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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.

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 imzalanmış bültenler eklenmelidir.

Tüm başvurular intihal araştırması 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 kriterle dayanmasını önerir:

1. Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması
2. Dergiye gönderilecek kopyanın hazırlanması veya bu kopyanın 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 şartlarını 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. Gerekliğinde, dergi içinde çözümlenemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararları ilgili nihai otoritedir.

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.

Yazıların sonuçlarının rapor edilmesi 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 belirtilen 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 (Aralık 2019'da güncellenmiştir - <http://www.icmje.org/icmje-recommendations>). Bu liste aşağıda görülebilir.

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

Yazarlar 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 tarafından önerilen Potansiyel Çıkar Çatışması Bildirim Formu ilk başvuru sırasında (katkıda bulunan tüm yazarlar tarafından doldurulmalıdır) sisteme yüklenmelidir. Bu formları www.dergipark.org.tr/tr/pub/tchd adresinden indirebilirsiniz.

Kapak Sayfasının Hazırlanması:

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 isim soy isim, e-posta adresi, telefon ve faks numaraları dahili iletişim bilgileri verilmelidir. Ayrıca yazı ile ilgili olarak 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 indeksledikleri için özetle önemli bulgular sunulmalıdır.

Makalenin diğer bölümleri Giriş, Gereç ve Yöntemler, Sonuçlar, Tartışma, Teşekkür (gerekirse) ve Kaynaklar’da 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 sınırı 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, araştırma ihtiyacı olan alanları içeren yazılardır. 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 gönderilmiş 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 yerleştirilmemelidir. 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 yerleştirilmemelidir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturacak şekilde birleştirilmemelidir, her alt birim, başvuru sistemi aracılığıyla ayrı ayrı yüklenmelidir. Resimlerin üzerine etiketleme (örneğin a,d,c,d gibi) yapılmamalıdır. Şekil alt yazılarını 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 kısıtlıtlıkları tartışma bölümü içinde sonuç paragrafından önce belirtilmelidir.

KAYNAKLAR

Yayınlar atfı yapılırken, en son ve en güncel yayınlar tercih edilmelidir. Yazarlar on yıldan eski referansları kullanmaktan kaçınmalıdır. Yazılarda 10 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 listendiği 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 pollen-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. Kaçınıcı 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. Kaçınıcı 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. Accessed 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."

Düzeltilme istenmesi aşaması:

Bir makalenin hakemler tarafından istenen değişiklikler yapılmış kopyası gönderilirken yazar, hakemler tarafından istenen her açıklama/düzeltilmeye cevap vermekle yükümlüdür. Yazarlar hakemlerin düzeltme/açıklama isteklerini her isteğin ardından olacak şekilde madde madde açıklamalı, 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 kopyası istenilen sürede gönderilmezse yazı sistemden otomatik 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" yüklenmelidir. 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 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 pediatric surgery, dentistry, public health, genetics, psychiatrics 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.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with the COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship should be based on the following 4 criteria:

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.

The Turkish Journal of Pediatric Disease requires and encourages the authors and the individuals who involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to the potential bias or a conflict of interest. Any financial grants or other supports received for the submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all of the contributing authors. Cases of the potential conflict of interest of the editors, authors, or reviewers are being resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

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.

Statements or opinions expressed in the manuscripts published in the Turkish Journal of Pediatric Disease reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

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 December 2019 - <http://www.icmje.org/icmje-recommendations>).

CONSORT	Randomised controlled trials
STROBE	Observational epidemiological research
STARD	Diagnostic accuracy
PRISMA	Systematic reviews and meta-analysis
ARRIVE	Experimental animal studies
TREND	Non-randomized public behavior

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at

www.dergipark.org.tr/en/journal/2846/submission/step/manuscript/new. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will go firstly through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions not conforming to the journal's guidelines will be returned to the submitting author with the technical correction requests.

Authors are required to submit the following:

Copyright Transfer and Acknowledgement of Authorship Form and ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all of the contributing authors) during the initial submission. These forms are available for downloading at www.dergipark.org.tr/en/pub/tchd

Preparation of the Manuscript Title page:

Title page should be submitted for all of the submissions and this page should include:

Title page of the manuscript should include the English title of the article. The title page should include the authors' names, degrees, ORCID number and the institutional/professional affiliations, a short title (max 50 character), abbreviations, financial disclosure statement, and the conflict of interest statement. For manuscripts sent by the authors in Turkey, a title in Turkish is also required. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to this/her institution, which is listed separately. Please provide a contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

Important Notice: The title page should be submitted separately.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (<https://www.nlm.nih.gov/mesh/MBrowser.html>). For manuscripts sent by the authors in Turkey, key words in Turkish are also required.

MANUSCRIPT TYPES

Original Articles:

Word count: up to 3,500 (Introduction, Methods, Results, Discussion)

Title: maximum of 20 words

Structured abstract: up to 250 (Objective, Materials and Methods, Results and Conclusion)

Keywords: 3-6 word, listed in alphabetical order.

Figures and tables: are not limited, but must be justified thoroughly

References: up to 40

Original articles should include; English title, English structured abstract (structured as, English key words. If the article is in Turkish, Turkish title and English title, Turkish structured summary and English summary

(structured as Purpose, Material and Method, Conclusion and Discussion), Turkish and English keywords are required.

for most readers, reading the abstract first, is critically important. Moreover, various electronic databases integrate only abstracts into their index, so important findings should be presented in the abstract.

The other sections of the manuscript should include Introduction, Materials and Methods, Results, Discussion, Acknowledgement (if required) and References. All sections of the manuscripts should start on a new page.

Review Articles:

Word count: up to 5000

Abstract: up to 500 (Objective, Materials and Methods, Results and Conclusion)

Keywords: 3-6 word, listed in alphabetical order.

Figures and tables: are not limited, but must be justified thoroughly

References: up to 80

Review articles are comprehensive analyses of the specific topics in medicine, which are written upon the invitation due to extensive experience and publications of authors on the review subjects. All invited review articles will also undergo peer review prior to the acceptance.

Review articles should include; English title, English abstract and English key words. For manuscripts sent by authors in Turkey, a Turkish title, Turkish abstract and Turkish key words are also required.

Case Reports:

Word count: up to 2000

Abstract: up to 200

Keywords: 3-6 word, listed in alphabetical order.

Figures and tables: total 5

References: up to 15

There is a limited space for the case reports in the journal and reports on rare cases or conditions that constitute challenges in the diagnosis and the treatment, those offering new therapies or revealing knowledge that are not included in the literature, and interesting and educative case reports are being/ will be accepted for publication. The text should include Introduction, Case Presentation and Discussion.

