düzeltilmiş kopyaya yazılacak metin bu açıklamanın altına eklemelidir. Düzeltme yapılmış kopya dergiye ayrı bir kopya olarak yüklenmelidir. Düzeltilmiş yazılar düzeltme isteğinin gönderilmesinden itibaren 30 gün içinde gönderilmelidir. Yazının düzeltilmiş kopyasıistenilen sürede gönderilmezse yazı sistemden ototmatik olarak düşürülecektir ve tekrar başvuru yapılması gerekecektir. Eğer yazarlar ek zaman talep ediyorlarsa bu taleplerini ilk 30 günlük süre sona ermeden önce dergiye iletmelidir.

Kabul edilen yazılar dilbilgisi ve noktalama işaretleri yönünden kontrol edilir. Kabul süreci ve düzenleme işlemleri tamamlandıktan sonra yazı dergi web sayfasında cilt ve sayfa numarası verilmeden DOI verilerek yayınlanır.

Yazar Listesi/Sırası Değişimi

Yazı gönderildikten sonra yazar listesinin/sırasının değiştirilmesi (yazar adlarının silinmesi veya yeni yazar adı eklenmesi gibi) talepleri yayın kurulunun onayına tabidir. Bu talep yazar değişiklik formunun doldurulup dergiye yüklenmesi ile talep edilebilir. Bu form aşağıdakileri içerecek şekilde doldurulmalıdır: Talebin gerekçesi, yani yazar listesi, tüm yazarlar tarafından (yeni ve eski) imzalanan yeni bir telif hakkı transfer formu, yeni yazar tarafından imzalanmış çıkar çatışması formu.

Yazının Geri Çekilmesi Talebi

Türkiye Çocuk Hastalıkları Dergisi yüksek kaliteli yazılar yayınlamayı ve yayın etiğini korumayı taahhüt etmektedir. Yazarlardan, yayın etiğinde ve yazıların kalitesinde tavsiye edilen kurallara uymaları beklenmektedir.

Yazının geri çekilme talebi olağanüstü durumlarda talep edilmelidir. Bir yazının geri çekilmesi için yazarların dergiye geri çekme nedenlerini belirten ve tüm yazarlar tarafından imzalanan bir "Makale geri çekme Formu" yüklemeleri gerekmektedir. Bu form derginin web sayfasından indirilebilir. Yazarlar dergiden bu konuda olumlu bir cevap alana kadar makalelerinin geri çekilme işleminin tamamlanmadığını bilmelidir.

Bir makalenin inceleme süreci altı aydan uzun bir zaman almış ve yazarlara karar bildirilmemişse yazının geri çekilme talebi olumlu karşılanır.

INSTRUCTIONS FOR AUTHORS

The Turkish Journal of Pediatric Disease is an open access and a scientific publication journal that is published from the Ankara Bilkent City Hospital, Children's Hospital. The journal is published in accordance with independent, unbiased, and double-blind peer review principles. The journal is published bimonthly (January, March, May, July, September, November)

The publication language of Turkish Journal of Pediatric Disease is English. However, the journal welcomes manuscripts both in Turkish and English for the evaluation. The authors of articles who had manuscript in Turkish are required to provide an English version of their accepted article before the publication.

In the Turkish Journal of Pediatric Disease original articles, reviews, case reports, editorials, short reports, book reviews, biographies and letters to the editor are also published in the journal. Besides if related with pediatrics, articles on aspects of pedatric surgery, dentistry, public health, genetics, pshyciatrics and nursery could be published.

The editorial and the publication processes of the journal are shaped in accordance with the guidelines of the World Association of Medical Editors (WAME), the Committee on Publication Ethics (COPE), the International Council of Medical Journal Editors (ICMJE), the Council of Science Editors (CSE), the European Association of Science Editors (EASE) and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The originality, high scientific quality, and the citation potential are the most important criterias for a manuscript to be accepted for the publication. Manuscripts submitted for the evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed if manuscript have been submitted to another journal for the evaluation and have been rejected for the publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with a detailed information of the organization, including the name, date, and location of the organization.

Manuscripts submitted to the Turkish Journal of Pediatric Disease will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field, in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of the research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for the experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts that are concerning experimental researchs on humans, a statement should be informed included that shows a written informed consent of the patients and the volunteers who were given a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information of the patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity carefully. For the photographs that may reveal the identities of the patients, releases signed by the patient or their legal representative should be enclosed.

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1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable of all aspects of the work in

ensuring that questions related to the accuracy or the integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she had done, an author should be able to identify which co-authors are responsible for the specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all of the four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all of the four criteria should be acknowledged in the title page of the manuscript.

The Turkish Journal of Pediatric Disease requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through https://dergipark.org.tr/en/pub/tchd) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without a further review. As a part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all of the responsibility for the authorship during the submission and review stages of the manuscript.

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The Editorial Board of the journal handles all of the appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office to regard their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all of the appeals and complaints.

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Statistical analysis to support the conclusions are usually necessary. Statistical analyses must be conducted in accordance with the international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information about the statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified certainly.

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MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with the ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in May 2022 - http://www.icmje.org/recommendations).

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Olgu Sunumları / *Case Reports*

Derleme / *Review*

An Oxidative Stress Marker in Pediatric Migraine Patients: Dynamic Thiol-Disulfide Homeostasis

Migren Tanılı Çocukların Tiyol/Disülfit Düzeylerinin Sağlıklı Çocuklarla Karşılaştırılması

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ABSTRACT

Objective: Migraine is a common disease in childhood. Oxidative stress has been implicated in the pathogenesis of migraine. Dynamic thiol/disulfide homeostasis is proven to be a marker of oxidative stress. We aimed to investigate the correlation between migraine and dynamic thiol/disulfide homeostasis.

Material and Methods: A total of 141 children (71 migrain and 70 controls) were included. The serum total thiol, native thiol, and disulfide levels were measured and the ratios of disulfide/native thiol, disulfide/total thiol and native thiol/total thiol were compared between migraine patients and healthy children during attack-free period.

Results: Native thiol levels and native thiol/total thiol ratio were significantly lower in the migraine group than the control group (p=0.022, p=0.005, respectively); whereas disulfide levels, disulfide/native thiol and disulfide/total thiol ratios were significantly higher in the migraine group than the control group (p=0.039, p=0.022, p=0.005 respectively).

Conclusion: Our results demonstrate that there is an ongoing oxidative process in pediatric migraineurs even during attack-free period. This result may shed light on further studies analyzing dynamic changes in the oxidant-antioxidant balance during the attack and the aura phase to support the presence and importance of oxidative stress in pediatric migraine.

Key Words: Children, Migraine, Thiol/disulfide

ÖZ

Amaç: Migren çocuk ve ergen yaş grubunda değişen yaşam tarzları ve psikososyal faktörler ile birlikte görülme sıklığı giderek artan önemli bir klinik problemdir. Birincil baş ağrıları arasında yer alan migrenin biyokimyasal, genetik ve çevresel faktörlerle ilişkili nörovasküler bir hastalık olduğu bilinmektedir. Son yıllarda yapılan birçok çalışmada migren patogenezinde oksidatif stres sorumlu tutulmuştur. Oksidatif stres varlığında tiyol/disülfit homeostazisinin disülfit yönünde bozulması beklenmektedir. Tiyol/disülfit homeostazisinin çocuklarda migren ile olan ilişkisini araştıran geniş

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çaplı araştırmalar mevcut değildir. Çalışmamızda migren tanılı çocuklarda dinamik tiyol/disülfit homeostazisi ilişkisini belirlemeyi ve bu dengede disülfit yönünde bozulma görülürse migren proflaksisi ve/veya tedavisinde oksidatif stresten korunma ve/veya antioksidan tedavi kullanımı ile ilgili literatüre katkı sağlanmasını amaçladık.

Gereç ve Yöntemler: Çalışmaya Sağlık Bilimleri Üniversitesi, Ankara Keçiören Eğitim ve Araştırma Hastanesi'nde Çocuk Nöroloji Polikliniği'nde değerlendirilerek migren tanısı alan 8-18 yaş arasındaki 71 hasta ve Genel Çocuk Polikliniği'ne başvuran 70 sağlıklı çocuk dahil edilmiştir. Toplanan örneklerde serum doğal tiyol, total tiyol, disülfit, disülfit/doğal tiyol yüzdesi, disülfit/total tiyol yüzdesi ve doğal tiyol/total tiyol yüzdesi ölçümleri yapılarak migren hastaları ve sağlam çocuklar karşılaştırılmıştır.

Bulgular: Migren sıklığı yaşla birlikte artmış; 8-12 yaş %18.3, 13-15 yaş %36.6, 16-18 yaş %45.1 olarak tespit edilmiştir. Ağrı şekli %85.9 ile en sık zonklayıcı olup ağrıların %59.2'si bilateral bulunmuştur. Hastaların %11.3'ü atak ağrısının 30 dakikadan kısa sürdüğünü belirtmiştir. Gruplar karşılaştırıldığında doğal tiyol, doğal tiyol/total tiyol değerleri kontrol grubunda anlamlı olarak yüksek saptanmıştır (sırasıyla p=0.022, p=0.005). Disülfit, disülfit/doğal tiyol, disülfit/total tiyol değerleri ise hasta grubunda anlamlı olarak yüksek bulunmuştur (sırasıyla p=0.039, p=0.005, p=0.005). İstatistiksel olarak anlamlı olmasa da kontrol grubunda total tiyol değerleri hasta grubundan yüksek bulunmuştur (p=0.115).

Sonuç: Migren hastalığı sık görülmesine rağmen çocuklarda bu konuda yapılmış prospektif çalışma oldukça az sayıdadır. Çalışmamızda migren tanılı çocuklarda migren hastalığı ile tiyol/disülfit homeostazisi arasındaki ilişki incelenmiş olup oksidatif strese yönelik parametreler yüksek bulunmuştur. Migren hastalarındaki yüksek oksidatif stres değerleri antioksidan etkili maddelerin hastalığın tedavisinde rol oynayabileceğini düşündürmektedir. Bu konuyla ilgili destekleyici çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Çocuk, Migren, Tiyol/Disülfit

INTRODUCTION

Migraine is one of the most common forms of primary headache in children. Two systematic reviews published in the last ten years have reported that the prevalence varies between 7.7% and 9.1% in children and adolescents (1,2). The pathophsiology of migraine remains unclear, however, increasing evidence indicates that it is related to the excitability of the cerebral cortex on the basis of genetic predisposition (3,4). In addition, oxidant/antioxidant imbalance has been shown to play an important role in the mechanism that initiates the migraine attack (5,6). Oxidative stress is defined as the disruption of the balance between reactive oxygen species (ROS) and antioxidant molecules in favor of ROS (7). Serum thiols are free radical scavengers under physiological conditions. The sulfhydryl groups they contain are mainly responsible from the antioxidant effects (8). ROS, which is formed as a result of metabolic events, transfer excess electrons to thiols to form oxides and disulfide bonds. As a result of the oxidant/antioxidant balance of the organism, these disulfide bonds can be converted back to thiols, indicating that they are reversible. This balance is called dynamic thiol/disulfide homeostasis. Thiol/disulfide homeostasis is expected to be affected in diseases caused by oxidative stress (9,10). When protein function disorders, channel disorders, transport and signal transduction disorders are considered, it may be suggested that thiol/disulfide homeostasis may be impaired in migraine.

The aim of this study is to compare the dynamic thiol/disulfide levels in pediatric migraine patients with healthy controls and to determine the possible relationship of this homeostasis with clinical features of migraine.

MATERIALS and METHODS

The study population included children diagnosed with migraine at Ankara Keçiören Training and Research Hospital, Health Sciences University, Department of Pediatric Neurology and healthy children admitted to the general pediatric outpatient clinic. Ethical approval for this study was obtained from the Ethics Committee of Keçiören Training and Research Hospital (27.12.2017-15/1571). Informed consents were obtained from all children or their parents.A total of 71 migraine patients and 70 healthy children during follow-up for routine control were included. The diagnosis of migraine was made according to International Classification of Headache Disorder - third edition (ICHD-3) (11). Both groups consisted of children aged between 8-18 years without any neurological or chronic systemic disease, history of recent infection or medication. Age, sex, height, body weight, blood pressure, detailed history of migraine (onset, frequency, duration of migraine, duration of attacks, location and type of pain, accompanying features, precipitating factors, aura, family history), physical and neurological examinations were recorded. The blood samples of the patients with migraine were collected in the attack-free period. Venous blood samples taken for thiol/disulfide measurement were centrifuged rapidly at 1500 rpm for 10 minutes, and incubated at-80°C to investigate oxidative markers. Serum thiol/disulfide levels were measured by a calorimetric and automatic method developed by Erel O et al. (9). We preferred this method because it is relatively inexpensive and easily accessible. In this method, by adding NaHB4, the dynamic disulfide bonds in the sera are reduced to form free functional thiol groups. The residues are removed by adding formaldehyde. Thus both reduced and native thiol groups are determined and the total thiol amount is reached. The amount of disulfide is obtained by substracting the native thiol from total thiol and dividing it into two. The

method automatically measures serum native thiol, disulfide and percentages of disulfide/native thiol, disulfide/total thiol and native/total thiol. All these values were compared between migraine patients and healthy children.

Statistical Analysis

Descriptive statistics of the normal distribution data were given as mean ± standard deviation (SD). The normality of the distribution of the groups was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics that do not fit to normal distribution were given as median, quartiles, maximum and minimum values. Pearson chi-square test was used to compare qualitative data. Mann Whitney U (between two groups) and Kruskal Wallis (more than two groups) tests were used for comparison of continuous variables that did not fit the normal distribution. Student t test (between two groups) and ANOVA (more than two groups) were used to compare the continuous distribution of databetween groups. SPSS 20.0 (SPSS Inc, Chicao, IL, USA) was used for statistical analysis. A p value <0.050 was considered statistically significant.

RESULTS

A total of 141 children (71 migraine patients and 70 healthy control) with a mean age of 14.7±2.32 years (range 8-17.9 years) were included. Female/male ratio was 1.51. The clinical characteristics of the patients are shown in Table I. No statistically significant difference was detected between the migraine and control groups in terms of gender, age, body weight, height or blood pressure.

In the migraine group, most of the patients had throbbing headache (85.9%) and 20.8% of the patients were diagnosed with migraine with aura. Characteristics of headache are shown in Table II.

The disulfide levels in the migraine group was statistically higher than the control group (p=0.039). Also, the disulfide/native thiol ratio and disulfide/total thiol ratio were significantly higher in the migraine group than the control group (p<0.05). Conversely, native thiol/total thiol ratio was detected significantly lower in the migraine group than the control group (p<0.05). Native thiol levels were higher in the control group than the migraine group (p=0.022). Patients in the control group were likely to have higher total thiol levels than the migraine group, but no statistical significant difference was detected (p=0.115) (Table III).

No statistically significant difference was detected between native thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native/total thiol levels and frequency of attacks (Table IV).

Table I: Clinical characteristics of the patients.

	Migraine group (n=71)	Control group (n=70)	p
Mean age ± SD (range, years)	14.82 ± 2.32 (8-17.7)	14.74 ± 2.72 (8.2-17.9)	0.629
Female/Male (ratio)	46/25 (1.84)	39/31 (1.25)	0.271
Body weight (range, kg)	56.89 ± 12.79 (27-84)	55.89 ± 13.87 (25-85)	0.650
Height (range, cm)	160.45 ± 11.64 (125-182)	158.0 ± 12.56 (126-181)	0.796

Table II: Characteristics of migraine.

	Number (n)	Percentage (%)
Generalized	12	16.9
Unilateral temporal	14	19.7
Bitemporal	15	21.1
Frontal	15	21.1
Occipital	15	21.1
Type of pain		
Throbbing	61	85.9
Pressing	4	5.6
Other	6	8.4
Duration of migraine attack		
≤ 30 min	8	11.3
31 min - 1 hr	11	15.5
1 - 2 hr	18	25.4
2 - 4 hr	10	14.1
>4 hr	24	33.8
Duration of migraine diagnosis		
≤ 2 mo	17	23.9
2- 6 mo	14	19.7
6 mo-1 year	19	26.8
1-2 y	14	19.7
>2 y	7	9.9
Frequency of attacks		
Daily	24	33.8
4-6 /pw	14	19.7
1-3 /pw	28	39.4
< 1/week	5	7
Total	71	100

min: *minutes,* ***hr:*** *hour,* ***mo:*** *months,* ***y:*** *years,* ***pw:*** *per week*

Table III: Comparison of thiol/disulfide levels in the migraine and control groups.

	Migraine Group		Control Group		p
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Native thiol	344.4±63.7	340 (112.9-480.4)	368.7±52.4	368.6 (246.6-507.4)	0.022
Total Thiol	387.2±54.2	387.2 (231.3-520.0)	401.5±53.1	401.5 (305.5-572.5)	0.115
Disulfide	21.6±10.1	20.2 (0.4-61.6)	18.5±7.3	17.9 (6.7-52.3)	0.039
Disulfide/ Native thiol	7.3±7.5	5.6 (0.1-52.4)	5.1±25	4.8 (1.9-21.2)	0.005
Disulfide/ Total thiol	5.8±3.9	5.1 (0.1-25.6)	4.5±1.8	4.4 (1.8-14.9)	0.005
Native Thiol/ Total Thiol	88.2±7.8	89.8 (48.8-99.8)	90.8±3.6	91.1 (70.2-96.3)	0.005

Table IV: Data concerning the comparison of frequency of attacks and thiol/disulfide levels.

	Median	1st and 3rd quarter	p
Native thiol			
Daily (n=24)	344.45	315.43 -375.38	
4-6/pw (n=14)	343.55	324.25 – 391.40	0.096
1-3/pw (n=28)	352.00	313.98 – 386.25	
<1/week (n=5)	285.90	127.95 – 333.40	
Disulfide			
Daily (n=24)	20.725	13.93 – 24.83	
4-6/pw (n=14)	16.925	15.00 – 23.40	0.201
1-3/pw (n=28)	19.70	16.80 – 23.58	
<1/week (n=5)	33.20	18.88 – 60.40	
Disulfide/native thiol			
Daily (n=24)	5.51	3.76 – 7.56	
4-6/pw (n=14)	4.98	3.89 – 7.01	0.136
1-3/pw (n=28)	5.96	4.59 – 7.36	
<1/week (n=5)	11.61	5.63 – 47.26	
Disulfide/total thiol			
Daily (n=24)	4.96	3.49 – 6.57	
4-6/pw (n=14)	4.525	3.60 – 6.15	0.135
1-3/pw (n=28)	5.325	4.20 – 6.42	
<1/week (n=5)	9.42	5.05 – 24.37	
Native thiol/total thiol			
Daily (n=24)	90.075	86.87 – 93.02	
4-6/pw (n=14)	90.945	87.70 – 92.79	0.136
1-3/pw (n=28)	89.35	87.17 – 91.60	
<1/week (n=5)	81.15	51.27 – 89.91	
	Mean	**Lower and Upper Bound**	
Total thiol*			
Daily (n=24)	391.24	367.41 – 415.07	
4-6/pw (n=14)	393.31	365.64 – 420.98	0.031
1-3/pw (n=28)	392.96	374.71 – 411.21	
<1/week (n=5)	318.42	235.57 – 401.26	

Pw: *per week* ****** *The mean/lower and upper bound were given for total thiol and also ANOVA was performed because total thiol levels were normally distributed.*

Table V: Comparison of frequency of attacks and total thiol levels.

	Mean Difference	Std. Error	p
Total thiol			
<1/week (n=5)			
Daily (n=24)	-72.82	25.53	0.035
4-6/pw (n=14)	-74.89	27.05	0.044
1-3/pw (n=28)	-74.54	25.21	0.026

Pw: *per week*

A statistically significant difference was found between total thiol levels of the patients and the frequency of attacks. Post-hoc analysis revealed that the group with attacks less than once a week had lower total thiol levels than the other three groups which was statistically significant (Table V).

DISCUSSION

In the recent years, mitochondrial dysfunction which tends to increase production of oxidants and downregulate antioxidant enzymes has been shown to play a role in the pathogenesis of migraine. Triggers of migraine have been also reported to increase oxidative stress. It has been suggested that oxidative stress may play a central role in the pathogenesis of migraine by deregulating brain blood flow. Therefore, the increase in free radicals has been reported to initiate a migraine attack (5,6,12,13). In this study, dynamic thiol/disulfide homeostasis developed by Erel O (9) et al. was used as an indicator of oxidative stress. This method has proven to be reliable and objective to measure dynamic thiol/disulfide balance. In diseases caused by oxidative stress thiol/disulfide homeostasis is expected to be affected and deteriorate in the disulfide direction. In the current study, we found disulfide levels, disulfide/native thiol and disulfide/total thiol ratios significantly higher in the migraine group than the control group which supported the presence of oxidative stress. There are also many tests that can measure levels of oxidant and antioxidant molecules. Endogenous antioxidant mechanisms in the body include antioxidant enzymes and various non-enzymatic molecules like catalase, superoxide dismutase, glutathione peroxidase and some peroxidation enzymes belong to the enzymatic group; uric acid, albumin, ascorbic acid, and vitamins E and C (14). However,

it is difficult to evaluate oxidative stress by measuring these molecules, since they are present in different tissues (9,15).

The increase in both native and total thiol values in the control group in our study was higher than the migraine group and the difference was statistically significant in terms of native thiol. Kurt ANC et al.(16) also found total and native thiol levels to be higher in the control patients than the migraine group, whereas the difference was not statistically significant. However, in a previous report in adults, total and native thiol levels were higher in the migraine group than the control group (17). Thiols are known to be physiological free antioxidants. However, it has been reported in the literature that they are biochemically very active and generally antioxidant but may be pro-oxidant due to the fact that they are sometimes affected by the oxidative stress level of the organism (8,18). The concentration of sulphur compounds can alter the antioxidant structure of enzymes and proteins and become pro-oxidative and participate in the structures. This equilibrium is dynamic and represents an assessment of the oxidative stress level of the organism for a given period of time (8,9). As the oxidative stress level is reported to increase with age, high level of thiols may be explained by acting of thiols as prooxidant molecules in the situation of adult migraineurs (19).

In our study, we found lower thiol and higher disulfide levels in children with migraine which demonstrate that there is an ongoing oxidative process in these patients. One of the reasons for low thiol level in pediatric migraine patients may be greater extent thiol consumption to remove excess free radicals generated. Also, dynamic changes in the oxidant-antioxidant balance may play a different role in pediatric patients than adults. We found high levels of disulfide in children with migraine during the attack-free period and according to the hypotesis that migraine is a response to increased levels of oxidative stress in the brain, further increase may be expected at the time of attack. However, some components of the migraine attack like substance P, platelet activation, serotonin are suggested to be neuroprotective by reducing oxidant production and delivering antioxidants to the brain (12). The choice of time is a limitation of our study. In which way the oxidant-antioxidant balance will shift during an attack can be demonstrated with future prospective studies.

The vascular theory of headache proposes that aura is represented as a consequence of vasoconstriction and cortical hypoxia. In animal models, intermittent hypoxia is reported to cause oxidative stress via mitochondrial dysfunction. Moreover, oxidative stress may help account for the relationship between cortical spreading depression and the subsequent attack in migraine with aura (20). Studies on the relationship between aura and oxidative stress are controversial. Tuncel et al. and Tripathi et al. reported that patients with aura were more prone to oxidative stress, however, Eren Y et al. (23) and Gümüşyayla et al. (17) did not find statistically significant relationship between migraine groups with and without aura (21,22). We did not find any correlation between presence of aura and thiol/disulfide parameters. If our study could be performed during the aura phase, more definite results could be reported on this issue.

Alp et al. (24) detected significant negative correlation between total thiol levels and the duration of headache in adult migraineurs. They suggested that oxidative stress may not only play a role in migraine pathogenesis but also is a triggering factor for attack severity and duration. In another study, there was no significant correlation between oxidative stress markers and duration of migraine attack (25). We also did not find any correlation between duration of attacks and thiol/disulfide parameters. Many studies about migraine and oxidative stress include adult patients. As defined in theInternational Headache Society (IHS) criteria and studies in the literature, the minimum duration of headache in adults is 4 hours, however in young children migraine attacks frequently last less than 4 hours (11,25). In our study, only 34% of the patients reported that the pain lasted more than 4 hours. The absence of a relationship between oxidative stress parameters and the duration of the attack in our study may be due to the fact that the duration of the attacks in children is not as long as in adults.

Erol et al. (26) reported that neither duration of disease nor frequency of attacks affected antioxidants in children with migraine. Similarly, there was no significant difference between the frequency of attacks and native thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native/total thiol levels in our study. However, the group with attacks less than once a week had lower total thiol levels than the other groups.

Female adults appear to have lower levels of oxidative stress compared to male adults. One reason for this apparent gender difference could be due to the anti-oxidant properties of estrogen (27). No statistically significant correlation was found between gender and thiol/disulfide values in our study. Approximately 65% of our patients were female and about 90% of them were pubertal and postpubertal. However, there was no difference between gender or puberty and thiol/disulfide parameters which might support that not only estrogen but also some other mechanisms are responsible for the lower levels of oxidative stress in adult females compared to male adults.

CONCLUSIONS

High oxidative stress values are determined in children with migraine which could play a role in migraine pathogenesis. Despite the limitations mentioned above, our data constitutes one of the largest studies investigating the relationship between pediatric migraine and oxidative stress in the literature. Prospective studies analyzing the dynamic changes in the oxidant-antioxidant balance during the attack and the aura phase are needed to support the presence and importance of oxidative stress in pediatric migraine.

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Evaluation of Primary and Secondary Raynaud's Phenomenon in Childhood

Çocukluk Çağı Birincil ve İkincil Raynaud Fenomeni Olgularının Değerlendirilmesi

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ABSTRACT

Objective: To evaluate the clinical, laboratory and capillaroscopic findings of pediatric patients with Raynaud's phenomenon.

Material and Methods: Ninety-five pediatric patients who were diagnosed with Raynaud's phenomenon between January 2014 and January 2021, were retrospectively examined. The demographic data, laboratory parameters and capillaroscopic findings of the patients were recorded. The capillaroscopic findings of the patients were classified as normal, nonspecific abnormalities and scleroderma pattern.

Results: Primary Raynaud's phenomenon was present in 84 (88.5%) patients, and secondary Raynaud's phenomenon was present in 11 (11.5%). Arthralgia, arthritis, rash and recurrent fever were significantly more common in secondary Raynaud's phenomenon (p=0.001, p=<0.001, p=0.01, p=0.035, respectively). Antinuclear antibody positivity >1/320 was significantly higher in the patients with secondary Raynaud's phenomenon (p=0.01). Of the 40 patients who had capillaroscopy performed, 2 had a scleroderma pattern, 19 had nonspecific changes, and 19 had normal nailfold capillaroscopic findings. Capillary irregularity, tortuous capillaries and increased branching were significantly higher in the secondary Raynaud's phenomenon cases (p=0.015, p=0.015, p=0.003, respectively).

Conclusion: Having antinuclear antibody titer >1/320 and detection of capillary irregularity, tortuous capillaries and increased branching may be useful in distinguishing primary and secondary Raynaud's phenomenon.

Key Words: Antinuclear antibody, Capillaroscopy, Pediatric, Raynaud's Phenomenon, Rheumatology

ÖZ

Amaç: Raynaud fenomeni ile takip edilen pediatrik hastaların klinik, laboratuvar ve kapilleroskopik bulgularını değerlendirmek.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles.The study was obtained from Ankara City Hospital, No. 2 Clinical Research Ethics Committee (Approval number: E2-21-258).

Contribution of the Authors / Yazarların katkısı*: *SEZER M: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***CELIKEL E:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AYDIN F:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study. ***EKICI TEKIN Z:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. KURT T: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***TEKGOZ N:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KARAGOL C:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***COSKUN S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KAPLAN MM:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***CELIKEL ACAR B:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Gereç ve Yöntemler: Ocak 2014 ile Ocak 2021 tarihleri arasında Raynaud fenomeni tanısı ile takip edilen 95 çocuk hasta geriye dönük olarak incelendi. Hastaların demografik verileri, laboratuvar parametreleri ve kapilleroskopik bulguları kaydedildi. Hastaların kapilleroskopik bulguları normal, nonspesifik anormallikler ve skleroderma paterni olarak sınıflandırıldı.

Bulgular: Birincil Raynaud fenomeni 84 hastada (%88.5), ikincil Raynaud fenomeni 11 hastada (%11.5) mevcuttu. Artralji, artrit, döküntü ve tekrarlayan ateş, sekonder Raynaud fenomeninde anlamlı olarak daha sıktı (sırasıyla p=0.001, p=<0.001, p=0.01, p=0.035). Sekonder Raynaud fenomeni olan hastalarda 1/320 titre ve üzerinde antinükleer antikor pozitifliği anlamlı olarak daha sıktı (p=0.01). Kapilleroskopi yapılan 40 hastanın 2'sinde skleroderma paterni, 19'unda nonspesifik değişiklik ve 19'unda normal kapilleroskopi bulguları vardı. İkincil Raynaud fenomeni olgularında kapiller düzensizlik, tortuyoz kapiller ve dallanma artışı anlamlı olarak daha sık saptandı (sırasıyla p=0.015, p=0.015, p=0.003).

Sonuç: Antinükleer antikor titresinin >1/320 olması ve kapiller düzensizlik, tortuyoz kapiller ve dallanma artışının saptanması, birincil ve ikincil Raynaud fenomenini ayırt etmede faydalı olabilir.

Anahtar Sözcükler: Antinükleer antikor, Kapilleroskopi, Pediatri, Raynaud Fenomeni, Romatoloji

INTRODUCTION

Raynaud's phenomenon (RP) is a vasospastic disorder characterized by recurrent transient vasospasm in the smaller arteries of the fingers and toes that results in triphasic color changes. The vasospasm causes blanching (whitening), followed by the dilation of the capillaries and venous stasis causing cyanosis (blue coloration). Finally, the arteries dilate, causing the return of blood flow and post-ischemic hyperemia (redness). The hands, feet, ears, nose and nipples can be affected (1). RP prevalence increases with age in children, especially among the girls (2). The prevalence of primary RP in the general population is 5-20%, while it is 15% in children who are 12-15 years old (3). In a multicenter report, the prevalence of RP was found to be 2.2% between 0 and 10 years of age and 20% between the ages of 10 and 20 (4).

Interactions between genetic, neural, vascular and intravascular factors are responsible for the pathogenesis of RP. The underlying defect in primary RP is considered to be a local fault in the vascular function of thermoregulation and excessive vasoconstriction (5). Secondary RP results out of acquired conditions involving endothelial damage that may be associated with structural deterioration (6).

According to its etiology, RP can be primary (80% of cases) or secondary. There is no associated disease in primary RP. Secondary RP is attributed to an underlying disease, most commonly connective tissue diseases (7). Risk factors for RP in children are living in cold climates, female sex, and positive family history. Some conditions associated with RP may be listed as rheumatological disorders (scleroderma, systemic lupus erythematosus, juvenile idiopathic arthritis, dermatomyositis, mixed connective tissue disease, Sjogren's syndrome, Takayasu arteritis), mechanical injury, arterial diseases, hematological diseases, infection, medication, and exposure to chemical agents (1, 8). The clinical symptoms of the underlying pathology are usually present at the time of examination. However, in connective tissue diseases like scleroderma, RP may occur as the first symptom years before other clinical findings (9). RP is a clinical sign in 70-80% of patients at presentation in juvenile systemic scleroderma (10). In several studies evaluating RP cases in children, the rates of connective tissue diseases were found to be 23.6% and 28% (11, 12).

The difference between secondary RP and primary RP is related to their severity and complications. Attacks in secondary RP are more severe and frequent, and they usually have an asymmetrical pattern. Primary RP usually develops at an earlier age than secondary RP. Digital ulceration, necrosis and ischemic self-amputations are common in secondary RP. Nailfold capillary microscopy is a powerful diagnostic tool that can be used for the differential diagnosis of primary and secondary RP (13, 14). In primary RP, capillaroscopic findings are likely to be normal. Antinuclear antibody (ANA) positivity and changes in capillaroscopy (capillary enlargement, decreased number of capillaries, avascular areas) are indicative of secondary RP (15). Primary RP patients may develop symptoms of collagen tissue diseases over time. Therefore, patients who are followed up with a diagnosis of RP should be evaluated in terms of systemic diseases and monitored carefully (16).

The aim of this study is to evaluate the clinical, laboratory and capillaroscopic findings of pediatric patients with primary and secondary RP.

MATERIAL and METHODS

Ninety-five patients diagnosed with RP in the pediatric rheumatology department of our hospital between January 2014 and January 2021 were included in the study. The international consensus criteria for the diagnosis of RP were used to diagnose the patients (17). The study was obtained from Ankara City Hospital, No. 2 Clinical Research Ethics Committee (Approval number: E2-21-258).

Patients over 18 years of age and those with secondary causes other than rheumatological diseases were excluded from the study. Patients who already had additional connective tissue disease at the time of diagnosis were excluded.

Data were collected from patient records retrospectively. Age at diagnosis, sex, clinical findings, duration of symptoms, trigger factors, concomitant diseases, family history and all initial laboratory parameters including hemoglobin (Hb), white blood

cell count (WBC), platelet counts (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complement 3 (C3), complement 4 (C4), ANA, anti-dsDNA, extractable nuclear antibody (ENA) panel, antiphospholipid antibodies and capillaroscopic findings were recorded. The laboratory parameters of the patients had been recorded at the time of their admission. ANA was evaluated with the IFA method and ENA panel was evaluated using the immunoblot method. Values above 1/100 were considered ANA-positive. Among the antiphospholipid antibodies, the lupus anticoagulant, beta 2 glycoprotein, and anticardiolipin antibodies were tested.

Capillaroscopy was performed by experienced specialist rheumatologists. The capillaroscopic findings of the patients were classified as normal (capillary count >7, capillary morphology normal, no capillary enlargement, no avascular area), nonspecific abnormalities (one of these following: decrease in capillary number, capillary enlargement, abnormal morphology or microhemorrhage) and scleroderma pattern (early, active or late stage). More specifically the presence of giant capillaries (capillaries with an apical diameter ≥50 µm) or the combination of abnormal shapes with an extremely lowered number of capillaries points to a 'scleroderma pattern' (18, 19).

The clinical and laboratory data of the patients with primary and secondary RP were compared.

Statistical analyses

The statistical analyses were performed using the SPSS software version 25. The normal distribution of the variables was investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Descriptive statics are presented using medians and interquartile ranges (IQR) for the non-normally distributed and ordinal variables and frequencies for the categorical variables. In the comparisons between groups, Mann-Whitney U test was used for the non-normally distributed variables and ordinal variables, and Chi-squared or Fisher's tests were used for the categorical variables. A p-value smaller than 0.050 was considered to show a statistical significance.

RESULTS

Ninety-five patients with RP, of which 68 (71.6%) were female patients (female-to-male ratio= 2.5:1), were included in the study. The median age of the patients was 15.5 years (IQR 13.9-16.5 years) at the onset of their disease. The patients were most frequently admitted to the hospital in February (n=15, 15.8%) and March (n=15, 15.8%). Where as cold was a trigger for all patients also, 3 (3.2%) patients were triggered by stress. The mean follow-up period for all patients was 2.6 months, where the mean follow-up period of the secondary RP patients was 7.9 months. The clinical and laboratory characteristics of the patients are shown in Tables I and II.

Primary RP was present in 84 (88.5%) patients, and secondary RP was present in 11 (11.5%). Among the secondary RP patients, the associated disease was SLE in 3 (27.2%) patients, scleroderma in 2 (18.2%) patients, juvenile dermatomyositis in 1 (9.1%) patient, and juvenile idiopathic arthritis in 5 (45.5%) patients.

Table I: Baseline clinical characteristics of Raynaud phenomenon patients.

	All patients (n=95)	Primary RP (n=84)	Secondary RP (n=11)	p
Gender, female*	68 (71.6)	59 (70.2)	9 (81.8)	0.723
Age at diagnosis (years) †	15.5 (13.9-16.5)	15.5 (13.9-16.6)	14.9 (12-16.4)	0.496
Duration of symptoms (month) † n=61	12 (2-24)	12 (2-24)	4 (1.6-12)	0.355
Biphasic pattern*	69 (72.6)	62 (73.8)	7 (63.6)	0.486
Triphasic pattern*	26 (27.4)	22 (26.2)	4 (36.4)	0.486
Arthralgia*	40 (42.1)	30 (35.7)	10 (90.9)	0.001
Arthritis*	17 (17.9)	8 (9.5)	9 (81.8)	<0.001
Skin eruption*	5 (5.3)	2 (2.4)	3 (27.3)	0.010
Malar rash*	5 (5.3)	4 (4.8)	1 (9.1)	0.467
Photosensitivity*	8 (8.4)	7 (8.3)	1 (9.1)	1.000
Dry mouth/dry eyes*	10 (10.5)	9 (10.7)	1 (9.1)	1.000
Apthous ulcers*	20 (21.1)	18 (21.4)	2 (18.2)	1.000
Alopecia*	3 (3.2)	2 (2.4)	1 (9.1)	0.312
Thickened of the skin*	4 (4.2)	1 (1.2)	3 (27.3)	0.004
Muscle weakness*	1 (1.1)	0 (0)	1 (9.1)	0.116
Headache*	6 (6.3)	6 (7.1)	0 (0)	1.000
Weight loss*	2 (2.1)	1 (1.2)	1 (9.1)	0.219
Recurrent fever/abdominal pain*	3 (3.2)	1 (1.2)	2 (18.2)	0.035

*****Number (percentage), †Median (Interquartile range)(IQR)*

Table II: Baseline laboratory characteristics of Raynaud phenomenon patients.

	All patients (n=95)	Primary RP (n=84)	Secondary RP (n=11)	p
WBC, 10^9/L*	6.64 (5.8-8)	6.62 (5.74-7.97)	6.68 (6.1-9.1)	0.926
Hemoglobin (g/dL)*	13.8 (13-14.8)	13.9 (13.1-14.9)	13 (12.9-14.1)	0.063
ESR, mm/h*	5 (4-8)	5 (4-7)	8 (4-15)	0.209
CRP, mg/dL*	0.07 (0.01-0.18)	0.03 (0.01-0.17)	0.18 (0.01-0.2)	0.213
C3 g/L*	1 (0.9-1.1)	1 (0.9-1.1)	0.9 (0.6-1.3)	0.383
C4 g/L*	0.19 (0.14-0.21)	0.18 (0.14-0.21)	0.2 (0.1-0.21)	0.671
ANA positivity† (>1/100 titer) n=94	40 (42.6)	32 (38.6)	8 (72.7)	0,050
ANA positivity† (>1/320 titer) n=94	20 (21.3)	14 (16.9)	6 (54.5)	0.010
Anti dsDNA positivity† n=86	1 (1.2)	0 (0)	1 (10)	0.116

Median (Interquartile range)(IQR), †Number (percentage), **ANA: Antinuclear antibodies, **C3:** Compleman 3, **C4:** Compleman 4, **CRP:** C-reactive protein, **ESR:** Erythrocyte sedimentation rate, **WBC:** White blood cell*

Table III: Capillaroscopic findings in RP patients.

	All patients (n=40)	Primary RP (n=35)	Secondary RP (n=5)	p
Capillaroscopy findings Normal*				0.049
Nonspesific changes and sclerodema pattern*	19 (47.5) 21 (52.5)	19 (54.3) 16 (45.7)	0 (0) 5 (100)	
Capillary loss*	1 (2.5)	0 (0)	1 (20)	0.125
Capillary disorganization*	11 (27.5)	7 (20)	4 (80)	0.015
Capillary enlargement*	16 (40)	13 (37.1)	3 (60)	0.373
Giant capillaries*	1 (2.5)	0 (0)	1 (20)	0.125
Tortuous capillaries*	11 (27.5)	7 (20)	4 (80)	0.015
Capillary branching*	8 (20)	4 (11.4)	4 (80)	0.003
Microhemoarrages*	7 (17.5)	5 (14.3)	2 (40)	0.204

Number (percentage)

Color changes were biphasic in 69 (72.6%) patients, and triphasic in 26 (27.4%) patients. Twenty-one (22.1%) patients had pain and 40 (42.1%) had numbness. The most common findings accompanying RP were arthralgia (n=40, 42.1%), arthritis (n=17, 17.9%) and oral ulcers (n=20, 21.1%). Nine (9.5%) patients had a family history of rheumatic diseases (including 4 RP, 2 SLE, 1 systemic sclerosis, 1 Sjogren's syndrome and 1 rheumatoid arthritis). All patients with a family history were primary RP patients.