Case reports should include; English title, English abstract and English key words. For manuscripts sent by authors in Turkey, a Turkish title, Turkish abstract and Turkish key words are also required.

Letters to the Editor:

Word count: up to 1500

Figures and tables: total 3

References: up to 15

This type of manuscript discusses about the important parts, overlooked aspects, or lacking parts of the previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a Letter to the Editor. Readers can also present their comments on published manuscripts in the form of a Letter to the Editor. An abstract and Keywords should not be included. Tables, Figures, Images, and other media can be included. The text should not include subheadings. The manuscript that is being commented on, must be properly cited in this manuscript.

Letters to the Editor should include; English title. For the letter to the editor sent by authors in Turkey, a Turkish title also required.

Study Protocols:

The Turkish Journal of Pediatric Disease welcomes study protocols to improve the transparency of research and inform the scholarly community about the trials that are being underway. Publication decision of study protocols will be by editorial decision. Study protocols for the pilot or feasibility studies are not generally taken into consideration.

Study protocol articles should follow the SPIRIT guidelines that provides a detailed account of the hypothesis, rationale, and methodology of the study. All study protocols must provide an Ethics Committee Approval. All protocols for the clinical trials require a trial registration number and the date of registration.

Tables

Tables should be included in the main document, presenting after the reference list, and they should be numbered consecutively in the order they are referred in the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by the footnotes (even if they were defined within the main text). Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text. The following symbols should be used for abbreviations in sequence: *, †, ‡, §, ||, ¶, **, ††, ‡‡.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or in the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures should also be blind. Any information within the images that may indicate an individual or an institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses as in the following format: The skin prick tests were performed using a multi-prick test device (Quantitest, Panatrex Inc, Placentia, California, USA).

All references, tables, and figures should be referred in the main text, and they should be numbered consecutively in the order that they are referred in the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

REFERENCES

While citing publications, the preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 20% in the journal. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of the references. Reference numbers should be indicated at the end of the sentences in the text as superscripts and references should be numbered consecutively

in the order that they are mentioned in the text. Journal names should be abbreviated as listed in "Index Medicus" or in "ULAKBİM/Turkish Medical Index". References should be typed in consistence with the following examples. Native references should be used as much as possible.

If the reference is a journal;

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of an article is more than 6 followed by "ve ark." in Turkish references and "et al." in international references). Title of the article, title of the manuscript abbreviated according to Index Medicus (<http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog>). Year; Volume: First and last page number.

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

If the reference is a journal supplement;

Author(s)' surname and initial(s) of the first name. Title of the article. Title of the manuscript abbreviated according to Index Medicus (<http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog>). Year; Volume (Suppl. Supplement number): First and last page number.

Example: Queen F. Risk assessment of nickel carcinogenicity and occupational lung cancer. *Environ Health Perspect* 1994;102 (Suppl. 1):S2755-S2782.

If the reference is a book;

Author(s)' surname and initial(s) of the first name. Title of the book. Edition number. City of publication; Publisher, Year of Publication.

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

If the reference is a book chapter;

Surname and initial(s) of the first name of the author(s) of the chapter. Title of the chapter. In: Surname and initial(s) of the first name(s) of the editor(s) (ed) or (eds). Title of the book. Edition number. City of publication: Publisher, Year of publication: First and last page numbers of the chapter.

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

If the reference is a conference paper presented in a meeting;

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of a conference paper is more than 6 followed by "et al." in Turkish references and "et al." in international references). Title of the conference paper, If applicable In: Surname and initial(s) of the first name(s) of the editor(s) (ed) or (eds). Title of the abstract book. Title of the meeting; Date; City of the meeting; Country. Publisher; Year: Page numbers.

Example: 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: 1561-5.

If the reference is an online journal;

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of an article is more than 6 followed by "ve ark." in Turkish references and "et al." in international references). Title of the article, title of the manuscript abbreviated according to Index Medicus Year; Volume (Number). Available from: URL address. Accessed date: day.month.year.

Example: 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. Accessed 20 January 2008.

If the reference is a website:

Name of the web site. Access date. Available from: address of the web site.

Example: Centers for Disease Control and Prevention (CDC). Access date: 12 March 2013. Available from: <http://www.cdc.gov/>

If the reference is a thesis:

Author's surname and initial of the first name. Title of the thesis (thesis). City; Name of the university (if it is a university); Year.

Example: Özdemir O. Fibrillin-1 gene polymorphism and risk of mitral valve disorders. (Thesis). Ankara: Gazi University, 2006.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue were raised by the reviewers, and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for the grammar, the punctuation, and the format. Once the publication process of a manuscript is completed, it will be published online on the journal's webpage as an ahead-of-print publication before being included in its scheduled issue. A PDF proof of the accepted manuscript will be sent to the corresponding author and their publication approval will be requested within 2 days of their receipt of the proof.

CHANGE OF AUTHORSHIP AND WITHDRAWAL REQUEST

Change of Authorship

Any request to change the author list after submission, such as a change in the order of the authors or the deletion or the addition of author names, is subject to the Editorial Board's approval. To obtain this approval, please find and complete the change of authorship form on the Journal's website and send it to the Journal's office. This form should include the following information: The reason for the change of authorship signatures of all authors (including the new and/or removed author)

Please note, if you are adding or removing author/authors, a new copyright transfer form signed by all authors should also be sent to the editorial office after the Editorial Board approves the change of the authorship.

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Demographics, Clinical and Treatment Characteristics of Children and Adolescents with Essential Tremor: A Retrospective Cross-Sectional Analysis

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ÖZ

Amaç: Çocukluk çağında gözlenen tremorların büyük kısmını esansiyel tremor (ET) oluşturmaktadır. Bu çalışmada bir eğitim araştırma hastanesinin çocuk nöroloji polikliniğinde esansiyel tremor tanısı konulan olguların demografik özellikler açısından geriye dönük bilgileri analiz edildi.

Gereç ve Yöntemler: Haziran 2016-Haziran 2019 yılları arasındaki 3 yıllık süre içinde çocuk nöroloji polikliniğine titreme şikâyeti ile başvuran olgulardan esansiyel tremor tanısı Hareket Bozuklukları Derneği (1998) tanı ölçütleri esas alınarak konulan olgular incelendi. SPSS 17.0 programı analizde kullanıldı. $p < .05$ anlamlılık düzeyi olarak kabul edildi.

Bulgular: Belirtilen süre içinde esansiyel tremor tanılı olguların toplam 93 olduğu, yaş ortanca değerinin 16 yıl (6-18 yaş) olduğu, % 54.8'inin ($n = 51$) kız ve % 45.2'sinin ($n = 42$) erkek olduğu saptandı. Olguların % 7.5'i ($n = 7$) çocuk yaş grubunda (6-11 yaş) iken % 92.5'i ($n = 86$) ergen yaş grubunda (12-18 yaş)'di. Olguların %17.2'sinde ($n=16$) esansiyel tremora sekonder gelişen psikiyatrik semptomlar nedeniyle çocuk-ergen psikiyatrisine danışıldığı saptandı. Olguların %11.8'ine ($n = 11$) dideral tedavisi önerildiği gözlemlendi. Çocuk yaş grubuna dideral tedavisi önerilmediği, çocuk ve ergen yaş gruplarının benzer oranlarda çocuk psikiyatrisi bölümüne yönlendirildiği saptandı ($p > .05$).

Sonuç: Esansiyel tremor benzer oranlarda kız ve erkek cinsiyetini etkilemekte ve dideral özellikle ergen grubunda tedavi seçeneği olarak gözlenmektedir. Kesitimizde hem kız-erkek cinsiyetlerinde, hem de çocuk-ergen yaş gruplarında benzer oranlarda psikiyatrik etkilenim olduğu gözlenmiştir. Bulgular literatür ile uyumludur.

Anahtar Sözcükler: Çocuk, Ergen, Esansiyel tremor, Propanolol

ABSTRACT

Objective: Most of the tremors observed in childhood constitute essential tremor (ET). In this study, retrospective information of the patients who were diagnosed with essential tremor by the pediatric neurology out patient clinic of an education and research hospital were analyzed.

Material and Methods: Patients who were admitted to the pediatric neurology out patient clinic with a complaint of tremor in the 3-year period between June 2016 and June 2019 were diagnosed based on the criteria of Movement Disorders Society (1998). SPSS 17.0 program was used in the analysis and $p < .05$ was accepted as the level of significance.

Results: It was determined that the cases diagnosed with essential tremor were 93 in total, the median age was 16 years (6-18 years), 54.8% ($n = 51$) were girls and 45.2% ($n = 42$) were boys. While 7.5% ($n = 7$) of the cases were in the child age group (6-11 years), 92.5% ($n = 86$) were in the adolescent age group (12-18 years). It was found that



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child-adolescent psychiatry was consulted due to psychiatric symptoms developing secondary to essential tremor in 17.2% (n = 16) of the cases. It was observed that 11.8% (n = 11) of the cases were prescribed dideral treatment. It was found that dideral treatment was not recommended for the childage group, and the child and adolescent age groups were directed to the child psychiatry department at similar rates (p> .05).

Conclusion: Essential tremor affects the gender of girls and boys in similar proportions and dideral is observed as a treatment option especially in adolescent group. In our cross-section, it was observed that there was a similar rate of psychiatric influences in both male and females exes and child-adolescent age groups. The findings are consistent with the literature.

Key Words: Child, Adolescent, Essential tremor, Propranolol

GİRİŞ

Tremor vücut bölümlerindeki antagonist kasların istemsiz ve ritmik bir şekilde kasılması sonucu gelişen bir hareket bozukluğudur. Çocukluk çağında tremor gözlenme sıklığı %5-20 oranlarına varan bir aralıkta bildirilmiş olup tek başına bir semptom olarak ortaya çıkabileceği gibi diğer nörolojik veya sistemik bozuklukların bir semptomu olarak da gözlenebilir (1, 2).

Esansiyel tremor (ET), tremor türleri içindeki en sık görülen hareket bozukluğudur. Patofizyolojisi tam olarak bilinmeyen bozukluk baskın ve poligenik nitelikte bir kalıtsal özellik göstermektedir (3). Etkilenen bireylerin %50-70'inde aile öyküsü vardır. Görülme sıklığı yaşla birlikte artan bozukluk, her iki cinsiyeti de eşit derecede etkilemektedir. Yaşın artmasıyla birlikte ET insidans ve prevalansının arttığını gösterilmiştir (4, 5).

ET'nin karakteristik bulgusu altta yatan başka bir nörolojik bulgu ya da bozukluk olmaksızın özellikle ellerde görülen postural ve/veya kinetik nitelikteki titremelerdir. Hareket Bozukluğu Derneği'nin Tremor Araştırma Grubu (The Movement Disorder Society's Tremor Investigation Group), esansiyel tremoru el titreme için başka bir açıklamanın olmadığı, başlıca ellerde ve kollarda iki taraflı, büyük ölçüde simetrik postural ya da kinetik titreme olarak tanımlamaktadır (6). Artmış katekolamin düzeyleri, stres, yorgunluk, santral sinir sistemini uyaran ilaçlar ve istemli hareketler titremelerin şiddetini artırırken, istirahat, β -blokerler, primidon ve alkolün tremorun şiddetini azalttığı gösterilmiştir (7).

ET'de tremor dışındaki nörolojik muayene bulguları normaldir. Hastalığın tanısı bazen tesadüfen ya da etkilenen kişinin işlevselliğinin olumsuz etkilenmesi nedeniyle başvurusu üzerine konur. Ellerin motor kontrolünün etkilenmesi nedeniyle birey yeme, içme, yazma gibi günlük aktivitelerinde ciddi sıkıntı yaşayabilir. Yaklaşık her üç ET'li olgudan ikisinin günlük yaşam aktivitelerinde önemli bozulmaların olduğu gösterilmiştir (8).

Tanısı öykü ve fizik muayene ile konulan ET'nin, tanıyı destekleyen özgül laboratuvar testi veya görüntüleme bulgusu yoktur. Yorgunluk, santral sinir sistemini uyaran ilaçlar, istemli hareketler ve stres esansiyel tremorun amplitüdünü artırırken, istirahat, β -blokerler, primidon ve alkol azaltmaktadır (1, 8).

ET'de motor belirtilere ek olarak bireyde bilişsel (kognitif) değişikliklerin ve psikiyatrik semptomların gözlenebilmektedir (9,10). Günlük yaşam aktivitelerini engelleyecek şiddette titremesi olan hastaların tedavi edilmesi önerilmektedir. Kesin

bir tedavisi olmayan ET'de ağır bileklik ve su içerken ağır bardak kullanma gibi yöntemler tremorun azaltılmasına katkı sunabilir. İlaç tedavisi hastaların %50'sinde tremorda kısmen bir azalma sağlar ve maalesef %30-50 hastada etkisizdir. İlk tercih edilen ilaç beta-adrenerjik blokerler (en sık propranolol)'dir (7).

Bu çalışmada çocuk nörolojisi polikliniğine başvuran ve esansiyel tremor tanısı konuşma olguların demografik, klinik ve tedavi özellikleri geriye dönük analiz edildi.