There was no significant difference between the primary RP and secondary RP patients in terms of their pattern of color changes, age of onset, complete blood count parameters or acute phase reactants. The positivity rate of ANA titer >1/100 was 42.6% (40 patients). The positivity rate of ANA titer >1/320 was significantly higher in the secondary RP patients (p=0.010). Positivity was detected in 27 of the 58 (46.6%) patients whose ENA panels had been tested. Of 27 patients with positive ENA panels, 8 (29.6%) had isolated DFS70, 3 (11.1%) had Scl70 or RNP-Sm or PCNA, 4 (14.8%) had CENP-B, 2 (7.4%) had Ribosomal P or SS-B or Ro-52 and 1 (3.7%) had Jo-1 positivity. There was no significant difference in terms of ENA panel positivity between primary and secondary RP. Antiphospholipid antibodies had been tested in 47 patients, and isolated Beta-2 glycoprotein IgM positivity was detected in 2 patients.

Among the 40 patients who had capillaroscopy performed, 2 had a scleroderma pattern, 19 had nonspecific changes, and 19 had normal nailfold capillaroscopic findings. Capillary irregularity, tortuous capillaries and increased branching were significantly higher in the secondary RP patients (p=0.015, p=0.015, p=0.003, respectively) (Table III).

Thirty-two (38.1%) of the primary RP patients and 5 (45.5%) of the secondary RP patients were treated with a vasoactive agent. Treatment response was observed in 90.3% of the primary RP patients and 80% of the secondary RP patients.

DISCUSSION

In our study, it was revealed that children diagnosed with RP with joint complaints, rash, fever, high-titer ANA positivity and capillaroscopy findings should also be followed up in terms of underlying rheumatological diseases. The importance of screening tests for ANA, more specific antibodies associated with connective tissue diseases, and nailfold capillaroscopy in

patients presenting with RP have been demonstrated in adult series, because the data suggest that these may be risk factors for developing a connective tissue disease. There are still no clear recommendations for RP in children, and the importance of screening tests and imaging techniques has been only partly elucidated.

In general, the prevalence of RP is higher in girls than boys and increases with age. Nigrovic et al. (11) reported that 80% of 123 children with RP were girls, with a mean age of symptom onset of 12.3±4.3 years. Pavlov-Dolijanovic et al. (12) showed that among 250 RP patients, 44% were between 10 and 16 years of age, and 140 (56%) were adolescents aged 17 to 20 years. Eighty-two percent of the patients were girls, and the female-to-male ratio was 5:1 (12). Similarly, in our study, RP was more common in girls (71.6%). The median age of the patients included in our study was 15.5 years at the onset of their disease.

It is sometimes difficult to diagnose RP in children, as some patients may not have triphasic color changes and parents may perceive the color changes in their child as a normal response to cold exposure. Although three-color changes are not experienced by every patient with RP, triphasic color changes in the fingers or toes may be seen with blanching followed by cyanosis and then reactive hyperemia. Monophasic color change is more common than biphasic and triphasic color changes which are typical attacks. "Definite RP" is defined as biphasic color changes in response to cold, while monophasic color changes accompanied by paresthesia or numbness are termed "possible RP". In any case, mainly disturbances of the cutaneous microcirculation lead to these color changes. Nigrovic et al. (11) showed the triphasic pattern in 24% of primary RP patients and 19% of secondary RP patients. Turan et al. (3) detected the triphasic pattern in 34.5% of patients. In our study, the triphasic pattern rate was found to be 26.2% in the primary RP patients and 36.4% in the secondary RP patients. There was no significant difference in the pattern of color changes between the primary and secondary RP patients. Similarly, Nigrovic et al. (11) reported that biphasic or triphasic color changes were less common than monophasic color changes and not more common in secondary than primary RP.

ANA positivity and capillaroscopic findings are the most important parameters associated with evaluating the progression of the condition connective tissue diseases (20). ANA positivity at low titers can also be found at different rates in the healthy population, depending on geographical differences (3, 21).

In our study, ANA was positive in 40 (42.6%) patients. While ANA positivity at a 1/100 titer was seen in 21.7% of the patients with primary RP, no significant difference was found between the primary and secondary RP patients. The rate of ANA positivity over 1/320 was significantly higher in the cases with secondary RP (p=0.010). Similarly, the rate of ANA positivity was found to be 25% in patients with primary RP in another study (11). A study in Italy found that 63% of patients with RP who developed rheumatological diseases at follow-up had an ANA titer above 1/160, and only 22% of patients with primary RP had this positivity (22). Patients with high-titer ANA positivity should be evaluated carefully in terms of underlying diseases.

Capillaroscopy is an important imaging technique in the differentiation of primary and secondary RP. According to the Pediatric Rheumatology European Society (PRES) Scleroderma Working Group recommendations, capillaroscopy should be performed at the time of diagnosis and the findings should be classified as normal, nonspecific changes and scleroderma pattern. Additionally, patients with ANA positivity, specific autoantibodies and/or nailfold capillary changes were considered to be at high risk and follow-up was recommended (20). Capillary enlargement, decreased number of capillaries, giant capillaries and avascular areas are indicative of secondary RP. In a large series of pediatric patients with RP, 211 of 250 children with RP were classified as having normal capillaroscopy findings, 29 patients were classified as having nonspecific capillary changes, and 10 patients had a scleroderma pattern according to capillaroscopy findings. The frequency of normal capillary findings in patients with primary RP was higher than that in patients with secondary RP. Nonspecific capillary changes had a similar distribution in both primary and secondary RP. A scleroderma pattern was found only in patients with secondary RP (12). Nigrovic et al. (11) stated that nailfold capillaries were nonspecific or abnormal in 23% of primary RP and 68% of secondary RP patients. In our study, 47.5% of the patients had normal findings, 47.5% had nonspecific changes, and 5% had scleroderma patterns among the 40 patients with capillaroscopy results. Capillary irregularity, tortuous capillaries and increased branching were significantly higher in the secondary RP cases.

Despite the large number of patients, the limitations of our study were its retrospective nature and limited number of secondary RP patients. Conducting the study with a larger number of patients with both primary and secondary RP would be more valuable in terms of the significance of the results. Because it was a retrospective study, only half of the patients had received capillaroscopy examination. Prospective, multicenter studies including long-term results of pediatric RP patients should be conducted.

In conclusion, having ANA titer >1/320 and detection of capillary irregularity, tortuous capillaries and increased branching may be useful to distinguish between primary and secondary RP. Patients with joint complaints, rash, fever, high-titer ANA positivity and capillaroscopy findings should be evaluated carefully in terms of underlying diseases.

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Etiological Assessment of Acute Urticaria in Children

Çocuklarda Akut Ürtikerin Etiyolojik Değerlendirilmesi

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ABSTRACT

Objective: Acute urticaria is one of the most common causes of admission to hospitals in children. The aim of the study is to evaluate the etiology of acute urticaria in patients who admitted to pediatric allergy outpatient clinics.

Material and Methods: The patients who were diagnosed as acute urticaria in pediatric allergy outpatient clinics between January 1, 2016 and December 31, 2016 were included in the study. Patient information was recorded retrospectively from medical files.

Results: In this study, 469 patients with acute urticaria were evaluated. The median (min-max) age of the patients was 7 years (2 months-18 years), and 48.8 % of them were male. Angioedema was accompanying in 20 % of the patients. Recurrent acute urticaria was seen in 33.5 % (n = 157) of the patients. In the history, infections were the triggers in 37.5 % (n=176) of the patients, drugs in 17.9 % (n=84), food in 10.9 % (n=51), insect bites in 3.2 % (n=15), and 0.2 % (n=1) of them had the vaccine. When the patients were evaluated with the medical histories, physical examination and laboratory findings; triggers could not be detected in 59 % (n=276) and these patients were diagnosed as idiopathic acute urticaria. Infections (37.5 %; n=176) were in the first place in patients with triggers. Food and drug allergies were confirmed in only one patient each. Considering the etiological distribution according to age groups, it was seen that idiopathic acute urticaria was more common in the 12-18 age group and infection-associated acute urticaria in the group under 2 years old (p=0.009).

Conclusion: Mostly, triggers cannot be found in children who apply to the allergy clinic due to acute urticaria. In patients who can be identified triggers, infections are in the first place. However, patients' clinical histories may also include food or drug(s) as a suspected trigger, and it is important to evaluate these patients with diagnostic allergy tests. Thus, misdiagnosis of patients and unnecessary food or drug restrictions would be prevented.

Key Words: Acute Urticaria, Children, Etiology, Infection, Trigger

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study has been approved by Health Sciences University Ankara Pediatric Health and Diseases Hematology Oncology Training and Research Hospital's ethical board (2017-073/ 12.06.2017).

Contribution of the Authors / Yazarların katkısı*: *ARI H: Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in the writing of the whole or important parts of the study. ***GUVENIR H:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, ***TOYRAN M:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***CIVELEK E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***BUYUKTIRYAKI B:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, ***GINIS T:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, ***KOCABAS CN:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***DIBEK MISIRLIOGLU E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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ÖZ

Amaç: Akut ürtike rçocuklarda hastane başvurularının en sık nedenlerinden biridir. Çalışmanın amacı çocuk alerji polikliniğinde akut ürtiker tanısı alan hastaların etiyolojik açıdan değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmaya 1 Ocak 2016 - 31 Aralık 2016 tarihleri arasında hastanemizin çocuk alerji polikliniklerinde akut ürtiker tanısı alan hastalar alındı. Hasta bilgileri dosya kayıtlarından geriye dönük olarak kaydedildi.

Bulgular: Çalışmada akut ürtiker tanısı alan 469 hasta değerlendirildi. Hastaların yaş ortancası (min-maks) 7 yıl (2 ay-18 yıl) olup, %48.8'i erkekti. Hastaların % 33.5'inde (n=157) tekrarlayan akut ürtiker öyküsü vardı ve % 20'sine anjiyoödem de eşlik ediyordu. Öyküde tetikleyici olarak hastaların % 37.5'ünde (n=176) enfeksiyonlar, % 17.9'unda (n=84) ilaç, % 10.9'unda (n=51) besin, % 3.2'sinde (n=15) böcek ısırığı ve % 0.2'sinde (n=1) aşı bulunuyordu. Hastalar anamnez, fizik muayene ve laboratuvar bulguları ile değerlendirildiğinde; %59'unda (n=276) tetikleyici saptanamadı ve bu hastalar idiopatik akut ürtiker olarak tanı aldılar. Tetikleyici saptanan hastalarda enfeksiyonlar (% 37.5; n=176) ilk sırada yer alıyordu. Besin ve ilaç alerjisi ise sadece 1'er hastada doğrulandı. Yaş gruplarına gore etiyolojik dağılıma bakıldığında, 12-18 yaş grubunda daha çok idiyopatik akut ürtiker, 2 yaş altı grupta ise enfeksiyonla tetiklenen akut ürtiker olduğu görüldü (p=0.009).

Sonuç: Akut ürtiker nedeniyle alerji kliniğine başvuran çocuklarda çoğunlukla tetikleyici bulunamamaktadır. Tetikleyici tespit edilebilen hastalarda ise enfeksiyonlar ilk sırada yer almaktadır. Ancak hastaların klinik öykülerinde şüpheli tetikleyici olarak yiyecek veya ilaç(lar) da bulunabilir ve bu hastaların tanısal alerji testleri ile değerlendirilmesi önemlidir. Böylece hastaların yanlış tanı almaları ve gereksiz besin veya ilaç kısıtlamaları önlenebilecektir.

Anahtar Sözcükler: Akut Ürtiker, Çocuk, Etiyoloji, Enfeksiyon, Tetikleyici

INTRODUCTION

Urticaria are skin lesions that can appear in any part of the body, they are characterized by itchy and erythematous plaques and usually they are healed within 24 hours. When the deeper of the dermis is involved and there is also a subcutaneous involvement accompanied by pain rather than itchiness, then this version is called angioedema. With a very rough definition, urticaria is a vascular reaction that develops against various stimulants and is formed with various mechanisms (immunologic or non-immunologic). Symptoms in acute urticaria last shorter than 6 weeks while in chronic urticarial they last longer than 6 weeks (1).

Acute urticaria can be observed in all age groups. It has been reported that around 20 % of the general population suffers at least one acute urticaria attack during their lifetime (2). There are not many studies available on acute urticaria prevalence in children but it is reported to be 2-6.7% (3).

Infections, drugs, food and bites are among the most common reasons behind acute urticaria. Acute urticaria may develop during or after viral or bacterial infections particularly in children. In some pediatric series, infections have been found to be related to more than 80 % of acute urticaria cases (8). However, it is not always possible to detect etiology in acute urticaria and in almost half of the cases etiology is never determined (4). The aim of this study is to make an etiology assessment of the patients applying to pediatric allergy outpatient clinics with acute urticaria.

MATERIAL and METHOD

The population of our study was <18-year-old patients who applied to our hospital's pediatric allergy outpatient clinic between 1 January 2016 and 31 December 2016 and received acute urticaria diagnosis.

The study has been approved by Health Sciences University Ankara Pediatric Health and Diseases Hematology Oncology Training and Research Hospital's ethical board (2017-073/ 12.06.2017).

Patient files have been reviewed to record their demographic characteristics (age, gender, family and individual atopy history), duration of urticaria, triggering factors, accompanying findings, physical examination and laboratory tests conducted to determine etiology (complete blood count, liver and kidney function tests, erythrocyte sedimentation rate, c reactive protein, full urine test, urine culture, throat culture, fecal parasite screening and lung X-rayresults).

Patients with suspected drugs or food in their history have been invited to clinic and diagnostic tests had been invited to the cliinic and had undregone allergologic tests to confirm or rule out allergy.

Skin prick test: Patients without dermographism have been subjected to skin prick test. Histamine (10 mg/mL) was used as a positive control and diluent (temolin) as a negative control for the test. Skin prick tests were performed on the volar forearm, and were read after 20 min. SPT results were considered positive if a wheal size was ≥3 mm compared with the negative control.

Allergens used in skin prick test (Stallergenes SA, 92160, Antony, France): - Food allergens (cow's milk, egg white and yolk, wheat, soya, hazelnut, peanut, orange, banana) - House dust mites (Dermatophagoides farinae, Dermatophagoides pteronyssinus) - Pollen: grass-pollen mixture of 5 (Perennial ryegrass, Cynodondactylon, Timothy grass, Sweet vernal grass, Bluegrass), grain-pollen mixture of 4 (oat, wheat, barley, maize), tree pollen mixture (Cupressus sempervines, Salix caprea, Olea europaea, Betula alba, Platanus vulgaris), weed polen (Salsola kali, Chenopodium album, Parietaria judaica, Artemisia vulgaris,

Ambrosia elatior, Plantago, Compositae) - Mold (Aspergillus mixture [Aspergillus fumigatus, Aspergillus niger, Aspergillus nidulans], Cladosporium mixture [Cladosporium cladospories, Cladosporium herbarum], Alternaria alternate) - Epithelium (cats and dogs) - Cockroach (Blatella germanica) - Latex.

Diagnostic assessment for drug allergy: A guide prepared by the European Academy of Allergy and Clinical Immunology (EAACI) association has been used for the drug allergy assessment of the patients (5). Accordingly, a skin prick test with the parenteral form of the suspected drug has been conducted, and if the skin prick test was negative, intradermal test has been conducted. If the intradermal test was also negative, drug provocation test has been conducted orally with the suspected drug. Patients who did not display any reactions during provocation have been kept under observation for at least 2 hours. Drug allergy has been ruled out if no reaction was detected. However, detection of any objective findings during or after the provocation led to the acceptance of drug allergy.

Diagnostic assessment for food allergy: Prick test has been performed with the suspected food. Patients with a negative skin prick test were subjected to food oral provocation test. Observing any findings in the patient related to skin (urticaria, angioedema), cardiovascular (hypotension, confusion, tachycardia), respiration (wheezing, hoarseness, cough, dyspnea), gastrointestinal (nausea, vomiting, stomach ache), neurologic (dizziness, vertigo, fainting) systems during provocation test or following the final dosage meant the test was deemed positive and terminated.

Consent of patients and / or their families has been taken prior to skin tests and provocation tests.

Statistical Analysis

All findings have been evaluated with SPSS 17 (SPSS Inc, Chicago, IL, 2009) program. Discrete variables are given in numbers and percentages, continuous variables are given in minimum, maximum, mean±standard deviation and median. Chi-square test has been used for the comparison of discrete variables. T-test has been for the comparison of continuous variables of the two groups conforming to normal distribution, and Mann Whitney-U test has been used for normal the comparison of continuous variables not conforming to normal distribution. $p<0.05$ value has been considered statistically significant.

RESULT

In this study, 469 patients with acute urticaria were evaluated. The median age (min-max) of the patients was 7 years (2 months-18 years) and 48.8% were male. Urticaria was generalized in more than half of the patients. Ninety-four (20%) patients had accompanying angioedema. The most accompanying extracutaneous symptom was fever (Table I).

Table I: Symptomsofpatients.

Symptoms	n (%)
Onlyskinsymptoms	293 (62.5)
Urticaria	199 (42.5)
Urticaria+Angioedema	94 (20)
Localization of urticaria	
Generalized	190 (40.5)
Extremities	129 (27.5)
Extremities + Trunk	65 (13.9)
Head and neck region	55 (11.7)
Trunk	30 (6.4)
Localization of angioedema	
Periorbital area	26 (27.7)
Periorbital area + lips	26 (27.7)
Extremities	21 (22.3)
Lips	20 (21.3)
Genital area	1 (1)
Skin +other symptoms	176 (37.5)
Fever	95 (20.3)
Fever+Cough	63 (13.2)
Dysuria	8 (1.7)
Diarrhea	5 (1.1)
Analzone itching	3 (0.6)
Toothache	2 (0.4)

Infections were the first (37.5%) among the possible triggers in the clinical history (Table II). In 17.9% (n=84) of the cases with acute urticaria, there was a history of drug use as a possible trigger (Table II). Diagnostic testing was planned for all patients with possible drug-related urticaria. However, 18 patients later had used the same drug without any reactions. The parents of 20 patients did not consent for drug tests. The remaining 46 patients were evaluated to drug allergy tests. 11 patients with suspected penicillin allergy were checked for specific IgE and it was found negative. Drug skin tests and provocation tests were negative in 45 patients while drug allergy was confirmed only in 1 patient. This patient was positive penicillin skin test.

In 10.9% (n=51) of the patients, there was food as a possible trigger in the history (Table II). 8 of those patients had not developed any symptoms when they consumed the same food afterward. No diagnostic test with suspected food was performed on these patients. The remaining 43 patients have been subjected to skin prick test and provocation test with suspected foods and only one case had a positive skin test result, who was tested with green lentil. The history of this patient included acute urticaria recurring with consumption of green lentils.

The most common abnormal laboratory findings were elevation in C-reactive protein. The other abnormal laboratory findings are shown in Table III.

Among patients evaluated with clinical history, physical examination, and laboratory data 58.8% (n=276) of the patients did not have any trigger, while there were 193 (41.2%) patients

Table II: Possible Triggers in History

	n (%)
Infection	176 (37.5)
Respiratory tract infection	163 (92.7)
Urinary tract infection	8 (4.5)
Acute gastroenteritis	5 (2.8)
Drug	84 (17.9)
Antibiotics	56 (66.7)
Amoxicillin clavulanate	44 (52.4)
Clarithromycin	4 (4.8)
Cefdinir	3 (3.6)
Metronidazole	2 (2.4)
Ceftriaxone	1 (1.2)
Cefixime	1 (1.2)
Cefuroxime	1 (1.2)
Nonsteroidal anti-inflammatory drugs	20 (23.8)
Ibuprofen	11 (13.1)
Paracetamol	8 (9.5)
Methimazole	1(1.2)
Others	8 (9.5)
Pseudoephedrine+Dextromethorphan	3 (3.6)
Fish oil	2 (2.4)
Sumitrin	1 (1.2)
Lidocaine	1 (1.2)
Carbamazepine	1 (1.2)
Food	51 (10.9)
Chocolate	11 (21.6)
Milk and products	5 (9.8)
Strawberry	3 (5.9)
Spice	3 (5.9)
Egg	3 (5.9)
Honey	2 (3.9)
Fish	2 (3.9)
Sunflower seeds	2 (3.9)
Hazelnut	2 (3.9)
Lentil	2 (3.9)
Dessert	2 (3.9)
Eggplant	2 (3.9)
Chicken	2 (3.9)
Other foods	20 (39.2)
Beeorin sectbites	15 (3.2)
Vaccine (Hepatitis Bvaccine)	1 (0.2)
Unknown	142 (30.3)

Table III: Patients with abnormalities in laboratory tests.

	Abnormal results / Number of patients under going test (%)
Complete Blood Count	
Leukocytosis	69/349 (19.8)
Anemia	61/349 (17.5)
Eosinophilia	39/349 (11.2)
Thrombocytosis	26/349 (7.5)
Thrombocytopenia	3/349 (0.9)
Biochemical tests	
Abnormal liver function tests	44/270 (16.3)
Abnormal renal function tests	2/164 (1.2)
Acute phase reactants	
Elevated C-reactive protein	53/137 (38.7)
Elevated erythrocyte sedimentation rate	7/57 (12.3)
Elevated total IgE	77/239 (32.2)
Abnormal lung X-ray	3/25 (12)
Microbiological tests	
Urine culture positivity	9/305 (3)
Throat culture positivity	8/30 (26.7)
Group Abetahemolytic streptococci	

Table IV: Confirmed etiology of acute urticaria (n=193).

	n (%)
Infection/infestation	176 (91.2)
Upper respiratory tract infection	149 (77.2)
Urinary tract infection	9 (4.7)
Acute otitis media	5 (2.6)
Acute gastro enteritis	4 (2)
Pneumonia	3 (1.6)
Parasitosis	3 (1.6)
Tooth abscess	2 (1)
Varicella	1 (0.5)
Insect bite	15 (7.8)
Food allergy (Green lentils)	1 (0.5)
Drug allergy (Penicillin)	1 (0.5)

Table V: Comparison of age groups by etiology.

Age groups	Idiopathic n (%)	Infection n (%)	Other n (%)	p
≤2 years (n=43)	15 (34.9)	31 (48.8)	7 (16.3)	0.009
2-6 years (n=94)	52 (55.3)	37 (39.3)	5 (5.3)	
6-12 years (n=203)	117 (57.6)	74 (36.4)	2 (1)	
12-18 years (n=129)	92 (71.3)	34 (26.4)	3 (2.3)	

with confirmed acute urticaria etiology. Infections were seen to be the first in the etiology of acute urticaria (Table IV).

In terms of age groups, most common triggers in patients under 2 years were infections while in 12-18 age group the most common trigger was idiopathic acute urticaria (Table V).

23.3% (n = 100) of the patients had recurrent acute urticaria. In these patients the urticaria recurrence median was 2 (minimum 1- maximum 5). There was no statistical difference between the patients with first episode acute urticaria and recurrent acute urticaria in terms of age, gender and etiology (Table VI).

DISCUSSION

Etiology was found in only 41% of the patients in the study assessed for acute urticaria. Infections were the leading factor triggering acute urticaria.

Table VI: Comparison of patients with first episode and recurrent acute urticaria.

	First episode (n=369)	Recurrent acute urticaria (n=100)	p
Age groups, n(%)			
≤2 years	30 (69.8)	13 (30.2)	
2-6 years	72 (76.6)	22 (23.4)	0.298
6-12 years	160 (78.8)	43 (21.2)	
12-18 years	107 (82.9)	22 (17.1)	
Gender, n (%)			
Male / Female	185 (50.1) / 184 (49.9)	44 (44) / 56 (56)	0.276
Etiology, n(%)			
Idiopathic	220 (59.6)	52 (52)	0.328
Infection	112 (30.4)	38 (38)	
Other	37 (10)	10 (10)	

Acute urticaria can be seen in both children and adults. It has been reported that around 20% of the general population suffers at least one acute urticaria attack during their lifetime (2). There are not many studies available on acute urticaria prevalence in children but it is reported to be 2-6.7% (3). A study conducted by Ricci et al. (6) reported that acute urticaria is observed at a higher rate in 0-24 months old children and prevalence is reduced by age. The age of the patients participating in our study ranged between 2 months and 18 years but the majority of the patients (39.7%) were between 6 to 12 year olds.

Acute urticaria in adults is mostly seen in women but in pediatric patients the distribution between genders is equal. Despite the fact that some studies on pediatric patients are reporting a higher incidence, there are no significant differences in terms of prevalence in pediatric patients (7). Our study group consisted of 48.8% of boys and 51.2% of girls and there was no significant difference between gender distributions in terms of age groups.

Determining etiology in patients with an acute urticaria diagnosis is important as it would have an impact on the treatment approach. However, it is not always possible to determine etiological. In a collection of studies on the subject, the rate of etiology in acute urticaria in pediatric age groups ranged between 20-90% determining (8). In our study, an etiologic cause was found only in 41% of the patients. Hence, majority of the patients were idiopathic cases. In etiology identified most common cause are infections. Over 80 percent of acute urticaria cases in some pediatric series have been found to be related to infections. Different studies have indicated that viral, bacterial and parasitic infections can be related to acute urticaria (9). Particularly in children, acute urticaria can develop during or after viral or bacterial infections. It is thought that this is related to complement activation resulting from immune complexes that develop during an infection (10). The most frequent infections in acute urticaria etiology are viral upper respiration tract infections. In 91.2% of the patients with a defined etiology in our study, infections and in particular upper respiratory tract infections are found to be acute urticaria triggers. A study by Sackesen et al. (4) has pointed out urinary tract infections in acute urticaria etiology. Interestingly, in about 70% of the patients with a diagnosed urinary tract infection (16.2%) there were no symptoms to indicate urinary tract infection and they suggested routine urinary test in etiologic assessment. There were 9 (4.7%) patients with a urinary tract infection diagnosis in our study. A symptomless urinary tract infection has been detected only in one of these patients.

Food and drugs are among the common suspicious agent in acute urticaria etiology in our study. However, confirming the allergy through allergy work-up indicates that these rates are not so high. It is difficult to distinguish the etiologic reason in urticaria that occurs after use of drug in acute infection. It is generally though that the reaction is due to infectious agents or the interaction between the drug and infectious agent (11). Confirming drug allergy in these patients is important as it will prevent getting a wrong drug allergy diagnosis. In our study the rate of drug allergy confirmation was only 1.2% (n=1), while the rate of food allergy confirmation was only 2% (n=1). A study by Sackesen et al. (4) reported a food allergy confirmation rate of 3% and a drug allergy confirmation rate of 5%. As it is seen, even though they are considered to be highly suspicious in etiology, drug and food allergy are actually very low in acute urticaria etiology. However, especially in etiology, it is very difficult to prove there is no drug allergy. There are drugs such as antibiotics and antipyretic (paracetamol, ibuprofen) that can be simultaneously used during acute infection. When acute urticaria occurs in such a case it is not possible to say that the only cause is infection. These patients must be subjected to allergy tests at least 4-6 weeks after the reaction to see whether there is any drug allergy.

Another cause in etiology is bite /sting. Papular urticarial resulting from bug bite is included in acute urticaria. Therefore, particularly in the presence of papular urticarial, bug bites must be taken into consideration. Papular urticaria frequency in children is ranging between 3.3 and 4.7% Similar to literature, popular urticaria rate has been concluded as 3.2% in our study (12).

Age seems to be an important factor in determining etiology in acute urticaria. Majority of the patients with defined etiology in our study are children under 2-year-old. The rate of determining etiology in under 2 year olds is 65.1% while the rate in patients

over 12 is 28.7%. Therefore, more detailed tests could be necessary when searching for etiology in younger children.

21.3% (n=100) of the patients assessed in our study for acute urticaria had recurring acute urticaria. No age, gender or etiologic differences have been observed in patients with first attack and recurring acute urticaria. A study conducted by Mortureux et al. (13) monitored post -acute urticaria children and reported chronic or recurring acute urticaria in 30% of the children.

It is a limitation that our study is retrospective. However, a high number patients were evaluated. Unlike other similar studies, allergy tests were performed on patients with suspected drug and / or food allergies to clarify whether there is an allergy. These are the strengths of our study.

In conclusion, the most important point in detecting etiology in acute urticaria is getting a detailed clinic history of the patient and performing a comprehensive physical examination. It is not necessary to have routine laboratory tests in all patients. Laboratory tests must be planned on the basis of clinical findings of each patient. Infections occupy an important place in etiology particularly in etiology in younger children. Therefore, infection-related tests could be performed on younger children even if there are no clinical suspicions. Unlike the popular belief, the rate of confirmed food and drug allergy is not very high. Diagnostic tests must be performed if there are suspected food or drugs in the story. This will prevent unnecessary food or drug restrictions.

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Evaluation of Knowledge Level, Perceptions and Attitudes of Families About Childhood Hypertension

Çocukluk Çağı Hipertansiyonu İle İlgili Ailelerin Bilgi Düzeyi, Algı ve Tutumlarının Değerlendirilmesi

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ABSTRACT

Objective: This study is carried out to evaluate the knowledge levels, perceptions and attitudes of families about childhood hypertension and to identify the sources that are effective in creating knowledge and awareness of childhood hypertension.

Material and Methods: This cross-sectional study was carried out with the families of children who applied to our children hospitals' outpatient clinics between January 15, 2018 and June 15, 2018.

Results: The participants who live in the city center compared to those living in other places ($p = 0.002$); health professionals compared to other occupational groups ($p < 0.001$); those with an income level of 5001 TL and above, compared to other income levels ($p < 0.001$); university graduates compared to other education categories ($p < 0.001$); those who had high blood pressure in their family or relatives compared to others ($p = 0.015$) and participants who had measured blood pressures compared to those who did not ($p < 0.001$) had higher number of correct answers and knowledge levels.

Conclusion: In this study it was determined that knowledge level of the families about childhood hypertension was found to be moderate to low. It has been determined that as the education levels of the individuals increase, their knowledge level generally increases. Considering that hypertension, which is an important public health problem in our country, is becoming more common in childhood and its morbidity is reflected in adulthood; there is a need for community-accepted and applicable community-based conservation and education projects. Family physicians, who have an extremely important role in informing the society, are thought to be the most effective, accessible and able to present scientific and updated information at this point

Key Words: Awareness, Childhood, Hypertension

ÖZ

Amaç: Bu çalışmada birincil olarak ailelerin çocukluk çağı hipertansiyonu konusundaki bilgi düzeyleri, algı ve tutumlarını değerlendirmeyi amaçladık. İkincil olarak ise çocukluk çağı hipertansiyonu bilgi ve farkındalığını oluşturmada etkili olan kaynakları belirlemeye çalıştık.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Permission for this study was obtained from the Clinical Research Ethics Committee of YBU Yenimahalle Training and Research Hospital (Protocol code: 2017/70; Date: 09/01/2018 Decision no: 2018/01/05). Written informed consent was obtained from all participants.

Contribution of the Authors / Yazarların katkısı: BAGCI H: Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***GULER SONMEZ T:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***YUKSEL S:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results. ***OZLU SG:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Gereç ve Yöntemler: Araştırmamız 15 Ocak-15 Haziran 2018 tarihleri arasında hastanemiz Çocuk Sağlığı ve Hastalıkları polikliniklerine başvuran ailelerle gönüllülük esas alınarak, yüz yüze anket çalışması şeklinde gerçekleştirildi.

Bulgular: Çalışmaya yaş ortalaması 37.6 ± 9.5 yıl olan 736 (%75.1) kadın, 244 (%24.9) erkek toplam 980 kişi dahil edildi. Katılımcıların %55'inin çocukluk çağında hipertansiyon olabilir mi sorusuna evet cevabı verdiği saptandı. Hipertansiyon ile ilişkili 8 bilgi sorusuna ise katılımcılar tarafından verilen doğru cevapların ortanca değerinin 5 olduğu tespit edildiİl merkezinde yaşama, sağlık çalışanı olma, gelir seviyesinin 5001 TL ve üzeri olması, üniversite mezunu olma, ailesinde veya yakınlarında hipertansiyon varlığı, daha önce tansiyon ölçtürme durumu ile katılımcıların cevapladıkları doğru soru sayısı arasında anlamlı ilişki saptandı. Katılımcıların bilgi edinme kaynakları açısından değerlendirildiğinde aile hekimlerinin katkısının %17 ile %31 arasında değiştiği saptandı.

Sonuç: Bu çalışmada çocukluk çağı hipertansiyonu konusunda ailelerin bilgi düzeylerinin orta-düşük düzeyde olduğu saptanmıştır. Bireylerin eğitim düzeyleri arttıkça genel olarak bilgi düzeylerinin de arttığı tespit edilmiştir. Ülkemizde önemli bir halk sağlığı sorunu olan hipertansiyonun çocukluk çağında da giderek yaygınlaştığı ve erişkin döneme yansıyan morbiditesi olduğu göz önüne alındığında; toplumca kabul görmüş ve uygulanabilir toplum tabanlı koruma ve eğitim projelerine ihtiyaç olduğu ortaya çıkmaktadır. Toplumun bilgilendirilmesi noktasında son derece önemli role sahip olan aile hekimlerinin bu noktada en etkin, ulaşılabilir, bilimsel ve güncel bilgileri sunabilecekleri düşünülmektedir.

Anahtar Sözcükler: Farkındalık, Çocukluk çağı, Hipertansiyon

INTRODUCTION

In recent years, incidence of childhood hypertension is gradually increasing; although there are differences between countries, its incidence is reported to be approximately 3-4% (1). It is a well-known and modifiable risk factor for atherosclerosis and cardiovascular disease in adults (1). Despite this increasing incidence; little attention has been paid to childhood hypertension and its long-term consequences (1,2) .

There are studies in the literature showing that the precursors of adult hypertension can also be observed in childhood. There is also evidence that hypertension in childhood and adolescence contributes to the early development of atherosclerosis and cardiovascular diseases in adulthood. Therefore, detecting and treating children with hypertension will make an important contribution in the follow-up of adulthood cardiovascular diseases (2,3).

Awareness is an important factor in health behavior to detect the diseases. Increasing awareness plays an important role especially in primary prevention. At the same time, having accurate and reliable information is a crucial step in creating behavioral changes. In the literature, there are few studies related with awareness and knowledge level about childhood hypertension reporting that the level of awareness is not high enough (4,5). In a study with adult patients in the United States, it was found that as the level of knowledge of individuals about hypertension increases, the awareness of the society, the treatment and control of the disease increase (6).

Childhood hypertension is an important public health problem due to the increasing frequency and being the basis of atherosclerotic and cardiac diseases in adulthood. In this regard, it is suggested, in this study, that the awareness and knowledge levels of families and general practitioner who take place in primary care should be increased. In order to achieve this, first information level of the families should be identified on the subject, and then solution suggestions should be provided to overcome the lack of information.

We aimed to determine parents' awareness of and knowledge about childhood hypertension and their main information sources, in an urban district of Ankara, the capital city of Turkey.

MATERIAL and METHODS

Permission for this study was obtained from the Clinical Research Ethics Committee of YBU Yenimahalle Training and Research Hospital (Protocol code: 2017/70; Date: 09/01/2018 Decision no: 2018/01/05). Written informed consent was obtained from all participants.

A cross-sectional survey was administered to families who attended outpatient pediatric clinics at our institute between January 15, 2018 and June 15, 2018. In total, we included 980 parents or guardians aged over 18-years, who had at least one child, and agreed to complete our survey.

Data collection was carried out as face to face questionnare with the parents of the children applied to our pediatric out patient clinics. A three-section, 29-item questionnaire was designed by the authors based on a review of the literature. In the first section, demographic characteristics were included (gender, marital status, number of children, place of residence, and occupation) and in the second section, knowledge of childhood hypertension was assessed through a series of "yes," "no/I have no idea" questions (Table I and II). After each knowledge question, the participants were asked to indicate the source of their information. In the third part of the questionnaire, four questions determined the participants' awareness of childhood hypertension.

The questionnaire was first pretested on ten volunteers in order to confirm its clarity and certainty. The median values of the knowledge questions were calculated for each demographic characteristic and compared with each other. The knowledge of parents whose scores were above the median value was considered "sufficient," whereas knowledge below the median value was determined "insufficient."

Statistical Analyses

Categorical variables are described using frequencies and percentages. Since the continuous variables were derived from a questionnaire, non-parametric statistics were used to describe the data and compare groups without testing for data distribution. That is, median (minimum–maximum) values are used to describe continuous variables. The Chi-square test was used to assess the relationship between two categorical variables.

For knowledge questions, we compared total scores of two and more than two groups using the Mann–Whitney U and Kruskal–Wallis tests, respectively. For hypothesis testing, the type I error rate was taken as 0.05.

RESULTS

This study included 980 people, of which 736 (75.1%) were women and 244 (24.9%) were men. The mean age was 37.6 ± 9.5 years, 94.5% were married, 25.7% had one child, 49.5%, 20.1%, and 4.7% had two, three, and four or more children, respectively. Altogether, 68% of the participants had a history of high blood pressure in their families or relatives, whereas 90.5% of the participants had had their blood pressure measured at least once previously. Other socio-demographic characteristics of the participants are summarized in Table I.

Table I: Distribution of Sociodemographic Characteristics of the Participants.

	Frequency (n)	Percent (%)
Gender		
Female	736	75.1
Male	244	24.9
Place of residence		
City Center	665	68.1
District	299	30.6
Village-Town	12	1.2
Occupation		
Health employee	48	4.9
Officer	103	10.5
Retired	39	4
Worker	107	10.9
Housewife	505	51.6
Others*	180	21.4
Monthly income		
0-1000 TL	178	18.4
1001-2500 TL	428	44.3
2501-5000 TL	295	30.5
5001 TL and over	66	6.8
Education Level		
Primary school	210	21.5
Secondary school	167	17.1
High School	321	32.7
University	281	28.7

**Lawyer; manager. self-employment etc.*

Table II: Descriptive Statistics of the Participants' Answers.

Information Questions	Frequency (n)	Percent (%)
Do you think hypertension or high blood pressure can be seen at any age?		
Yes	771	79
No /No idea	205	21
At which age will hypertension be detected?		
From Birth	224	22.9
Age 6 and Over	66	6.7
Age 12 and Over	112	11.5
Age 18 and Over	95	9.7
Age 40 and Over	113	11.6
No idea	368	37.6
Should blood pressure be measured in childhood?		
Yes	668	68.7
No/No idea	304	31.3
Is hypertension symptomatic in children ?		
Yes	427	43.9
No/No idea	546	56.1
Does measuring blood pressure harm children?		
Yes	277	28.6
No/No idea	700	71.4
Does hypertension improves spontaneously as the child grows up?		
Yes	634	64.8
No/No idea	344	35.2
Should hypertension be treated in children?		
Yes	809	83.1
No	165	16.9

Whereas 694 (71.2%) of the participants stated that hypertension can be seen in children with a family history of hypertension, only 668 (68.7%) stated that blood pressure measurement should be done in childhood. In total, 83.4% participants had children aged over 3 years, and among these only 219 (25.6%) stated that their child's blood pressure was measured during routine childhood examinations.

The median value for the correct answers to the information questions about childhood hypertension was found to be five. In total, 367 (37.4%) participants answered correctly six or more questions indicating that these participants had a higher awareness of childhood hypertension. Participants who previously had their child's blood pressure measured were more likely to answer information questions correctly than participants whose children did not have/or were not remembered as having their blood pressure measured ($p < 0.001$).