GEREÇ ve YÖNTEMLER

Çocuk nörolojisi bölümüne Haziran 2016 – Haziran 2019 yılları arasındaki toplam üç yıllık süre içinde başlıca ellerde titreme yakınması ile başvuran olgulardan esansiyel tremor tanısı konulmuş olanların dosyaları geriye dönük analiz edildi. Olguların EEG, Kranial MR, Kranial Diffüzyon MRI sonuçları ve rutin biyokimyasal parametreleri incelendi.

Çalışmaya kabul edilme ölçütleri: iki taraflı el ve önkolların bilateral titremesi ve diğer nörolojik bulguların olmaması iken, **Çalışmadan dışlama ölçütleri:** Titreme dışında anormal nörolojik muayene varlığı, ailede veya kişide tiroid disfonksiyonu varlığı, psikomotor veya motor gelişimsel gecikmenin varlığı, titremeye neden olabilecek ilaçlar almak, ağır metaller, bizmut, civa, metilbromid tarafından zehirlenme, titremenin şiddetli görünümü, psikojenik kökenli titreme, ailesel tremor varlığı, anormal MRI bulgusu varlığı olarak belirlendi.

İstatistiksel Analizler: Analizlerde SPSS 17.0 (Chicago Inc., 2008) programı kullanıldı. Kategorik değişkenler sıklık (n) ve yüzde (%) cinsinden ifade edildi. Sürekli değişken olan yaş (yıl) ortanca, minimum ve maksimum değerler cinsinden ifade edildi. Kategorik değişkenler için Pearson- χ^2 ve Fisher's exact testleri kullanıldı. p<.05 anlamlılık düzeyi olarak kabul edildi.

Çalışma için Ankara Eğitim ve Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu'ndan 21.04.2020-245 karar numarası ile onay alınmıştır.

BULGULAR

İki yıllık süre içinde esansiyel tremor tanılı olguların toplam 93 olduğu, yaş ortanca değerinin 16 yıl (6-18 yaş) olduğu, % 54.8'inin (n = 51) kız ve %4 5.2'sinin (n = 42) erkek olduğu saptandı.

Tablo I: Esansiyel tremorlu 93 olgunun demografik özellikleri.

	n (%)
Yaş (yıl) ^a	16 (6-18)
Yaş grup [†]	
Çocuk (6-11 yaş)	7 (7.5)
Ergen (12-18 yaş)	86 (92.5)
Cinsiyet [†]	
Kız	51 (54.8)
Erkek	42 (45.2)

a: Medyan (minimum-maksimum), †: n(%)

Tablo II: Esansiyel tremorlu olguların cinsiyet açısından tedavi ve psikiyatriye yönlendirilme dağılımları.

	Toplam n = 93	Kız n = 51	Erkek n = 42	χ ²	p
Dideral, [†]				.390*	.749
Yok	82 (88.2)	44 (86.3)	38 (90.5)		
Var	11 (11.8)	7 (13.7)	4 (9.5)		
Psikiyatri kons, [†]				.183	.669
Yok	77 (82.8)	43 (84.3)	34 (81.0)		
Var	16 (17.2)	8 (15.7)	8 (19.0)		

*: Fisher's exact test, †: n(%)

Tablo III: Esansiyel tremorlu olguların cinsiyet açısından tedavi ve psikiyatriye yönlendirilme dağılımları.

	Toplam n = 93	Çocuk n = 7	Ergen n = 86	χ ²	p
Dideral [†]				1.015*	.593
Yok	82 (88.2)	7 (100.0)	0		
Var	11 (11.8)	0	11 (12.8)		
Psikiyatri kons [†]				.687*	.346
Yok	77 (82.8)	5 (71.4)	72 (83.7)		
Var	16 (17.2)	2 (28.6)	14 (16.3)		

*: Fisher's exact test, †: n(%)

Olguların %7.5'i (n = 7) çocuk yaş grubunda (6-11 yaş) iken %92.5'i (n =86) ergen yaş grubunda (12-18 yaş)'tı. Çocuk/ Ergen oranı: 1/12.1 bulundu.

Olguların %17.2'sinde (n=16) esansiyel tremora sekonder gelişen psikiyatrik semptomlar nedeniyle çocuk-ergen psikiyatrisine danışıldığı saptandı. Olguların %11.8'ine (n = 11) dideral tedavisi önerildiği gözlemlendi (Tablo I).

Esansiyel tremor olgularının cinsiyet açısından ilaç kullanımı ve psikiyatri bölümüne yönlendirilmesi değişkenleri ile arasındaki ilişki analiz edildiğinde, kız olguların %11.8'ine (n = 11) ve erkek olguların %9.5'ine (n = 4) propranolol ilacı önerildiği saptandı (p>.05) (Tablo II).

Esansiyel tremor olgularının yaş grupları açısından ilaç kullanımı ve psikiyatri bölümüne yönlendirilmesi değişkenleri ile arasındaki ilişki analiz edildiğinde, çocuk olguların %15.7'sinden (n = 8) ve erkek olguların %9.5'ine (n = 4) propranolol ilacı önerildiği saptandı (p>.05) (Tablo III).

TARTIŞMA

Esansiyel tremor (ET), tremorun en yaygın şeklidir ve muhtemelen tek bir hastalık varlığı yerine klinik bir sendromla karakterize edilen en yaygın hareket bozukluğudur.

Çalışmamıza ait kesitteki ET varlığı kız ve erkek cinsiyetinde birbirine benzer oranlarda bulundu. Literatürde cinsiyetin benzer oranda etkilendiğini söyleyen çalışmalar (3,11) daha ağır basmakla birlikte, çalışmaların yaklaşık üçte birinde ET'nin erkek cinsiyetinde daha sık görülme eğiliminde olduğu bildirilmektedir (12,13). Uzunlamasına çalışmalarda ET'li kadın cinsiyetinde kafa tremorunun daha sık olduğu da bildirilmiş ve bu durumun açıklanması için ileri çalışmalara gereksinime işaret edilmiştir (13). Bizim geriye dönük kesitimizde böyle bir ayırım saptanmamıştır.

Çalışmamızda ergen yaş grubunda ET varlığının 12 kat daha fazla olduğu gözlemlendi. Esansiyel tremorun yaşı artmasıyla birlikte arttığı literatürde çok çalışmada tutarlı bir şekilde vurgulanmıştır (3,14,15). Yaşın ilerlemesi ile birlikte ET'nin şiddetinde artış ve başın tremoru gibi bulguların eklendiğini bildiren epidemiyolojik çalışmalar mevcuttur (15).

Esansiyel tremor olgularında sadece hareket bozukluğuna ilişkin semptomlar değil aynı zamanda bilişsel değişiklikler ve psikiyatrik semptom ve bulguların eklenebildiği, anksiyete ve depresyon semptomlarının kliniğe en sık eşlik eden psikiyatrik durumlar olduğu gösterilmiştir (9, 16). Sengul ve ark. (17) ET'li gençlerde bilişsel işlevlerde bozulmanın olduğunu, depresyon, anksiyete semptomlarında artış bulunduğunu, uyku kalitesinin düştüğünü göstermişlerdir. Psikiyatrik değerlendirme açısından kesitimize bakıldığında, hem kız-erkek cinsiyetlerinde, hem de çocuk-ergen yaş gruplarında benzer oranlarda psikiyatrik konsültasyon gereksinimi olduğu gözlemlenmiştir.

Hastanın, hastanın yaşamında neden olduğu bozulmaya ve bozulmaya ilişkin öznel deneyimi, hastanın klinik ziyareti sırasında objektif değerlendirmeden daha önemlidir. Bu tür bir değerlendirme zor olabilir. Çalışmalar, temel tremor hastalarında fiziksel insanın zihinsel yaşam kalitesi ölçümlerinin ortalama olarak sağlıklı bireylere göre daha düşük olduğunu göstermiştir (17).

Bireyin günlük işlevselliğini olumsuz etkilediği durumlarda ET'ye yönelik tedavi seçenekleri düşünülebilir. Uygulanan tedaviler semptomatik düzeyde etkili olup küratif nitelikte değildir. ET'li olguların yaklaşık %50'sinde tremorda kısmen bir azalma sağlayan bu ilaçların, maalesef olguların %30 ila 50'sinde etkisiz olduğu konusunda olgular iyice bilgilendirilmelidir (18).

Bugüne kadar ET tedavisinde kullanılan ilaçlar örneğin hipertansiyon gibi başka bir hastalığın tedavisi için uygulanırken ET'de de etkili olduğu şans eseri fark edilen ilaçlardır. β-blokerler ilk seçenek olup en sık kullanılanı propranololdür. Dirençli tremorlu olgularda cerrahi tedavi bir seçenek olup bu amaçla talamotomi

veya talamusun derin beyin stimulasyonu ile uyarılması teknikleri uygulanmaktadır (18).

Propranolol, bir non-selektif beta adrenerjik reseptör antagonisti olup Amerikan Yemek ve İlaç Birliği (FDA) tarafından ET tedavisi için onaylanan tek ilaçtır. Oral yolla, günde 2 kez 40 mg'a kadar uygulanabilmektedir. Kabaca her üç ET'li olgunun biri propranolol tedavisine cevapsızdır (4). Bizim kesitimizde ilaç başlama oranı %11.8 olup tümüne propranolol uygulanmıştır.

Atenolol, metoprolol, verapamil ve klonidin gibi diğer antihipertansif tedavi seçeneklerinin plaseboya göre ET belirtilerinde azalmaya neden olduğu ortaya konulmuş olsa da bu konuyla ilgili çalışmalar sınırlı sayıdadır ve daha geniş sayılı ve kontrollü çalışmalara ihtiyaç vardır (18). Bizim kesitimizde propranolol dışında uygulanan başka bir ilaç seçeneği olmamıştır.

Çalışmamızın kısıtlılıkları: Geriye dönük bir analizdir. Tremorun şiddeti değerlendirilememiştir. Kesitsel nitelikte olduğu için sonuçlar genellenemez. Bununla birlikte yaşla arttığı, kız-erkek cinsiyetin benzer oranda ET sergilediği ve benzer oranda psikiyatri desteğine gereksinim duyduğu bulgularımız, literatür ile uyumludur.

Sonuç olarak, Esansiyel tremorlu olguların yaş ve cinsiyetten bağımsız psikiyatrik semptomlar göstermesi, böylesi olguların psikiyatri bölümüne danışılmasının gerekliliğine işaret edebilir.

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Evaluation of Children with Cystine Stones: A single-Center Experience

Sistin Taşı Olan Çocuk Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Cystinuria is a rare genetic disorder. Many patients suffer from significant recurrent urolithiasis, repeated surgical interventions, and the risk of progressive renal impairment. In the current study, the outcomes of patients with cystine stones were investigated.

Material and Methods: A total of Twenty-six cystinuria patients with cystine stones, aged between 3 months and 18 years, in our Pediatric Nephrology Department, were retrospectively analyzed.

Results: The mean age of patients at diagnosis was 45.2±45.5 months and 88,5% were male. Sixteen (62%) children had recurrent urinary tract infections. Only 10 (38%) patients showed additional metabolic abnormalities. The urinary pH had significantly increased with treatment and the number of stone recurrence was lower in the patients with urinary pHs ≥ 6.5. There was a significant positive correlation between the last-visit serum creatinine level and the number of surgical interventions. There was no significant correlation between the last-visit eGFR and the number of surgical interventions. On the other hand, eGFR values decreases as the total number of surgical interventions increases. No stone events were observed at the end of the follow-up period in 10 patients (38%) and the stone events per patient-year were 0.36 for all patients. Four patients with low eGFRs at the beginning of the study get normal with treatment after the follow-up period.

Conclusion: Cystinuria has significant morbidity if not controlled properly. Despite all treatments, it should be kept in mind that renal impairment may develop in cystine stones with cystinuria and surgical treatment should be planned by considering minimally invasive options.

Key Words: Child, Cystinuria, Urolithiasis, Kidney stones

ÖZ

Amaç: Sistinüri nadir görülen bir genetik hastalıktır. Birçok hasta, önemli ölçüde tekrarlayan ürolitiazis, tekrarlayan cerrahi müdahaleler ve ilerleyici böbrek yetmezliği ile karşı karşıya kalmaktadır. Bu çalışmada sistin taşı olan hastaların sonuçları değerlendirildi.



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Contribution of the Authors / Yazarların katkısı: **CAYCI FS:** 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. **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, 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. **TIRYAKI HT:** 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 necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **BAYRAKCI US:** 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.

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Gereç ve Yöntemler: Çocuk Nefroloji Bölümümüzde, yaşları 3 ay ile 18 arasında değişen, sistin taşı olan toplam 26 sistinürlü hasta retrospektif olarak incelendi.