Altogether, 534 (55.0%) participants answered "yes" to the question, "Will children be hypertensive?"; while 427 (43.9%) answered "yes" to the question, "Will the children be

Table III: Comparison of demographic characteristics categories according to information questionnaire correct answer total score.

	n	Median	Min.	Max.	p
Gender					
Male	244	5	0	8	0.283
Female	736	5	0	8	
Total	980	5	0	8	
Marital Status					
Married	926	5	0	8	0.294
Single	54	6	0	8	
Total	980	5	0	8	
Number of Children					
1	252	5	0	8	0.709
2	485	5	0	8	
3	197	5	0	8	
4	46	5	0	8	
Total	980	5	0	8	
Place of Residence					
City Center	665	5	0	8	0.002
District	299	4	0	8	
Town-Village	12	4	0	7	
Total	976	5	0	8	
Occupation					
Health Worker	48	7	2	8	<0.001
Officer	103	5	1	8	
Retired	39	4	0	7	
Worker	107	5	0	8	
Self-employment	73	5	0	8	
Housewife	505	4	0	8	
Other	102	5	0	8	
Total	977	5	0	8	
Monthhly Income (TL)					
0-1000	178	5	0	8	<0.001
1001-2500	428	4	0	8	
2501- 5000	295	5	0	8	
5000 -	66	6	1	8	
Total	967	5	0	8	
Educational Status					
Primary school	210	4	0	8	<0.001
Secondary School	167	4	0	7	
High school	321	5	0	8	
University	281	5	0	8	
Total	979	5	0	8	
Are there any hypertensive patients among your family or relatives?					
Yes	667	5	0	8	0.015
No	235	4	0	8	
No Idea	78	5	0	8	
Total	980	5	0	8	
Have you had your blood pressure measured by now?					
Yes	886	5	0	8	<0.001
No	92	4	0	8	
Total	978	5	0	8	

Min: *Minimum,* ***Max:*** *Maxsimum*

symptomatic?" and 373 (77.7%) answered "headache" to the question, "What could this symptom be?" The distribution of answers given to the information questions is shown in Table 2 and the distribution of the number of questions answered correctly is shown in Figure 1.

It was found that the participants with greater childhood hypertension knowledge were more likely to live in the city center compared to those living in other areas (p=0.002); were more likely to be health professionals compared to other occupational groups (p<0.001); had an income of ≥5001 Turkish lira compared to lower income groups (p< 0.001); were more likely to be university graduates than other educational categories (p<0.001); were more likely to have high blood pressure in their family or relatives compared to others (p= 0.015), and were more likely to have had their blood pressure measured compared to those who did not (p<0.001) (Table III). Gender, marital status, and number of children did not affect parents' knowledge (p=0.283, p=0.294, and p=0.709, respectively) (Table III).

Descriptive statistics regarding the source of parents' information are given in Table IV. Parents were able to choose more than one option while specifying sources.

DISCUSSION

In this study, knowledge and awarenesss of parents about childhood hypertension were evaluated in an urban area of Ankara the capital city of Turkey. We have highlighted that parents are insufficiently aware of childhood hypertension and that the source of this information mainly comes from written or visual media rather than from healthcare professionals. Significant relationships were found between parents' knowledge and the following: living in the city center, being a healthcare professional, income of ≥5001 Turkish lira, being a university graduate, presence of hypertension in family or relatives, and those who had had previous blood pressure measurement. No significant differences were found between the gender and age of participants and their knowledge.

Hypertension is an important health problem of childhood and may occur as early as the first day of postnatal life. There is mounting evidence that hypertension in childhood may precede hypertension in adulthood and may be a precursor of adulthood atherosclerosis; an important risk factor for cardiovascular disease (7,8). Effective steps to diagnose and manage adulthood hypertension have been taken globally, but little attention has been paid to this problem in childhood (7). Although there are many studies addressing awareness of adulthood hypertension, there are few studies dealing with awareness of childhood hypertension (7). One of the few studies exploring adults' awareness of childhood hypertension was carried out by Odely et al.(8) in Cameroon. They discovered that there was insufficient knowledge of the presence, diagnosis,

Table IV: Sources of Information Regarding Childhood Hypertension.

Information	Sources					
	Relatives - Friends*	General Practitioners*	Written Press*	TV*	Internet*	Other*
Hypertension can be detected at any age	386 (49.2)	140 (17.9)	175 (22.3)	217 (27.9)	207 (26.4)	112 (14.2)
Blood pressure should be measured in childhood	245 (36.1)	165 (24)	137 (20.2)	162 (23.9)	172 (25.4)	131 (19.3)
Children may have hypertension	205 (6.8)	130 (23.3)	139 (25)	174 (31.2)	175 (31.4)	97 (17.4)
If children have hypertension, they will be symptomatic	140 (30.9)	134 (29.6)	98 (21.6)	124 (27.4)	116 (25.6)	107 (23.6)
Hypertension in children improves spontaneously as the child grows up	48 (24.1)	62 (31.2)	39 (18.6)	44 (21.6)	48 (24.1)	54 (26.6)
Hypertension must be treated in children	199 (26.2)	215 (28.3)	161 (21.2)	203 (26.7)	227 (29.9)	199 (26.2)

**n(%)*

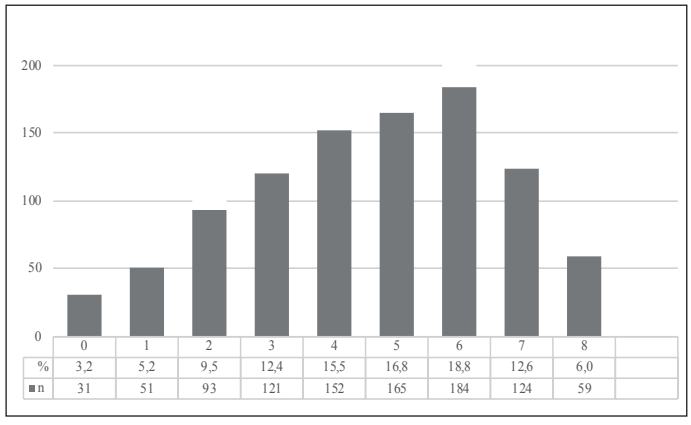

Figure 1: Distribution of Information Questionnaire Correct Answer Total Score.

and management of childhood hypertension (8). In agreement with these findings, we found only 367 (37.4%) of participants answered knowledge questions sufficiently indicating that knowledge was low among our study population. When evaluated according to demographic features, living in the city center was associated with increasing knowledge compared with living in other areas. Yao et al. (9) similarly found that knowledge of adulthood hypertension in people living in rural areas was lower than in those living in city centers and towns. This difference is explained by the reduced ability of rural residents to access educational tools (9). Studies performed in developing countries have consistently found that those with higher incomes have better awareness of hypertension compared with those with lower incomes (10). This was similarly observed in our study and may be explained by those with a higher income having better access to healthcare and treatment, as well as having better control of disease.

University graduates in our study had greater awareness and knowledge of childhood hypertension than other educational grades. These findings were corroborated by Viera et al. (6) who found that individuals with a low level of education had a low level of hypertension knowledge. However, Grad et al.(11) found that there was no significant relationship between the educational background of adolescents and their knowledge of hypertension. Although it was determined in our study that the level of knowledge of the participants increased as the level of education increased, it should be noted that this study was performed in adults. We suggest that people should be informed about hypertension during secondary education in order to increase the awareness of the society based on the data in our study and the literature.

Previous studies in adults have demonstrated that smokers and overweight people are more aware of the diagnosis, management, and consequences of hypertension (12). Physicians pay more attention to patients with hypertension who are overweight (12). In our study, in addition to these previous findings in literature, we noted that those who had their blood pressure measured previously and who had hypertensive relatives had a higher awareness of childhood hypertension.

We explored the sources of our participants' information on childhood hypertension. We demonstrated that the social environment (relatives, friends, neighbors etc.), written and visual media, and the internet were the most common information sources. Oskay et al. (13) found that the most common source of hypertension knowledge in those who attended family medicine outpatient clinics was health professionals (52.2%); however knowledge was still not at the desired level. In addition, relatives were found to be an important and active source of information, although they may also be a source of unreliable and pseudoscientific information (13). In recent years, with an increasing focus on disease prevention and maintaining a healthy lifestyle, health communication and education has gained increasing importance. Promoting and improving health is based on health education, and health information is the basis for this. The authority of the information source is important; the more reliable the source and the stronger its authority the greater likelihood of behavior change. Family physicians have an important role in informing their patients and may provide effective, accessible, scientific, and up-to-date information.

The main limitation of this study is that it was conducted in a single center. Therefore, we are aware that it may not reflect the national data. Another limitation of our study is that while applying the questionnare we did not discriminate the presence of hypertension in the family according to the ages of the patients. Presence of a hypertensive child or adolescent in the family or among relatives could have effect the knowledge of the parents. Despite these limitations ,since there are not many studies on the level of parental knowledge about childhood hypertension, we think that our study will still give an important preliminary idea.

In conclusion, hypertension is an important public health problem in Turkey, as in other parts of the world. It is becoming more prevalent in childhood and can cause morbidity in adulthood; there appears to be a need for community-based prevention and education campaigns. Above all, we suggest that healthcare professionals should be informed more effectively about childhood hypertension in conjunction with an effective healthcare education program involving the all aspects of news media to raise public awareness.

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Clinical Characteristics of COVID-19 in Children Compared with Their Families in Turkey: A Tertiary-Care Hospital Experience

Türkiye'de Aileleriyle Kıyasla Çocuklarda COVİD-19'un Klinik Özellikleri: Bir Üçüncü Basamak Hastane Deneyimi

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ABSTRACT

Objective: The COVID-19 outbreak that has spread all around the world is still a threat for humankind. Epidemiological, clinical, laboratory, and radiological features of the disease are enlightened day by day. It was aimed to evaluate the characteristics of children and their parents with COVID-19 to aid in diagnosis and treatment.

Material and Methods: A retrospective review of the medical records of pediatric patients and their parents who were confirmed as COVID-19 positive, between April 23, and May 28, 2020, was conducted.

Results: A total of 93 children and 81 adults were evaluated in the present study. Asymptomatic and mild cases accounted for 63.5% of the children and 50% of the parents. Of the children, 3.2% had moderate illness, whereas this was 9.8% for the parents There was a statistically significant difference in terms of the severity of illness between the children and their parents (p =0.01). Although it had a milder clinical course in children, one child died. Increased levels of C-reactive protein (CRP) were observed in 8.6% of the children and 48.1% of the patients, and there was statistically significant difference in terms of CRP levels between the children and their parents (p =0.001).

Conclusion: The clinical, laboratory, and radiological features of COVID-19 showed differences in the children and their parents. It should be kept in mind that COVID-19 can be fatal in children, although the course of the disease appears to be milder in children than in their parents

Key Words: Adults, Children, COVID-19

ÖZ

Amaç: Tüm dünyaya yayılan COVİD-19 salgını, insanlık için hala bir tehdittir. Hastalığın epidemiyolojik, klinik, laboratuvar ve radyolojik özellikleri gün geçtikçe gün yüzüne çıkmaktadır. Tanı ve tedaviye yardımcı olmak için COVİD-19'lu çocuk ve ebeveynlerinin özelliklerini değerlendirmeyi amaçladık.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ankara Training and Research Hospital, Clinical Research Ethics Committee. (10.07.2020/ E-20/303).

Contribution of the Authors / Yazarların katkısı*: *CURA YAYLA BC: Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AYKAC K:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, , Taking responsibility in the writing of the whole or important parts of the study. ***ESEROGLU F:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***DEMIR A:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***OZTOPRAK SIYAH U:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***TUNCER ERTEM G:*** Reviewing the article before submission scientifically besides spelling and grammar. ***CESUR S:*** Reviewing the article before submission scientifically besides spelling and grammar. ***KARAKAYA J:*** Taking responsibility in logical interpretation and conclusion of the results. ***TASAR MA:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.

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Gereç ve Yöntemler: 23 Nisan-28 Mayıs 2020 tarihleri arasında COVİD-19 olduğu doğrulanan pediatrik ve onların ebeveyni olan yetişkin hastaların tıbbi kayıtlarının retrospektif olarak incelendi.

Bulgular: Bu çalışmada toplam 93 çocuk ve 81 yetişkin değerlendirildi. Asemptomatik ve hafif vakalar çocuklarda %63.5, ebeveynlerde ise %50'di. Çocukların %3.2'si orta şiddette hastalığa sahipken, ebeveynlerin %9.8'inde vardı. Çocuklar ve ebeveynler arasında hastalık şiddeti açısından istatistiksel olarak fark vardı (p=0.01). Çocuklarda daha hafif klinik seyretmesine rağmen bir çocuk öldü. Çocukların %8.6'sında ve ebeveynlerin %48.1'inde C-reaktif protein (CRP) düzeylerinde artış görüldü, çocuklar ve ebeveynler arasında CRP açısından istatistiksel olarak anlamlı fark vardı (p=0.001).

Sonuç: COVİD-19'un klinik, laboratuvar ve radyolojik özellikleri çocuklarda ve yetişkinlerde farklılıklar göstermektedir. COVİD-19'un hastalık seyri çocuklarda yetişkinlere göre daha hafif gibi görünse de, COVİD-19'un çocuklarda ölümcül olabileceği akılda tutulmalıdır.

Anahtar Sözcükler: Erişkin, Çocuk, COVİD-19

INTRODUCTION

A new underlying cause of pneumonia, called coronavirus disease 2019 (COVID-19) has spread across the world (1). Reports from both the Centers for Disease Control and Prevention (CDC) and China have concluded that a small amount of the infected population was children, at a rate of 1.7 and 8.7%, respectively (2–4). Additionally, the severity of symptoms was different between children and their parents (5). In a study from China, which included 2143 infected children, only one 14-year-old child died and 94.1% of the children were reported to be either asymptomatic or followed a moderate clinical course (6). Wending et al.(5) reported that although there is substantial lung injury among children, the disease was milder, perhaps due to less pronounced inflammatory response. These data suggested that the clinical and radiological features of children differ from those observed in adults, which indicates that disease management and treatment in children may require a different approach from that used in adults.

Herein, the clinical features and management strategies of COVID-19 in children when compared with their families was reported. Few data are available on children who have COVID-19 when compared with adults (5,7). Therefore, it is believed that sharing the available data on families will be beneficial in understanding the epidemiological and clinical features of the disease in both children and their parents.

MATERIAL and METHODS

The retrospective study was performed at a tertiary-care hospital in Ankara, the capital of Turkey, between April 23 and May 28, 2020. The medical records of the pediatric patients enrolled in the study and their parents, including age, sex, signs and symptoms, exposure history, pre-existing co morbidities (i.e. heart disease, chronic lung disease, neurologic diseases), laboratory findings, chest computer tomography (CT) and X-ray results, complications, treatments, and clinical outcomes of patients who were confirmed as COVID-19-positive were evaluated. Total radiological imaging defined x-ray or chest CT. The study was approved by the Ankara Training and Research Hospital, Clinical Research Ethics Committee. (10.07.2020/ E-20/303).

Suspected cases of COVID-19 were diagnosed according to national COVID-19 guidelines. Patients suspected of having COVID-19 via positive reverse transcriptase-polymerase chain reaction (RT-PCR) results were accepted as confirmed cases (8). The severity of COVID-19 was categorized based on the clinical characteristics and the results of laboratory examinations and radiologic imaging, and were defined as asymptomatic, mild, moderate, severe, and critical. Asymptomatic included cases with positive diagnoses but without any clinical or radiological findings; mild disease included cases with acute upper respiratory tract infections but without clinical and radiological pneumonia; moderate disease included cases with pneumonia and symptoms of respiratory tract infection; severe disease included cases with progressive respiratory disease, dyspnea, and central cyanosis; and critically ill included cases presented with acute respiratory distress syndrome or respiratory failure, shock, and organ dysfunction, including encephalopathy, myocardial injury, coagulation abnormalities, and acute kidney injury (6, 9).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the participants' baseline characteristics, including medians and interquartile ranges for continuous variables and frequency distributions for categorical variables. P-values were calculated using the chi square or Fisher exact tests for the categorical variables and the student tor Mann-Whitney U tests for the continuous variables according to the normality assumption. $p<0.05$ was accepted as statistically significant.

RESULTS

We obtained and compared the clinical data of pediatric patients (n=93) and their parents (n=81) who had COVID-19 in our hospital. Detailed data regarding the demographic, clinical characteristics, treatment, and outcomes of the patients are summarized in Table I. The median (minimum-maximum) age of the pediatric patients was 8 (0–17) years and 48.4% were male. The median age (minimum-maximum) of the parents was 36 (31–79) years and 37% were male. Only 8.6% of the pediatric patients had underlying disease, whereas this rate

Table I: Demographic, clinical and laboratory data of patients with COVID-19.

	Children (n=93)	Parents (n=81)	p
Age, years*	8 (0–17)	36 (31–79)	NA
Male†	45 (48.4)	30 (37)	0.08
Underlying disease‡			
None	85 (91.4)	62 (76.5)	
Neurologic disease	4 (4.3)	2 (2.4)	
Asthma	1 (1.1)	1 (1.2)	
Hypothroidism	2 (2.3)	0	NA
FMF	1 (1.1)	1 (1.2)	
Hypertension	0	6 (7.3)	
Asthma+Hypertension	0	2 (2.4)	
Diabetes+ Hypertension	0	3 (3.7)	
Hepatitis B	0	1 (1.2)	
Symptoms‡			
Fever	34 (36.6)	38 (46.9)	0.16
Cough	37 (39.8)	41 (50.6)	0.15
Dyspnea/tachypnea	5 (5.4)	13 (16)	0.02
Myalgia/fatigue	16 (17.2)	23 (28.4)	0.07
Sore throat	15 (16.1)	14 (17.3)	0.83
Headache	9 (9.7)	13 (16)	0.20
Diarrhea	6 (6.5)	7 (8.6)	0.58
Abdominal pain	7 (7.5)	1 (1.2)	0.06
Vomiting	6 (6.5)	1 (1.2)	0.12
Loss of smell/taste	5 (5.4)	1 (1.2)	0.2
Conjunctivitis	1 (1.1)	0	1
Laboratory findings‡			
Leukocytosis	0	0	NA
Neutropenia	10 (10.8)	2 (2.5)	0.03
Lymphopenia	12 (12.9)	16 (19.8)	0.22
Increased CRP	8 (8.6)	39 (48.1)	0.001
Increased Procalcitonin	0/72 (0)	1/69 (1.2)	NA
Increased LDH	27/74 (36.5)	35/79 (44.3)	0.24
Increased D dimer	7/27 (25.9)	13/78 (16.6)	0.29
Increased troponin	3/53 (5.6)	3/71 (4.2)	1
Total Radiologic imaging‡	92	74	0.01
Normal	59 (63.4)	33 (44.6)	
Anormal	34 (36.6)	41 (55.4)	

NA: *Nonapplicable,* ***FMF:*** *Familial Mediterranean Fever,* ***CRP:*** *C-Reactive Protein,* ***LDH:*** *Lactate Dehydrogenase,* ***CT:*** *Computer Tomography, *Values were given at median (min-max), † %, ‡Values were given at number (percentage).*

was 23.5% in the parents. The most common underlying disease was neurologic diseases in the pediatric patients, while it was hypertension in their parents. Moreover, 5 of the mothers were pregnant.

The most common symptoms were cough and fever in the children, similar to the parents; however, there was a statistically significant difference between the parents and children in terms of the rate of dyspnea/tachypnea, as dyspnea/tachypnea were more common in the parents than in the children (p=0.02, Table I). The rate of the other symptoms, such as fatigue/myalgia, sore throat, diarrhea, headache, vomiting, loss of smell or taste, and conjunctivitis were similar between the parents and the children.

Table II: Severity of illness, treatment, and outcomes of patients with COVID-19.

	Children (n=93)	Parents (n=81)	p
Severity*			0.01
Asemptomatic	22 (23.7)	7 (8.5)	
Mild	37 (39.8)	31 (41.5)	
Moderate	31 (33.3)	35 (47.6)	
Severe/ Critical	3 (3.2)	8 (9.8)	
Antiviral treatment*			0.001
Hq	0	60 (74.0)	
Favipiravir	0	8 (9.8)	
Favipiravir+azithromycin	0	1 (1.2)	
Hq+Favipiravir	3 (3.9)	3 (3.7)	
Hq+azithromycin	0	6 (7.4)	
ICU*	1 (1.1)	0	NA
Outcome*			NA
Recovered	92 (98.9)	100	
Death	1 (1.1)	0	

Hq: *Hydroxychloroquine,* ***ICU:*** *Intensive care unit,* ***NA:*** *Nonapplicable, * Values were given at number (percentage).*

Neutropenia was detected in 10.8% of the children and 2.5% of the parents (p=0.03). Lymphopenia was present in 12.9% of the children and 19.8% of the parents. There were no statistically differences in terms of lymphopenia and leukocytosis between the children and the parents.

Increased levels of C-reactive protein (CRP) were seen in 8.6% of the children and 48.1% of the parents, and this difference was statistically significant (p=0.001). The parents with severe clinical condition had high CRP levels. However, there was no statistically significant difference in terms of CRP levels and severity of the parents or the children (Figure 1).

Increased lactate dehydrogenase (LDH) levels were detected in 44.3% of the parents and 36.5% of the children. The D dimer level was increased in 25.9% of the children and 16.6% of the parents. There were no statistically differences in terms of increased LDH, D dimer, and procalcitonin, and troponin levels between the children and the parent groups.

All of the children and 14.8% of the parents were evaluated via chest X-ray. In the children, 23.6% were evaluated with CT, whereas in the parents, 91.3% were evaluated with thorax CT. Total of 55.4% children and 36.6% of parents presented remarkable abnormalities on X-ray or chest CT. There was a statistically significant difference in terms of the radiologic abnormalities between the groups (p=0.01). Asymptomatic and mild cases accounted for 63.5% of the children and 50% of the parents. In the children, 3.2% had severe/critical illness, whereas this rate was 9.8% for the parents. There was a statistically significant difference in terms of the severity of illness between the children and their parents. Clinical severity, treatment, and outcomes are shown in Table II.

Antiviral treatment was used in only 3.9% of the children who had critical disease, whereas 96.2% of the parents received antiviral treatment (p=0.001). A combination of hydroxychloroquine (hq)

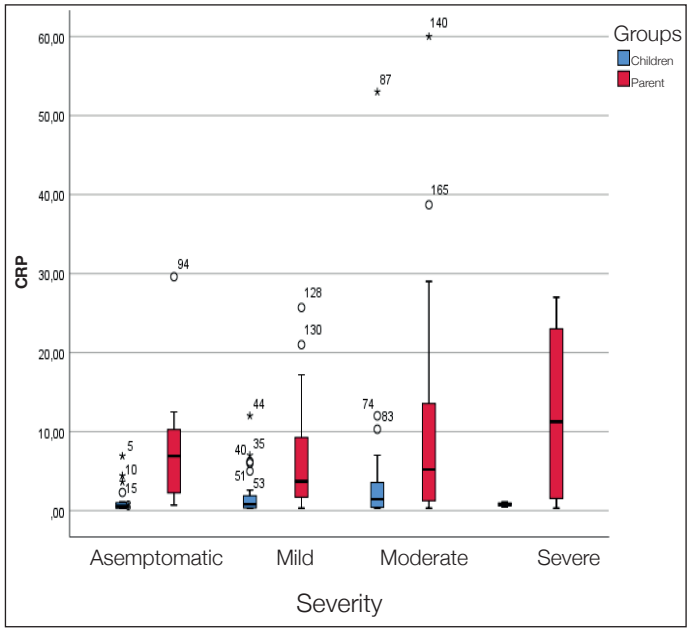

Figure 1: CRP levels and severity of parents and children.

+ favipiravir in children and hq in the parents were the most common antiviral treatments. Patients were admitted to either inpatient wards or the intensive care unit (ICU), according to the course of the disease. Only 1 (1.1%) child was admitted to the ICU, while none of the parents were. All of the parents recovered; however, 1 child died due to myocarditis.

DISCUSSION

To the best of our knowledge, this study was one of the very few studies in the literature that focused on the epidemiological, clinical, and management strategies in families with COVID-19. The findings highlighted the fact that the rate of asymptomatic patients with COVID-19 infection was higher in the children than the adults, whereas the rate of severe/critical patients was higher in the adults than the children, similar to the literature (5, 10). Due to the asymptomatic clinical condition, it is difficult for health care workers to recognize the disease early and control the spread of the virus. Hypotheses related to differences in immunity, microbiota, intensity of exposure to SARS-CoV-2, endothelial damage and clotting function, ACE-2 receptors, and co morbidities for the age-related difference in the severity of COVID-19 are still under consideration (11).

Herein, fever and cough were the two most common clinical manifestations presented by both the children and the adults, similar to the literature, whereas dyspnea/tachypnea was more frequent in the adults than the children (12, 13). Clinicians should pay attention as the differences in the signs and symptoms to diagnosis the disease in children and adults.

Included in this study were 5 pregnant women. It is known that pregnant women are likely to be a high-risk population for COVID-19 (14). Fortunately none of the pregnant patients herein had severe disease.

Since the pandemic outbreak of COVID-19, investigations including laboratory tests and radiologic findings have played an important role in the early diagnosis and treatment monitoring of COVID-19. However, many of the previous reports on COVID-19 laboratory results were based on data from the general population. Additionally, limited information is available based on age differences (15). The most useful and reliable laboratory markers are CRP, LDH, lymphocyte, and procalcitonin levels (15). The expert consensus statement for children with COVID-19 has stated that most patients display increased CRP and LDH levels, but normal procalcitonin levels (16). In contrast to adult patients, only a small number of children with COVID-19 had increased CRP in the current study. This result suggested that inflammation caused by viral infection, especially in the lungs, is less severe in children than in adults, similar to findings of Wenjun et al. (5). Furthermore, radiologic abnormalities in adults were more common in the children than in the adults in the current study.

Several studies have determined that lymphopenia is rarely observed in infected children. However, in adults, lymphopenia occurs more frequently, especially in severe cases (17). In the findings herein, lymphopenia occurred in the adults more than in the children. This may have been attributed to the fact that severe disease was seen at a higher rate in the adults than in the children.

In a retrospective cohort study of 12.306 pediatric COVID-19 patients in the USA, the hospitalization frequency was 5.3%, with 17.6% requiring critical care services and 4.1% requiring mechanical ventilation (18). Only 1 child died among 2.143 children in one of the largest pediatric series from China, and in another study from the USA/Canada, the pediatric ICU (PICU) mortality rate was 4.2% (6, 19). In the most recent CDC data on May 20th, 2021, a total of 391 deaths were reported among pediatric cases in the USA (20). In the cohort herein, of the 93 patients, 1 (1.0%) was admitted to the PICU and died, whereas all of the adults recovered. This mortality rate in the children appeared to be high when compared with reports from other countries; however, the true death rate in Turkey must be clarified by performing studies with larger populations.

No antiviral treatment was used in most of children in contrast to their parents. A huge knowledge gap exists regarding the treatment of patients, especially in children with COVID-19, due to a lack of clear evidence regarding the safety and efficiency of targeted therapies.

In conclusion, clinicians should consider that not only the clinical features, but also the laboratory data are different for different age groups. The disease course of COVID-19 appears to be milder in children than in adults. However, it should keep in mind it can be fatal in children. Increased data regarding the disease

course in children and the outcomes of therapeutic options will guide us in the accurate management of future cases.

This study has some limitations. Firstly, it has a small sample size and single center data. A larger, cohort study population will be needed. Secondly, we could not perform variant analysis and examine its course according to age.

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Transcatheter Closure of Patent Ductus Arteriosus in Infants Between 2-10 Kg

Patent Duktus Arteriozus'un Transkateter Kapatılması; 2-10 Kg Arası Bebeklerde

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ABSTRACT

Objective: The aim of this study was to present our experiences on transcatheter patent ductus arteriosus (PDA) closure with different devices, mostly the Amplatzer Piccolo Occluder, in infants weighing between 2-10 kg.

Material and Methods: In this study, the files of 31 patients who underwent transcatheter PDA closure between December 2019 and August 2022 were reviewed retrospectively.

Results: Transcatheter PDA closure was performed on 31(14 female) infants weighing between 2-10 kg. The mean age of patients was 10.7±6.7 months (2-28), and the mean weight was 6.6±2 kg (3-9.9). The median narrowest diameter of the ductus was 2.2 mm (IQR 2-3) and the median ductus length was 6 mm (IQR 4.75-8). The procedural success rate of all interventional procedures was 88% (30 of 34). Complications occurred in a total of four patients including failure of device implantation in one patient, post-procedural device embolization in 2 patients, and the significant residual shunt in one patient. None of the patients required surgery. In 34 interventional procedures, 3 of which were reintervention, 34 devices were used. Twenty-seven (79%) of them were Amplatzer Piccolo Occluder. The median fluoroscopy and procedural times were 10.5 minutes (IQR 7.25-18.5) and 40 minutes (IQR 35-57.5) respectively. The mean duration of follow-up was 10.3±8.8 months (1-32 months).

Conclusion: In our experience, transcatheter treatment of PDA with the Amplatzer Piccolo Occluder device which was our first choice for appropriate duct anatomy and size in infants weighing between 2-10 kg, is safe and effective.

Key Words: Amplatzer occluder device, Patent ductus arteriosus, Premature infant

ÖZ

Amaç: Bu çalışmanın amacı, 2-10 kg arası bebeklerde çoğunlukla Amplatzer Piccolo Occluder olmak üzere farklı cihazlarla transkateter patent duktus arteriyozus (PDA) kapatma konusundaki deneyimlerimizi sunmaktır.

Gereç ve Yöntemler: Bu çalışmada Aralık 2019-Ağustos 2022 tarihleri arasında transkateter PDA kapatılan 31 hastanın dosyaları geriye dönük olarak incelendi.

Bulgular: Toplam 31(14 kadın), 2-10 kg ağırlığındaki, bebeğe transkateter PDA kapaması yapıldı. Hastaların yaş ortalaması 10.7±6.7 ay (2-28) ve ortalama ağırlık 6.6±2 kg (3-9.9)'du. Duktusun en dar ortanca çapı 2.2 mm (IQR 2-3)

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0000-0003-0375-1726 : BAGRUL D
0000-0002-0707-2678 : GURSU HA
0000-0002-3657-2209 : ECE I
0000-0001-9480-8278 : CETIN II

Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Approval for this study was obtained from the Ankara City Hospital Ethics Committee 2 and the Ministry of Health (07/09/2022 decision number E2-22-2324).

Contribution of the Authors / Yazarların katkısı*: *KAVURT AV: Constructing the hypothesis or idea of research and/or article, planning methodology to reach the conclusions, taking responsibility in logical interpretation and conclusion of the results. taking responsibility in the writing of the whole or important parts of the study. ***SAYIN S:*** Taking responsibility in patient follow-up, data management and reporting, taking responsibility in logical interpretation and conclusion of the results. ***OZELCE B:*** Taking responsibility in patient follow-up, data management and reporting, taking responsibility in logical interpretation and conclusion of the results. ***BAGRUL D:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, taking responsibility in necessary literature review for the study. ***GURSU HA:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, taking responsibility in necessary literature review for the study. ***ECE I:*** Planning methodology to reach the conclusions, taking responsibility in logical interpretation and conclusion of the results, taking responsibility in necessary literature review for the study, reviewing the article before submission scientifically besides spelling and grammar. ***CETIN II:*** Planning methodology to reach the conclusions, taking responsibility in logical interpretation and conclusion of the results, taking responsibility in necessary literature review for the study, reviewing the article before submission scientifically besides spelling and grammar.

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ve ortanca duktus uzunluğu 6 mm (IQR 4.75-8)'di. Tüm girişimsel prosedürlerin prosedürel başarı oranı %88'di (30/34). Bir hastada cihaz implantasyonu başarısızlığı, 2 hastada işlem sonrası cihaz embolizasyonu ve bir hastada önemli rezidüel şant olmak üzere toplam dört hastada komplikasyon meydana geldi. Hiçbir hastada ameliyat gerekmedi. Üçü yeniden müdahale olmak üzere 34 girişimsel işlemde 34 cihaz kullanıldı. Bunların 27'si (%79) Amplatzer Piccolo Occluder'dı. Ortanca floroskopi ve prosedür süreleri sırasıyla 10.5 dakika (IQR 7.25-18.5) ve 40 dakika (IQR 35-57.5)'dı. Hastaların ortalama takip süresi 10.3±8.8 ay (1-32 ay)'dı.

Sonuç: Deneyimlerimize göre 2-10 kg arası bebeklerde uygun duktus anatomisi ve boyutu için ilk tercihimiz olan Amplatzer Piccolo Occluder cihazı ile PDA'nın transkateter tedavisi güvenli ve etkilidir.

Anahtar Sözcükler: Amplatzer tıkayıcı cihaz, Patent duktus arteriozus, Prematüre bebek

INTRODUCTION

Transcatheter device closure of patent ductus arteriosus (PDA) is the standard of care in infants, children, and adults in the last few decades (1). In recent years, transcatheter PDA closure in small babies and premature infants with new devices is a candidate to be the standard treatment. The AmplatzerTM Piccolo Occluder (Abbott Structural Heart, Plymouth, MN), previously called the AmplatzerTM Duct Occluder II Additional Sizes (ADO II AS) obtained CE-Mark in Europe in 2011 for PDA closure in patients ≥6 kg. United States Food and Drug Administration (FDA) approval of the Amplatzer Piccolo Occluder for use in premature infants ≥700 g was obtained on January 11, 2019 (2). ADO-II AS has been used with high procedural success in transcatheter PDA closure in larger, small babies, and premature infants in many centers in the United States and Europe (3-12). After the FDA approval of The Amplatzer Piccolo Occluder in premature infants ≥700 g, it has been widely used as a good alternative to surgery in premature PDA that does not respond to conservative and medical treatments (13,14). Today, transcatheter PDA closure is performed in babies with different devices such as AmplatzerTM Duct Occluder I or II (ADO; AGA Medical Corporation, Golden Valley, MN, USA), KONAR-Multifunctional™ Occluder (MFO) (Lifetech, Shenzhen, China) (15,16). However, it is mostly preferred in patients whose duct size or anatomy is not suitable for transcatheter PDA closure with Amplatzer Piccolo Occluder.

Here, we present our findings on transcatheter PDA closure with different devices, mostly the Amplatzer Piccolo Occluder, in infants weighing between 2 and 10 kg.

MATERIALS and METHODS

Study population

This was a retrospective study including infants weighing between 2 and 10 kg who underwent transcatheter PDA closure in the pediatric cardiology department of Ankara City Hospital, University of Health Sciences between December 2019 and August 2022. This study was conducted in accordance with the Helsinki Declaration Principles. Approval for this study was obtained from the Ankara City Hospital Ethics Committee 2 and the Ministry of Health (07/09/2022 decision number E2-22-2324).

Patient records were reviewed for demographic data also including previous echocardiograms and catheterization reports and angiograms. Patients' age, weight, height, narrowest diameter of the ductus, ductus length, type of ductus, vascular access, femoral sheath size used, device implantation approach, type and diameter of device procedure, and fluoroscopy time, length of follow-up were all recorded.

Procedural and follow-up complications including device implantation failure, post-procedure or intra-procedural device embolization, aortic or pulmonary artery occlusion due to device protrusion, residual shunt, device-induced endocarditis and hemolysis, large blood loss, transient weak arterial pulse were recorded.

Pre-interventional evaluation with transthoracic echocardiography

Cardiac and ductal anatomy were evaluated by two dimensional transthoracic echocardiography (2D-TTE) using a Vivid-S60N machine (General Electric, Norway) before the procedure in all patients. PDA measurements and additional cardiac defects were noted.

Infants weighing ≤ 2 kg or ≥10 kg who underwent transcatheter PDA closure were excluded in this study.

The interventional procedure

Duct morphology was determined according to the classification used in investigational device exemption (IDE) and the continued access protocol (CAP) studies (2). This classification was created by adding fetal-type ductal morphology (17) to the Krichenko classification (18) (Figure 1).

Informed consent was obtained from the parents of all infants before transcatheter PDA closure.

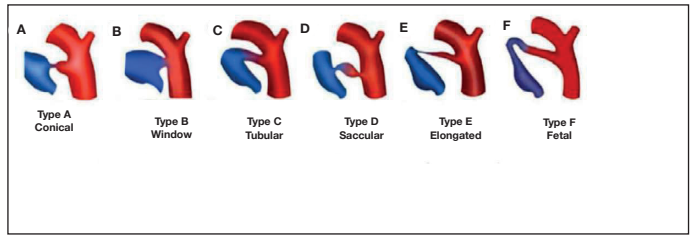

Figure 1: Six morphologic types of Patent Ductus Arteriosus. This classification has been used in the investigational device exemption (IDE) and the continued access protocol (CAP) studies (2). It was created by adding fetal-type ductal morphology (17) to the Krichenko classification (18). [Color figure can be viewed at wileyonlinelibrary.com]

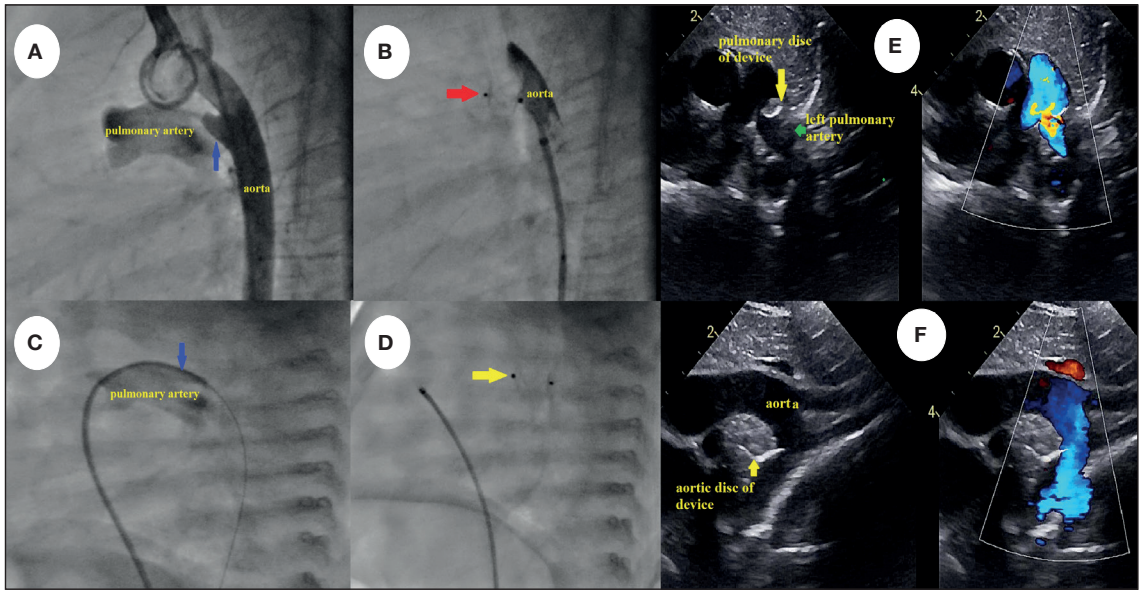

Figure 2: Transcatheter Patent Ductus Arteriosus (PDA) closure by retrograde transarterial approach; aortography in left lateral view shows conical type (Type-A) of PDA (**A**). Aortography in the left lateral view shows the implanted Amplatzer Piccolo Occluder 4/4 mm which is in the proper position within the duct and extraductal disc placement with no residual shunt and no protrusion into the aorta (**B**). Transcatheter PDA closure by anterograde transvenous approach and only by femoral vein access; a straight lateral image; while manually injecting the contrast, the catheter is withdrawn and the central diameter and length of the PDA [fetal type (Type-F)] are determined (**C**). The left lateral view shows the implanted Amplatzer Piccolo Occluder 5/4 mm in the proper position within the duct and extra ductal disc placement (**D**). The control echocardiography during the procedure revealed that the device did not protrude into the descending aorta or pulmonary artery (**E,F**). On all fluoroscopy images, the red arrowhead points to Amplatzer Piccolo Occluder 4/4 device, the yellow arrowhead points to Amplatzer Piccolo Occluder 5/4 mm device, and the blue arrowhead points to PDA.