Bulgular: Hastaların, tanı anındaki ortalama yaşı 45.2 ± 45.5 aydı ve % 88.5'i erkekti. On altı (% 62) çocukta tekrarlayan idrar yolu enfeksiyonu vardı. Sadece 10 (% 38) hastada ek olarak diğer metabolik anormallikler mevcuttu. Tedavi ile idrar pH'sının anlamlı olarak arttığı saptandı ve idrar pH ≥ 6.5 olan hastalarda taş tekrarlama sayısı daha düşük bulundu. Son-geliş serum kreatinin düzeyi ile cerrahi müdahale sayısı arasında anlamlı bir pozitif korelasyon mevcuttu. Son-vizit eGFR ile cerrahi girişim sayısı arasında anlamlı bir ilişki bulunmazken, toplam cerrahi girişim sayısı arttıkça eGFR değerleri azalmaktaydı. Takip süresi sonunda 10 hastada (% 38) taş olayı görülmedi ve tüm hastalarda hasta-yılı başına taş olayı 0.36'dı. Çalışmanın başlangıcında düşük eGFR'li dört hastanın eGFR'sinin takipte tedavi ile normale geldiği görüldü.

Sonuç: Sistinüri, düzgün kontrol altına alınmazsa önemli morbiditeye sahiptir. Tüm tedavilere rağmen sistinürde böbrek yetmezliği gelişebileceği akıld tutulmalı ve minimal invaziv seçenekler düşünülerek cerrahi tedavi planlanmalıdır.

Anahtar Sözcükler: Çocuk, Sistinüri, Ürolitiazis, Böbrek Taşı

INTRODUCTION

Cystinuria is an autosomal recessive disease that is characterized by elevated urinary excretion of dibasic amino acids (lysine, arginine, ornithine, and cystine) (1,2). Although urolithiasis is the most clinical manifestation of cystinuria, repeated stone formation in affected patients often causes considerable morbidity (3-5). In the general population, cystine stones account for 0.9 to 2% of all cases of urolithiasis (6). On the other hand in Turkey, there is a frequency of cystine stones between 7-17% of urinary stones (8). For the management of cystine stones, forced hydration, urinary alkalization and the administration of sulfhydryl compounds have been recommended for the prevention of stone recurrence. However, the effectiveness of these treatments remain controversial, and surgery is frequently required to remove urinary stones (9-12). In addition, it is also accompanied by the risk of progressive renal impairment (13-15).

Our study aimed to assess the impact of medications and surgical interventions on renal function in cystinuric patients with cystine stones, which determine the prognosis in long term follow up.

MATERIAL and METHODS

The present study was carried out at the Ankara City Hospital (previously called Ankara Child Health Hematology-Oncology Training and Research Hospital) Pediatric Nephrology Department. The study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Medical Research Ethics Committee of Ankara Child Health Hematology-Oncology Training and Research Hospital (Protocol Number:2014-041).

A total of 26 cystinuria patients with cystine stones, aged between 3 months and 18 years, were retrospectively analyzed.

The diagnosis of cystinuria was made based on elevated urine dibasic amino acids and cystine levels according to normal

values for age in urine amino acid analyzes. Normal urine cystine excretion was reported as 30 mg/L per day (0– 100 $\mu\text{mol/g}$ creatinine) (3). The diagnosis of the cystine urolithiasis (stones) was based on an analysis of stone samples that obtained by spontaneous passage or surgery using the X-ray absorption method at the Institute of Mineral Inspection and Research Laboratory.

The blood urea nitrogen, serum levels of creatinine, sodium, potassium, chloride, calcium, uric acid, phosphorous, magnesium, arterial blood gas, urine analysis, parathyroid hormone and vitamin D were also recorded. Urine cultures were reviewed for bacteriological examination to check for urinary tract infections (UTIs).

Metabolic evaluations were performed for all patients. To define the metabolic abnormalities, the levels of calcium, oxalate, citrate, cystine, and uric acid were calculated by 24 hours urine analysis or by spot urine analysis. The absolute urine concentration of metabolic variables in the 24-hour urine or the mineral-to-creatinine ratio in spot urine was analyzed and compared with reference values (16).

Estimated glomerular filtration rates (eGFRs) were calculated using the bedside Schwartz creatinine-based formula ($\text{eGFR (mL/min/1.73 m}^2\text{)} = \text{k} \cdot \text{height (cm) / plasma creatinine (mg/dl)}$; where k is a constant = 0.413) at the beginning of the diagnosis and at the last visit (17).

For all patients, urinary ultrasonography (US) examinations were performed every 3-6 months.

Stone events were defined by the appearance of new stone or radiological evidence of stone growth.

All patients were advised to increase their fluid intake and to restrict their sodium intake (18). Trimethoprim-Sulfametoksazol (1-2 mg/kg/day) in a single dose was given to the patients with recurrent UTIs (16). Oral potassium citrate was prescribed for all patients at a dose of 1-2 mmol/kg per day in 3 divided doses to alkalize the urine to a pH of 7 or 8 (18). Cystine-binding drugs were also given to all patients. Alpha-mercaptopyrionylglycine at a dose of 10-20 mg/kg/day was our first drug of choice (18).

D-penicillamine treatment was started for two patients; however, due to the side effects of the drug (diarrhea, nephrotic syndrome), this treatment was replaced with alpha-mercaptopyronyl glycine (Thiola). We did not see any side effects with Thiola. Additionally, patients with other metabolic risk factors were treated according to their risk factors. Chlorothiazide (1-2 mg/kg day) was offered for hypercalciuria and pyridoxine (10 mg/kg/day) was also administered for hyperoxaluria (16).

Surgical management of cystine stones was performed by pediatric urology in our hospital depending on the size of the stone, its location and any signs of obstruction.

Data analysis and statistics

Data were evaluated using SPSS for Windows 11.5 (Chicago, Inc.) packet program. To compare the two groups, we used independent samples t-test if continuous variables have normal distributions, Mann-Whitney U test if continuous variables have not normal distributions. Chi-square test was used to evaluate categorical data. The relationship between variables was evaluated via Spearman Correlation analysis. The statistical boundary was accepted as 0.05.

RESULTS

Of the 26 patients with cystine stones, 23 were male (88.5%), and three were female (11.5%). The mean age at diagnosis was 45.2 ± 45.5 months (range: 3 months-12 years), and the mean follow-up duration was 64.7 ± 64.3 months (range: 7-204). On admission, five children (19%) were <1-year-old, fifteen (58%) were 1-5 years, and six (23%) were > 5 years.

Twelve children (46%) had positive family histories of urolithiasis. Consanguinity was also present in nine (35%) patients.

The most common presenting symptoms on admission were abdominal and flank pain (69%). The presenting symptoms and characteristics of the patients are shown in Table I. Sixteen (62%) children had also recurrent UTIs during their follow-up.