The Vivid-7 machine (General Electric, Norway) was used for TTE assessment during the procedure in all patients.

Prophylactic antibiotics were administered. Cardiac catheterization was performed under deep sedation or general anesthesia. The Seldinger technique was used for vascular access. The 4F and 5F sheaths were placed arterial only, venous only, or both. Then, heparin sulfate (100 IU/kg) was administered.

Oximetric and some hemodynamic studies (eg pulmonary to systemic flow ratio or pulmonary vascular resistance) were performed only if there was an additional cardiac anomaly detected or suspected in echocardiography or when moderate or significant pulmonary hypertension is detected by invasive measurements.

Transcatheter PDA closure was performed by anterograde transvenous or retrograde transarterial approach.

Retrograde transarterial approach

The ductus was visualized with contrast injections to the descending aorta at the lateral and right oblique positions with a 4-5f pigtail catheter or Amplatzer TorqVue LP catheter (Abbott Structural Heart, Plymouth, MN). From the aorta the 0.014-inch coronary wire was gently advanced into the pulmonary artery through the PDA; a 4F Judkins catheter or 4F Amplatzer TorqVue LP catheter were then slid over the guide wire and advanced to the pulmonary artery. Devices were delivered through a 4 F or 5F Amplatzer TorqVue LP catheter (Abbott Structural Heart, Plymouth, MN). This system was connected to a Y-connector, and the position of the implanted device was verified by injecting the contrast material with hand. After confirming that the device was in the proper position, it was released under fluoroscopy. Then, the position of the device in the duct and the presence of residual shunt were checked with contrast injection into the descending aorta (Figure 2 a,b).

Anterograde transvenous approach

A 4F Judkins catheter was advanced into the right atrium and its tip was turned toward the tricuspid valve. The hydrophilic guide wire (Terumo Medical Corporation, Somerset, NJ, USA) or 0.014-inch coronary wire inside the catheter was advanced into the right ventricle and the pulmonary artery. From the pulmonary artery, the hydrophilic wire was gently advanced into the aorta through the PDA; the catheter was then slid over the guide wire and advanced to the aorta. If there is an arterial sheath, the duct was visualized as described in the retrograde transarterial approach. If there is a venous sheath, this system was connected to a Y-connector and the catheter was withdrawn while injecting the contrast material by hand, the central diameter and length of the PDA were determined at the left anterior oblique view with slight caudal angulation (15 LAO-15 CAU), and straight lateral positions. After determining the appropriate device to use based on the PDA measures, the device was implanted into the duct with an Amplatzer TorqVue LP catheter (Figure 2c, d). The location of the device and whether it protruded into the aorta/ the pulmonary artery

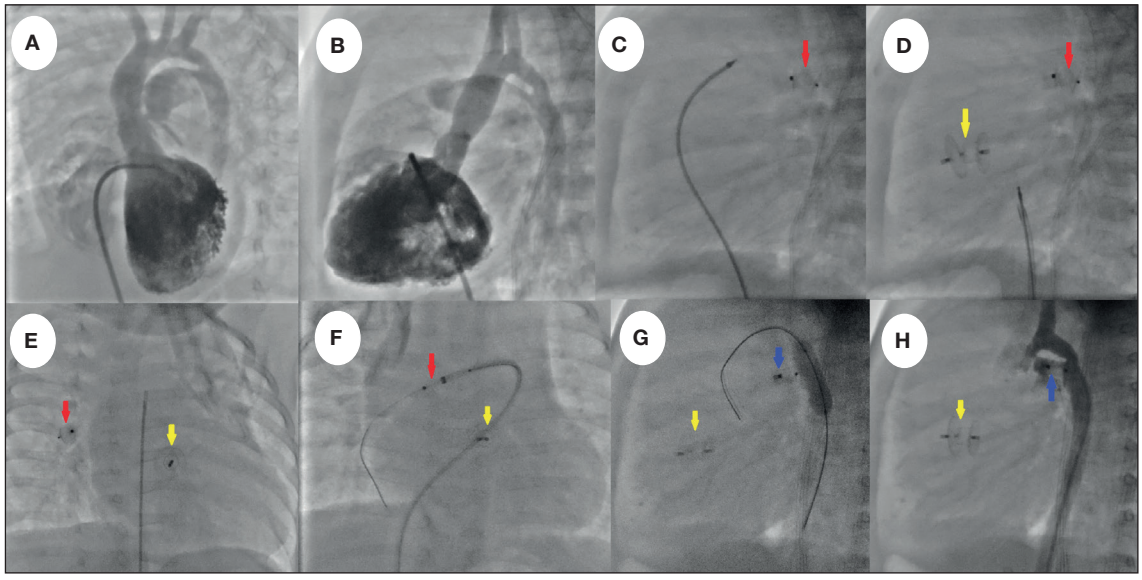

Figure 3: Left lateral and frontal views of Patent Ductus Arteriosus (PDA) and Ventricular Septal Defect (VSD) by left ventricular contrast agent injection (**A,B**). Left lateral views of the Amplatzer™ Piccolo Occluder 5/4 device in the duct, and the KONAR-Multifunctional™ VSD Occluder (MFO) implanted into the VSD anterogradely (**C,D**). Frontal views of the embolized Amplatzer™ Piccolo Occluder into the right pulmonary artery (**E**), and retrieval into the 5F long sheat with gooseneck snare (**F**). Left lateral views of the Amplatzer Duct Occluder-I (ADO-I)6/4 device in the duct, and balloon angioplasty with Tyshak balloon catheter 7/20 mm (**G**). The final position of ADO-I 6/4 device in lateral view with aortogram (**H**). In all images, the red arrowhead points to Amplatzer Piccolo Occluder 5/4 device, the yellow arrowhead points to the KONAR MFO device, and the blue arrowhead points to ADO I 6/4 device

were determined by transthoracic echocardiography using a high parasternal short axis and suprasternal windows (Figure 2 e,f). If there is an arterial sheath, the position of the device in the duct and the presence of residual shunt were checked with contrast injection into the descending aorta.

Procedural success

Procedural success was defined as the presence of all three following criteria: successful device implantation, no major complications and requiring no reintervention during follow-up.

Device Specifications

In this study, devices whose technical specifications are described below were used for transcatheter PDA closure.

The Amplatzer Piccolo Occluder device

The Amplatzer Piccolo™ Occluder is a self-expandable, nitinol mesh device with a central cylindrical waist and low-profile retention discs that are marginally larger than the waist, resulting in a nearly isodiametric device. The device comes pre-loaded on a delivery wire, which has a soft floppy distal end with a microscrew attachment at the tip. It can be delivered through a 4 F Amplatzer TorqVue LP catheter. The Amplatzer Piccolo Occluder is available in nine sizes comprised of three waist diameters (3, 4, and 5 mm) and three lengths (2, 4, and 6 mm). This device is not recommended for PDA >4mm in diameter or <3mm in length.

The Amplatzer Piccolo Occluder can be delivered either antegrade via the femoral vein or retrograde via the femoral artery because of the symmetrical configuration. In infants ≤2 kg, special procedural modifications were utilized to avoid the need for vascular access into the femoral artery in order to maximize safety and avoid complications. Both retention discs can be completely implanted into the canal (intraductal placement) or the central waist can span the entire length of the duct with retention discs placed just outside the canal (extraductal disc placement) (2).

The Amplatzer duct occluder-I device

The ADO-I is a mushroom-shaped device made of 0.004-inch nitinol wire mesh. A 2-mm retention skirt extends radially around the distal part of the device, assuring secure fixation in the mouth of the PDA. Prostheses are available in five different sizes (5/4, 6/4, 8/6, 10/8, and 12/10). The largest measurement is at the aortic site and the narrowest is at the pulmonary end. The device is attached by a recessed microscrew to a 0.038-inch delivery cable made of stainless steel; it is delivered through a 5F to 7F long sheath with anterograde transvenous route (19).

The Amplatzer duct occluder-II device

The ADO-II is a self-expanding nitinol device with a central waist and two symmetrical retention discs (both 6 mm larger than the central waist). The central waist is designed to fill the defect, and the two retention discs are designed to be deployed on the aortic and pulmonary sides of the defect. The occluder has a multilayered, multisegmented design creating six potential planes of occlusion with no central fabric. This design decreases the profile of the occluder and is deliverable with either a 4F or 5F delivery system. The ADO II is available in two lengths (4 and 6 mm) and four waist diameters (3, 4, 5, and

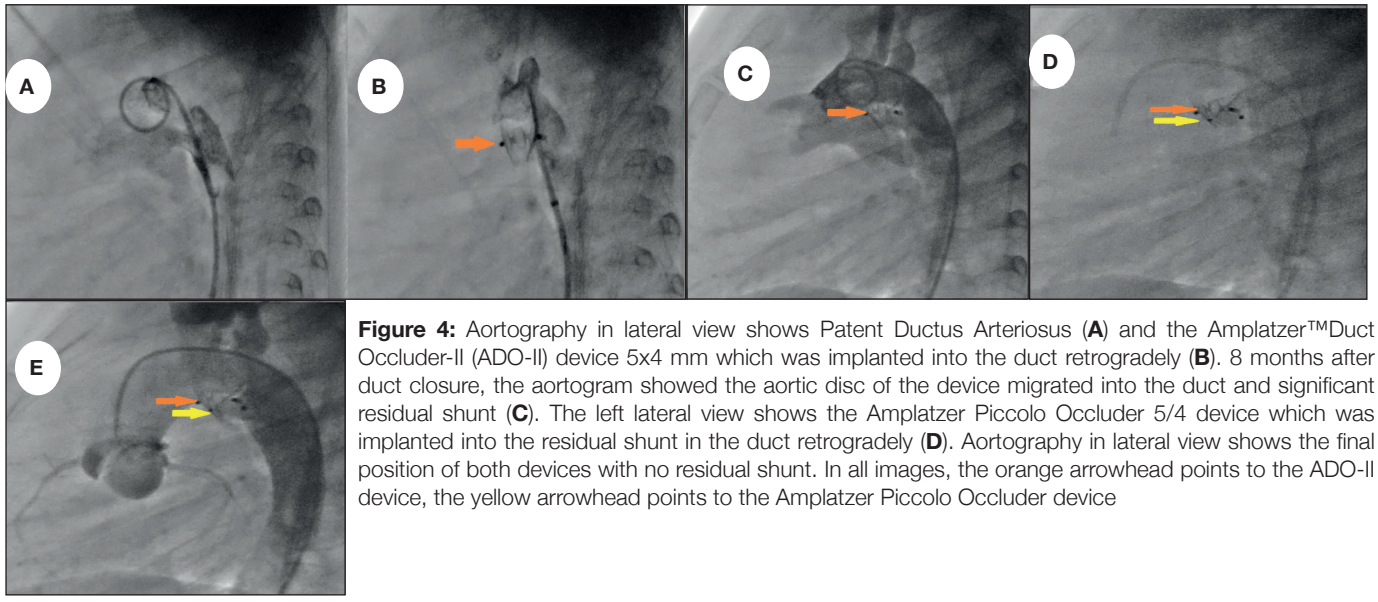

Figure 4: Aortography in lateral view shows Patent Ductus Arteriosus (**A**) and the Amplatzer™Duct Occluder-II (ADO-II) device 5x4 mm which was implanted into the duct retrogradely (**B**). 8 months after duct closure, the aortogram showed the aortic disc of the device migrated into the duct and significant residual shunt (**C**). The left lateral view shows the Amplatzer Piccolo Occluder 5/4 device which was implanted into the residual shunt in the duct retrogradely (**D**). Aortography in lateral view shows the final position of both devices with no residual shunt. In all images, the orange arrowhead points to the ADO-II device, the yellow arrowhead points to the Amplatzer Piccolo Occluder device

6 mm). This occluder has a screw attachment for a delivery wire and radiopaque markers. The ADO-II device can be implanted either the anterograde transvenous route or the retrograde transarterial route (19).

The Lifetech Konar-MF device

The KONAR- MFO device is a self-expandable, double-disc device made from double nitinol wire mesh layers with 144 threads of nitinol wires. It is designed as a hybrid of single-disc and double-disc PDA devices. Two discs are linked together by a cone-shaped waist and there are two screws on the left and right disc. It can be screwed together at both sides and therefore its placement can be anterograde transvenous route or the retrograde transarterial route. Device sizes are given as LV waist diameter and then RV waist diameter. The sizes start from 5/3 mm and up to 14/12 mm, the length in total being 4 mm without stretching. In total, eight sizes are available. The waist of the four largest models is sewn with PTFE membranes, whereas the four smaller models have no membrane. The device is used through a 4–7 F sheath (20). This device was used off-label in one patient.

Follow-up

Transthoracic echocardiography was performed immediately after the procedure, at the 24th hour, and 1, 3, and 6 months after the procedure in all patients to evaluate the therapeutic effects and complications of transcatheter PDA closure. A residual shunt was considered if Doppler color flow mapping showed an aorta-to-pulmonary shunt across the ductus.

Complications

Major and minor complications at the peri-procedural period or during follow-up were recorded for all patients. Major complications included death, cardiac arrest, device embolization, failure of device implantation, significant residual shunt, device-related endocarditis, significant obstruction of the aorta or the pulmonary artery due to device protrusion, massive blood loss, device-related hemolysis; minor complications included mild narrowing of the left pulmonary artery or descending aorta due to device protrusion, transient weak arterial pulse.

Statistical analysis

Statistical Package for the Social Science (SPSS_17.0.1 for Windows; SPSS Inc) was used for statistical analysis. The normal distribution test of continuous variables was performed by using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean ± standard deviation (SD) (minimum-maximum) and the nonnormally distributed continuous data were reported as median {interquartile range (IQR)}. Categorical data are presented as numbers (n) and percentages (%). Statistical signifcance was defined as a two-tailed p value of<0.05.0

RESULTS

Transcatheter PDA closure was performed on 31(14 female) infants weighing 2-10 kg between December 2019 and August 2022. The mean age of patients was 10.7±6.7 months (2-28), and the mean weight was 6.6±2 kg (3-9.9). The median narrowest diameter of the ductus was 2.2 mm (IQR 2-3) and the median ductus length was 6 mm (IQR 4.75-8). A conical PDA (type A) was observed in 64% of patients (Figure 1a), while a fetal, tubular, and elongated PDA (type F, C, or E) were observed in 16%, 13%, 6.5% of patients respectively (Figure 1f, c, e). The demographic and ductus characteristics of the patients are given in table I.

Procedural characteristics and outcomes are shown in table II. Thirty-four interventional procedures, 3 of which were reintervention, were performed on 31 patients and 34 devices

Table I: General characteristics of the patients and ductal morphology

	Patients (n=31)
Age (months)	10.7 ± 6.7 (2-28)
Gender (female), n (%)	14 (45)
Body weight (kg)	6.6 ± 2 kg (3-9.9)
Narrowest diameter of the ductus (mm)	2.2 (2-3)
Ductus Length (mm)	6 (4.75-8)
Type of ductus * n (%)	Type A (n=19) (64) Type B (n=1) (0) Type C (n=4) (13) Type D (n=0) (0) Type E (n=2) (6.5) Type F (n=5) (16)

Values are presented as mean ± SD (minimum-maximum) or median (interquartile range). ***** *This classification has been used in the US IDE and the CAP studies (2). It was created by adding fetal-type ductal morphology to the Krichenko classification (17,18).*

Table II: Procedural characteristics and outcomes

	Patients (31), Procedure (34)*
Procedural success, n (%)	30 (88)
Access	Only venous in 3, only arterial in 24, and both in 7
Device implantation approach	Retrograde (n=27) Anterograde (n=7)
Sheath size used	4F (n=23, arterial 19 vein 4) 5F (n=18, arterial 12 vein 6)
Fluoro time (min)	10.5 (7.25-18.5)
Procedure time (min)	40 (35-57.5)
Length of follow-up (months)	10.3 ± 8.8 (1-32)

Values are presented as mean ± SD (minimum-maximum) or median (interquartile range). ***34 interventional procedures were performed on 31 patients and 34 devices were used.*

were used. None of the patients required surgery. Failure of device implantation occurred in one patient. In this patient, the ductus closed spontaneously after the interventional procedure. The rate of procedural success was 88% (30 of 34). An antegrade and a retrograde implant approach were used in 7 and 27 procedures respectively. The median fluoroscopy and procedural times were 10.5 minutes (IQR 7.25-18.5) and 40 minutes (IQR 35-57.5) respectively. The mean duration of follow-up for our patients was 10.3±8.8 months (1-32 months).

In addition to transcatheter PDA closure, transcatheter ventricular septal defect (VSD) closure was performed in one patient in the same session.

Specifications of the devices used and the procedural characteristics of device types are shown in table III. When comparing the device types, the use of the Amplatzer Piccolo Occluder was significantly higher than the other device types ($p< 0.001$). Twenty-seven (79%) Amplatzer Piccolo Occluder was used. Of the patients who underwent transcatheter PDA closure with the Amplatzer Piccolo Occluder device, 8 were ≤ 6 kg, and 19 were >6 kg. The most preferred implantation approach in this device was retrograde route (n= 23, 85%). The most frequently used sizes of Amplatzer Piccolo Occluder were 4/4 mm (37%) and 5/4 mm (37%). Post-procedural device embolization occurred in two patients. Therefore, the success of the procedure was 89%. The procedural success was 87.5% in infants ≤ 6 kg and 90% in infants > 6 kg. The MFO occluder device was used off-label in one patient.

Procedural and follow-up complications are shown in table IV. One patient had an unsuccessful implant. After the Amplatzer Piccolo Occluder 4/4 device was released, it was found to protrude into the descending aorta and create a 20 mmHg gradient. The device was retrieved with a gooseneck snare and successfully removed from the body. Control angiography showed that the duct was restricted. Then the procedure was postponed to a future date. In this patient, the ductus closed spontaneously during follow-up.

Post-procedural device embolization occurred in two patients. In the first patient weighing 5.6 kg, transcatheter VSD and PDA closures were performed in the same session using only the venous route. The duct was visualized by left ventricular contrast injection (Figure 3a, b). Transcatheter PDA closure was performed with the Amplatzer Piccolo Occluder 5/4 mm device with an antegrade transvenous route (Figure 3 c, d). At 12 hours after the procedure, it was observed that the device was embolized into the right pulmonary artery. We thought that embolization was due to the underestimation of ductal dimension due to incomplete visualization of the ductus. The device was retrieved with a gooseneck snare into the 5F long-sheath placed in the main pulmonary artery and was successfully removed from the body (Figure 3e, f). Then, transcatheter PDA closure was performed with ADO1 6/4 device. After the procedure, a peak-to-peak 15 mmHg gradient was obtained in the aortic isthmus, which was also present before the procedure. Balloon angioplasty was performed with a Tyshak balloon catheter 7/20 mm covering the aortic isthmus and the aortic disc of the device. After balloon angioplasty, the peak-to-peak gradient decreased to 8 mmHg (Figure 3 g, h). Also, the control echocardiogram revealed a mean Doppler gradient of 10 mmHg in the aortic isthmus without a diastolic tail. No Doppler gradient showing significant aortic stenosis was obtained during follow-up echocardiograms. In the second patient weighing 6.1kg, transcatheter PDA closure was performed with the Amplatzer Piccolo Occluder 4/2 device. On the 1st post-procedure day, it was observed that the device was embolized to the left pulmonary artery. We speculate that the device embolization is due to the fact that the implanted device is too small for the encountered anatomy. The device was retrieved with a gooseneck micro snare into the 5F long-sheath placed in the main pulmonary artery and was successfully removed from the body. Then, transcatheter PDA closure was performed with Amplatzer Piccolo Occluder 5/4 device. After

Table III: Specifications of the devices used and procedural characteristics

Devices*	Amplatzer Piccolo Occluder (n=27)† (79)	ADO II (n=4) (12)	ADO I (n=2) (6)	LT-MFO (n=1) (3)‡
Device diameter (mm), n(%)	4/2 (n=2) (7) 5/2 (n=1) (3) 4/4 (n=10) (37) 5/4 (n=10) (37) 4/6 (n=1) (3) 5/6 (n=4) (15)	3/4 (n=1) 6/6 (n=1) 5/4 (n=2)	8/6 (n=1) 6/4 (n=1)	6/8 (n=1)
Sheath size used	4F (n=19), 5F (n=11)	4F (n=2), 5F (n=3)	4F (n=2), 5F (n=2)	5F (n=2)
Device implantation approach	Retrograde (n=23) (85) Anterograde (n=4) (15)	Retrograde (n=4)	Anterograde (n=2)	Anterograde (n=1)
Access	Only venous in 3, only arterial in 21, and both in 3 (two are retrograde)	Only arterial in 3, venous and arterial in 1	Venous and arterial in 2	Venous and arterial
Major Complication	Device embolization (n=2) Failure of device implantation (n=1)	Significant residual shunt (n=1)		

Thirty four interventional procedures were performed in 31 patients and 34 devices were used. †The use of the Amplatzer Piccolo Occluder was statistically significantly higher than other device types (p< 0.001). ‡The LifeTech™ multifunctional occluder device was used off-label in one patient.* ***ADO:* *Amplatzer™ duct occluder,* ***LT-MFO:*** *LifeTech™ multifunctional occluder device.*

Table IV: Procedural and Follow-up complications

	Patients (n=31)
Major complications, n(%)	
Failure of device implantation	1 (3.2)
Post-procedure device embolization	2 (6.5) *
Significant residual shunt	1 (3.2) †
Device -related endocarditis	0 (0)
Significant obstruction of the aorta or the pulmonary artery due to device protrusion,	0 (0)
Massive blood loss	0 (0)
Device -related hemolysis	0 (0)
Total events	4 (13)
Minor complications, n(%)	
Mild narrowing of the left pulmonary artery due to device protrusion	0 (0)
Mild narrowing of descending aorta due to device protrusion	1 (3.2)
Transient weak arterial pulse	0 (0)
Total events	1 (3.2)

**Two Amplatzer Piccolo Occluder devices were replaced with the ADO-I device and the larger Amplatzer Piccolo Occluder device. †The residual shunt was closed by implanting a second device (Amplatzer Piccolo Occluder) during follow-up.*

the second procedure, no complications were observed during the follow-up.

In another patient who underwent transcatheter PDA closure, second device implantation was performed due to progressively increasing residual shunt during follow-up. In this patient weighing 6 kg, transcatheter PDA closure was performed with an ADO-II device at the age of 5.5 months(Figure 4 a, b). Eight months after the first procedure, the patient was taken to the catheter room because of a moderate-to-significant residual shunt that gradually increased on echocardiography. In aortography, it was observed that the aortic disc of the device migrated into the duct in an inappropriate position and there was a significant residual shunt at the edge of the device (Figure 3c). We thought that device malposition developed due to a mismatch of the implanted device with the shape of the ductus. Then a transcatheter Amplatzer Piccolo Occluder 5/4 device was successfully implanted by retrograde route into the residual duct (Figure 3d, e). After the second procedure, no complications were observed during the follow-up.

DISCUSSION

Transcatheter closure of the PDA has been the mainstay of treatment in infants, children, and adults. In addition, as a result of the developments in the industry, the widespread use of Amplatzer Piccolo Occluder in premature babies and its equivalence with surgical ligation are the subject of debate today (12,14,21,25).

The most common type of ductus was conic PDA in our study, consistent with the literature (2, 19).

Sathanandam SK et al. (2) reported a 92% success of implant for the Amplatzer Piccolo Occluder over 2 kg infants. Similarly, in our study, transcatheter PDA closure was performed with a procedural success rate of 88% in infants weighing between 2 and 10 kg. According to data obtained from 277 patients receiving ADO II AS in 10 European medical centers, the successful implantation rate was reported as 93.2% in infants 2-6 kg and 100% in infants >6 kg. In our study, the rate of procedural success with the Amplatzer Piccolo Occluder device was 87.5% in infants ≤ 6 kg and 90% in infants with >6 kg, these results are comparable to the results of the European medical centers, considering the learning curve and the number of patients (3-12).

In our study, a retrograde device implantation approach was preferred in 27 (70%) procedures. Amplatzer Piccolo Occluder device was implanted in 23(85%) of these procedures and the ADO-II device was implanted in 4 (15%) of them. In addition, 24 of these procedures had only a femoral arterial sheath. 5F arterial sheaths were not used in any infant weighing less than 6 kg. The smallest infant who underwent the transcatheter PDA closure using a 4f femoral arterial sheath weighed 4 kg. Moreover, all sizes of the Amplatzer Piccolo Occluder device are delivered through a 4 F Amplatzer TorqVue LP catheter. In the study of Sathanandam SK et al. (2) transcatheter PDA closure was performed with a retrograde approach in 26% of patients > 2 kg (but, femoral arterial access was used in 48%). In the same study, it has been stated that femoral artery access must be avoided in preterm infants <2 kg. In another study, 89% of transcatheter PDA closures with the ADO-II AS device were performed by retrograde arterial route in infants >6 kg (10).

The use of the retrograde arterial routes shortens the procedure and fluoroscopy times, provides better visualization of the duct angiographically, allows to perform aortography to check the placement of the device in the duct, and also avoids cardiac injury and tricuspid valve regurgitation. However, it can cause femoral artery injuries. In our comment absence of vascular complications in this study was due to not using femoral artery sheaths in infants weighing less than 4 kg. Nevertheless, in our opinion, the anterograde route under transthoracic echocardiography guidance should be preferred without using a femoral arterial sheath, especially in small infants.

The procedure and fluoro times in our study (median 40 and 10.5 min respectively) were comparable with the procedure time and fluoro time of transcatheter PDA closure in the study of Sathanandam SK et al. (2) (mean 57.1 and 10.1 min respectively) and in the study of Park YA et al (22) (mean 48.6 and 13.4 min respectively).

Sathanandam SK et al. (2) reported that the intra-procedural device embolization rate was 3% and the post-procedure device migration rate was 1% in patients >2 kg in whom the Amplatzer Piccolo Occluder device was implanted. On the other hand, Baspinar et al reported one major complication (device embolization) in a group of 53 patients who were under 6 kg (8). Also, a large meta-analysis of ductus arteriosus occlusion reported adverse event rate of 10% (23). Similarly, in our study, post-procedure device embolization occurred in 2(7.4%) of 27 procedures in which the Amplatzer Piccolo Occluder device was implanted, and failure of device implantation occurred in one (3.7%) patient. Méot M et al. (22) reported that in the case of transcatheter PDA failure, mechanically induced spontaneous closure may occur early after the procedure. They also suggested that surgical ligation should be postponed when clinically tolerated (24). In our study, during the follow-up the patient who had failed device implantation, the duct closed spontaneously.

CONCLUSION

In our study, the Amplatzer Piccolo Occluder device has been our first choice in properly sized ducts because it requires a smaller delivery sheath, can be implanted with antegrade and retrograde approaches, is a nearly isodiametric device, and complications can be managed more easily. In our experience, the transcatheter treatment of PDA with Amplatzer Piccolo Occluder is safe and effective in appropriate anatomy and size in infants with 2 -10 kg.

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Determining the Relationship between the Influenza Vaccination and Disease Control in Children with Asthma

Astımlı Çocuklarda İnfluenza Aşısı İle Hastalık Kontrolü Arasındaki İlişkinin Belirlenmesi

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ABSTRACT

Objective: The influenza vaccine's effect on the control of asthma is debatable. The purpose of this study was to investigate the effect of the influenza vaccine on disease control in children with asthma.

Material and Methods: Children with a diagnosis of asthma were prospectively included in this study. The socio-demographic characteristics of the patients, the status of influenza vaccination within the previous year, the use of bronchodilators and systemic steroid therapy, the frequency of hospitalization, risk factors which may affect the disease's control status, and the effects of vaccination status were investigated.

Results: A total of 187 asthmatic children with a median age of 11 years were included in this study. Almost half of the patients (47.6%) did not have their asthma under control. In the last year, 14.4% had one asthma attack, 14.4% had two attacks, 19.3% had ≥3 attacks, while 51.9% had no asthma attack. In the previous year, 52.4% of the patients received an influenza vaccination. Influenza vaccination was equally common in those patients with controlled and uncontrolled asthma (54.1% vs 50.6%), and vaccination had no effect on disease control (p=0.662). Those patients with allergic rhinitis and atopy had a significantly higher uncontrolled asthma status than those without allergic rhinitis (p=0.027 and p=0.041, respectively). Children with uncontrolled asthma used less prophylactic drugs than those with controlled asthma (p<0.001).

Conclusion: The influenza vaccine has no effect on disease control in children with asthma. Having allergic rhinitis and atopy reduces the control of this disease.

Key Words: Asthma, Allergic rhinitis, Child, Influenza, Vaccine

ÖZ

Amaç: İnfluenza aşısının astım kontrolü üzerindeki etkisi tartışmalıdır. Bu çalışmanın amacı astımlı çocuklarda influenza aşısının hastalık kontrolüne etkisini araştırmaktır.

Gereç ve Yöntemler: Astım tanısı alan çocuklar prospektif olarak çalışmaya dahil edildi. Hastaların sosyo-demografik özellikleri, bir önceki yılda influenza aşısı olma durumu, bronkodilatatör kullanımı ve sistemik steroid tedavisi, hastaneye yatış sıklığı, aşılam durumunu ve hastalığın kontrol durumunu etkileyecek risk faktörleri araştırıldı.

Bulgular: Çalışmaya ortanca yaşı 11 olan toplam 187 astımlı çocuk dahil edildi. Hastaların yaklaşık yarısında (%47.6) astım kontrol altında değildi. Son bir yılda %14.4'ü, %14.4'ü iki, %19.3'ü ≥3 atağı geçirirken, %51.9'u astım atağı

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital (2012-009/ 29.02.2012).

Contribution of the Authors / Yazarların katkısı*: CAPANOGLU M:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***CIVELEK E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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geçirmedi. Bir önceki yılda hastaların %52.4'ü grip aşısı olmuştu. İnfluenza aşılaması, kontrollü ve kontrolsüz astımı olan hastalarda eşit oranda yaygındı (%54.1'e karşı %50.6) ve aşılamanın hastalık kontrolü üzerinde etkisi yoktu (p=0.662). Alerjik riniti ve atopisi olan hastalarda, alerjik riniti olmayan hastalara göre anlamlı olarak daha yüksek kontrolsüz astım durumu vardı (sırasıyla p=0.027 ve p=0.041). Kontrolsüz astımı olan çocuklar kontrol grubuna göre daha az profilaktik ilaç kullanmışlardı (p<0.001).

Sonuç: İnfluenza aşısının astımlı çocuklarda hastalık kontrolüne etkisi yoktur. Alerjik rinit ve atopiye sahip olmak hastalığın kontrolünü azaltır.

Anahtar Sözcükler: Astım, Allerjik rinit, Çocuk, İnfluenza, Aşı

INTRODUCTION

Asthma is the most common chronic disease in children in developed countries, and it is one of the leading causes of paediatric hospitalization (1,2). Although its prevalence varies by country, it has been reported to occur at a rate of 1-18% (3-5). Acute asthma attacks are a clinical picture which has a significant impact on both children and their parents. In children, asthma is usually diagnosed after the first attack, and these attacks account for the vast majority of subsequent hospitalizations (6). Poor asthma control can lead to severe asthma exacerbations (7). In terms of asthma control, Peters S.P. et al. (8) reported in a study with 1.003 patients in the United States that the rates of unplanned physician and emergency department visits in children with uncontrolled and controlled asthma were 70%-43% and 36%-10%, respectively.

For asthmatic patients of all ages, viral upper respiratory tract infections (URTIs) are accepted as the primary trigger (>80%) factors (9,10). In children aged 6-17 years (55%) and infants/pre-schoolers (33%), rhinovirus was the most common virus identified in asthma exacerbations of proven viral origin. However, influenza is only responsible for 0-7% of virus-induced asthma exacerbations, and there is insufficient evidence that it poses an additional risk in asthmatic children (12). Although the influenza vaccination is recommended in many countries in order to reduce asthma exacerbations in children, most children do not get vaccinated (13,14). Furthermore, the effect of the influenza vaccine on the frequency of attacks in children with asthma throughout the year is controversial. Although there are some studies that demonstrate that the influenza vaccine reduces the number of attacks in children with asthma, there are also other studies which have shown that it has no effect (15,16).

Our primary aim in this study was to examine the effects of the influenza vaccine on attack frequency and asthma control in children with asthma.

MATERIALS and METHODS

This study included all asthma patients who had been followed up at a paediatric allergy outpatient clinic for at least one year. The patients were contacted by phone, and after providing the parents with verbal information about this study, written/verbal consent was obtained from those parents who agreed to participate in this study. Those patients who could not be reached by phone or who provided incomplete data were excluded from this study. The hospital's ethics committee granted approval for this study.

The patients' socio-demographic data were recorded and included in this study. The patients were called and asked questions from questionnaire forms. The patients contacted by phone were asked about their influenza vaccination status in the previous year, their use of bronchodilator and systemic steroid therapy, any emergency service admissions, their frequency of hospitalizations, and any risk factors (atopy, smoking, crowded environment, school situation) affecting disease control. All data were recorded by a paediatric allergist.

Statistical Analysis

The data were analysed using the program SPSS 25.0 (IBM, Armonk, NY: IBM Corp.). Mean ± standard deviation for parametric tests, as well as median and categorical variables for non-parametric tests are expressed as numbers and percentages in the presentation of continuous variables. The Kolmogorov-Smirnov test was used to determine whether the data conformed to the normal distribution. To assess the relationship between two variables, a simple correlation test was used. To examine the differences between categorical variables, chi-square analysis was used. In all analyses, $p<0.050$ was considered statistically significant.

RESULTS

203 patients were included in this study. This study excluded 14 patients who could not be reached by phone and two patients who had missing data (Figure 1). In this study, which was completed with a total of 187 patients, the M/F ratio was 1.5/1, the median age was 11.0 years (min 5.0 - max 19.0, IQR 9.0-14.0), and 61.5% (n=115) of the patients were in the 5-12 years old age range (Table I). Almost half of the patients (47.6%) did not have their asthma under control. Having only one asthma attack in the previous year was observed with a frequency of 14.4%, two attacks with a frequency of 14.4%, and ≥3 attacks with a frequency of 19.3%, while 51.9% of the patients had no asthma attack with the previous 12 months (Table I). Furthermore, when the patients' asthma attacks during influenza infections were examined, 58.8% had no

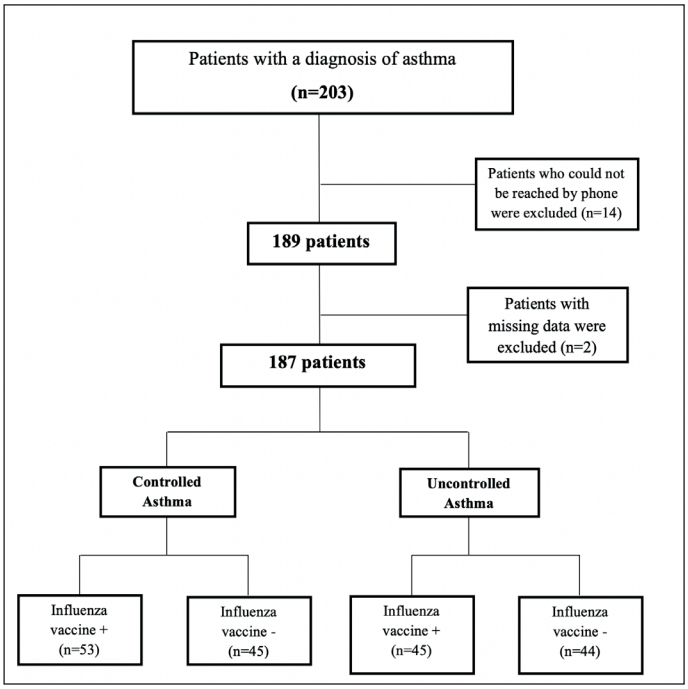

Figure 1: Distribution of patients included in the study.

Table I: Demographic data of patients, disease and vaccination status

Gender (M/F)	1.5 / 1
Age (Year) [median (min-max)]	11.0 (5.0 – 19.0)
Age groups(year)*	
5-12	115 (61.5)
≥12	72 (38.5)
Asthma control status*	
Under control	98 (52.4)
Uncontrolled	89 (47.6)
Frequency of asthma attacks*	
0	97 (51.9)
1	27 (14.4)
2	27 (14.4)
≥3	36 (19.2)
Frequency of asthma attacks during influenza infection*	
0	110 (58.8)
1	23 (12.3)
2	25 (13.4)
≥3	29 (15.5)
Influenza vaccination in the last 1 year*	
No	89 (47.6)
Yes	98 (52.4)

M: *male,* ***F:*** *female,* ***max:*** *maximum,* ***min:*** *minimum,* *******: (n,%)*

attack, 12.3% had only one attack, 13.4% had two attacks, and 15.5% had at least 3 asthma attacks. Furthermore, when the risk factors which may cause an asthma attack were investigated, 44.9% of the patients had risk factors such as cigarette smoke exposure, 54.0% had allergic rhinitis, 70.0% had school-age siblings, and 41.2% had risk factors such as living in a crowded environment (Table II). While 47.1% (n=88) of the patients received prophylactic treatment, only 26.7% (n=50) of them were receiving it on a regular basis.

Table II: Asthma attack risk factors in patients

Risk factors	n (%)
Cigarette smoke exposure	
Yes	84 (44.9)
No	103 (55.1)
Allergic rhinitis	
Yes	101 (54)
No	86 (46)
Siblings attending school	
Yes	131 (70)
No	56 (30)
Living in a crowded environment	
Yes	77 (41.2)
No	110 (58.8)

Table III: Comparison of patients' influenza vaccination with asthma status, exacerbation and hospitalization frequency

	influenza vaccine		p
	-	+	
Asthma control status*			
Under control	45 (50.6)	53 (54.1)	0.662
Uncontrolled	44 (49.4)	45 (45.9)	
Having an asthma attack during an influenza infection*			
No	51 (57.3)	59 (60.2)	0.766
Yes	38 (42.7)	39 (39.8)	
Hospitalization*			
No	3 (3.4)	3 (3.1)	0.841
Yes	86 (96.6)	95 (96.9)	

******* *n(%)*

It was observed that 52.4% (n=98) of the patients in this study had received an influenza vaccination within the previous year (Table I). The rate of influenza vaccination was 54.1% in those patients with controlled asthma and 50.6% in those with uncontrolled asthma, and it was determined that the influenza vaccination had no effect on disease control (Table III) (p=0.662). In terms of having an asthma attack during an influenza infection, there was no significant difference between the groups of patients with or without the influenza vaccine (39.8% vs 42.7%, respectively) (Table III) (p=0.766). The influenza vaccine had no effect on the annual number of attacks, absenteeism from school, or hospitalization rates due to asthma attacks in the children with asthma (Table III).

When the risk factors for asthma attacks were examined, those patients with allergic rhinitis were statistically significantly more likely than those without allergic rhinitis to have uncontrolled asthma (55.4% vs 38.3%, respectively) (p=0.027) (Table IV). Furthermore, uncontrolled asthma was observed to be more prevalent in those patients with atopy than in the asthmatic patients without atopy (55.7% vs 40.4%, respectively) (p=0.041) (Table IV). There was no statistically significant difference in cigarette smoke exposure between those with controlled asthma and those with uncontrolled asthma (p=0.244).

Prophylactic drug use was found to be significantly lower in those children with uncontrolled asthma than in those with

Table IV: The effect of risk factors on patients' asthma status

Risk factors	Asthma control status		Total*	p
	Under control*	Uncontrolled*		
Allergic rhinitis				
No	53 (61.7)	33 (38.3)	86 (100)	0.027
Yes	45 (44.6)	56 (55.4)	101 (100)	
Atopy				
No	59 (59.6)	40 (40.4)	99 (100)	0.041
Yes	39 (44.3)	49 (55.7)	88 (100)	
Exposure to cigarette smoke				
No	58 (3.4)	45 (3.1)	103 (100)	0.244
Yes	40 (96.6)	44 (96.9)	84 (100)	
Prophylactic drug use				
No	67 (67.7)	32 (32.3)	99 (100)	<0.001
Yes	31 (35.2)	57 (64.8)	88 (100)	

***** *n(%)*

controlled asthma (p<0.001) (Table IV). It was observed that the influenza vaccine had no effect on prophylactic drug use (p=0.187).