The mean serum creatinine levels at the first visit were 0.5 ± 0.7 mg/dl (median: 0.40 mg/dl). At the time of the patients' last outpatient visits, the mean serum creatinine level was 0.57 ± 0.28 mg/dl (median: 0.56 mg/dl). A significant difference was detected between the first and the last visit creatinine levels ($p=0.0008$). Other serum biochemical values, parathyroid hormone levels, and vitamin D levels were within the normal ranges.

The mean first-visit eGFR and last-visit eGFR were 141.8 ± 55.2 ml/min/1.73 m² (range: 10-244 ml/min) and 149.3 ± 48.4 ml/min/1.73 m² (range: 61-266 ml/min), respectively, and these were not significantly different ($p>0.05$).

Four patients with eGFRs <90 ml/min/1.73 m² at the beginning of the study, used thiol drugs regularly, and the eGFR values of these patients increased to >90 ml/min/1.73 m² after the follow-up period.

The mean pre-treatment and last-visits' urinary pH levels were 5.5 ± 0.63 (5-7) and 6.4 ± 0.74 (5-8), respectively, and the urinary pH also significantly increased with treatment during the follow-up period ($p<0.001$).

Urinary evaluations revealed additional metabolic abnormalities in 10 patients. Only 16 (62%) children had isolated cystinuria.

Stone analyses were available for all children. One had both uric acid and cystine stones, and two had calcium oxalate stones in addition to cystine stones. The other children had only cystine stones.

Table I: Characteristics of patients with cystine stones.

Patients Characteristics (n=26)	
Male/Female	23/3
Age at diagnosis, months*	45.2 ± 45.5 (3-144)
Follow-up period, months*	64.7 ± 64.3 (7-204)
Age distribution	
<1 years	5 (19%)
1-5 years	15 (58%)
>5 years	6 (23%)
Positive family history	12 (46%)
Consanguinity	9 (35%)
Symptoms of patients at first presentation	
Abdominal/flank pain	18 (69%)
Restlessness	16 (62%)
Urinary tract infection	16 (62%)
Hematuria	15 (58%)
Stone passage	7 (27%)
Enuresis	2 (8%)

*Mean $\pm$ SD (min-max)

Table II: Correlation between the last-visit serum creatinine, eGFR levels and the number of surgical interventions.

		Correlations	
		Last-visit serum creatinine	Last-visit eGFR*
Number of surgical interventions	r	0.578	-0.169
	p	0.002	0.410
	N	26	26

*eGFR: estimated glomerular filtration rate.

In 10 patients (38%), no stone events were observed during the follow-up period, and the stone event per patient-year was 0.36 for all patients.

There was no relation between family history of urolithiasis and the recurrence of stones in the patients ($p=0.247$). However, 75% of the patients with family histories of urolithiasis exhibited recurrence of cystine stones.

Moreover, there was no significant relation between UTI and stone size ($p>0.05$) or between UTI and the recurrence of stones ($p=0.108$). However, UTI was more common in patients with high numbers of stone recurrence.

An insignificant correlation was also observed between last visits' serum creatinine and number of stone recurrence ($r=0.273$, $p=0.178$)

The numbers of stone recurrences in patients with urinary pHs ≥ 6.5 were not significantly different ($p>0.05$). Although it is not significant, the number of stone recurrences in the patients with urinary pHs ≥ 6.5 was lower than that in the patients with pHs <6.5 . In addition, the patients who used thiol drugs experienced a lower number of stone recurrence ($r=0.491$, $p=0.011$)

Twenty-one patients received alpha-mercaptopropionylglycine as the first choice thiol-group drug. However, 3 patients did not receive thiol therapy despite being advised. Two separate patients also used it irregularly. D-penicillamine was given to two patients due to a lack of alpha-mercaptopropionylglycine, but during the follow-up period, the treatment was changed to alpha-mercaptopropionylglycine. The median duration of thiol drug usage was 27 months (minimum 1- maximum 201 months).

Prior to referral to our department, some of the patients had surgical interventions. Based on the available documents, of the 26 patients who were prescribed combined medical therapy, 2 patients only underwent ESWL, 4 had ESWL and surgery, and 17 patients underwent only surgical management that depended on the sizes and locations of the stones. Three patients had received neither ESWL nor surgery. Additionally, 9 patients required more than 1 surgical operation, and the patients underwent a total of 46 procedures and averaged 1.8 procedures per patient for 51 stone events.

There was a significant positive correlation between the last-visit serum creatinine level and the number of surgical interventions ($p=0.002<0.05$; $r=0.578$). On the other hand, there was no significant correlation between the last-visit eGFR and the number of surgical interventions ($p=0.410>0.05$; $r=-0.169$) (Table II). Although not statistically significant, eGFR values decrease as the total number of surgical interventions increases.

DISCUSSION

Approximately 6-10% of all urinary stone causes in children are cystine stones due to cystinuria (18). However, in Turkey, the frequency of cystine stone in Central Anatolia (within the area of our hospital) was reported as 3 to 12.5% (8). Therefore, cystinuria must be suspected in every pediatric stone patient with a family history of urinary stones. In cystine stones, regular follow-up and treatment are important due to the risk of high recurrence rates. On the other hand, it has also the risk of progressive renal failure (1-8,13-15,18,19).

Today, the management of cystinuria includes the elimination of stones and underlying metabolic disorders, prevention of the formation of new stones, control of UTIs, and also the preservation of renal function. However, the factors that directly cause cystine stone formation in childhood have not been clearly identified. Several studies have reported that high volume cystine excretion in the urine is a risk factor. It is known that cystine is insoluble at the physiological pH of urine. Thus, medical treatment should aim to reduce the cystine level and to increase the solubility of cystine in the urine. High levels of fluid intake, dietary sodium restriction, alkalization of the urine with potassium citrate to maintain a urine pH >6.5 and the usage of thiol drugs are the main treatments (5,14-20).

In our study, a combination of potassium citrate and citric acid was used for alkalization to maintain the urine pH >6.5 . Moreover, we restricted the sodium intake of our patients and recommended increased fluid intake. At the end of the follow-up period, we found a significant increase in urinary pH levels compared to the pre-treatment pH levels ($p<0.001$).