DISCUSSION

Asthma is the most common chronic respiratory disease in children and adolescents around the world (1,2,17). Despite its high prevalence, poor results are still obtained in cases of childhood asthma, and even child death is reported each year, despite the fact that it is preventable (17). Asthma management's main goals are to provide good control of asthma-related symptoms while minimizing the risk of exacerbations and/or complications (18). The World Health Organization (WHO), the United States of America (USA), and some European countries (19,20) recommend the influenza vaccination for aetiology to ensure asthma control. In addition, influenza infections may lead to severe asthma attacks, which usually require hospitalization (11). On the other hand, the rate of influenza vaccination in high-risk groups, such as those with asthma, remained far below the 75% target (58.6% between the ages of 6 months and 17 years in 2020-2021) (21,22). Parental and physician confusion about the benefits of the influenza vaccination and the role of immunization in preventing asthma attacks in this population is one of the barriers to compliance (23). The effect of the influenza vaccine on disease control and attack frequency in children with asthma was investigated in this study.

While asthma is more common in males in childhood, it is more common in females in adulthood. The reversal of this gender disparity in prevalence suggests that pubertal hormones may be involved in the aetiology of asthma (24). As in the literature, patients with asthma were found to be males more frequently in our study. According to the Centres for Disease Control and Prevention (CDC), half of all children with asthma (50.3%) do not have the disease under control (25). In our study, asthma was not under control in almost half of the patients (47.6%). This result supported the literature.

Many guidelines recommend an annual influenza vaccination for children with asthma, but there is insufficient clinical evidence to support this (26,27). In recent years, the findings of studies investigating the effect of the influenza vaccine on the number of attacks and disease control in children with asthma have remained contentious. Although there are some publications stating that the influenza vaccine reduces asthma attacks, health-care utilization, other respiratory diseases, and the number of asthma medications used, the fact that the majority of these are observational studies with low-quality evidence has led to biased and controversial results (28-31). Watanabe S. et al. (31) identified that the influenza vaccine reduced the incidence, frequency, and duration of attacks in 201 asthmatic children aged 1-15 years compared to a control group in a randomized controlled study. Additionally, Smitz et al. (32) reported in their retrospective study of preschool children with asthma that the influenza vaccine reduced the number of lower respiratory tract infections and acute otitis media. According to Ong et al. (33), the influenza vaccine reduced the use of oral steroids in children with asthma. In our study, asthmatic children who received or did not receive the influenza vaccine had similar attack frequencies and disease control. In contrast to the literature, our study showed that the influenza vaccine had no effect on the frequency of attacks in children with asthma. This can be attributed to the fact that our study was based on a questionnaire which obtained information from the families about the past, which may have resulted in insufficiently accurate information.

Aside from viral infections, atopic structure and allergic rhinitis have been identified as risk factors for asthma attacks in children, making the disease difficult to control (34,35). Uncontrolled disease was more common in those children with allergic rhinitis and atopic structure according to our study, which supports the literature. Additionally, it was discovered in the study conducted by JR DiFranza et al. (36) that exposure to cigarette smoke may trigger asthma attacks in children, making it challenging to control this disease. In our study, it was observed that exposure to cigarette smoke had no effect on the control of asthma or the frequency of attacks. The failure of families in our study to adequately explain their smoking/child exposure may have contributed to this result.

Limitations of this study include: (1) the single-centre nature of our study, which limits the generalizability of our findings; and (2) being a survey study with no face-to-face interviews resulting in concerns regarding the proficiency of our data.

In conclusion, it was observed in our study that the influenza vaccine had no effect on attack frequency or disease control in

children with asthma. However, based only on the data of our study, we cannot generalize that children with asthma do not need to be vaccinated against influenza. Larger, multicentre, and randomized controlled studies on this subject are needed.

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Clinical Characteristics and Possible Risk Factors of Epilepsy in Children with Cerebral Palsy: A Tertiary-Center Experience

Serebral Palsili Çocuklarda Epilepsinin Klinik Özellikleri ve Olası Risk Faktörleri: Üçüncü Basamak Merkez Deneyimi

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ABSTRACT

Objective: The aim of this study was to evaluate the clinical characteristics of children with cerebral palsy (CP) and to investigate possible risk factors and prognosis of epilepsy in children with cerebral palsy (CP) with a special emphasis on drug-resistant epilepsy (DRE).

Material and Methods: A total of 145 pediatric patients who were followed up with a diagnosis of CP between 2019 and 2022 were evaluated. Demographic features, prenatal/perinatal history, etiology and type of CP, degree of impairment in motor and cognitive functions, seizure type, neuroimaging, and electroencephalography (EEG) findings were obtained retrospectively from hospital records. The patients were divided into two groups: CP patients with epilepsy and patients without epilepsy. Study variables were compared between these two groups and also between DRE and controlled epilepsy groups.

Results: There were 91 (63%) boys and 54 (37%) girls with a mean age of 11.1±4.2 years (3-18 years). Epilepsy was present in 107 (73.7%) cases and 40.1% of them had refractory epilepsy. Epilepsy was most common in the tetraplegic form of CP (p=0.028). Term gestation, birth weight of ≥2500 g, and history of neonatal seizures were significantly higher in patients with epilepsy (p=0.030, 0.010, and 0.030, respectively). Children with DRE were more likely to have tetraplegic CP (50%) and severe intellectual disability (56%).

Conclusion: Determination of potential risk factors is important in predicting the development of epilepsy in patients with CP, as it may provide closer follow-up of patients at high risk. Particular attention should be paid to the early identification and treatment of comorbid epilepsy in children with CP.

Key Words: Cerebral palsy, Epilepsy, Risk factors, Refractory epilepsy, Pediatric

ÖZ

Amaç: Bu çalışmada serebral palsili (SP) çocuklarda klinik özellikler ile epilepsi gelişiminde olası risk faktörlerinin ve epilepsi prognozunun değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: 2019-2022 yılları arasında SP tanısı ile takip edilen toplam 145 çocuk hasta değerlendirilmiştir. Olguların demografik bilgileri, prenatal/perinatal öyküsü, SP etiyolojisi ve tipi, motor ve bilişsel fonksiyonlardaki bozukluğun derecesi, nöbet tipi, nörogörüntüleme ve elektroensefalografi (EEG) bulguları hastane kayıtlarından retrospektif olarak toplanmıştır. Olgular epilepsisi olan ve epilepsisi olmayan SP hastaları olmak üzere iki gruba ayrılmıştır. Çalışma değişkenleri bu iki grup arasında ve ayrıca dirençli epilepsi ile kontrollü epilepsi grupları arasında karşılaştırılmıştır.

Bulgular: Olguların 91'i (%63) erkek, 54'ü (%37) kız ve ortalama yaşı 11.1±4.2 yıl (3-18 yaş)'tı. Toplam 107 (%73.7) olguda epilepsi mevcuttu ve bunların %40.1'i dirençli epilepsiydi. Epilepsi grubunda en sık SP tipi tetraplejik SP'di (p=0.028). Term gebelik, ≥2500 g doğum ağırlığı ve neonatal nöbet öyküsü epilepsili SP grubunda anlamlı olarak daha fazlaydı (sırasıyla p=0.030, 0.010 ve 0.030). Dirençli epilepsi grubunda tetraplejik SP tipi (%50) ve ağır zihinsel yetersizlik (%56) görülme oranı kontrollü epilepsi grubuna göre daha yüksekti.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study is approved by the institutional ethical committee of Ankara City Hospital (E2-22-2147).

Contribution of the Authors / Yazarların katkısı*: *ARDICLI D: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***DEDEOGLU O:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study.

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Sonuç: Serebral palsili hastalarda epilepsi gelişiminin öngörülmesinde olası risk faktörlerinin belirlenmesi, yüksek riskli hastaların yakın izlemi açısından önemlidir. Serebral palsili çocuklarda komorbid epilepsinin erken tanımlanması ve tedavisine özellikle dikkat edilmelidir.

Anahtar Sözcükler: Serebral palsi, Epilepsi, Risk faktörleri, Dirençli epilepsi, Pediatrik

INTRODUCTION

Cerebral palsy (CP) is the most common chronic neurodevelopmental disorder in childhood and occurs at a frequency of 1.5-3 per 1000 live births. Cerebral palsy is caused by damage to the developing brain before or during birth or in the first months of life, affecting muscle tone, movement, and posture, that is not progressive, but symptoms and signs may change with age (1). In addition to motor functional disabilities, children with CP are at increased risk for impairments in visual, auditory, sensory, cognitive, and behavioral functions and development of epilepsy.

It is well known that the general incidence of epilepsy in children with CP is high, ranging between 15-60% (1). Depending on the type of CP and accompanying comorbidities, the incidence of epilepsy may reach up to 90% (3, 4). The frequency of epilepsy has been reported as particularly more common in children with severe motor (tetraplegic CP) and cognitive impairments (4, 5). There are numerous reports on the predictive risk factors for the development of epilepsy in children with CP, including prenatal risk factors, perinatal complications, and history of neonatal seizures (3). Later in childhood, epileptic seizures may become resistant to anti-seizure medications and uncontrolled seizures put an extra burden with unfavorable impacts on neurodevelopment and quality of life.

Herein, we aimed to evaluate the clinical characteristics of patients with CP and to investigate possible correlations between pre/perinatal risk factors and epilepsy, with a special emphasis on drug-resistant epilepsy (DRE) in a group of children with cerebral palsy recruited from a single tertiary center in Turkey.

MATERIALS and METHODS

This is a single-center, cross-sectional, retrospective study including 145 children with CP followed at Ankara Bilkent City Hospital, Department of Pediatric Neurology between 2019-2022. Patients with CP diagnoses were extracted from the electronic-based hospital data system according to the ICD-10 classification, as code of G80 and subtypes were included. Patients aged 3-18 years with a follow-up of at least 12 months were included. Children initially diagnosed with CP and later had another diagnosis mimicking CP, such as neurometabolic or neurodegenerative disorders were excluded. The following data variables were collected: age, gender, type of CP, prenatal risk factors, natal history, postnatal complications, presence of neonatal seizures, the level of motor and cognitive impairment, neuroimaging results, data regarding epilepsy such as age at seizure onset, seizure type, frequency of seizures, number of anti-seizure medications (ASMs), and electroencephalography (EEG) findings.

Clinical diagnosis of CP was defined as non-progressive, static encephalopathy presenting with motor and postural disabilities, caused by damage to the developing brain. Types of CP were grouped as diplegic, hemiplegic, tetraplegic, dyskinetic, ataxic, and mixed form. The level of motor functional severity was based on the Gross Motor Function Classification Scale (GMFCS) (6). The cognitive status of patients was evaluated based on age-appropriate standardized psychometric tests in available patients. Gestational age of ≤37 weeks was considered prematurity and the age of gestation was categorized into the following groups: ≤30 weeks, 30–37 weeks, and >37 weeks. Birth weight was grouped as <1000 g, 1000–1499 g, 1500–2499 g, and ≥2500 g. Brain neuroimaging findings were classified according to the Magnetic Resonance Imaging Classification System (MRICS) proposed by Surveillance of Cerebral Palsy in Europe (SCPE): maldevelopments (disorders of cortical formation and other maldevelopments), predominant white matter injury (periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH) or periventricular hemorrhagic infarct), predominant gray matter injury (basal ganglia/thalamus lesions, arterial infarctions or watershed lesions in parasagittal distribution), miscellaneous (nonspecific cerebral or cerebellar atrophy, ventriculomegaly) and normal (7). We classified types of seizures and epilepsies based on the 2017 International League against Epilepsy (ILAE) classification (8). Epilepsy types were classified into four groups: focal, generalized, combined focal and generalized, and unknown. Drug-resistant epilepsy was defined as persistent seizures despite the proper use of at least two ASMs. Controlled epilepsy was defined as having no seizures for more than 6 months. Patients whose antiseizure treatment was discontinued were also included in the controlled epilepsy group. EEG abnormalities were classified in the form of focal, generalized or multifocal epileptogenic activities and other abnormalities, including abnormal background activity and a history of specific patterns such as hypsarrhythmia or electrical status epilepticus during sleep -ESES.

Patients were divided into the following groups; Group 1: CP with epilepsy (n=107) and Group 2: CP without epilepsy (n=38). Demographic characteristics, prenatal/natal history, postnatal complications, type of CP, level of motor disabilities, and cognitive functional status of the two groups were compared. Those variables were also compared between the subgroups of DRE and controlled epilepsy.

Statistics

SPSS software, version 23.0 (SPSS, Chicago, IL), was used for the statistical analysis of the data. The variables were

investigated using visual (histograms, probability plots) and analytical methods (Kolomogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed and medians and interquartile range (IQR) for the non-normally distributed and ordinal variables. Numbers and percentages are used for categorical variables. Median scores of all groups were compared with the nonparametric Mann-Whitney U test. The proportions of patients were compared by using the Chi-square test or Fischer's exact test in different groups. A p-value of <0.050 is considered to be statistically significant.

The study is approved by the institutional ethical committee of Ankara City Hospital (E2-22-2147).

RESULTS

A total of 145 patients (91 boys and 54 girls) were included. Mean age of the patients at last clinical visit was 11.1±4.2 years (3-18 years). The median duration of follow-up was 3.2 years. Parental consanguinity was present in 19 (13.1%) patients. The demographic and clinical features of our patients are demonstrated in Table I.

Eighty-three (57.2%) patients were born at term and 62 (42.8%) were born at preterm. The mode of delivery was vaginal in 73 (50.3%) and cesarean section in 72 (49.7%). Multiple gestation pregnancy was present in 11 (7.5%) patients. Data on birth weight was available in 109 patients, including ≥2500 g in 61 (55.9%), 1500-2499 g in 24 (22.0%), 1000-1499 g in 13 (11.9%,) and <1000 g in 11 (10.1%). A total of 107 (73.7%) patients had a history of hospitalization in the neonatal intensive care unit (NICU), with a median period of 21 days (IQR 11-45). Thirty-three patients (22.7%) had history of neonatal seizures and seven (4.8%) had history of neonatal hypoglycemia.

The most common etiologies of CP were hypoxic-ischemic encephalopathy (HIE) in 55 (37.9%) patients, followed by prematurity in 49 (33.8%). Other etiologies were stroke (n=14; 9.7%), brain malformations (n=11; 7.6%), neonatal sepsis/meningitis (n=6; 4.1%), and kernicterus (n=5; 3.4%). The etiology of CP was undetermined in 5 (3.4%) cases.

The most common CP types were spastic tetraplegia (n=39; 26.9%) and spastic hemiplegia (n=37; 25.5%) in our study. Children with tetraplegic and hemiplegic CP were mostly full-term babies (58.8% and 72.7%, respectively), while diplegic and dyskinetic CP forms were more frequent in the group of preterm births (73.3% and 66.7%, respectively). A statistical difference was observed between gestational age and type of CP (p=0.008). Birth weight was ≥2500 g in most of the patients with tetraplegic and hemiplegic CP (63% and 70%, respectively) compared to the other forms (p=0.013). Results of psychometric assessments were available in 112 (77.2%) cases. Patients with tetraplegic CP had more severe cognitive impairment compared to other types, as 67% of tetraplegic CP

Table I: Baseline clinical characteristics of patients with cerebral palsy (n=145)

Sex*	Male Female	91 (62.8) 54 (37.2)
Age at last clinical visit	Mean ± SD (min-max), years	11.1 ± 4.2 (3-18)
Etiology*	Hypoxic-ischemic encephalopathy (HIE) Prematurity Stroke Structural malformations Neonatal sepsis/meningitis Kernicterus Undetermined	55 (37.9) 49 (33.8) 14 (9.7) 11 (7.6) 6 (4.1) 5 (3.4) 5 (3.4)
Type of CP*	Diplegia Hemiplegia Tetraplegia Mixed Dyskinetic Ataxic	31 (21.4) 37 (25.5) 39 (26.9) 31 (21.4) 6 (4.1) 1 (0.7)
GMFCS scores*	GMFCS I GMFCS II GMFCS III GMFCS IV GMFCS V	14 (9.7) 40 (27.8) 24 (16.7) 44 (30.6) 22 (15.3)
Cognitive impairments*	Normal Mild impairment Moderate impairment Severe impairment	10 (8.9) 41 (36.6) 29 (25.9) 32 (28.6)

***:** *n (%),* ***SD:** standart deviation,* ***GMFCS:** gross motor function classification scale*

Table II: Comparison of study parameters in Group 1 (CP patients with epilepsy) and Group 2 (CP patients without epilepsy)

	Group 1 (n=107)	Group 2 (n=38)	p
Sex, n (%)			
Male	66 (61.7)	25 (65.8)	0.653
Female	41 (38.3)	13 (34.2)	
Age at last clinical visit (years)			
Median (IQR)	11.7 (8-15)	10.9 (5.9-13)	0.060
Etiology of CP, n (%)			
HIE	45 (42.1)	10 (26.3)	
Prematurity	31 (29.0)	18 (47.4)	
Stroke	11 (10.3)	3 (7.9)	
Structural malformations	10 (9.3)	1 (2.6)	0.031
Neonatal sepsis/meningitis	5 (4.7)	1 (2.6)	
Kernicterus	1 (0.9)	4 (10.5)	
Undetermined	4 (3.7)	1 (2.6)	
Gestational age			
Term (>37 w)	69 (64.5)	14 (36.8)	0.003
Preterm (≤37 w)	38 (35.5)	24 (63.2)	
Birth weight			
≥2500 g	51 (63.8)	10 (34.5)	
1500-2499 g	14 (17.5)	10 (34.5)	0.014
1000-1499 g	10 (12.5)	3 (10.3)	
<1000 g	5 (6.3)	6 (20.7)	
Mode of delivery			
Normal vaginal	43 (46.2)	13 (37.1)	0.355
Cesarean section	50 (53.8)	22 (62.9)	
History of NICU hospitalization			
Yes	78 (80.4)	29 (80.6)	0.985
No	19 (19.6)	7 (19.4)	
History of neonatal seizures			
Yes	29 (27.4)	4 (10.5)	0.034
No	77 (72.6)	34 (89.5)	
Type of CP			
Diplegia	22 (20.6)	9 (23.7)	
Hemiplegia	26 (24.3)	11 (28.9)	
Tetraplegia	33 (30.8)	6 (15.8)	0.028
Mixed	24 (22.4)	7 (18.4)	
Dyskinetic	1 (0.9)	5 (13.2)	
Ataxic	1 (0.9)	0	
GMFCS classification scores			
I	9 (8.5)	5 (13.2)	
II	29 (27.4)	11 (28.9)	0.536
III	16 (15.1)	8 (21.1)	
IV	33 (31.1)	11 (28.9)	
V	19 (17.9)	3 (7.9)	
Cognitive impairment			
Normal	6 (7.3)	4 (13.3)	
Mild	27 (32.9)	14 (46.7)	0.245
Moderate	22 (26.8)	7 (23.3)	
Severe	27 (32.9)	5 (16.7)	
MRI findings (MRICS classification)			
Normal	3 (2.9)	1 (2.6)	
Maldevelopments	11 (10.8)	0	0.036
Predominant white matter injury	43 (42.2)	26 (68.4)	
Predominant gray matter injury	36 (35.3)	9 (23.7)	
Miscallaneous	9 (8.8)	2 (5.3)	

***CP:** cerebral palsy, **IQR:** interquantile range, **HIE:** hypoxic ischemic encephalopathy, **NICU:** neonatal intensive care unit, **GMFCS:** gross motor function classification scale, **MRI:** magnetic resonance imaging, **MRICS:** magnetic resonance imaging classification system*

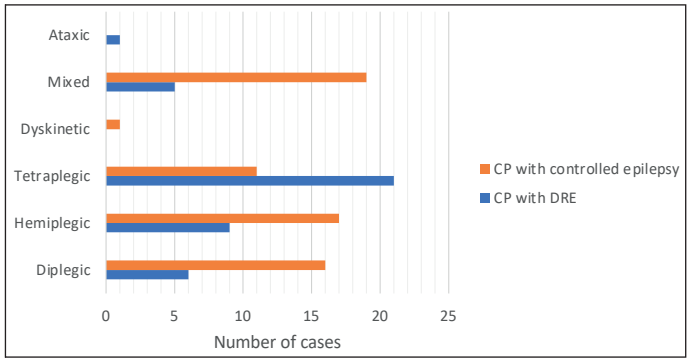

Figure 1: The distribution of cerebral palsy (CP) types in children with drug-resistant epilepsy (DRE) and controlled epilepsy.

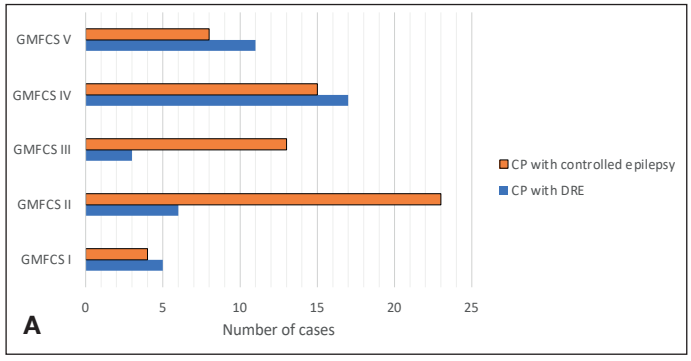

Figure 2A: The distribution of GMFCS levels in children with DRE and controlled epilepsy (GMFCS: Gross Motor Function Classification Scale, DRE: Drug-resistant epilepsy)

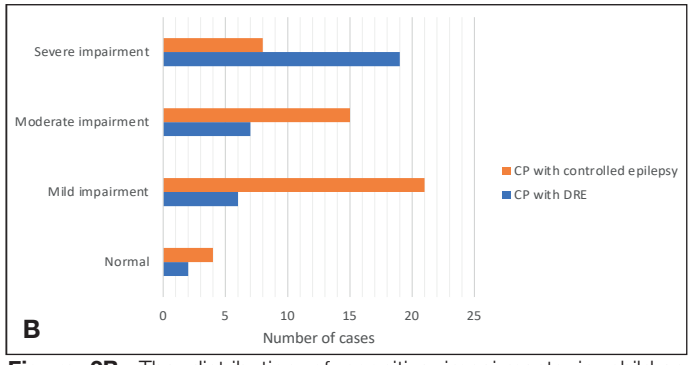

Figure 2B: The distribution of cognitive impairments in children with DRE and controlled epilepsy (GMFCS: Gross Motor Function Classification Scale, DRE: Drug-resistant epilepsy.

had a severe intellectual disability. In terms of motor functional status, 91 (63%) patients had a score of ≥ III, which indicated severe gross motor dysfunction.

Brain magnetic resonance imaging (MRI) data was available for 140 (97%) cases, which showed white matter predominance injury as the most common pathology (n=69; 49.3%), followed by gray matter predominant lesions (n=45; 32.1%), maldevelopments (n=11; 7.9%), other miscellaneous findings (n=11; 7.9%), and was normal in 4 patients (2.9%). The most common MRI abnormality among patients with diplegic CP was predominant white matter lesions (82.1%), mostly periventricular leukomalacia. Gray matter involvement was more common in cases with hemiplegic and tetraplegic CP, whereas white matter injury was predominant among patients with diplegic CP (p=0.003).

Among the included patients, epilepsy was diagnosed in 107 children (73.7%). Median age at study onset and male/female ratio was similar between the groups of CP patients with and without epilepsy (Table II). The median age at epilepsy-onset was 13 months (IQR 4-48) and the onset of seizures was before 24 months of life in 66 (61.6%) patients. Only four patients developed epileptic seizures beyond 10 years of age. Types of CP were diplegia in two, hemiplegia, and mixed form each in one patient. History of status epilepticus (SE) was noted in 12 patients (8.3%). A total of 73 patients (68.2%) were on polytherapy at the time of study enrollment.

Patients with epilepsy were mostly full-term (64.5% vs 36.8%, p=0.030) and had a birth weight of ≥2500 g (p=0.014). The history of neonatal seizures was statistically more frequent among patients with epilepsy (27.4%) compared to those without epilepsy (10.5%) (p=0.034). The most common etiologies of CP in Group 1 and Group 2 were HIE (42.1%) and prematurity (47.4%), respectively. Among the seven patients with a history of neonatal hypoglycemia, six had epileptic seizures during follow-up. In terms of mode of delivery and history of hospitalization in the NICU, there was no statistical difference between the groups (p=0.330 and 0.980, respectively). The most common CP forms were tetraplegic (30.8%) and hemiplegic (24.3%) in Group 1, whereas hemiplegic (28.9%) and diplegic (23.7%) in Group 2 (p=0.080). The distribution of GMFCS scores was similar between the groups (p=0.536). In terms of the degree of cognitive impairments, no statistical difference was detected between patients with and without epilepsy. MRI findings showed that predominant gray matter injury was more frequent in the epilepsy group than in CP without epilepsy (p=0.036). Majority of our cases (62%) had generalized tonic/tonic-clonic seizures as the predominant seizure type. According to epilepsy classification, 51 (47.7%) had generalized epilepsy, 34 (31.8%) had focal epilepsy, 9 (8.4%) had combined focal and generalized epilepsy, and the type of epilepsy was undetermined in 13 (12.1%) patients. Data regarding EEG results were available in 122 cases, of those, 91 (74.5%) showed abnormal findings. EEG abnormalities were as follows: focal (n=46; 50.5%), generalized (n=12; 13.2%), multifocal (n=19; 20.9%) epileptogenic activities, and other abnormalities (n=14; 15.3%).

Of the 107 children with epilepsy and CP, 43 (40.2%) had DRE. The median age of seizure-onset was earlier in patients with DRE than in controlled epilepsy (7 mo vs 24 mo, p=0.002). Neonatal seizure history was more common in patients with DRE than in controlled epilepsy (41.5% vs 18.8%, p=0.011). Eight of the 12 patients with a history of status epilepticus developed DRE during follow-up. Most common etiology of CP was HIE in the DRE group (52.4%). When the etiology of CP was compared with epilepsy outcome, seizure control was achieved in most

of those with prematurity and kernicterus etiology (p<0.001). The most common CP types were tetraplegic CP in the DRE group and mixed CP in the controlled epilepsy group (p=0.002) (Figure 1). Children with DRE were more likely to have GMFCS level >III (66.7%), and severe intellectual disability (56%) (Figures 2A-B). Predominant gray matter injury was the most frequent MRI abnormality among patients with DRE (42.5%). In terms of epilepsy type, there was no statistical difference between DRE and controlled epilepsy groups (p=0.158). Multifocal epileptic activities and a history of specific EEG patterns (hypsarrhythmia and ESES) on EEG were more frequent in patients with DRE (p=0.038)

DISCUSSION

Epilepsy has been considered one of the most common comorbidities among children with CP. The presence of epilepsy in CP, especially if refractory, significantly affects neurodevelopment and quality of life. The prevalence of epilepsy in CP has been reported in the literature varies widely; ranging from 15 to 90% (2-4). In the present study, 74% of the CP patients had epilepsy. Prevalence of epilepsy in our cohort was higher than in previous reports from different parts of our country, ranging between 50-57% (9-12). However, a similar rate of epilepsy was reported in the study of Bearden et al. (13), the prevalence of epilepsy was also found as high as 77%. These differences between the studies may be due to the different methodology, sample size, the average age of the patients at the enrollment, and variable duration of follow-up periods. Such a high percentage of patients with CP and concomitant epilepsy can be explained by the higher rate of severe SP patients are often referred to tertiary-center hospitals.

Numerous studies have investigated potential risk factors for epilepsy development in children with CP. The history of neonatal seizures is one of the most emphasized risk factors (3, 9-11). Our study revealed that neonatal seizure history was statistically higher in the epilepsy group compared to the patients without epilepsy, which is consistent with the previous literature. Additionally, neonatal seizures were more common in the DRE (42%) group than in patients with controlled epilepsy (19%). A similar relationship was also indicated by Mert et al.(9), children with neonatal seizures were 3.3 times more likely to have a poor epilepsy prognosis. Data on perinatal risk factors that may contribute to the occurrence of epilepsy in children with CP are relatively conflicting. Some of the studies revealed prematurity and low birth weight as possible risk factors for both epilepsy and CP (3, 4). In contrast, our study demonstrated that the percentage of term delivery and normal birth weight was higher in CP patients with epilepsy compared to those without epilepsy. Similar to our report, Zelnik et al. (14) showed that epilepsy was more common in term infants than in preterms. These results can be attributed to the fact that epilepsy is mostly caused by gray matter lesions, which are more common in full-term infants, while white matter lesions are more frequent in premature babies. In the study of Maksoud et al. (15), low Apgar scores were associated with an increased risk of epilepsy in CP in particular with DRE. In the current study, there was no significant difference between patients with and without epilepsy in terms of sex, parental consanguinity, and mode of delivery (p>0.050). Similar to our results, Gurkan et al. (11) found no significant association between epilepsy development and history of NICU hospitalization. In our study, six of seven patients with a history of neonatal hypoglycemia had epilepsy during follow-up. A similar relationship was also reported by Indian authors, as epilepsy occurred in 14 of the 30 (46.7%) CP children with a history of neonatal hypoglycemia (16). In children with CP, the perinatal insults are multi-factorial and further worsened by secondary injury to the brain such as hypoglycemia.

Our data showed that epilepsy was particularly more frequent in children with spastic tetraplegic CP, while it was less common in patients with dyskinetic or diplegic CP. Tetraplegic CP has been frequently reported to be a risk factor for epilepsy in previous studies (3, 15, 17). Most of our patients with DRE had tetraplegic CP. This is most likely linked to the higher rate of individuals with spastic quadriplegia in cerebral palsy populations in general, who are mostly affected by diffuse brain injury. However, in the study of Singhi et al.(18), the rate of epilepsy was the highest among patients with spastic hemiplegia (65.9%). Mert et al. (9) reported no significant difference between the type of CP and epilepsy development. These variations between studies can be attributed to the applied methodologies and sample size.

Similar to previous reports, the onset of epilepsy in the current study occurred at a young age (13 months) and more than half of our patients had their first seizures during the first two years of life (11, 16). In addition, the median age of seizure-onset was earlier in patients with DRE (7 months) than in the controlled epilepsy group (24 months). Some of the studies also mentioned that the age at seizure-onset might differ depending on the CP type.

Several reports showed a significant relationship between intellectual disability, motor impairment and epilepsy development (3, 13, 17). Although no statistical difference was detected between the level of motor and cognitive dysfunction and the development of epilepsy in our study, we found an association between these variables and intractable epilepsy. Patients with DRE were more likely to have higher GMFCS scores and moderate/severe cognitive impairments compared to the controlled epilepsy group. Contrary to our findings, Maksoud et al. (16) found an insignificant association between GMFCS score and intractable epilepsy.

Regarding MRI data, white matter predominance injury was the most common pathology (49%) in our entire cohort, while gray matter involvement was more frequent in the epilepsy group.

This finding was not surprising, as it is well known that cortical involvement plays a role in epileptogenesis.

With respect to the characteristics of epilepsy, the majority of individuals in our cohort had generalized epilepsy with a predominance of generalized tonic/tonic-clonic seizures (62%). Similarly, Gurkan et al. found generalized tonic-clonic seizures (46.6%) as the most frequent seizure type among their study population (13). However, in another report from our country, focal seizures were predominant (48.2%), probably due to their study consisted 42.9% of spastic hemiplegics (9). Focal seizures have been reported as one of the most important predictive factors of intractable epilepsy in children. However, we found no statistical difference in terms of seizure type and the subgroups of DRE and controlled epilepsy. The literature evaluating the predictive importance of EEG in CP patients with DRE is scarce. We detected multifocal epileptic discharges and a history of hypsarrhythmia or ESES more frequently in the DRE group. In the study of Tokatly Latzer et al, focal, multifocal discharges, and focal background slowing has been reported as predictive EEG abnormalities of intractable epilepsy (19). Another report acknowledged hypsarrhythmia as a poor prognostic factor (3).

Our study has some limitations, including the retrospective nature, relatively small sample size, and heterogeneity of the etiological factors of CP, limiting the statistical power. Other mentioned predictive factors for epilepsy development, such as family history of epilepsy or having a low Apgar score were not included in our analysis, due to the large size of missing data.

CONCLUSIONS

In summary, our study revealed that the frequency of epilepsy is higher than most reports. Epilepsy is common in certain forms of CP. The history of neonatal seizures appears to be the most significant risk factor for both epilepsy development and poor epilepsy prognosis in patients with CP. While term gestational age and normal birth weight were associated with epilepsy development, mode of delivery and the presence of consanguinity were not found to be risk factors in our cohort. Determination of potential risk factors is important in predicting the development of epilepsy in patients with CP, as it may provide closer follow-up of patients at high risk. Particular attention should be paid to the early identification and treatment of comorbid epilepsy in children with CP.

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Testicular Torsion in Children: A 10-Year Clinical and Histological Evaluation

Çocuklarda Testis Torsiyonu: 10 Yıllık Klinik ve Histolojik Değerlendirme

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ABSTRACT

Objective: The purpose of the present study is to determine the clinical, radiological and pathological characteristics of testicular torsion patients, the intervention techniques applied according to time to hospital admission of the patient and testis-saving rates in the childhood age group.

Material and Methods: This retrospective study included the patients aged between 0-18 years who applied to pediatric surgery clinic due to the complaint of abdominal pain or scrotal pain between January 2011 to January 2021 and were diagnosed with testicular torsion after evaluation. The patient age, hospital admission complaint, duration of the symptoms, month of hospital admission, lateralization of the affected testicle, preoperative diagnostic studies, type of the implemented intervention (orchiectomy/detorsion) and postoperative diagnosis were determined. Hematoxylin-Eosin-stained archive slides of the materials sent to pathology department for examination were reviewed by two pathologists.

Results: In this period of 10 years; 28 patients aged between 0-18 years admitted to our hospital because of testicular torsion. Scrotal pain and tenderness were present in all the patients (100%). Of the patients; 4 (14.3%) were neonatal and 21 (75%) were between the ages 12-18 years. Testicular parenchyma could not be macroscopically selected in the examination of orchiectomy materials and the materials were hemorrhagic. Hemorrhagic infarction was detected by microscopic examination.

Conclusion: Acute scrotum is a frequently seen surgical emergency in the childhood period. There are many entities that may cause acute scrotum; performing differential diagnosis accurately and timely can protect the patient from unnecessary surgery and testicular loss.

Key Words: Acute Scrotum, Child, Testicular Torsion

ÖZ

Amaç: Bu çalışmanın amacı çocuk yaş grubunda testis torsiyonlu hastaların klinik, radyolojik ve patolojik özelliklerini, hastaların hastaneye başvuru zamanına göre müdahale yöntemlerini ve testis kurtarma oranlarını belirlemektir.

Gereç ve Yöntemler: Bu retrospektif çalışma Ocak 2011-Haziran 2021 yılları arasında karın ağrısı veya skrotal ağrı ile çocuk cerrahisi kliniğine başvuran ve değerlendirme sonrası testis torsiyonu tanısı alan 0-18 yaş arası hastaları kapsamaktadır. Hastaların yaşı, hastaneye başvuru şikayeti, semptomların süresi, hastaneye başvurduğu ay, etkilenen testisin lateralizasyonu, preoperatif tanı çalışmaları, yapılan müdahalenin tipi (orşiektomi/detorsiyon) ve postoperatif tanı

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belirlendi. Patoloji birimine inceleme için gönderilen materyallere ait Hematoksilen-Eozin boyalı arşiv preparatları iki patolog tarafından yeniden gözden geçirildi.

Bulgular: Bu 10 yıllık dönemde 0-18 yaş arası 28 hasta testis torsiyonu nedeni ile hastanemize başvurmuştu. Hastaların hepsinde (%100) skrotal ağrı ve hassasiyet mevcuttu. Hastaların 4 tanesi (%14.3) yenidoğandı ve 21 hasta (%75) 12-18 yaşları arasındaydı. Orşiektomi materyallerinin incelenmesinde makroskopik olarak testis parankimi seçilemiyordu ve materyaller hemorajikti. Mikroskopik incelemede hemorajik enfarktüs saptandı.

Sonuç: Akut skrotum çocukluk çağında sık görülen cerrahi acillerdir. Akut skrotuma neden olabilecek çok sayıda antite mevcuttur; ayrıcı tanının doğru ve zamanında yapılması hastayı gereksiz cerrahiden kurtaracak ve testis kaybını önleyecektir.

Anahtar Sözcükler: Akut skrotum, Çocuk, Testis Torsiyonu

INTRODUCTION

The presence of pain, swelling and redness in the scrotum is defined as acute scrotum. There are many important or non-important causes of acute scrotum and acute scrotum is the most commonly seen emergency in the childhood period. Testicular torsion is the most important and most emergency cause of acute scrotum (1). Since time loss may result testicular loss, the diagnosis of testicular diagnosis should be absolutely eliminated in each male child with the complaint of acute scrotum (2).

Testicular torsion (TT), testicular appendage torsion (TAT), epididymo-orchitis (EO), scrotal trauma, idiopathic scrotal edema, varicocele, inguinal hernia, hydrocele, pyocele and tumors are the pathologies that should be considered in the differential diagnosis of acute scrotum. Acute scrotum is a real phenomenon and the studies have shown that hemorrhagic testicular infarction, irreversible testicular injury and complete testicular infarction are observed 2 hours, 6 hours and 24 hours after the onset of the symptoms, respectively. The testicles could not be saved if the treatment of TT is not initiated in the first 6 hours. Early diagnosis and management are necessary to prevent the complications such as testicular infarction and infertility. Scrotal Doppler ultrasonography (USG) is the primarily applied imaging technique in case of sudden-onset scrotal pain in both children and adults since it is non-invasive and easy accessible (3,4).

The purpose of the present study is to determine the clinical, radiological and pathological characteristics of TT patients, the intervention techniques applied according to time to hospital admission of the patient and testis-saving rates in the childhood age group.

MATERIALS-METHOD

This retrospective study included the patients aged between 0-18 years who applied to pediatric surgery clinic due to the complaint of abdominal pain or scrotal pain between January 2011 to January 2021 and were diagnosed with TT after evaluation. The patients were diagnosed based on anamnesis, physical examination and scrotal Doppler USG. The low amount or absence of blood supply was evaluated in favor of TT. The patient age, hospital admission complaint, duration of the symptoms, month of hospital admission, lateralization of the affected testicle, preoperative diagnostic studies, type of the implemented intervention (orchiectomy/detorsion) and postoperative diagnosis were determined. The duration of symptoms was considered as the time interval between onset time of complaints and time to hospital admission. Hematoxylin-Eosin-stained archive slides of the materials sent to pathology department for examination were reviewed by two pathologists (DG, IES). The study was approved by Hatay Mustafa Kemal University, Tayfur Ata Sökmen Medical Faculty, Non-Interventional Clinical Research Ethics Committee with the decision number 26.08.2021-01.

Statistical Analysis:

The present study was conducted with 28 patients. The categorical variables were presented as numericals and percentages. The Shapiro Wilk test was used to test distribution normality and continuous variables such as age and duration were expressed as median and interquartile range (IQR).

RESULTS

In this period of 10 years; 28 patients aged between 0-18 years admitted to our hospital because of TT. Scrotal pain and tenderness were present in all the patients (100%). Of the patients; 4 (14.3%) were neonatal and 21 (75%) were between the ages 12-18 years. The median age of all the patients was 15.50 (11.00-17.00) years. The time to hospital admission ranged between 3-240 hours among the patients and the median time to hospital admission was 23.50 (5.50-60.00) hours. May (14.3%) and July (17.7%) were the most frequent months of hospital admission. Only one patient (3.6%) had admitted to the hospital in June. All the patients (100%) were undergone color Doppler USG at the time of their admission to the hospital. The left and right testes were affected in 21 (75%) and 7 (25%) patients, respectively. Orchiectomy was performed in 14 (50%) patients at the time of admission while 14 (50%) patients were undergone detorsion procedure. Contralateral testis fixation was performed in 4 patients in whom time to hospital exceeded 24 hours after onset of admission complaints and who were undergone orchiectomy. Orchiectomy was applied postoperatively one month later since necrotic leakage was detected in the surgery site and no blood supply was

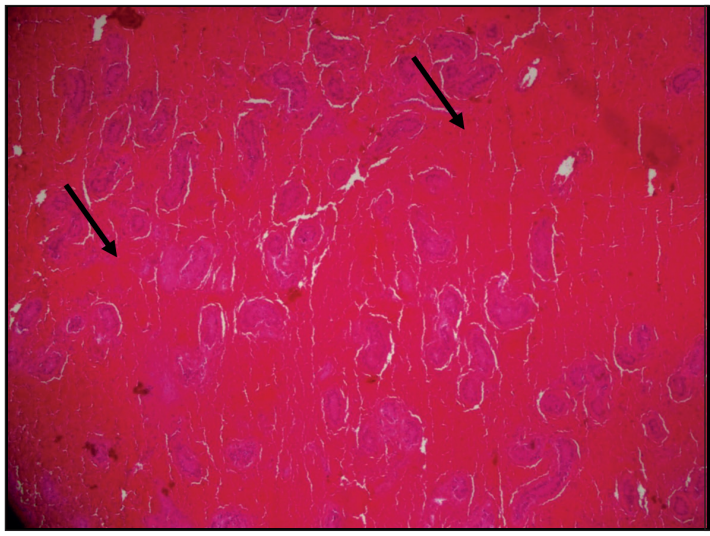

Figure 1: Hemorrhage in testicular parenchyma (arrow) (H+E, x40)

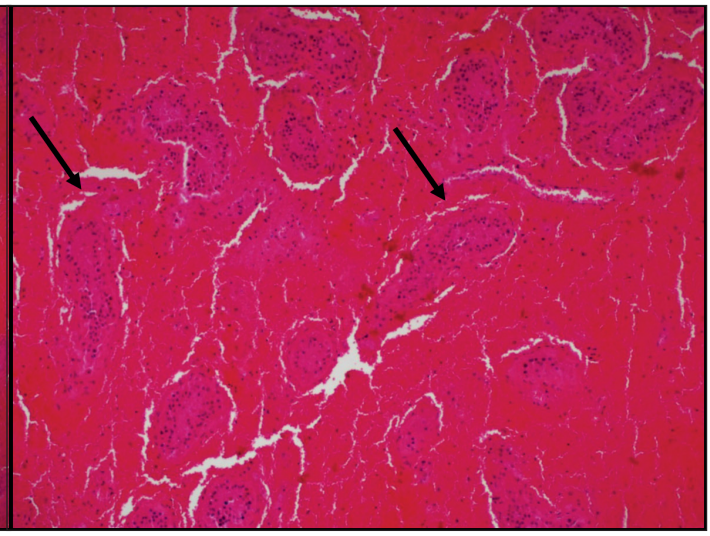

Figure 2: Infarct in seminiferous tubules (arrow) (H+E, x100)

encountered by Doppler USG in one patient (3.6%) who had undergone detorsion procedure at the time of admission. Testicular parenchyma could not be macroscopically selected in the examination of orchiectomy materials and the materials were hemorrhagic. Hemorrhagic infarction was detected by microscopic examination (Figure 1-2). The results were evaluated to be consistent with TT. Perioperative morbidity or mortality was observed in none of the patients.

DISCUSSION

Acute scrotal pain and swelling are the commonly seen phenomena among children and frequently require surgical consultation in the emergency service. TT, TAT and EO are the most prevalently seen causes of acute scrotum in the childhood period (5). Although, TT and TAT have been reported to be the most frequently detected pathologies in the prepubertal men, however, prevalence of each pathological diagnosis present variety among regions (6). Perinatal torsion is not frequently seen and make up 10% of pediatric cases (7). In our study, 4 (14.3%) of the cases were neonatal and our result was similar with the literature. It has been found in a study that the rate of TT was 35.5% in the children with acute scrotum (8). On the other side, that rate was found to be 23% in another study (9). Beside these outcomes, the rates of TT, TAT and EO were determined to be 74.2%, 8.2% and 3.4%, respectively (10).

Acute scrotum is observed most commonly between the ages of 12-18 years and first year of the life representing a bimodal distribution (4,11). In also our study, 75% of the cases were between 12-18 years of age. Acute scrotum is usually observed in the winter months. On the other side, torsion was frequently observed in January and August in a study and this result was attributed to the decreased atmospheric pressure (12). Of the patients included in our study, 14.3% and 17.7% had admitted to the hospital in May and July, respectively. This result suggested us that seasons had no effect on the development of acute scrotum. It has been identified in a study that left testicle was more frequently torsioned (58%) (13). In also our study, TT was more frequently encountered in the left testicle in (75%) consistently with the literature.

According to the literature, testis-saving rates range between 30-70% in the patients with TT. The differential diagnosis of acute scrotum may be difficult because of similar clinical and examination findings. Although, acute phase reactants are adequate for diagnosis of acute epididymitis, they may not provide adequate data in its differentiation from TT (16). It has been reported in many papers that color Doppler USG can be used preoperatively as a sensitive and reliable diagnostic method with respect to prevention of unnecessary surgical treatment (14, 15). It has been reported that sensitivity and specificity of color Doppler USG were 96-100% and 84-100% in diagnosis of torsion, respectively (16, 17). Nuclear testicular flow studies performed as another technique for evaluation of blood flow of the testicles are not currently preferred since it is a long-lasting procedure and also not always available (18). The popularity of color Doppler USG has progressively increased because it is a non-invasive procedure and contributes to accurate diagnosis at least as much as nuclear scan. Beside this, it can easily differentiate the other pathologies in the scrotum. However, it may occasionally cause erroneous results since it is a operator-dependent technique. Diagnostic failings resulting from the experience of the radiologist in scrotal USG, the fact that torsion may be occasionally intermittent and difficulty in performing USG in little kids are the factors that decline diagnostic strength of color Doppler USG (19). Color Doppler USG was performed in all the patients with TT included in our study. The successful treatment of TT can be obtained by early diagnosis and scrotal fixation of bilateral testes via the fastest surgical removal of testicular torsion. The most important factors for determination of testicular loss are the degree of testicular torsion and its duration in hours. Testis can

be saved if the appropriate intervention could be performed in the first 6 hours. Extreme testicular atrophy has been found due to torsions that exceeded 360 degrees and lasted longer than 24 hours (20). According to the results, orchiectomy was not performed in 46.4% patients and the testes could be saved by detorsion. Our testis-saving rate was consistent with the literature.

CONCLUSION

Acute scrotum is a frequently seen surgical emergency in the childhood period. There are many entities that may cause acute scrotum; performing differential diagnosis accurately and timely can protect the patient from unnecessary surgery and testicular loss. Every child who admitted to the emergency service due to the complaint of acute scrotum should be absolutely performed color Doppler ultrasonography since it is a non-invasive and reliable diagnostic method. Multicenter studies involving a large number of patients are needed to determine the causes and incidence of acute scrotum and also to assess the importance of Doppler Ultrasonography.

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Dynamic Thiol-Disulfide Homeostasis in Children with Newly Diagnosed Iron Deficiency Anemia

Yeni Tanı Almış Demir Eksikliği Anemisi Olan Çocuklarda Dinamik Tiyol-Disülfid Homeostazisi

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ABSTRACT

Objective: Iron is an element, which is found in the structure of antioxidant enzymes and has an important role in the inactivation of reactive oxygen species. Disruption of oxidant-antioxidant balance may be playing a role in the pathogenesis of iron deficiency anemia (IDA). Dynamic thiol-disulfide homeostasis (DTDH) and serum ischemia-modified albumin (IMA) levels are important indicators of pro-oxidant/antioxidant status. In this study, we aimed to evaluate DTDH parameters and serum IMA levels in children with newly diagnosed IDA, who did not receive iron therapy.

Material and Methods: Fifty patients diagnosed with IDA and 33 healthy age- and sex-matched control patients were included in the study. DTDH parameters and IMA levels of the patients and control groups were measured. The same parameters were also compared in patients with Hb<7 g/dl (profound IDA) (n:14/50, 28%) and Hb≥7 g/dl (mild-moderate IDA) (n: 36/50, 72%) in the IDA group. The relationship between DTDH parameters in these groups were investigated.

Results: Native thiol, total thiol, native thiol/total thiol levels, constituting antioxidant capacity indicators, were found to be significantly lower in IDA patients; while oxidant disulfide, disulfide/native thiol, disulfide/total thiol, and IMA levels were found to be statistically higher compared to those in the control group (p<0.050). When DTDH parameters and IMA levels were examined; there was a positive correlation between antioxidant parameters and a negative correlation between oxidative parameters with hemoglobin and ferritin levels (p<0.050). Also, oxidative parameters were found to be much higher in profound IDA group than in the group with Hb>7 g/dl (p<0.050).

Conclusion: In this study, increase in serum disulfide and IMA levels with the decrease in serum native thiol and total thiol levels indicated oxidative stress in IDA patients before treatment, compared to the control group. Evaluation of these indicators in children is important in predicting the toxicity due to IDA.

Key Words: Hemoglobin, Iron deficiency anemia, Ischemia modified albumin, Oxidative damage, Thiol-disulfide

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ÖZ

Amaç: Demir, antioksidan enzimlerin yapısında bulunan ve reaktif oksijen türlerinin inaktivasyonunda önemli rolü olan bir elementtir. Oksidan-antioksidan dengenin bozulması demir eksikliği anemisinin (DEA) patogenezinde rol oynuyor olabilir. Dinamik tiyol-disülfid homeostazisi (DTDH) ve serum iskemi modifiye albümin (IMA) seviyeleri prooksidan/antioksidan durumun önemli göstergeleridir. Bu çalışmada, demir tedavisi almayan, yeni tanı almış demir eksikliği anemisi olan çocuklarda DTDH parametreleri ve serum İMA düzeylerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Demir eksikliği tanısı almış 50 hasta ile yaş ve cinsiyet açısından uyumlu 33 sağlıklı kontrol çalışmaya dahil edildi. Hasta ve kontrol gruplarının DTDH parametreleri ve İMA düzeyleri ölçüldü. Aynı parametreler, Hb<7 g/dl (derin DEA) (n:14/50, %28) ve Hb≥7 g/dl (hafif-orta DEA) (n:36/50, %72) olan DEA grubundaki hastalarda da karşılaştırıldı. Bu gruplarda DTDH parametreleri arasındaki ilişki araştırıldı.

Bulgular: Antioksidan kapasite göstergelerini oluşturan nativ tiyol, total tiyol, nativ tiyol/total tiyol seviyeleri DEA hastalarında anlamlı olarak daha düşük bulunurken; oksidan disülfid, disülfid/nativ tiyol, disülfid/total tiyol ve İMA seviyeleri kontrol grubundakilere göre istatistiksel olarak anlamlı daha yüksek bulundu (p<0.050). Dinamik tiyol-disülfid homeostazisi parametreleri ve IMA seviyeleri incelendiğinde; hemoglobin ve ferritin seviyeleri ile antioksidan parametreler arasında pozitif bir korelasyon ve oksidatif parametreler arasında negatif bir korelasyon vardı (p<0.050). Ayrıca derin DEA grubunda oksidatif parametreler, Hb>7 g/dl olan gruba göre çok daha yüksek bulundu (p<0.050).

Sonuç: Bu çalışmada, DEA hastalarında tedavi öncesi kontrol grubuna göre serum nativ tiyol ve total tiyol düzeylerindeki düşüşle birlikte serum disülfid ve IMA düzeylerindeki artış oksidatif strese işaret etti. Çocuklarda bu göstergelerin değerlendirilmesi DEA'ya bağlı toksisiteyi öngermede önemlidir.

Anahtar Sözcükler: Hemoglobin, Demir eksikliği anemisi, İskemi modifiye albümin, Oksidatif hasar, Tiyol-disülfid

INTRODUCTION

Iron deficiency (ID) is the most common nutritional deficiency globally, especially in developing countries. Iron deficiency anemia (IDA) is a condition that develops with a decrease in red blood cell mass or hemoglobin (Hb) amount, depending on ID. This clinical manifestation may occur due to increased iron requirement, malabsorption or chronic blood loss. In children, it is mostly detected during infancy and school-age, when rapid growth occurs, or in adolescence due to menstrual bleeding in girls (1).

Iron is an element that has an important role as catalyst for enzymes, involved in energy production, electron transport chain, inactivation of reactive oxygen species (ROS), deoxyribonucleic acid (DNA), ribonucleic acid (RNA) production and protein synthesis (2). The production of hemoglobin and other iron-containing proteins such as cytochrome, myoglobin, catalase and peroxidase is also affected in ID (3,4). In addition, studies have shown decreases in concentrations and activities of antioxidant enzymes such as glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD) in patients with IDA, thus reducing the total antioxidant capacity (TAC) (5,6).

It is thought that oxidative stress increases with the elevation in pro-oxidant levels or decrease in antioxidant enzyme capacities in IDA. Due to oxidative stress, the loss of balance between free radicals or ROS production and the antioxidant system leads to deterioration in molecular and cellular functions (7,8). Thiols, a group of organic sulfur compounds, occupy an important place in the antioxidant system and protect the organism against the harmful effects of ROS by coordinating the antioxidant defense (9). Oxygen radicals, ROS and thiol groups are oxidized to form reversible disulfide bonds. The disulfide bonds are reduced back to thiol groups, ensuring dynamic thiol-disulfide homeostasis (DTDH). Dynamic thiol-disulfide homeostasis is one of the most important indicators of the oxidant/antioxidant status in the body. Thiol-disulfide balance measurements are used to evaluate native thiol (-SH), disulfide (-SS), total thiol [(-SH)+(-SS)] levels and dynamic thiol-disulfide (-SH/-SS) homeostasis (10). Ischemia-modified albumin (IMA) is an altered form of albumin, characterized by decreased cobalt-binding affinity, mainly occurring in ischemic conditions and due to free radical damage. It has been shown that there is an increase in IMA levels in cases of oxidative damage (11).

Evaluation of thiol-disulfide homeostasis and IMA levels in IDA-related oxidative damage in children, can predict future toxic effects and indicates the importance of early diagnosis and appropriate treatment. Therefore, in our study, we aimed to evaluate thiol-disulfide homeostasis and serum IMA levels in patients with newly diagnosed IDA, who had not received iron therapy.

MATERIALS and METHODS

The study was conducted between June 2020 and January 2021 at Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Department of Pediatric Hematology and Oncology, Ankara, Turkey. Fifty patients, diagnosed with IDA and 33 healthy age- and sex-matched control group patients were included. The patients and control group did not have any acute or chronic diseases or medication use during the evaluation. The diagnosis of IDA (with Hb value below -2SD according to age group and ferritin below 12 ng/ml) was made by evaluating the patients' complete blood count and iron parameters. In addition, patients in the IDA group were divided according to their hemoglobin levels as Hb<7g/dl (profound IDA) (n:14/50, 28%) and Hb≥7 g/dl (mild-moderate IDA) (n:36/50, 72%). Dynamic thiol-disulfide homeostasis

parameters and IMA levels of the patients and control group were measured.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Hospital's Clinical Research Ethics Committee approved the study (numbered 18.03.2021, E-21/03-135). Informed consent was obtained from all participants and their parents.

Peripheral venous blood samples were taken to measure complete blood count, ferritin, DTDH parameters and IMA levels. To measure DTDH parameters and IMA levels, additional 3 ml samples were taken from blood samples, taken from children with IDA and the control group, during their routine controls.

Collected blood samples were centrifuged at 3600 rpm for 10 minutes in the biochemistry laboratory and stored at -80°C. After completion of sample collection, all of them were thawed simultaneously and studied on a Roche Hitachi Cobas c501 automatic analyzer, usinga new spectrophotometric method defined by Erel and Neşelioğlu (10). Accordingly, disulfide bonds (SS) were reduced to free thiol groups (SH) with sodium borohydride. Total thiol (SH + SS) amount was measured using 5,5'-dithiobis-(2 nitrobenzoic) acid. Half the difference between total thiol and native thiol provided the dynamic disulfide amount. After measuring these levels, the percentage ratios of disulfide/native thiol (SS/SH), disulfide/total thiol (SS/SH+SS), and native thiol/total thiol (SH/SH+SS) were calculated. IMA was measured by a colorimetric method developed by Bar-Or et al. (12), based on the measurement of unbound cobalt after incubation with patient serum, and the results were reported in absorbance units (ABSU). Serum ferritin level was measured by immunoassay on Advia Centaur XPT analyzer (Siemens IRL08191533).

Statistical Analysis

Statistical analyses were performed using the SPSS software version 20. Frequency and percentage values were calculated with the Kolmogorov-Smirnov test for categorical variables; mean±standard deviation (SD), median, minimum and maximum values were calculated for continuous variables. The significance of the difference between groups was evaluated using Student's t-test or Mann-Whitney U test. Nominal variables were compared using Pearson Chi-Square or Fisher's exact probability test. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. $p<0.050$ values were considered statistically significant.

RESULTS

Fifty patients diagnosed with IDA and 33 healthy controls were included in the study. Twenty one (42%) of the patients in the study group and 18 (54%) of the control group were female.

Table I: Comparison of the demographical characteristics and hematological parameters of children with IDA and control group.

	IDA* (n=50)	Controls (n=33)	p
Gender: Female/Male	21 / 29	18 / 15	0.262
Age (year)	3.7±2.6	3.7±1.2	0.969
Hemoglobin (Hb) (g/dL)	8.95±1.84	12.57±0.85	<0.001
Hematocrit (Hct) (%)	29.63±4.17	41.81±2.15	<0.001
Mean Corpuscular Volume (MCV) (fL)	62.87±7.43	83.81±1.60	<0.001
Red blood cell (RBC) ($x10^{12}$/L)	4.21±0.19	4.90±0.13	<0.001
(Red Cell Distribution Width (RDW) (%)	17.54±1.54	12.12±1.08	<0.001
Platelet count ($\times10^3$/µL)	375.80±84.77	265.87±54.69	<0.001
Ferritin (ng/mL)	4.59±3.15	30.90±12.07	<0.001

***IDA:** Iron deficiency anemia*

Table II: Comparison of DTDH parameters and IMA levels of children with IDA and control group

	IDA* (n=50)	Control group (n=33)	p
Native thiol (µmol/L)	430.07±63.02	476.58±38.36	<0.001
Total thiol (µmol/L)	451.23±59.80	489.41±42.31	<0.001
Disulphide (µmol/L)	11.74±6.0	6.10±4.30	<0.001
Disulphide/native thiol†	2.81±1.97	1.33±1.01	<0.001
Disulphide/total thiol†	2.61±1.65	1.27±0.94	<0.001
Native thiol/total thiol†	95.11±3.36	97.44±1.89	<0.001
Ischemia modified albumin (IMA) (ABSU)	0.79±0.29	0.57±0.20	<0.001

**IDA: Iron deficiency anemia, †:(%)*

Table III: Comparison of DTDH parameters and IMA levels of children with profound IDA (Hb below 7 g/dL) and Mild-moderate IDA (Hb above 7 g/dL) groups.

	Profound IDA* group (n=14/50, %28)	Mild-moderate IDA* group (n=36/50, %72)	p
Native thiol (µmol/L)	426.53±57.34	431.44±65.81	0.503
Total thiol (µmol/L)	448.58±57.46	452.26±61.45	0.574
Disulphide (µmol/L)	15.17±4.95	10.41±5.85	0.004
Disulphide/native thiol†	3.27±1.34	2.63±2.16	0.036
Disulphide/total thiol†	3.08±1.21	2.43±1.77	0.034
Native thiol/total thiol†	95.03±2.93	95.14±3.55	0.635
Ischemia modified albumin (IMA) (ABSU)	0.79±0.20	0.80±0.32	0.738

**IDA: Iron deficiency anemia, †: (%)*

While the mean age of the patients was 3.7±2.6 years in the study group, it was 3.7±1.2 years in the control group. There was no significant difference between the two groups regarding

Table IV: Correlation analyses between hemoglobin, ferritin and platelet values with DTDH parameters and IMA levels.

	Native thiol	Total thiol	Disulphide	Disulphide/ native thiol	Disulphide/ total thiol	Native thiol/ total thiol	IMA*
Hemoglobin							
r	0.329	0.297	-0.261	-0.260	-0.271	0.256	-0.248
p	0.002	0.006	0.017	0.018	0.013	0.019	0.024
Ferritin							
r	0.282	0.247	-0.320	-0.241	-0.255	0.240	-0.301
p	0.010	0.024	0.003	0.028	0.020	0.029	0.006
Platelet							
r	-0.257	-0.191	0.269	0.285	0.284	-0.274	0.209
p	0.019	0.084	0.014	0.009	0.009	0.012	0.058

IMA: *Ischemia modified albumin*

gender distribution and age (p >0.050). The study group had significantly lower Hb, hematocrit (Hct), mean corpuscular volume (MCV), red blood cell (RBC) counts, ferritin levels and higher red cell distribution width (RDW) and platelet levels compared to the control group. Demographic characteristics and hematological parameters of patients and the control group are presented in Table I.

Antioxidant capacity indicators of native thiol, total thiol, native thiol/total thiol levels were significantly lower in IDA patients than in controls. In contrast, oxidant disulfide, disulfide/native thiol, disulfide/total thiol and IMA levels were found to be statistically significantly higher (p<0.050) in IDA patients (Table II). In addition, when oxidative stress markers were evaluated in patients with profound anemia with Hb below 7 g/dL and patients with IDA with Hb above 7 g/dL; disulfide, disulfide/native thiol, disulfide/total thiol levels were found to be statistically significantly higher in patients with profound anemia, but no significant difference was found in terms of IMA levels (p=0.004; p=0.036; p=0.034; p=0.738, respectively) (Table III).

There was a weak negative correlation between disulfide, disulfide/native thiol, disulfide/total thiol and IMA levels with serum hemoglobin levels. However, there was a moderate-weak positive correlation between native thiol and weak positive correlation between total thiol, native thiol/total thiol with serum hemoglobin levels. Also, these relationships were statistically significant (p<0.050). When correlation analyses were performed between ferritin levels and these parameters; a moderate-weak negative correlation between disulfide and IMA, and weak negative correlation between disulfide/native thiol, disulfide/total thiol were found. Also, a weak positive correlation between native thiol, total thiol, and native thiol/total thiol were found. This relationship was statistically significant, as well (p<0.050). Moreover, there was a weak negative correlation between native thiol, total thiol, native thiol/total thiol, and a weak positive correlation between disulfide, disulfide/native thiol, disulfide/total thiol, and IMA levels with platelet count. Among them, native thiol, native thiol/total thiol, disulfide, disulfide/native thiol, disulfide/total thiol correlations were found to be statistically significant (p<0.050) (Table IV).

DISCUSSION

Iron is an element that is essential for human life. It is found in the structure of Hb, which provides oxygen transport in the body, participates in the structure of enzyme systems in some tissues and ensures the complementation of iron-related functions (1).

Iron deficiency anemia, which is very common in the world and especially in developing countries, occurs with the decrease in the amount of Hb as a result of ID. Since ID is a systemic disease that affects all bodily functions, many complications such as growth retardation, neurocognitive deficiencies, impaired immune system and learning disabilities can occur. Especially in childhood, oxidative damage in IDA may contribute to deterioration in neurocognitive functions (13,14). Therefore, understanding the pathogenesis, early detection and prevention of IDA are important in terms of child health (15,16).

In oxidative stress caused by increased free radicals and ROS, the oxidant-antioxidant balance is disrupted in favor of oxidation. Membrane changes and damage to erythrocytes due to ROS-induced oxidative stress, have been demonstrated (17). Several studies have reported that the concentrations and activities of antioxidant enzymes such as glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD) decreased and oxidant stress increased in IDA (18, 19). Aycicek et al. (20), have found that total oxidant status (TOS) and oxidative stress index (OSI) were higher in patients with IDA, while total thiol (–SH) and total antioxidant capacity (TAC) levels were lower than in the control group. Similarly, Akça et al. (21), have reported that oxidative stress parameters increased in children with IDA. In addition, Akarsu et al. (22), have stated that in IDA, the total antioxidant capacity measurements were low.

Dynamic thiol-disulfide homeostasis is one of the indicators, playing an important role in intracellular signal transduction, apoptosis, and many antioxidant and enzyme activities (9). Topal et al. (23), have reported that disulfide, disulfide/native thiol, and disulfide/total thiol levels were significantly higher in the IDA group. Consistent with previous reports, in our study, we found that DTDH parameters of native thiol, total thiol, native thiol/total thiol levels showing antioxidant capacity

decreased and oxidative stress indicators (disulfide, disulfide/native thiol, disulfide/total thiol, and IMA levels) increased in IDA patients compared to in control group. Also, we showed in our study that the increase in oxidant parameters due to oxidative damage could be higher especially in profound anemia where the Hb value is below 7 g/dL.

IMA is caused by chemical changes in albumin, which, in turn, is caused by oxidative free radicals during ischemia. IMA is one of the earliest markers of ischemia (24). Therefore, elevated IMA levels have been associated with increased oxidative stress in IDA, which can be considered a chronic hypoxic state. Bilgili et al. (25), in their study on adults, have reported high IMA levels in the patient group with IDA. Topal et al. (23), have reported relatively elevated IMA levels in children with IDA compared to in healthy controls. Similar to the literature, in our study, we found higher levels of IMA indicating oxidative damage in the IDA group compared to in control group. Also, there was a positive correlation between antioxidant parameters with hemoglobin and ferritin levels in the current study, while oxidative parameters showed a negative correlation with both hemoglobin and ferritin levels.

Causes of reactive thrombocytosis in children include infections, malignancies, splenectomy, acute blood loss, and iron deficiency anemia. Although the mechanisms are not fully known, it is thought that the similar amino acid sequence of thrombopoietin and erythropoietin may explain reactive thrombocytosis in children with iron deficiency anemia (26-28). Durmuş et al. (29), have reported that oxidative stress increased in patients with essential thrombocythemia, but there is no study showing the oxidant-antioxidant balance in reactive thrombocytosis due to iron deficiency anemia in children. In our study, we found a positive correlation with disulfide, disulfide/native thiol, disulfide/total thiol, possibly due to the increase in platelet count and oxidative stress.

In literature, there is limited data on DTDH and IMA levels in children with IDA. This study has some limitations, such as having a small sample group and avoidance of evaluation of antioxidant enzyme levels. However, our study found statistically significantly lower DTDH parameters, showing antioxidant capacity and higher DTDH parameters and IMA levels, showing oxidative damage in patients with IDA compared to healthy controls. Evaluation of thiol-disulfide homeostasis in oxidative damage due to IDA in children, is important in predicting the toxic effects, to which the patient will be exposed to in the subsequent period. Otherwise, the relationship between thrombosis and neurocognitive functions and oxidative stress in patients with IDA needs to be investigated. Therefore, further studies are needed to elucidate this situation. In addition, these results will guide hematologists in the management of children diagnosed with IDA.

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Evaluation of Patients with Chronic Cough Referred to Pediatric Pulmonology Outpatient Clinic

Kronik Öksürük Şikayeti ile Çocuk Göğüs Hastalıkları Polikliniğine Başvuran Hastaların Değerlendirilmesi

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ABSTRACT

Objective: A cough that lasts longer than four weeks in children is called chronic cough. The aim of this study is to determine the underlying causes of chronic cough.

Material and Methods: Patients aged 0-18 years who were referred to Şanlıurfa Training and Research Hospital pediatric pulmonology outpatient clinic between 27 December 2021 and 30 June 2022 due to chronic cough were enrolled. Patients with known cystic fibrosis, primary ciliary dyskinesia, interstitial lung disease, asthma, bronchopulmonary dysplasia were excluded from the study. The "CHEST Guideline and Expert Panel Report" guideline was used in the approach to chronic cough.

Results: 153 patients were included in this study. The most common causes of chronic cough were asthma (30.7%), protracted bacterial bronchitis (20.3%), and upper respiratory tract cough syndrome (11.1%). Wet cough was present in 60.8% of the patients with chronic cough and the most common diagnosis in patients with wet cough were protracted bacterial bronchitis (33.3%), pneumonia and other lung infections (17.2%) and bronchiectasis (12.9%). The most common diagnoses were asthma (68.3%), upper airway cough syndrome (6.7%), and natural recovery (6.7%) in patients with dry cough. Failure to thrive was more common in patients with wet cough than patients with dry cough ($p<0.030$) and fever, weight loss and desaturation were only present in patients with wet cough.

Conclusion: The most common reasons are asthma, protracted bacterial bronchitis and upper airway cough syndrome. The differential diagnosis should be made by pediatricians based on specific cough pointers, careful physical examination and tests performed in line with the recommendations of the guidelines.

Key Words: Asthma, Bronchitis, Child, Chronic Cough, Pneumonia

ÖZ

Amaç: Çocuklarda dört haftadan uzun süren öksürük kronik öksürük olarak adlandırılmaktadır. Bu çalışmada kronik öksürüğün altta yatan nedenlerinin saptanması amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya kronik öksürük nedeniyle 27 Aralık 2021- 30 Haziran 2022 tarihleri arasında Şanlıurfa Eğitim ve Araştırma Hastanesi Çocuk Göğüs Hastalıkları Polikliniğine başvuran 0-18 yaş arası hastalar dahil edildi.Bilinen kistik fibrozis, primer silyer diskinezi, interstisyel akciğer hastalığı, astım, bronkopulmoner displazi tanısı olan hastalar çalışma dışı bırakıldı. Kronik öksürüğe yaklaşımda "CHEST Guideline and Expert Panel Report" kılavuzu örnek alındı.

Bulgular: Çalışmaya 153 hasta dahil edildi. Bu çalışmada kronik öksürüğün en sık nedenleri astım (%30.7), uzamış bakteriyel bronşit (%20.3), üst solunum yolu öksürük sendromu (%11.1) olarak sıralandı. Kronik öksürük olan hastaların %60.8'inde ıslak öksürüğün mevcut olduğu, ıslak öksürüğü olan hastalarda ise en sık tanıların uzamış bakteriyel

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Harran University Ethics Committee approved the study (Decision number: HRU/22.13.09).

***Contribution of the Authors / Yazarların katkısı*: OZSEZEN B:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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bronşit (%33.3), pnömoni ve diğer akciğer enfeksiyonları (tüberküloz ve kist hidatik) (%17.2) ve bronşektazi (%12.9) olduğu görüldü. Kuru öksürüğü olan hastalarda ise en sık tanılar astım (%68.3), üst solunum yolu öksürük sendromu (%6.7) ve doğal iyileşme (%6.7) olarak sıralandı. Islak öksürük olan hastalarda kilo alamama şikayeti kuru öksürük olan hastalara göre daha belirgin iken (p<0.030) ateş, kilo kaybı ve desaturasyon sadece ıslak öksürük olan hastalarda mevcuttu.

Sonuç: Kronik öksürüğün en sık nedenleri astım, uzamış bakteriyel bronşit, üst solunum yolu öksürük sendromudur. Kronik öksürüğü olan hastalarda dikkatli fizik muayene ve rehberlerin önerileri doğrultusunda yapılan tetkikler ile hastalara tanı konulup tedavi kararı verilmelidir.

Anahtar Sözcükler: Astım, Bronşit, Çocuk, Kronik öksürük, Pnömoni

INTRODUCTION

Cough is one of the most common causes of hospital admission during childhood. It negatively affects the quality of life of both the child and the family. A cough that lasts more than four weeks is called chronic cough (1).

A detailed history along with detailed physical examination is necessary to determine the underlying cause of chronic cough. Early detection of the underlying cause of chronic cough can provide early intervention for preventable or progressive lung diseases. The frequency of chronic cough varies among populations and is reported at a rate of 1% in India, 9% in Eastern Europe, and 5-12% in China (2-4). The frequency of chronic cough increases in regions where air pollution is more intense (4).

The most common causes of chronic cough are nonspecific causes such as prolonged bacterial bronchitis, upper airway cough syndrome, natural healing. Apart from this, asthma, gastroesophageal reflux, infections, immune deficiencies, cystic fibrosis, primary ciliary dyskinesia, airway malacia , trachea-esophageal fistula (TEF), congenital heart diseases, foreign body aspiration and psychogenic cough (5).

The aim of this study is to define the underlying causes of chronic cough.

MATERIALS and METHODS

Patients aged between 0-18 years who applied to Şanlıurfa Training and Research Hospital pediatric pulmonology outpatient clinic between 27 December 2021 and 30 June 2022 due to chronic cough were included in this study. Patients with known cystic fibrosis, primary ciliary dyskinesia, interstitial lung disease, asthma and bronchopulmonary dysplasia were excluded.

The “CHEST Guideline and Expert Panel Report” guideline was conducted in the approach to chronic cough. (6) Detailed history of the patients (cough duration, cough character, wheezing, snoring, foreign body aspiration, drug use, rhinitis, sinusitis, respiratory tract infection history, presence of concomitant diseases, presence of allergic disease in the family, exposure to secondhand tobacco smoke) was taken and physical examination and additional tests (chest radiography, chest computed tomography (CT) in selected patients, nasal endoscopy in patients with suspected upper airway cough syndrome, flexible bronchoscopy in cases with suspected malaise and foreign body aspiration, genetics analysis in patients suspicious of cystic fibrosis and primary ciliary dyskinesia) were performed. The physical examination of the patients was performed in two-week intervals until the cough resolved.

A cough with sputum or productive due to airway secretions was defined as wet cough, and cough without sputum or non-productive was defined as dry cough (7). Presence of more than two episodes of wheezing and/or increase in forced expiratory volume in one second (FEV1) of 12% predicted or more by spirometry after administration of bronchodilator therapy (400µg salbutamol or equivalent) was considered as asthma. The modified asthma prediction index or response to treatment was used to diagnose asthma in children who could not perform spirometry (8). Protracted bacterial bronchitis diagnosed was made if the wet cough resolved in two to four weeks of treatment with amoxicillin-clavulanate and there were no alternative causes of cough (1). Upper airway cough syndrome was diagnosed if there were findings such as hyperemia in the pharynx or nasal mucosa, postnasal discharge in the history and physical examination compatible with the diagnosis, and a response to nasal saline solution and oral or nasal decongestant treatment within 2-4 weeks. Recovery of cough under medical supervision without any treatment was defined as natural recovery (9). Mycoplasma pneumonia was diagnosed if there was serological positivity for Mycoplasma pneumonia IgM antibody, findings consistent with atypical pneumonia in physical examination and chest X-ray, and cough responding to clarithromycin treatment (9). Psychogenic cough diagnosis was made in patients when organic causes were excluded (10). The diagnosis of bronchiectasis was confirmed with thorax CT in patients who had persistent wet cough and abnormal chest X-ray findings, who did not respond to antibiotic treatment (11).

Statistical analysis was evaluated in SPSS 23 package program. Data were given as mean ± standard deviation (SD), median (interquartile range (IQR), number (percent)). Chi-square test was used to compare qualitative data. The Mann Whitney U test was used to compare the median values between the two groups. Significance level was taken as p<0.050.

The study was carried out in accordance with the principles of the Declaration of Helsinki. Harran University Ethics Committee approved the study (Decision number: HRU/22.13.09).

RESULTS

153 patients were included in this study. Eighty patients (52.3%) were boys. The median cough interval was 12 weeks (IQR: 7-29). The parental consanguinity rate was 32.7% (50 patients). Mean gestation age and birth weight was 38.2 weeks (SD: 2.7) and 3159.2 kg (SD:0.4) respectively. The symptoms accompanying cough, physical examination findings, tobacco smoke exposure, environmental and personal factors triggering cough such as pet (such as cat, dog, bird), family history, and laboratory findings are summarized in Table I.

Sixty patients (39.2%) had dry; 93 patients (60.8%) had wet cough. Daytime and night cough was present is 149 patients (97.4%). Thirty-two patients (20.9%) had seasonal, 83 patients (54.2%) had exertional cough, and four patients (2.6%) had a cough associated with feeding. Seasonal cough was present in 40% of the patients with dry cough and 8.6% of the patients with wet cough (p<0.001). Exercise induced cough was present in 78.3% of the patients with dry cough and 38.7% of the patients with wet cough (p<0.001). Thirty percent of the patients with dry cough had secondhand tobacco smoke exposure whereas this ratio was 9.7% in patients with wet cough (p<0.001). There was no significant difference in findings such as cough related with feeding, mouth breathing, snoring, and accompanying wheezing in patients with dry and wet cough. Shortness of breath was detected in 13.3% of patients with dry cough and 9.7% of patients with wet cough, failure to thrive was present in 1.7% of patients with dry cough and 10.8% of patients with wet cough (p=0.500 and p=0.030 respectively). Desaturation was present in three patients (3.2%) with wet cough. Fever and weight loss was detected in only one patient (1.1%) with wet cough. None of the patients with dry cough had crackles, clubbing or tachypnea, whereas among patients with wet cough 39.8% had crackles, 7.5% had clubbing and 6.5 % had tachypnea (p<0.001, p=0.030, p=0.050 respectively). Rhonchus rates were similar in patients with dry and wet cough; rhonchus was present in 11.7% of the patients with dry cough and 18.3% of the patients with wet cough (p=0.300).

Table I: The symptoms accompanying cough, physical examination findings, environmental factors, and laboratory findings in patients with chronic cough.

Symptoms accompanying cough*	
Wheeze	16 (10.5)
Dyspnea	17 (11.1)
Loud snoring /mouth breathing	21 (13.7)
Failure to thrive*	11 (7.2)
Weight loss*	1 (0.7)
Fever*	1 (0.7)
Allergic rhinitis findings*	29 (19)
Family history- Environmental exposure*	
Asthma/ atopy history in the family	33 (21.6)
Presence of pet at home	10 (6.5)
Secondhand tobacco smoke exposure	27 (17.6)
Physical findings	
Desaturation*	3 (2)
Tachypnea*	6 (3.9)
Oxygen saturation, mean (SD)	97.5 (1.4)
Crackles*	37 (24.2)
Rhonchus*	24 (15.7)
Clubbing*	7 (4.6)
Laboratory, median (IQR)	
Hemoglobin g/dl†	12.6 (11.7- 14.0)
White blood cell mm^3†	8.9 (7.5-12.6)
Platelets mm^3†	329 (282-386)
IgA mg/dL‡	116 (79-297)
IgG mg/dL‡	947 (891-1460)
IgM mg/dL‡	83 (63-142)

Ig: *immunoglobulin,* ***IQR:*** *interquartile range,* ***SD:*** *standard deviation,* ****:*** *n(%),* ***†:*** *Complete blood count was performed in 35 patients.* ***‡:*** *Quantitative immunoglobulins were available in 15 patients.*

Table II: Thorax CT findings of patients with chronic cough

Thorax computed tomography findings	n (%)
Pectus carinatum	1 (0.7)
Hilar/ mediastinal lymphadenopathy	4 (2.6)
Mosaic attenuation	2 (1.3)
Consolidation	5 (3.3)
Ground glass opacity	3 (2)
Atelectasis	14 (9.2)
Infiltration	3 (2)
Bronchiectasis	14 (9.2)

All patients had a chest X-ray and it was normal in 74 patients (48.4%). The frequency of pathological findings were as follows: peribronchial thickening in 27 patients (17.6%), infiltration in 17 patients (11.1%), chronic changes in 10 patients (6.5%), bronchiectasis in nine patients (5.9%), atelectasis in nine patients (5.9%), bilateral hyperinflation in six patients (3.9%), unilateral hyperinflation in one patient (0.7%).

A thorax CT was present in 34 patients (22.2%). Chest CT findings is shown in Table II. A flexible bronchoscopy was performed in 11 patients (7.2%) in which two patients had tracheomalacia, four patients had bronchomalacia and two patients had infection. The final diagnosis of the two patients with infection were protracted bacterial bronchitis and primary ciliary dyskinesia. Two patients were referred to pediatric surgeons because of findings resembling TEF. In one patient macroscopic flexible bronchoscopy findings were normal but Mycobacterium tuberculosis culture was positive in bronchoalveolar lavage sample. This patient was diagnosed with tuberculosis.

The final diagnosis of the patients is shown in Table III. The longest duration of cough was seen in the patients with bronchiectasis (median 48 weeks (IQR: 34-130), whereas shortest duration of cough was seen in patients with pneumonia (median 4 weeks (IQR:4-8) (p<0.050).

Table III: The final diagnosis of patients with chronic cough

Diagnosis	n (%)
Asthma	47 (30.7)
Protracted bacterial bronchitis	31 (20.3)
Upper airway cough syndrome	17 (11.1)
Pneumonia	14 (9.2)
Bronchiectasis	12 (7.8)
Malacia	6 (3.9)
Interstitial lung disease	5 (3.3)
Gastroesophageal reflux -Swallow dysfunction	4 (2.6)
Natural healing	4 (2.6)
Post infectious cough	3 (2)
Immunodeficiency	2 (1.3)
Tuberculosis	2 (1.3)
Tracheoesophageal fistula	2 (1.3)
Psychogenic cough	2 (1.3)
Foreign body aspiration	1 (0.7)
Hydatic cyst	1 (0.7)

The most common diagnoses in patients with wet cough were protracted bacterial bronchitis (33.3%), pneumonia and other lung infections (tuberculosis and hydatid cyst) (17.2%), and bronchiectasis (12.9%). The most common diagnoses in patients with dry cough were asthma (68.3%), upper airway cough syndrome (6.7%), and natural recovery (6.7%).

Reversibility test was performed in 17 (36.2%) of 47 patients diagnosed with asthma and reversibility was positive in all of them. Inhaled fluticasone treatment was initiated to these patients. Thorax CT was performed in one patient who did not respond to treatment. In the thorax CT, there was a hyperechoic appearance in the mediastinal window and a localized increase in aeration was present in the right middle lobe in the parenchyma window consistent with a foreign body in the right intermediate bronchus. The foreign body in the right intermediate bronchus was removed by the pediatric surgeons by rigid bronchoscopy. After rigid bronchoscopy the corticosteroid therapy was discontinued.

In 31 patients diagnosed with protracted bacterial bronchitis cough resolved in 22 patients after two weeks of oral antibiotic treatment. Among the remaining eight patients cough resolved in 7 of them after four weeks of oral antibiotic treatment. Infection was detected by flexible bronchoscopy in one patient who did not respond the standard therapy. During follow up four patients had recurrent protracted bacterial bronchitis. None of the patients with recurrent protracted bacterial bronchitis had bronchiectasis on chest CT.

Nasal saline and nasal steroid treatments were started by the otorhinolaryngologists in patients who were diagnosed with upper airway cough syndrome. The details history of the patients diagnosed with pneumonia revealed that seven patients applied to the hospital within the two days of the onset of complaints, oral antibiotic treatment was initiated for these patients, but none of them received treatment for more than seven days. Mycoplasma IgM/ IgG positive was positive in nine patients. Patients diagnosed with mycoplasma pneumonia received oral macrolide therapy for ten days. Patients diagnosed with non-mycoplasma pneumonia received oral amoxicillin-clavulanate therapy. All patients responded to antibiotic treatment.

Among patients with bronchiectasis two of them were diagnosed with cystic fibrosis based on history, physical examination and cystic fibrosis genetic analysis. Of the remaining ten patients nine of them had a PICADER score above seven. These nine patients were diagnosed with primary ciliary dyskinesia by whole exome sequencing. The remaining one patient was diagnosed with non-cystic fibrosis and non-primary ciliary dyskinesia. This patient had bronchiectasis localized to the right lower lobe, and no anatomical abnormality was detected by flexible bronchoscopy, except for purulent secretion. Staphylococcus aureus growth was detected in the bronchoalveolar lavage sample.

The diagnosis of interstitial lung disease patients were as follows: hypersensitivity pneumonia, bronchiolitis obliterans, Rubinstein Taybi related interstitial lung disease, cutis laxa related interstitial lung disease and immunodeficiency related interstitial lung disease. Chest physiotherapy was initiated for all patients with interstitial lung disease. Patients with hypersensitivity pneumonia and bronchiolitis obliterans responded to clinical treatment. No specific treatment was given for the remaining patients with interstitial lung disease.

Two patients were diagnosed with tuberculosis. Flexible bronchoscopy was performed first patient with prolonged cough and sputum who had hilar after hilar lymphadenopathy, atelectasis, consolidation and bronchiectasis on thorax CT. Tuberculosis acid-resistant bacillus and polymerase chain reaction was positive and Mycobacterium tuberculosis culture growth was detected in the bronchoalveolar lavage.

The second patient had chronic cough with a family history of tuberculosis. She had

hilar lymphadenopathy and atelectasis in the right middle lobe on thorax CT. Mycobacterium tuberculosis culture growth was positive in sputum culture. Both patients recovered at the end of six months.

DISCUSSION

Cough in childhood is one of the most common reasons for referral to the pediatrician. Chronic cough is burdensome for patients and their families. At the same time, it increases health expenditures due to frequent hospital admissions (5). Because of the significant anatomical and physiological differences between children and adults, and existence of different diseases

and treatment approaches, the first pediatric-based guideline the American College of Chest Physicians, was published in 2006 (2). Cough may be caused by a simple disease such as upper respiratory tract infection or it can be an indicator of a systemic illness such as underlying chronic lung disease, immunodeficiency and heart diseases (12). Since cough can sometimes be the only indicator of respiratory disease, it should be carefully evaluated. Otherwise, it may lead to delayed diagnosis and progression of the disease. In this study, the most common causes of chronic cough were asthma, protracted bacterial bronchitis, and upper airway cough syndrome. Wet cough was present in 60% of patients with chronic cough, and the most common diagnoses in patients with wet cough were protracted bacterial bronchitis, pneumonia and other lung infections (tuberculosis and hydatid cyst), and bronchiectasis, respectively. In patients with dry cough, the most common diagnoses were asthma, upper airway cough syndrome, and natural recovery. While failure to thrive was more frequent in patients with wet cough than patients with dry cough, fever, weight loss and desaturation were only present in patients with wet cough. In addition, crackles, clubbing and tachypnea were prominent findings in patients with wet cough. Seasonal and exercise-induced cough was more frequent in patients with dry cough.

The most common cause of chronic cough was asthma in this study. In the first study which examined the etiology of chronic cough in children, the most common cause of chronic cough was asthma (2). In a systematic review evaluating 14 studies, asthma and protracted bacterial bronchitis were stated as the most common causes of chronic cough (6). Different studies from our country evaluated the reasons of chronic cough., Pedük et al. (13) showed that 23.4% of the children with chronic cough were diagnosed with asthma, whereas this ratio was 39% in the study by Asilsoy et al. (9). Both of the studies stated the most common cause of chronic cough was asthma followed by protracted bacterial bronchitis. Similar results, were reported by Çullas İlarslan et al. (14) where asthma, protracted bacterial bronchitis, pneumonia and obstructive sleep apnea were the most common causes of chronic cough. In studies conducted abroad, both Marchant et al. (7) as well as Chang et al. (15) showed that protracted bacterial bronchitis was the most common cause of chronic cough. Different results between studies can be explained by the different age groups and regional prevalence of diseases. When Turkish studies supporting this idea are compared with American and Australian studies, it is seen that asthma is the most frequent cause of chronic cough in Turkey (7,9,15,16).

In this study, 60% of patients with chronic cough had wet cough. The frequency of wet cough was similar in studies conducted by Çullas İlarslan et al. (14) and Gedik et al. (17) study. In a patient with chronic wet cough, clinical evaluation and the improvement of cough with antibiotic treatment suggests the diagnosis of protracted bacterial bronchitis. CHEST guidelines recommend a two-week course of treatment for protracted bacterial bronchitis (6,10). It is recommended to repeat the course of antibiotics in persistent cough and to perform further investigations such as flexible bronchoscopy only in persistent cases after four weeks of treatment in the same guideline. Common bronchoscopy findings of protracted bacterial bronchitis are purulent airway secretions and airway malaise. While the diagnosis of protracted bacterial bronchitis was based on the results of bronchoscopy and bronchoalveolar lavage in the study by Marchant et al. (7), Asilsoy et al. (9) and Chang et al. (15) diagnosed patients based on clinical findings and response to treatment. In this study, similar to the study by Asilsoy et al. (9) the diagnosis of protracted bacterial bronchitis was made clinically and with response to treatment, and flexible bronchoscopy was performed in only one patient because there was no adequate antibiotic response.

In the differential diagnosis of chronic cough, additional diagnostic methods such as thorax CT and or flexible bronchoscopy can be performed in cases where there is no response to standard treatments or when there is a suspicion of an additional disease. Suppurative lung disease, non-healing pneumonic consolidation and vascular anomalies can be detected with thorax CT (6). In this study, thorax CT was performed in 20% of the patients for diagnostic purposes. The diagnosis based on thorax CT were bronchiectasis, interstitial lung disease, and aspiration suggesting swallowing dysfunction. In addition, foreign body aspiration was diagnosed by thorax CT in a patient who was diagnosed with asthma and did not respond to treatment. The patients were diagnosed with malacia and TEF by flexible bronchoscopy. The thorax CT and flexible bronchoscopy was also helpful in diagnosing psychogenic cough by excluding other etiological causes of chronic cough.

In this study, one of the common causes of chronic cough was pneumonia (9%). M. pneumoniae IgM or IgG antibodies were positive in nine of 14 patients diagnosed with pneumonia. In studies conducted in our country on chronic cough, Çullas İlarslan et al.(14) stated the incidence of pneumonia as 7.6%, and Gedik et al. (17) found it to be 3%. In the study by Asilsoy et al. (9) it was stated that one of the common causes of chronic cough was pneumonia and 17 of 41 patients were positive for M. pneumonia IgM or IgG antibodies. The authors stated that although these results suggest acute infection in only some of the patients, such factors may cause chronic cough. The different follow-up periods in the studies may explain pneumonia frequency in patients with chronic cough. In this study, which had a shorter follow-up period, patients were frequently diagnosed with pneumonia, while in the study of Gedik et al. (17) where patients were followed up for a longer period of time the frequency of pneumonia was much lower. In the presence of recurrent pneumonia, the underlying etiological causes are investigated and patients can be diagnosed with different diseases such as chronic suppurative lung disease

and immunodeficiency. These findings suggest that patients with pneumonia in should to be followed up for recurrent pneumonia, and further investigations should be performed in the presence of recurrent pneumonia.

Smoking is one of the leading causes that triggers cough. In this study, while 18% of children with chronic cough had secondhand tobacco smoke exposure, this rate increased to 30% in the group with dry cough. Secondhand tobacco smoke exposure is a modifiable risk factor affecting long-term lung health. By preventing secondhand tobacco smoke exposure, lung infections and progression of chronic lung diseases can be prevented.

This study has some limitations. First, a validated cough questionnaire was not used in this study and patients did not keep a cough diary. In addition, a longer follow-up period may allow a better understanding of the natural history of cough, recurrence rates, and diagnostic changes. Finally, the fact that the study was conducted in the pediatric pulmonology outpatient clinic may not reflect the real population.

In conclusion, chronic cough is an important health problem that patients frequently seek medical consult. The most common reasons are asthma, protracted bacterial bronchitis and upper airway cough syndrome. The differential diagnosis should be made by pediatricians based on specific cough pointers, careful physical examination and tests performed in line with the recommendations of the guidelines.

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Infantile Chronic Subdural Hematoma Secondary to Brain Atrophy

Beyin Atrofisine Sekonder İnfantil Kronik Subdural Hematom

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ABSTRACT

Chronic subdural hematoma (CSH) may develop in infants as a result of some accompanying circumstances of brain atrophy. A six-month-old boy with mental and motor retardation and increased head circumference was admitted in our hospital. His head circumference was over 97 percentile. Hypotonic and hypoactive baby couldn't hold his head and wasn't interested in surrounding enviroment. He had a history of aspiration pneumonia with no history of head trauma. MRI showed acute elements over chronic subdural hemorrhage spread almost all over the supratentorial area with severe cerebral atrophy. The brain volume was 95.252 mm^3 and it was around 1/6-1/8 of normal volume. It is thought that, chronic subdural hematoma was developed due to cerebral atrophy as a cascade started with chronic hypoxia and resulted as an increase in the head circumference and panhypopitruitism.

After 10 days of subdural drainage, subduroperitoneal shunt was placed'. At the end of second month, head circumference stopped increasing, the patient could hold his head and started to be partially interested in the surrounding objects, however the change in the brain volume was not significant.

Cognitive and motor functions progress very rapidly in the first two years of life. Early evacuation of CSH has a positive effect on prognosis and most commonly used method is subduraperitoneal shunt insertion.

Key Words: Brain Atrophy, Infantile panhypopituitarism, Subdural hematoma

ÖZ

İnfantlarda kronik subdural hematom beyin atrofisi ile ilişkili bazı durumlara bağlı olarak gelişebilir. Altı aylık bebek hasta mental ve motor retardasyon ve baş çevresinde artış bulguları ile kliniğimize sevk edildi. Baş çevresi 52 cm (97 persentil üstü) olarak ölçüldü, fontanelinin açık, gergin olduğu ve pulse etmediği görüldü. Nörolojik muayenesinde çevre ile ilgisiz olduğu, başını serbest kaldıramadığı görüldü. Öyküsünden 2 aylıkken aspirasyon pnömonisi geçirdiği ve kafa travması öyküsü olmadığı öğrenildi. Manyetik Rezonans Görüntülemede kronik üstü akut kısımlar içeren subdural kanamanın tüm supratentorial alana yayıldığı, beyinin supratentorial kısmının çok ciddi şekilde global atrofiye uğradığı görüldü. Hesaplamada hastanın beyin hacmi 95.252 mm^3 olarak ölçülmüş ve normal hacim yaklaşık 1/6-1/8 oranında azalmıştır. Hastanın öyküsünden, bir kaskat halinde; pnomoniye bağlı kronik hipoksi ile başlayan sürecin, buna bağlı beyin atrofisi gelişimi ve sonrasında subdural hematom, panhipopitruitizm ve baş çevresinde artış ile sonuçlandığı düşünülmüştür.

Hastaya subdural drenaj takılmış, drenajının 10. gününde reopere edilerek subduroperitoneal şant yerleştirilmiştir. Ameliyattan sonraki ikinci ayda baş çevresi artışı durmuş, hastanın başını tutabildiği ve çevresiyle kısmi ilgili olmaya başladığı görülmüştür. Ancak beyin hacminde önemli değişiklik olmamıştır.

Kognitiv ve motor işlevler hayatın ilk iki yılında hızla gelişir. Bu nedenle hematomun erken boşaltılmasının prognoza olumlu etkisi vardır ve bu amaçla en sık kullanılan yöntem subduraperitoneal şant yerleştirilmesidir.

Anahtar Kelimeler: Beyin atrofisi, İnfantil panhipopituitarizm, Subdural hematom

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INTRODUCTION

Chronic subdural hemorrhage can occur due to several causes (trauma, hemorrhagic diathesis, cerebrovascular events, vascular anomalies, arachnoid cysts, infections, tumor, and surgery) (1,2). During development of a chronic subdural hematoma; after enough blood is accumulated in the subdural space, it can make a pressure especially on the cortex, impair brain blood supply, especially the cortical part of it due to inflammation caused by hemorrhage material. Activated inflammatory cascade on the brain tissue can create a toxic-inflammatory effect (3). The fibroblasts located in the mechanically thin layer between dura and the arachnoid layers play the most important role in this process.

Growth factors released from fibroblasts increase neoangiogenesis and tissue plasminogen activator fibrinolysis. Developing immature vessels and increasing fibrinolysis may cause new bleeding and enlargement of the size of hematoma (4).

As hemorrhage becomes chronic, released VEGF and IL 6 may activate pathways like JAK-STAT and MAPK causing the formation of new membranes. Membranes formed between arachnoid and dura may cause new hemorrhage, thus the size of hematoma increases and vicious cycle may start (5). While the size of hematoma is small, the patient is usually asymptomatic; hence the size of hematoma increases as other space occupying lesions it may cause increased intracranial pressure. Since unilateral hemorrhage has a risk of uncal, subfalcine herniation, while bilateral hemorrhage has central transtentorial one (6,7). If uncal and central herniations cause brain stem compression and dislocation, it may affect respiratory function, loss of consciousness and paresis (8).

Chronic subdural hematoma is mostly seen in elder age group but seldom cases in infants are also reported (9,10). Infantile chronic subdural hematomas cause neurological symptoms and affect motor and mental development in most cases but some asymptomatic cases with no progression may be observed.

CASE REPORT

A six-month-old baby boy with mental and motor retardation and increased head circumference was admitted in our hospital. He referred to our hospital with chronic subdural hematoma and severe cerebral atrophy after taken CT scan due to these symptoms.

His medical history showed that he had no prenatal or early postnatal problem, had normal development for up to two months, was treated in the ICU of another hospital due to aspiration pneumonia when he was second months old and received respiratory support due to asphyxia and long-term antibiotic therapy. After age of two months, he

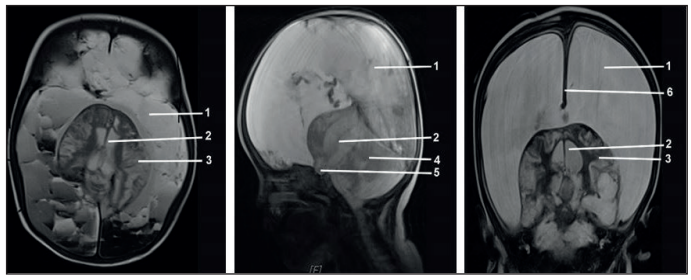

Figure 1: Patient's MRI done at the arrival to our clinic (1-subdural hematoma 2-shrunken ventricle, 3-atrophic cortex, 4-cerebellum 5-atrophic diencephalon 6-falx).

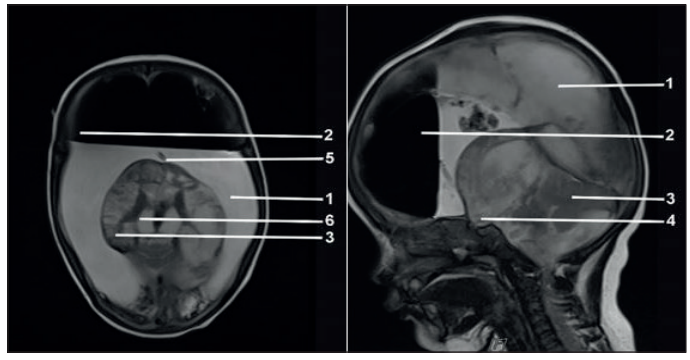

Figure 2: Post-operative MRI after inserted subdural peritoneal shunt (1- subdural hematoma 2-remaining space after hematoma drainage 3-cortex 4-diencephalon 5- proximal catheter of subdural peritoneal shunt 6-ventricle).

showed progressive worsening of neurological status and regression of development. It was reported that he was on hormone replacement therapy due to panhipopituitarism and phenobarbital treatment was started for seizures.

On neurological examination, the head circumference was 52 cm (over 97 percentile) and the fontanel was open, bulging and non-pulsatile. Hypotonic and hypoactive baby could not sit and bilateral pupillary light reflexes could not be obtained. He couldn't hold his head, had sucking and searching reflexes. He responded to the painful stimulus by pulling four limbs. Extensor plantar responses were positive.

We performed cranial magnetic resonance imaging (MRI) which confirmed diagnosis. The result showed subdural hemorrhage containing chronic, subacute and acute phase blood elements spread almost all over the supratentorial area that created severe atrophy of the brain. The cortical and subcortical areas were severely thinned and the diencephalic structures decreased in volume due to global atrophy in the brain. Infratentorial areas was not affected (Figure 1).

MRI examination of the patient was performed under sedation with a 3T MRI device (Verio; Siemens Medical System). The obtained images were processed on the workstation and measurements were made on axial T2 weighted images (Syngo. via, Siemens Work Sitation) (Section thickness: 5 mm Gap: 6.5 mm). In the axial images, the total volume was calculated from the internal tabula level of the calvarium with the free

hand drawing technique. ((Slice thickness + amount of gap) X number of slice). Total brain volume was likewise calculated in the cortical area using free hand drawing technique with the relevant formula: ((Slice thickness + amount of gap) x number of slice). Brainstem and cerebellum were not included into total brain volume calculation.

The patient's brain volume was measured as 95.252 mm^3 and normal volume decreased by approximately 1/6-1/8 in calculation.

Subdural drainage was placed in order to prevent growth of head circumference and to reduce pressure on the brain as much as possible. During the surgery, dark brown blood in the chronic subdural hematoma setting with occasionally contained acute bleeding foci is evacuated from burr hole. On the 10^{th} day of the drainage when the colour of the drainage was more serous, the patient was re-operated and a subduroperitoneal shunt was placed. At the end of the second month, patient's head circumference stopped increasing, it was seen that the patient could hold his head and started to be partially interested in the surrounding objects, however the change in the brain volume was not significant (Figure 2).

DISCUSSION

Chronic subdural hematoma is a lesion that can lead to serious neurological complications in infants. Neurological follow-up becomes difficult in patients with asphyxia as they should be intubated and sedated in intensive care hospitalization period. Reducing sedation as much as possible and performing frequent neurological examinations, controling the head circumference and fontanel tension may be useful for early diagnosis especially in intubated and sedated cases.

Brain development reaches 80-90% volume of adult brain in the first 2 years of life (11). Especially myelinization starts at birth and is completed mostly at the age of 2 (12). Cognitive and motor functions progress very rapidly in the first two years of life hence atrophy and other organic disorders that occur during this period affect both functions seriously (13,14). Therefore, for the prevention of cognitive and motor retardation early evacuation of chronic subdural hematoma has a positive effect on prognosis at first two years of age (12).

In our case, the possible trigger for the happened sequential events was brain atrophy due to asphyxia and secondary subdural hemorrhages that the patient had at the age of 2 months. Hemorrhages secondary to atrophy caused an increase in cortical and subcortical atrophy, shrinking of the brain caused growth of subdural hematoma and consequently formation of a rare and uncommon form of cerebral atrophy. While normal human brain volume should be 425.000-855.000 mm^3 in the first 0-12 months of life in our patient it was 95.252 mm^3 (12). Apart from the cortical and subcortical layer, atrophy of the diencephalon suggests that the initial asphyxia attack played a role in the event.

On time and appropriately done surgical treatment should be used in order to preserve motor and mental development. Immediate surgical treatment is essential in patients with subdural hemorrhage that cause shift and neurological losses. Although approaches such as Burr Hole drainage, hematoma evacuation with craniotomy are feasible in surgical treatment, the most commonly used recent method is subduraperitoneal shunt insertion (15).

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Necrotizing Fasciitis Following Tetanus Vaccination

Tetanoz Aşısı Sonrası Nekrotizan Fasiit

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ABSTRACT

Necrotizing fasciitis (NF) is a rare infection that is characterized by rapidly progressing necrosis into the superficial and deep tissues. NF can result in serious morbidity and mortality as a life-threatening condition. Early diagnosis is one of the most important factors in reducing mortality. Therefore, we aimed to describe a case of severe necrotizing fasciitis in the left arm after tetanus vaccination administration and to discuss the benefits of early surgical management in the light of the literature.

Key Words: Children, Necrotizing Fasciitis, Tetanus Vaccine

ÖZ

Nekrotizan fasiit (NF), yüzeyel ve derin dokulara hızla ilerleyen nekroz ile karakterize nadir görülen bir enfeksiyondur. NF, yaşamı tehdit eden bir durum olarak ciddi morbidite ve mortaliteye neden olabilir. Mortaliteyi azaltmada en önemli faktörlerden biri erken tanıdır. Bu olgu sunumunda, tetanoz aşısı sonrası sol kolda şiddetli nekrotizan fasiit gelişen bir olguyu sunmayı ve literatür ışığında erken cerrahi tedavinin faydalarını tartışmayı amaçladık.

Anahtar Kelimeler: Çocuk, Nekrotizan Fasiit, Tetanoz Aşısı

INTRODUCTION

Necrotizing fasciitis (NF) can be defined as a severe bacterial infection that occurs as a result of soft tissue infection. NF, which may also be caused by ischemia and/or lack of defense mechanisms, can become a vicious circle causing tissue necrosis (1). NF is more likely to affect adults than children. But, healthy children appear to be affected more often by NF, which is in contrast to the association of adults with NF (2). Identification of a small lesion that triggers the progression to fasciitis can be possible in 50-80% of children (3). Circumcision, umbilical vein catheterization, inguinal hernia operation, chickenpox superinfection, omphalitis, limb lesions, perineal infections, head-neck lesions, trauma, and insect bites can be the cause of NF. In most cases, the virulent form of group A *Streptococcus* is responsible for the development of NF. Clinical suspicion may be useful for the early diagnosis and treatment. If not treated in the early period, morbidity and mortality increase significantly in cases where the diagnosis is delayed. Besides the use of broad-spectrum antibiotics, aggressive surgical debridement constitutes the main principles of treatment. Negative Pressure Wound Therapy (NPWT) is an efficient treatment in the case of acute and chronic wounds and this treatment method accelerates healing by the topical negative pressure (4). This case report presents the management of NF in a pediatric case that developed after tetanus vaccination administration.

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CASE REPORT

A 13-year-old patient with no known systemic diseases in his medical history presented with a rash and pain in the left upper arm. Upon questioning, it was learned that he had a tetanus vaccination at school one week earlier. He presented to an external medical center with complaints of pain, redness, and fever, and his complaints did not regress despite oral amoxicillin/clavulanic acid and intravenous ampicillin/sulbactam treatment.

On the 17th day after vaccination, his complaints continued and he was transferred to our hospital. The patient was admitted to the infection service, and intravenous ampicillin/sulbactam and clindamycin treatments were initiated. Upon arrival, his body temperature was 37.4°C, respiratory rate was 24/minute, and heart rate was 72/minute. We were consulted because of the rapid increase in redness and pain. There was no pathology in the other system examinations. The principal findings were swelling, hyperemia, increased temperature, and tenderness in the anterolateral region of the left arm.

It was observed that the abscess drained spontaneously in the anterolateral aspect of the left arm, and fluctuation and crepitation were palpated around it, and the patient was taken into emergency operation (Figure 1). During the surgical exploration performed in the area with tissue defects, it was observed that the infection and necrosis progressed from the graft site to the proximal shoulder, distal to the forearm, and into the subcutaneous, fascia, and muscle tissues, with the infection dissecting the tissues (Figure 2). Extensive purulent discharge between the muscle tissues was drained, necrotic tissues were debrided in places reaching the bone tissue, and the entire region was washed with antiseptic solutions. Subsequently, all dead tissues were removed by debridement two more times at 24-hour intervals (Figure 3). On the third day, when it was seen that the inflammation had regressed, the tissue defect in the shoulder area was approximated somewhat, and TNP vacuum-assisted closure (VAC; Kinetic Concepts Inc., San Antonio, TX) was applied to the remaining open areas. Intravenous teicoplanin was added to the treatment. Due to the limitation of movement in his left elbow, he began a physical therapy program. VAC was repeated for three sessions, four days apart. *Bacillus flexus* growth was observed in the pus culture sample obtained during the first debridement, so treatment was continued. No growth was observed in subsequent pus and blood cultures. Thirteen days after the first debridement, when the patient's VAC was opened, it was observed that granulation tissue was developing. A partial thickness skin graft was taken from the right thigh and applied to the patient, and VAC was placed on the graft again. When the VAC was opened four days later, it was seen that the grafts were adapted. The patient did not need a blood transfusion during this period. He was treated with clindamycin for 19 days, teicoplanin for 16 days, and ampicillin/sulbactam for 16 days. Physical therapy recommendations were provided, and Vaseline application

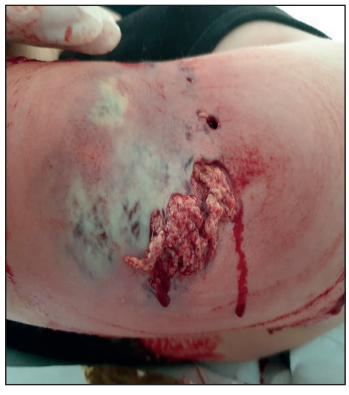

Figure 1: The abscess drained spontaneously in the anterolateral region of the left arm, and an obvious exposed subcutaneous fat is also seen.

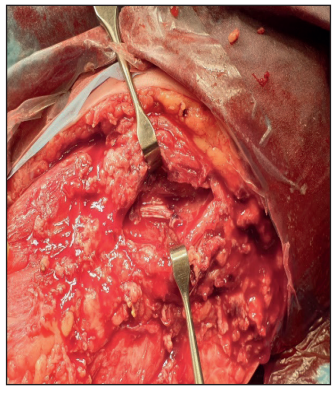

Figure 2: The deep tissue infection and necrosis progressing through the fascia planes extending to the bone.

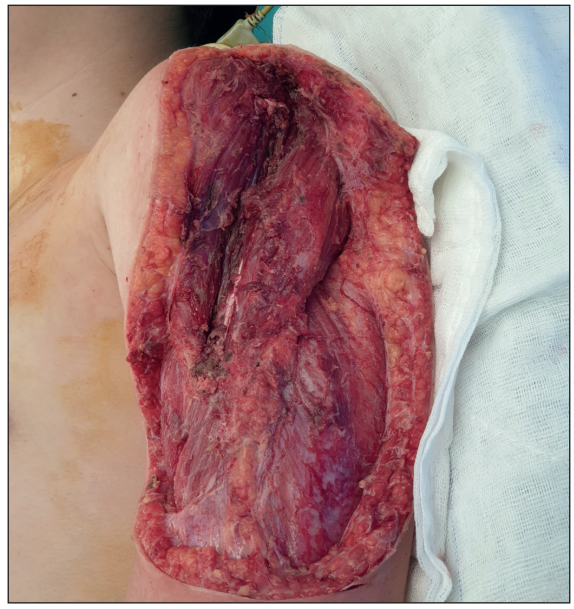

Figure 3: View after serial debridement.

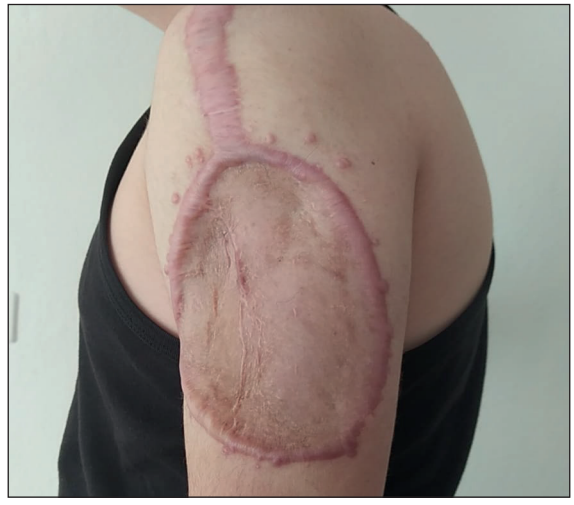

Figure 4: Final outcome of reconstruction with a free skin graft in postoperative 6th month.

was recommended to the graft areas. It was observed that the patient had no problems during the follow-up appointment 10 days after discharge (Figure 4).

DISCUSSION

NF is a rare bacterial infection that has many etiologies. Although it is frequently seen in the extremities and perineum, it can occur anywhere in the body. The most important factor affecting the treatment process is early diagnosis, which is mainly based on clinical findings. It can easily be confused with other soft tissue infections associated with clinical erythema. NF should be suspected if there is pain and sensitivity in the affected area that is accompanied by a subfebrile fever and rapid clinical deterioration despite antibiotic treatment. Radiological imaging methods alone are not diagnostic due to nonspecific findings.

Because of the high morbidity and mortality caused by NF, emergency treatment should be started immediately after diagnosis. Broad-spectrum antibiotherapy that includes coverage of various organisms, including *Streptococcus*, *Staphylococcus*, gram-negative bacteria, and anaerobes, should be initiated, and immediate, effective, and adequate debridement should be performed. The only way to control infection in NF is to debride all necrotic tissue effectively and adequately. In our case, debridement continued until live bleeding tissue was reached, and all necrotic tissue was removed. There are many publications in the literature suggesting that early aggressive debridement decreases the mortality rate (5). It should be performed by an experienced surgeon who is familiar with the anatomy of the region in order to protect functional structures during debridement. The patient should be followed up closely, and debridement should be repeated if necessary. Some authors recommend mandatory reassessment in the operating room within 24 hours to ensure adequate debridement (3). Rabuel at al. (6) shows that patients who do survive NF have decreased (self-reported) quality of life in multiple domains with a focus on decreased physical functioning.

A plan should be made to close the defect after the necrotic tissue is cleaned and the spread of the infection is under control. We applied VAC in this patient to support granulation development. This application reduces bacterial load by removing exudate in the environment, increases local blood flow, causes the release of growth factors, removes proteases that prevent wound healing, contributes to the development of granulation tissue, and ensures rapid and high-quality wound healing (7). The tissue defect in this patient was approximately 40 cm^2. Some tissue defects were primarily closed, VAC was applied to the remaining area, the defect area was reduced, and then a partial thickness skin graft was applied. The application of VAC on the graft facilitated the adaptation of the graft in the current infectious environment by ensuring its safety.

CONCLUSION

NF is a rapidly progressing and life-threatening infection that involves soft tissues and fascia. If not treated promptly and correctly, the mortality rate can be high. Amputation can be life-saving, especially in NF cases occurring in the extremities. After the diagnosis is made, early and serial debridements and acute treatment with appropriate antibiotic therapy should be instituted.

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Çocukluk Çağı Aşıları ve Covid-19 Enfeksiyonu

Childhood Vaccines and Covid-19 Infection

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ÖZ

Koronavirus 2019 hastalığı (COVİD-19) Aralık 2019 da Wuhan/ÇİN' de başlayıp, kısa sürede küresel halk sağlığı krizine dönüşerek Mart 2020 de pandemi olarak kabul edilmiştir. Özellikle akciğerleri tutarak ciddi ve ölümcül sonuçlara neden olabilmektedir. Tüm dünyada çocukların bu hastalıktan daha az veya daha hafif etkilendikleri görülmüştür. Etkin bir tedavisi veya COVİD-19'a karşı özel bir aşısı bulunana kadar, çocuklardaki bu iyi seyirden çeşitli ipuçları bulunmaya çalışılmıştır. Ve çocukluk çağı aşılarının koruyucu etkisi olabileceği hipotezi ortaya atılarak çeşitli çalışmalar yapılmıştır. Bu durum daha önceki pandemilerden elde edilen 'Eğitilmiş immün yanıt' mekanizması ile veya önceki endemik hastalıklarda gösterilen 'çapraz koruma' ile açıklanmaktadır. Fakat etkili olmadığına dair karşıt görüşler de mevcuttur. Bu yazıda, ülkemiz aşı programında da yer alan, çocukluk çağı canlı aşıları olan KKK, BCG ve inaktif aşıları olan influenza, hepatit A ve Boğmaca aşılarının, COVİD-19'a karşı bağışıklık cevabı gelişmesinde, etkilerinin belirlenmesi ve gelecekteki olası yeni pandemiler için de yön gösterici olabilmesi için literatür gözden geçirilmiştir. Tümü 2020 de yayınlanan bu konu ile ilgili makalelerin bulguları özetlenmiştir.

Anahtar Sözcükler: Aşı, BCG aşısı, Çocukluk çağı aşıları, HAV aşısı, İnfluenza aşısı, KKK aşısı

ABSTRACT

Coronavirus 2019 disease (COVİD-19) started in Wuhan/ China in December 2019 and turned into a global public health crisis in a short time and was accepted as a pandemic in March 2020. It can cause serious and fatal consequences, especially by involving the lungs. All over the world, ıt has been observed that children are less and mildly affected by this disease. Until an effective treatment or a special vaccine against COVID-19 was found, several clues were sought from this good prognosis of children. And various studies have been carried out by putting forward the hypothesis that childhood vaccines may have a protective effect. This is explained by the 'trained immune response' mechanism obtained from previous pandemics or the 'cross protection' shown in previous endemic diseases. But there are also opposing views that it is not effective. In this article, we will discuss the effects of alive vaccines MMR vaccines and BCG vaccines and inactive vaccines, influenza, hepatitis A and whooping cough vaccines, which are also included in the vaccination program of our country, on the development of immune response against COVID-19 and a direction for possible new pandemics in the future. The literature has been reviewed to be illustrative for this issue.The findings of the articles on this subject,all published in 2020, are summarized.

Key Words: Vaccine, BCG vaccine,Childhood vaccines, HAV vaccine, İnfluenza vaccine, MMR vaccine

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GİRİŞ

Akut şiddetli respiratuar sendrom koronavirüs-2 (SARS-CoV-2)'in yol açtığı COVİD-19 hastalığı 11 Mart 2020'de Dünya Sağlık Örgütü (DSÖ) tarafından pandemi olarak kabul edilmiştir (1). DSÖ 22 Kasım itibari ile yaklaşık 57.8 milyon kişinin hastalığa yakalandığını ve yaklaşık 1.3 milyon kişinin öldüğünü bildirmiştir (2). COVİD -19 hastalığı, yaş, cinsiyet ve sağlık durumuna göre çeşitli klinik bulgularla ortaya çıkabilmektedir. İlerleyici akciğer hastalığı, sepsis ve ölüm gibi kötü etkilere yol açabilen bu virüsün çocukları daha az enfekte ettiği ve enfekte çocuklar arasında ise daha az şiddetli klinik bulgulara neden olduğu görülmüştür (3-5). Örneğin, Çin, italya ve Güney Kore'de 10 yaş altı çocukların daha az hastalandığı veya hastalığı daha hafif geçirdikleri bildirilmiştir (6). Yine, Çin'de enfekte kişilerin %0.9'unun çocuk olduğu ve çocuklarda mortalitenin olmadığı, buna karşın yenidoğanlarda daha semptomatik ve daha ağır seyirli olduğu görülmüştür (4,5). Bu durum COVİD-19'un neden yenidoğan dışındaki çocuklarda daha az sıklıkta veya daha az kötü seyirli olduğu sorusunu gündeme getirmiştir. Bunun üzerine 'Çocukluk çağı aşılarının spesifik olmayan veya çapraz koruması olabileceği' hipotezi ortaya çıkmıştır (7). Bu nedenle KKK, BCG gibi çocukluk çağı aşılarının COVİD-19 ve kötü etkilerine karşı koruyucu olup olmadığı konusunda çeşitli araştırmalar yapılmıştır.

Aşıların, spesifik olmayan bağışıklık ve çapraz koruma özelliklerinin COVİD-19 gibi büyük bir pandemiye yol açan SARS-COV2'ye karşı da sağlandığının gösterilmesi, tüm dünyadaki aşı politikalarını güçlendirerek olası yeni pandemilerin kontrolde tutulmasını sağlayabilir. Bu açıdan yol gösterici olması için; bu çalışmada, literatürdeki çocukluk çağı aşılarının COVİD-19'a karşı koruyuculuğu olduğunu savunan veya bu hipoteze karşı olan çalışmalar özetlenmiştir. Bu sayede çocukluk çağı aşılarının farklı bir etkisini hatırlatarak, ulusal aşı programlarının önemini vurgulamak ve etkin tedavi ve aşısı uygulanana kadar COVİD-19 için geçici bir çözüm ihtimalini değerlendirmek amaçlanmıştır.

YÖNTEM

Bu derleme yazılırken, sağlık bilimleri veri tabanı 'PUBMED'de' 'COVİD-19 ve çocukluk çağı aşıları', COVİD-19 –KKK, COVİD-19 –BCG, COVİD-19 oral polio virus, COVİD 19-influenza, COVİD-19 hepatit A, COVİD-19-hepatit B anahtar sözcükleri ile tarama yapılarak, İngilizce literatürdeki çalışmalar incelenmiştir. Aynı anahtar sözcükler ile 'google akademik' sitesinden hem İngilizce hem Türkçe dilinde arama yapılarak bulunan makale, mektuplar ve diğer çalışmalar gözden geçirilmiştir.

Yapılan taramalar sonucunda bu konuda İngilizce literatürde yayınlanmış makalelerden 40 makalenin derlemesi yapılmıştır. Türkçe dilinde makale bulunamamıştır. Dahil edilen makalelerin kısa özeti Tablo I' de verilmiştir, hipotez ve yorumdan ibaret olan makaleler tabloya dahil edilmemiştir. Bu konuda 'clinical trial' sitesinde halen devam etmekte olup sonuçları henüz yayınlanmayan 17 çalışma bulunmakta olduğu görülmüştür.

Çocukluk Çağı Aşılarının Covid-19'a Karşı Etkinliğini Sağlayabilecek Olası Mekanizmalar

Heterolog Koruma: Rutin zayıflatılmış ve canlı çocukluk çağı aşılarının aşı ilişkili olmayan diğer enfeksiyöz hastalıklar sebebi ile olan hastane yatışlarını ve mortaliteyi azaltmak gibi non spesifik koruyucu etkileri olduğuna dair çeşitli çalışmalar mevcuttur (8-10). Bunun gibi, bir aşının spesifik kullanım amacının ötesinde bir koruyucu etki sağlamasına heterolog koruma denilmektedir. Bu hipotez ilk kez 1990'larda Peter Aaby tarafından Bandim Health Projesinde Batı Afrika'da öne sürülmüştür (11). 1980 yılında çiçek aşının non-spesifik hastalık morbiditesinde azalma sağladığı, 1920-1930'larda ise BCG aşısının non-spesifik enfeksiyöz hastalıkların mortalitesini azaltabildiği ve 1960'larda ise OPV aşısının hem non-spesifik morbiditeyi hemde mortaliteyi azalttığı görülmüştür (11). Çiçek, BCG, oral polio ve kızamık aşıları beklenenin ötesinde bir mortalite azalmasına yol açmıştır. BCG ve çiçek aşılarının doğal ölümleri de azaltarak yaşam süresini arttırdığı görülmüştür (12). Yine BCG aşısının solunum yolu enfeksiyon sıklığını ve sepsis nedeni ile hastane yatışını azalttığı gösterilmiştir. 2019 yılında yayınlanan bir çalışmada ise BCG'nin viral enfeksiyonlara karşı koruma sağladığı, latent virüs enfeksiyonlarındaki reaktivasyonu engellediği, viral enfeksiyon ilişkili morbidite ve mortaliteyi azalttığı saptanmıştır (9). Kızamık aşısının ise çocukluk döneminde (3 veya 5 yıla kadar) % 30-86 arasında değişen mortalite azalmasına neden olduğu gösterilmiştir (8). Benzer şekilde, BCG aşısı olanlarda da, diğer hastalıklara karşı ölüm oranında % 25'lik bir azalma bildirilmiştir (13). Aşıların bu, eğitilmiş bağışıklık ve çapraz koruma ile sağladığı heterolog etkisinin COVİD-19 için de etkili olabileceği düşünülmüştür (14-16). Aşıların bu heterolog etkilerinin daha sonra yaşlanma, immünosupresyon ve komorbidite durumları ile azalabildiği görülmüştür, bu da çocukları çocukluk çağı aşılarının korumuş olabileceği hipotezini destekleyebilir (3).

a. Eğitilmiş Bağışıklık: BCG aşısının non-spesifik, koruyucu etkilerinin ağır kombine immün yetmezlikli farelerde de gözlenmesi; bu korumanın T ve B lenfositlerden bağımsız bir yol ile olduğunu göstermiştir (17). Bu non-spesifik koruyucu etkinin, monosit, makrofaj ve NK hücreleri gibi doğal immün hücrelerin fonksiyonel ve epigenetik olarak yeniden programlanması sonucu ortaya çıkan 'eğitilmiş immunite" aracılığı ile olduğu düşünülmüştür (18,19). Çünkü aşıların; innate hücrelerin epigenetik trankripsiyonel olarak yeniden programlanmasını sağlayarak, micro RNA artışına yol açıp, myeloid hücre proliferasyonunu arttırdıkları ve aorobik glikolizasyona doğru metabolik kayma sağladıkları ve tüm bunların sonucunda ise eğitilmiş innate immün hafızayı indükledikleri gözlenmiştir (20). Eğitilmiş bağışıklığın indüksiyonunun ise, ilişkili olmayan patojenler ile ikincil uyarım sonucunda; makrofaj ve monositlerin tepkisini, sitokin salınımını ve reaktif oksjien üretimini arttırdığı gözlenmiştir (19). Ek olarak, daha önce fare modelinde

Tablo I: Literaturde cocukluk cağı aşıları ve covid_19 enfeksiyonu.

Konu	İlk Yazar İsmi	Ülke	Yöntem	Vaka Sayısı	Vakaların Yaş Aralığı	Sonuç	Yorum
Mekanizma	Young A	Birleşik krallık	KKK ile SARS-COV2 arasındaki homoloji araştırılmış. Ayrıca COVİD-19 hastalık şiddeti ile Rubella IGG arasındaki ilişkiye bakılmış tır	6 hasta	-	*Rubella ve SARS-COV2arasında %29 aminoasit(aa) sekans homolojisi *Kızamık ve kabakulak ile de füzyon protein homolojisi *Rubella antikorları ile korele olarak KKK aşısı yaptırmayanlarda COVİD-19 seyrinin daha kötü olduğunu göstermişlerdir.	KKK aşısının aa sekans homolojisi sebebi ile COVİD-19'un hastalık şiddetinin azalttığını belirtmişlerdir.
	Nuova G	USA	İmmünhistokimyasal olarak SARS-COV2 ve mycobacterium Bovis arasındaki sekans homolojisi araştırılmıştır	-	-	SARS-COV2 zar proteini ile mycobacterium bovise özgü LTRY C proteini arasında 12 ardışık aa'in benzer olduğu görülmüş	BCG aşısının SARS-COV2 ye karşı spesifik immüniteyi indüklediğini belirtmişlerdir
	Kandeil A	Global	BCG, Pnomokok, Rotavirüs, Difteri, Tetanoz, Pertusis, Hepatit B, Hemofilus influenza, Hepatit B, Meningokok, KKK aşılarının SARS-COV2 ye karşı nötrolizan antikor sağlayıp sağlamadıklarını BALB/c farelerde değerlendirilmiştir.	140 serum örneği değerlendirilmiştir.	-	İnaktif SARS-COV 2 aşısı nötralizan antikor oluşturabilirken, Çocukluk çağı aşılarının SARS COV2 ye karşı nötralizan antikor oluşturamadığı gösterilmiştir.	Eğer bu aşıların COVİD-19 a karşı herhangi bir koruyuculuğu varsa bile bunun antikor ilişkili olmadığını belirtmişler.
BCG (koruyucu)	Gursel M	Türkiye	BCG aşı kampanyası olan ve olmayan ülkelerdeki COVİD-19 ilişkili ölümlerle ilgili veriler karşılaştırılmıştır	-	-	Ülkelerin nüfus büyüklüğüne göre COVİD-19 ilişkili ölümlerin, BCG aşısı olmayan ülkelere göre ulusal BCG aşılaması olan ülkelerde önemli ölçüde daha düşük olduğunu göstermişlerdir.	BCG aşısının COVİD-19' a karşı koruyucu olabileceğini öne sürmüşlerdir.
	Escobar LE	ABD	BCG aşısının Ülkelerdeki covid-19 ilişkili ölüm oranları üzerindeki etkileri değerlendirilmiş.	-	Her yaş grubu	BCG indeksindeki her %10 luk artışın COVİD-19 mortalitesinde 10,4 kat azalma sağladığını saptamışlardır.	BCG aşısının COVİD-19 mortalitesini azalttığını belirtmişlerdir.
	Ventura L	İtalya	121 ülkenin BCG aşı şeması ile COVİD-19 vaka ve ölümleri epidemiyolojik olarak incelenmiştir.	121 ülke verileri	-	BCG aşılamasının son 10 yılda zorunlu olan ülkelerde, COVİD 19 vaka sayısının (ortalama %50) ve mortalitesinin (ortalama %80) önemli ölçüde azaldığını tespit etmişler. Ve bu azalmaya hastalığın yaz mevsiminde başlamasının da katkı sağladığını belirtmişler.	BCG aşısı ve çeşitli sosyo-ekonomik faktörlerin COVİD-19 vaka ve mortalitesi arasında güçlü bir ilişki olduğunu belirtmişlerdir.

Konu	İlk Yazar İsmi	Ülke	Yöntem	Vaka Sayısı	Vakaların Yaş Aralığı	Sonuç	Yorum
BCG (koruyucu)	Weng CH	ABD	Kohort, 19 Mart- 29 nisan 2020 tarihleri arasında ABD Rhode adasındaki bir sağlık merkezindeki COVİD-19 pozitifliği saptanan hastalar BCG aşılanma durumlarına göre analiz edilmiştir.	120	>18 yaş	BCG aşısı yaptıranlarda COVİD-19 hastalığı seyri sırasında hastaneye yatış daha düşük bulunmuştur (%3,7 ye karşı %15,8). Bu ilişki çok değişkenli regresyon analizi ile demografik bulgular ve komorbiditeler ile değerlendirildiğinde de değişmeden kalmıştır.	BCG aşısının COVİD-19 hastalığının ağır geçirilmesini önlediğini saptamışlardır.
	Moorlag SCFM	Çok merkezli	Son 5 yılda BCG aşısı olan ve olmayan sağlıklı gönüllülerden oluşan 3 kohortta COVİD-19 ve semptomları geriye dönük olarak değerlendirilmiş.	430	>18 yaş (23-80 IQR)	Bu çalışmadaki veriler BCG aşılamasının COVİD-19 döneminde güvenli olduğunu gösterirken, hastalığa karşı potansiyel yarar konusunda net bir bilgi sunamadığı belirtilmiştir.	BCG aşılaması COVİD-19 döneminde güvenli bulunmuş fakat SARS-COV2 ye karşı potansiyel bir yayarının olup olmadığına ilişkin randomize klinik çalışmalar ihtiyaç vardır.
	Kinoshita M	Japonya	Japonya'daki BCG aşı kapsamı ile SARS-COV2 hastalık ilişkisi değerlendiirlmiş.	-	>18 yaş	1999-2002, 2004 ve 2012 dönemlerinde BCG aşısı yapılmayanlarda yapılanlara göre COVİD-19 sıklığı daha yüksek bulunmuştur.	CIOVİD-19'a karşı koruyucu bulunmuştur.
	Shet A	ABD	Kamuya açık veriler kullanılarak ülkenin ekonomik durumu, yaşlıların oranı dahil karışıklık yaratan faktörleri düzenledikten sonra BCG ile COVİD-19 a atfedilen ölüm oranları arasındaki ilişki değerlendirilmiş.	-	-	BCG aşılaması yapılan ülkelerde COVİD-19 a atfedilen ölüm oranı BCG kullanmayan ülkelere göre 5,8 kat daha düşüktür.	BCG aşılaması ile COVİD-19 a bağlı ölüm oranı arasında ters ilişki saptanmıştır.
BCG (Koruyucu değil)	Hamiel U	İsrail	BCG aşılamasının yapıldığı son 3 yıl ile (1979-1981) ve aşılamanın durdurulduğu yapılmadığı ilk 3 yıl (1983-1985) doğumlulardaki COVİD-19 sıklığı PCR sonuçlarına göre değerlendirilmiş.	5933 (3064 aşılı/2869 aşısız)	35-41 yaş	COVİD-19 sıklığı ile BCG aşılanması arasında istatistiksel olarak anlamlı bir bağlantı saptanamamıştır.	BCG aşısının COVİD-19 a karşı koruyucu olmadığı belirtilmiştir.
	Hensel J	ABD	2017 de güncellenen BCG atlasına göre COVİD-19 yayılım ve mortalitesi arasındaki ilişki analiz edilmiş.	-	-	Karıştırıcı değişkenler dikkate alındığında BCG aşılama politikası ile COVİD-19 yayılma oranı ve ölüm yüzdesi arasında bir ilişki olmadığı gözlenmiş. Ayrıca kardiyovasküler hastalıklar, sigara ve yandaş hastalıkların COVİD-19 yayılma oranı ve ölüm yüzdesi üzerinde önemli ölçüde etkili olduğu görülmüştür.	BCG aşılaması COVİD-19 a karşı koruyucu bulunmamış.

Konu	İlk Yazar İsmi	Ülke	Yöntem	Vaka Sayısı	Vakaların Yaş Aralığı	Sonuç	Yorum
BCG (Koruyucu değil)	Miller A	Newyork/ABD	Dünya BCG aşısı atlasındaki veriler ile COVİD-19 ve mortalitesi arasındaki ilişki analiz edilmiştir.	-	Her yaş	Karıştırıcı değişkenler için düzenleme yapıldıktan sonra BCG aşılaması ile COVİD-19 yayılma oranı ve ölüm oranı arasında bir ilişki olmadığı saptanmıştır.	BCG aşısı COVİD-19 ve mortalitesine karşı koruyucu değil demişlerdir.
	Allam F	Mısır	BCG aşısının koruyucu olduğunu öne süren çalışmalara karşı, koruyucu olmadığına dair görüş bildirmiştir.	-	-	*BCG aşısının Çin'in de rutin aşı şemasında olması *en çok etkilenen ülkelerden biri olan İran'da BCG aşılama oranının neredeyse %99 olması *Afrika'da en çok etkilenen ülke olan Mısırda da BCG aşılanmasının %95 olması *İspanyada 1924-1980 arasında BCG aşılamasının olmasına rağmen yaşlı popülasyonun çok etkilendiği belirtilmiştir.	BCG aşısı COVİD-19 a karşı koruyucu değildir diye görüş belirtmişlerdir.
	Asahara M	Japonya	1.Diamond Prenses gemisindeki insanların COVİD-19 enfeksiyon ve ölüm oranları, 2.ülkeler arasındaki ölüm sayılarını 3. Uluslar arasındaki toplam ölümlerin maksimum günlük artış oranları değerlendirilmiştir.	-	-	1.Gemide bulunan BCG aşısı yapılan ülkelerden olan kişiler ile yapılmayan ülkelerden olan kişiler arasında kişi başına COVİD-19 enfeksiyonu ve ölüm oranı benzer bulunmuş 2.ülkeler COVİD-19 geliş zamanlarına göre değerlendirildiğinde ölüm sayıları farklı bulunmadı 3.ölümlerdeki maksimum günlük artışlar BCG yapılan ve yapılmayan ülkelerde benzer bulunmuştur	BCG aşısı COVİD-19 a karşı koruyucu bulunmamıştır.
KKK Aşısı (Koruyucu)	Young A	Birleşik krallık	KKK ile SARS-COV2 arasındaki homoloji araştırılmış. Ayrıca COVİD-19 hastalık şiddeti ile Rubella IGG arasındaki ilişkiye bakılmış tır	6 hasta		*Rubella ve SARS-COV2 arasında %29 aminoasit sekans homolojisi *Kızamık ve kabakulak ile de füzyon protein homolojisi *Rubella antikorları ile korele olarak KKK aşısı yaptırmayanlarda COVİD-19 seyrinin daha kötü olduğunu göstermişler.	KKK aşısının aa sekans homolojisi sebebi ile,COVİD-19 un hastalık şiddetini azalttığını belirtmişlerdir.
	Gold JE	Çok merkezli-merkezleri yazabiliriz ülke olarak	KKK IGG titre düzeyi ile COVİD-19 hastalık şiddeti arasındaki ilişki değerlendirilmiş.	80	>18 (mean 30.6)	*Kabakulak IGG titreleri ile COVİD-19 şiddet ve semptom skorunun ters orantılı olduğu tespit edilmiştir	*KKK aşısı ile kabakulak antikor titrelerinin ; COVİD-19 hastalık şiddetini azalttığı bulunmuştur

Konu	İlk Yazar İsmi	Ülke	Yöntem	Vaka Sayısı	Vakaların Yaş Aralığı	Sonuç	Yorum
İnfluenza-Koruyucu	Ragni P	italya	influenza aşısının SARS-COV-2 enfeksiyonuna duyarlılığı ve klinik sonuçları etkileyip etkilemediği, COVİD-19 PCR negatif ve pozitif olanlardan oluşan 2 grup arasında araştırılmıştır	17680	COVİD-19 testi yapılanlar yaş aralık olarak vermemiş gruplamış	İnfluenza aşısı yapılanlarda COVİD-19 pozitifliği daha yüksek (%34,2 a %29,5)saptanmış fakat bu grubun daha yaşlı ve daha çok morbiditeye (hipertansiyon, kanser gibi) sahip olduğu görülmüş. COVİD-19 salgını ile paralel olarak aşılanan küçük grupta ise koruyucu olduğu görüldü.	İnfluenza aşısı yapılma zamanına göre COVİD-19 a karşı koruyabilir. Bunun dışında ise hastane yatışı ve mortalitesi üzerinde bir etkisi gösterilememiştir.
	Thindwa D	Çok merkezli-global	WHO'nun verilerine göre influenza ve pnömonok aşılamasının hem hedeflenen hastalık üzerindeki hem de COVİD-19 üzerindeki etkileri değerlendirilmiştir.	-	-	İnfluenza ve pnömokok aşıları influenza ve pnömokok hastalıklarını ve hastane yatışlarını azaltarak dolaylı olarak COVİD-19 bulaşını azaltabilir ve COVİD-19 için ayrılabilecek sağlık imkan ve harcamalarını arttırabilir.	İnfluenza ve pnömokok aşıları hedeflenene hastalıkların yükünü azalttığı gibi COVİD-19 morbiditesini de önleme potansiyeline sahiptir demişlerdir.
	Amato M	İtalya	İnfluenza aşısının 65 yaş ve üzerindekilerde COVİD-19 yayılımını azaltıp azaltmadığı değerlendirilmiş. Sars cov2 seroprevelansı, hastane yatışı, yoğun bakım yatışı ve mortalite olmak üzere 4 parametre değerlendirilmiştir.	Toplum verileri ulusal web sitesinden incelenmiş	65 yaş ve üzeri	*İnfluenza aşısı ile aşılanma ile COVİD-19 seroprevelansı, hastaneye ve yoğun bakıma yatış sıklığı ve ölüm oranı arasında ters ilişki olduğunu saptamışlar	65 yaş ve üzerinde influenza aşısının COVİD-19 hastalık yayılımını ve şiddetini azalttığını belirtmişlerdir
Hepatit-A-Koruyucu	Massoudi N	İran	2019 Yılında influenza aşısı yapılan ve yapılmayan Halk sağlığı çalışanları arasındaki COVİD-19 insidansına bakılmıştır	261	Median 40 Erişkin hasta	80 COVİD-19 vakası içinden sadece 3'ünün influenza aşısı yaptırdığı, ama 181 sağlıklı kontrolden ise 87'sinde aşının yapılmış olduğunu görmüşlerdir.	İnfluenza aşısının COVİD-19 'a karşı koruyucu olduğunu belirtmişlerdir.
	Sarıalioğlu F	Türkiye	Takip ettikleri diyaliz hastalarında COVİD-19 görülme sıklığının yaklaşık olarak 1/1000 (3/2450) saptanması üzerine, randomize seçtikleri hastalardaki HAV antikor düzeyine bakılmıştır	227	-	Randomize seçilen 227 hastanın %94,7 sinde HAV antikorunu pozitif saptamışlardır.	HAV aşısının COVİD-19'a karşı koruyucu olabileceğini belirtmişlerdir.

gösterilen; ölümcül polimikrobial sepsise karşı canlı zayıflatılmış mantar suşu ile aşılamanın, uzun ömürlü myeloid türevi baskılayıcı hücreler aracılığı ile septik inflamasyonu ve mortaliteyi azaltmasından yola çıkılarak; aşılar ile ortaya çıkan eğitilmiş immün yanıtın indüklediği uzun ömürlü myeloid supresan hücrelerin, COVİD-19 ilişkili septik inflamasyonu ve mortaliteyi azaltabileceği öne sürülmüştür (15). Fakat bu eğitimli bağışıklık hücrelerin aşıdan sonra yalnız 1 yıl boyunca dolaşımda kaldığı gözlenmiştir, bu da; bu konudaki görüş ayrılıklarına yol açmıştır (21).

b. Çapraz Reaksiyon: Başlangıçta hedeflenen bir T klonundan farklı hedeflerde de beklenmedik reaktivite oluşması olarak tanımlanmaktadır. Yani bir T hücresinin birden fazla epitopu tanıyabilmesidir. CD8-T hücrelerinin aynı viral protein üzerindeki iki epitop arasında, yakından ilişkili virüslerin benzer proteinleri arasında veya aynı virüs içindeki benzer iki protein arasında çapraz reaktivite gösterebildiği görülmüştür (22). Lenfosit bağımlı bu mekanizma ile sekonder enfeksiyonun daha hızlı temizlenmesinin sağlanabileceği görülmüştür (23). COVİD-19 ile de çocukluk çağı aşıları arasındaki bezer protein ve epitoplar sayesinde T lenfosit yanıtının tetiklenebileceğini öne süren çalışmalar mevcuttur (14). Bu mekanizmalar ile çocukluk çağı aşılarının COVİD-19'a ve şiddetli akciğer-sistemik etkilerine karşı da koruma sağlayabileceği ileri sürülerek çeşitli çalışmalar başlatılmıştır.

ÇOCUKLUK ÇAĞI AŞILARI VE COVİD-19'A KARŞI ETKİLERİ

I. BCG Aşısı

BCG aşısı tüm dünyada en çok kullanılan aşılardan birisidir (16). Çeşitli çalışmalar BCG aşılama programı olan ülkelerde, olmayanlara göre COVİD-19 morbidite ve mortalitesinin azaldığını göstermiştir (24-32). Örneğin, Shet A ve ark. (33) BCG aşısı yapılanlarda yapılmayanlara göre mortalitenin 5.8 kat azaldığını bulmuşlardır. Escobar ve ark. (25) ise çalışmalarında sosyoekonomik olarak benzer olan Avrupa ülkelerindeki BCG aşılanma indeksleri ile COVİD-19 ilişkili mortalite oranlarını karşılaştırmışlardır. BCG indeksindeki her %10'luk artışın COVİD-19 mortalitesinde %10.4 azalma ile ilişkili olduğunu gözlemlemişlerdir. Ayrıca hastalığın yayılmasını da engellediği düşünülmüştür, örneğin Kinoshita ve ark. (34), çalışmalarında 1999-2002, 2004 ve 2012 yıllarındaki rutin infant BCG aşılama kapsamına göre, Japonyadaki iller arası COVİD-19 prevelanslarını değerlendirmişlerdir; 1999-2002 arasında aşılama kapsamı %40'lardayken, 2006-2010 yılları arasında ülkede, bu oran giderek arttırılmıştır. BCG aşısının kapsamının artması ile COVİD-19 prevelansı arasında negatif korelasyon saptadıkları gibi genç nesil arasında (20-34 ve 40-54 yaş gruplarında, 65 yaş ve üstüne göre karşılaştırıldığında) da yerel COVİD-19 yayılmasının önlenmesinde önemli bir etkisinin olduğunu öne sürmüşlerdir.

Bunların dışında, BCG aşısının, daha önce sağlıklı gönüllülerdeki sarı humma aşısının viremisini azaltmasından yola çıkılarak; COVİD-19 virüse karşı oluşturulan aşırı immün yanıtı da önleyerek süper inflamasyonu azaltabileceği ve bu yolla da mortaliteyi azaltabileceği önesürülmüştür (35,36). Çünkü SARS-CoV-2'nin hiperinflamasyon ile sitokin fırtınasına yol açarak, COVİD-19 ile ilişkili akut solunum sıkıntısı sendromuna ve bununla da mortaliteye yol açtığı gözlenmiştir (36,37).

Pereria M ve ark. (26) ise, farklı bir konuya değinerek, orijinal BCG suşlarını kullanan ülkelerde, değiştirilmiş BCG suşları kullanan Avrupa ülkelerine kıyasla daha düşük COVİD-19 vaka ölüm oranı kaydedildiğini (Japonya -% 5.4; Brezilya -% 4,7 ve Fransa -% 15.1'e karşı Rússia -% 1.4, İtalya- % 14.5 ve Birleşik Krallık% 14.0) belirterek, bu durumun farklı BCG suşlarının COVİD-19 şiddeti ve mortalitesi üzerinde farklı etkilere sahip olabileceğini düşündürdüğünü vurgulamışlardır. Bütün bu çalışmaların aksine; BCG aşısının COVİD-19 a karşı koruyuculuğunu desteklemeyen çalışmalar da mevcuttur (38-41). Hamiel ve ark. (38) İsrailde BCG aşısı başlanmadan 3 yıl önce (1979-1981 doğumlular) ve başlangıcından 3 yıl sonra (1983-1985 doğumlular) doğan 2 grubu birbiri ile karşılaştırdıkları çalışmalarında, hem COVİD-19 + sıklığında, hem de ağır hastalık sıklığında fark bulamamışlardır. Yine çeşitli çalışmalarda gelir seviyesi, COVİD-19 test yapılma oranları, COVİD-19'un ülkelere geliş zamanı gibi faktörler dikkate alınarak aşı yapılma oranları ile COVİD-19 prevelans ve ölüm oranlarının tekrar değerlendirilmesi ile BCG aşısının koruyuculuğunun saptanmadığı belirtilmiştir (39,40,42). Ayrıca BCG aşı kampanyası olan ülkelerde de ağır vakaların ve ölümlerin olması veya tam tersi aşı politikası olmayan ülkelerde de korunan insanların olmasının BCG'nin koruyuculuğu hipotezine ters düştüğü belirtilmiştir (23,41). Bunların dışında, öne sürülen BCG-KKK aşılarının eğitilmiş immünite ile COVİD-19'a karşı koruma sağladığı görüşüne karşıt olarak ta, eğitilmiş immünitenin 3ay veya 1 yıla kadar sürebildiği, sonrasında azalarak kaybolduğu belirtilerek, dolayısı ile adölosanlardaki hastalığın daha az ve daha iyi olmasının bunun ile açıklanamayacağı öne sürülmüştür (23). BCG yapılan ve yapılmayan bazı ülkeler arasında COVİD-19'a bağlı mortalitelerde çok küçük bir farklılık olsa da, bunun ulusal enfeksiyon kontrol politakaları, sosyal mesafe, insanların davranış değişiklikleri, önceki yerel enfeksiyonlar, ACEI2 genetik polimorfizmi gibi çeşitli faktörlerden etkilenmiş olabileceği belirtilerek bu konuda daha fazla çalışmaya ihtiyaç olduğu vurgulanmıştır (42). Ayrıca BCG'nin çeşitli faktörler tarafından maskelenmiş küçük bir koruyucu etkisinin olabileceği, fakat bunun netleştirilmeden gündemde tutulmasının BCG aşı politikası olan ülkeleri iyimserliğe iterek onlar için zararlı sonuçlara yol açabileceği konusunda da uyarıda bulunulmuştur (42).

II. Kızamık Kızamıkçık Kabakulak (KKK) Aşısı

KKK aşısı, tüm dünyada uzun yıllardır güvenilir bir aşı olarak uygulanmaktadır. Bazı yazarlar, bilinen bir aşı olması ve riskli bir aşı olmaması sebebi ile, COVİD-19 ve KKK aşısı arasındaki öne sürülen ilişkiyi göz önüne alarak, COVİD-19'un yol açtığı kötü

tablolar ve mortaliteye karşı geçici bir çözüm ve profilaksi olarak risk grubunun KKK ile aşılanmasını önermişlerdir (15,43,44).

Adam young ve ark. (14), SARS-CoV-2 ve kızamıkçık virüsünün Makro (ADP-riboz-1"- fosfataz) alanları arasında % 29'luk bir amino asit dizisi homolojisi olduğunu belirlemişlerdir. Bu homolog sekansların sağladığı aktivasyonun antikor seviyesini arttırarak hastalık yükünü azaltabileceğini bildirmişlerdir. Ve risk grubunun KKK aşısı ile aşılanmasının, COVİD-19'dan korumasa da, hastalığın kötü gidişini azaltabileceğini öne sürmüşlerdir (14). Benzer şekilde Sidiq ve ark. (45) SARS-COV2 virüs spike glikoproteini ile hem kızamık füzyon proteini hem de kızamıkçık glikoprotein zarfı arasındaki homoloji sayesinde, KKK aşısı ile oluşan humoral bağışıklığın COVİD-19'a karşı koruma sağlayabileceği görüşünde olduklarını ancak deneysel analiz yapılması gerektiğini belirtmişlerdir (45).

Gold JE ve ark. (46) ise kabakulak IgG titresi ile COVİD-19 şiddetinin ters orantılı olduğunu göstererek, KKK aşısı ile COVİD-19 şiddeti arasındaki teorik ilişkiyi desteklediklerini bildirmişlerdir.

Fidel ve ark. (15), yetişkinlerde KKK aşılamasının düşük riskli olduğunu ve eğitilmiş immün sistem hipotezi doğru çıkarsa; yetişkinlerde KKK (pekiştirici) aşılamasının, COVİD-19 pandemisinin kritik bir döneminde hayat kurtarmak için "düşük riskli yüksek ödüllü" bir önleyici tedbiri temsil edeceğini belirtmişlerdir. Aslında KKK aşısının, zaten yüksek riskli yetişkinlerde (yani sağlık çalışanları) ve 1957'den önce doğmuş ve aşıyı çocukken almamış kişilerde tavsiye edilmekte olduğunu belirtmişlerdir. KKK aşısını çocuklukta almış olan yetişkinlerin muhtemelen hala hedeflenen virüslere karşı antikor titrelerine sahip olabileceği, ancak daha kısa ömürlü eğitimli doğuştan gelen lökositlere sahip olmadıklarını vurgulamışlardır. Bu nedenle, KKK aşısı, yaşlı yetişkinler için en azından kızamık, kabakulak ve kızamıkçığa karşı ek koruma sağlayacakken; eğitimli doğuştan gelen hücrelerin eklenmesi ile COVID-19'un en kötü sekellerine karşı da koruma sağlayabileceğini vurgulamışlardır (15). Anbarassu A ve ark. (43), aşı suşları tarafından ortaya çıkarılan IFN'lerin, koruma sağlamada vahşi tip hastalık suşlarından daha verimli olduğunu ve yine aşıyla indüklenen NK hücrelerinin, antiviral aktivitelerinin de daha güçlü ve sağlam olduğunu vurgulayarak KKK aşısı ile indüklenen IFN'lerin, NK hücrelerinin ve çapraz koruyucu antikorların başarılı bir şekilde S-CoV2'yi önleyip, iyileştirebileceğini belirtmişlerdir. Ayrıca COVİD-19 a karşı bir immun-profilaksi için KKK aşısının yeniden tasarlanabileceğini önermişlerdir (43).

Nazrul İslam ve ark. (44) ise artan kızamık insidansı ve son baharda görülen influenza ataklarına dikkat çekerek, bu iki hastalığın yol açacağı alt solunum yolu enfeksiyonları ve hastane yatışlarının gerek hastaları gerekse risk altındaki bakıcı ve ebeveynlerini, hastaneden COVİD-19 bulaşı riski ile karşı karşıya getirebileceğini belirtmişlerdir. KKK aşısının kızamıktan, influenza aşısının ise influenzadan hastane yatışları azalttığı bilinmektedir, KKK ve influenza aşılarının bu yönü ile de COVİD-19 a karşı toplumsal bir koruyuculuk sağlayabileceği vurgulanmıştır (43). Ayrıca Kızamık hastalığının influenza gibi diğer hastalıkların gelişimini kolaylaştırdığını, bu yüzden COVİD-19'a da yatkınlığı arttırabileceği konusunda uyarıda bulunarak KKK aşısının bu yönüyle de korumaya katkı sağlayabileceğini belirtmişlerdir (44).

Larenas-Linnemann DE ve ark. (47) ise hipotezden öteye giderek COVİD-19 başlangıcında 255 kişiyi KKK aşısı ile aşılamışlardır. Bu gruptan 36 kişinin COVİD-19'a yakalandığını, hepsinin de hafif olarak geçirdiğini bildirmişlerdir (sadece 1 hastada 1 günlük oksijen ihtiyacı oldugunu onunda öncesinde astımının olduğunu belirtmişler). Benzer şekilde, USS Roosevelt'teki ABD donanmasındaki, 955 denizcide COVİD-19'un hafif şiddette görülmesinin (yalnızca bir hastaneye yatış) KKK aşılarının yapılmasının bir sonucu olabileceği öne sürülmüştür (48).

Bunların aksine, KKK aşısının COVİD-19 a karşı koruyuculuğuna eleştirel veya karşıt görüş sunan yazarlar da olmuştur (49-50). Desphande S ve Balaji S, Hindistanda Edmonston-Zagreb suşunu içeren KKK aşısının kullanıldığını ve bunun da seropozitifliğinin erişkin yaşlara kadar devam ettiğini, bu yüzden booster doz gerekmediğini belirtmişlerdir (49). Ayrıca, sekans homoloji benzerliği çalışmalarına atfen ise aynı homolojinin E.Coli ile veya diğer bir çok coronavirüs tipleri ile sağlanabileceği bunun COVİD-19'dan korumayacağı, ama enfeksiyonun kötü gidişatına faydalı olabileceğini ancak klinik çalışmalar olmadan her birinin birer spekülasyondan ibaret olduğunu vurgulamışlardır (49).

III. İnfluenza Aşısı (IA)

Dünya sağlık örgütü mevsimsel influenza aşısını hamileler, 65 yaş üstü olanlar, kronik hastalıkları olanlar ve sağlık çalışanları olmak üzere risk grubuna rutin olarak önermektedir (51). Bazı çalışmalarda %60'a kadar varan COVİD-19, influenza koenfeksiyonu bildirilmiştir (52).

İnfluenza aşısının influenzaya karşı koruyuculuğu ve hastane yatışlarını azalttığı bilinmektedir. COVİD-19 ile benzer sezona denk gelen ülkeler için influenza vakalarının azalması, COVİD-19 olmayan hastalara bakmak için gereken kaynakları ve iş gücünü azaltarak ülkelere ek fayda sağlayabileceği öne sürülmüştür (53).

Ayrıca COVİD-19 ve influenza, benzer semptomlar ile ortaya çıkabileceği için, influenza virüsünün azaltılmasının, COVİD-19'un özgüllüğünü de arttıracağı vurgulanmıştır (53).

Pietro Ragni ve ark. (54), İtalyanın Reggio Emilia eyaletinde17608 kişide influenza aşısının COVİD-19 tanısı ve gidişatına etkisini değerlendirdikleri çalışmalarında; influenza aşısının hastaneye yatış ve ölüm üzerinde etkisinin olmadığını ama özellikle >65 yaştaki kişilerde COVİD-19 pozitifliğini azalttığını bildirmişlerdir. Amato M ve ark. (55) ise çalışmalarında, 65 yaş ve üzerindekilerde influenza aşısının; COVİD-19 seroprevelansı ve hastane yatışı, yoğun bakım gereksinimi ve mortalitesi

üzerindeki etkilerini regresyon analizi ile değerlendirmişlerdir. 65 yaş ve üstünde aşılama kapsamında %1'lik artışın, İtalyan populasyonda seropozitiflikte 78560, hastaneye yatışta 2512, yoğun bakım ihtiyacında 353 ve mortalite de1989 kişi azaltabileceğini saptamışlardır. Bu bulgular sonucunda da, influenza aşısının COVİD-19'un yayılmasını ve şiddetli klinik bulgu vermesini azalttığını rapor etmişlerdir. Massoudi ve ark. (56) halk sağlığı çalışanları arasında COVİD-19 hastalığına yakalanan ve yakalanmayanları 2019-2020 sezonunda influenza aşısı yaptırma durumlarına göre değerlendirdikleri çalışmalarında, COVİD-19 pozitifliği olan 80 kişiden sadece 3'ünün influenza aşısı yaptırmış olduğunu ama COVİD-19 negatif olan 181 kişiden ise 87'sinin aşılı olduğunu gözlemlemişlerdir. Kontrollerle karşılandığında aşılanmanın COVİD-19'a yakalanmayı azalttığını (OR: 0.04 (95% CI: 0.01-0.14) vurgulayarak risk gruplarının aşılanmasını önermişlerdir (56).

Yazarlar aşı planlamalarının gözden geçirilmesini tavsiye etmişlerdir (53-56).

Iv. Hepatit A (Hav) Aşısı

Faik sarıalioğlu ve ark. (57), hepatit A duyarlılığı ile ülkeler arasındaki ölüm oranlarındaki farklılıkları analiz ettiklerinde; hepatit A duyarlılığı yüksek (bağışıklığı düşük) ülkelerde COVİD-19 ilişkili ölüm riskinin 27.8 kat yüksek olduğunu tespit etmişlerdir. Bağışıklık yanıtı bozulduğu için diyaliz hastaları ağır hepatit A enfeksiyonu için risk grubundadır bu yüzden HAV aşısı ile aşılanmaktadırlar (58). Faik sarialioğlu ve ark. (57) 2420 diyaliz hastalarından sadece 30 kişinin (yaklaşık 1/1000) COVİD-19 hastalığına yakalandığını, ve bu gruptan randomize seçilen 227 hastada bakılan HAV antikorlarının %94.7'sinde pozitif olduğunu görmüşlerdir. Bu çalışmaları hala devam ediyor olsa da HAV antikorlarının COVİD-19'a karşı koruyucu olabileceğini belirtmişlerdir. Ayrıca aynı ekip yazılarında 'Princess Diamond' seyehat gemisinde bulunan 3711 mürettebat ve yolcudan 712'sinin hastalandığını ve 60 yaş üstü hastalardan %57'sinin asemptomatik geçirdiğini dünya geneline göre yüksek olan bu oranın gemiye binmeden önce yapılan Hepatit –A aşısı ile ilişkili olabileceğini belirtmişlerdir. HAV aşısının neden olduğu immün yanıtın, adaptif bir çapraz reaksiyon ile COVİD-19 enfeksiyonuna karşı koruyucu olabileceğini belirtmişlerdir (57). Fakat bu çalışmalar henüz HAV aşısının COVİD-19'a karşılığı koruyuculuğunu göstermek için yeterli düzeyde olmayıp yeni klinik ve moleküler düzeyde çalışmalara ihtiyaç duyulmaktadır.

V. Pertusis (Boğmaca) Aşısı

Ismail ve ark. (23), tüm dünyada çocukların COVİD-19'dan daha az etkilenmesini sağlayabilecek bir aşının, tüm dünyada yaygın yapılan ve çocukluk döneminde koruma sağlarken, erişkin dönemde hatırlatıcı doza gereksinimin olduğu bir aşı olması gerektiği görüşünü ortaya koymuşlardır. Bu kriterlere pertusis aşısının uyabileceğini belirtmişlerdir. Pertusis ve COVİD-19 arasındaki olası sekans benzerliği ve çapraz reaktif antikorların ve T hücrelerinin, koruyucu olabileceğini belirtmişlerdir (23). Fakat bu çalışma hipotez üzerine yapılabilecek çalışmaları belirtmektedir. Bu konuda yapılmış klinik çalışma şuanda İngilizce literatürde bulunamamıştır.

SONUÇ

Çeşitli çalışmalarda, çocukluk çağı rutin aşılarının, COVİD-19'a ve diğer olası yeni pandemik enfeksiyonlara karşı spesifik tedavi ve aşılar geliştirilene kadar geçici koruma sağlayabileceği belirtilmektedir. Fakat çalışmalar genellikle hipotez şeklinde olduğu için koruyucu olup olmadığı konusunda kesin bir kanıya varabilmek için klinik ve moleküler düzeyde çalışmalar gerekmektedir. Fakat konunun ehemmiyeti göz önüne alınarak, ulusal aşı programlarına önem verilerek, bu konuda yeni stratejiler geliştirilebilir. Aşıların rapel dozlarının yapılması, sağlık çalışanları gibi risk gruplarının aşılanması denenebilir.

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