Tekin et al. (21) reported that 66.7% of children with cystine stones who used alpha-mercaptopropionylglycine and potassium citrate had no stones at the end of the mean follow-up of 15 months. Furthermore, in another study, Izol et al. (22) demonstrated a 16.6% recurrence rate in patients who were receiving medical treatment and 100% in patients who did not receive any medical treatment. In our study, 20 of the 26 children received combined medical treatment regularly, and the mean follow-up period was 64.7 ± 64.3 (range: 7-204) months. At the end of the follow-up period, 10 patients (38%) had normal urinary US with no stone formation. On the other hand, the stone events per patient-year in our study was 0.36, which is higher than reported in Japan (0.19) but lower than reported from the Cleveland Clinic (0.84 stone events per patient-year) (23,24). These differences may be attributed to the differences in the definitions of stone events, the subjective nature of stone growth assessment with the US, the efficiency of combined therapy, differences in diet, and differences in genetics. In addition, regular, long-term therapy is important for stone prevention. In the current study, we recommend thiol drugs for all patients during the follow-up period regardless of stone events, but three patients did not use thiol drugs.

Despite all of these combined therapies, many patients may require various surgical procedures, such as ESWL, percutaneous nephrolithotomy, retrograde intrarenal surgery, and rarely, open surgery, due to the high rate of stone recurrence, which is accompanied by a high risk of renal impairment (18,19,25,26). In a previous study, it was reported that male gender, high numbers of interventions, and histories of solitary kidneys are prognostic risk factors for renal insufficiency (21). Previous studies have also reported that serum creatinine levels are significantly higher in patients with cystine stones compared to those with calcium oxalate stones (22). In our study, 2 of the 26 patients underwent only ESWL, 4 underwent ESWL and surgery, and 17 patients underwent surgical treatment. Additionally, 9 patients required more than one surgical operation, and the patients underwent a total of 46 procedures and averaged 1.8 procedures/patient for 51 stone events, which is less than has been reported in some other studies (7.9 procedures/patient for 126 stone episodes) (26). Due to the risk of renal impairment, minimally invasive surgical interventions are preferable. In our study, some patients received some surgical procedures prior to referral to our hospital, and there was a significant positive correlation between the number of surgical interventions and the last-visit serum creatinine values. In contrast, there was no significant correlation between the last-visit eGFR and the number of surgical interventions ($p=0.410>0.05$; $r=-0.169$), eGFR values decrease as the total number of interventions increases. Whether this finding was coincidental or due to risk factors such as the high number of male patients and/or the high number of surgical interventions

among our sample is unknown. It is difficult to resolve these questions due to the lack of genetic evaluations and the low number of female patients in this study.

CONCLUSION

It is important to remember metabolic diseases, such as cystinuria, as a cause of recurrent urolithiasis in children. Despite all treatments, it should be kept in mind that renal impairment may develop in cystinuria and surgical treatment should be planned by considering minimally invasive options.

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Postneonatal Epilepsy and Psychomotor Developmental Retardation Risk Factors in Term Neonatal Convulsions Without Hypoxic Ischemic Encephalopathy

Doğumsal Hipoksik İskemik Ensefalopatiye Bağlı Olmayan Term Yenidoğan Konvülsiyonlarında Psikomotor Gerilik ve Epilepsi Gelişim Risk Faktörleri

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ABSTRACT

Objective: Neonatal convulsions may be an early sign of brain injury and the presence of convulsions in the neonatal period has been associated with long-term sequelae such as mental retardation, postnatal epilepsy and death. We aimed to determine associations of etiological factors with neurodevelopment and postneonatal epilepsy and evaluate the risk factors in newborns with neonatal convulsions that were not related to hypoxic-ischemic encephalopathy.

Material and Methods: This study included full-term infants who were born between January 2010 and December 2014 and had neonatal convulsion history, had no history of hypoxic-ischemic encephalopathy and were followed for at least 1 year at our neurology clinic.



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Results: Forty-nine patients were included to the study. Among the identified etiologies on first clinical visit, hypoglycemia was the most common cause which was presented in 11 (40.74%; 11/27 patients) patients. During follow-up, 22.4% (n=11) of patients developed postneonatal epilepsy. In 4 of 7 patients with abnormal Bayley II test results, epilepsy developed in the follow-up. The risk for development of postneonatal epilepsy was significantly associated with abnormal neurological findings, such as cerebral palsy or significant delays in developmental stages; being not benefited from acute treatment and follow-up abnormal EEG findings of the patients.

Conclusion: Hypoglycemia should be primarily investigated and treated in term neonatal seizures without hypoxia. Abnormal neurological findings, being not benefited from the acute treatment and follow-up EEG findings were associated with developing epilepsy. In the literature, most of the studies were limited due to short follow-up periods. More information about prognostic factors in neonatal convulsions and the occurrence of postneonatal epilepsy is needed.

Key Words: Neonatal seizures, Hypoglycemia in newborn seizures, Postneonatal epilepsy

ÖZ

Amaç: Yenidoğan konvulziyonları, yenidoğan döneminde akut nörolojik hastalıkların en yaygın semptomlarından biridir. Hastalarda ölüm, mental retardasyon ve postneonatal epilepsi riskini arttırdığı bilinmektedir. Bu çalışmada sebebi doğumsal hipoksik iskemik ensefalopati olmayan ve hastanemizde yenidoğan konvulziyonu sebebiyle takip edilmiş hastalarda etyolojik faktörler ile nörolojik muayene bulgularının ve risk faktörlerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya hastanemiz nöroloji polikliniğinde takipli, Ocak 2010 - Aralık 2014 tarihleri arasında miadında doğan, doğumsal hipoksik iskemik ensefalopati öyküsü olmayıp, yenidoğan döneminde nöbet öyküsü olan, en az 1 yıl takibimizde kalan hastalar dahil edildi.

Bulgular: Çalışmaya 49 hasta dahil edildi. İlk başvuru sırasında saptanabilen en sık etyolojik faktör, 11 (%40.74) hastada saptanan hipoglisemiydi. İzlemde hastaların %22.4'ünde (n=11) postneonatal epilepsi geliştiği görüldü. Bayley II testleri anormal saptanan 7 hastanın 4'ünde epilepsi geliştiği belirlendi. Yenidoğan döneminde başlanan tedaviye yanıtın olmaması, anormal nörolojik muayene bulgularının varlığı ve izlemde anormal EEG bulgularının olması, hastalarda postneonatal epilepsi gelişimi için risk faktörleri arasındaydı.

Sonuç: Hipoglisemi, yenidoğan nöbetlerinde saptanabilen ve tedavi edilebilen sebeplerden bir tanesidir. Anormal nörolojik muayene bulguları, başlanan tedaviye alınan yanıtlar ve izlem EEG bulguları epilepsi gelişimi ile ilişkili görüldü. Bu konuda yapılmış olan çalışmaların çoğu, kısa gözlem süreleri sebebiyle sınırlıdır. Yenidoğan konvulziyonları ve postneonatal epilepsi gelişimi açısından daha fazla prognostik faktör belirlemek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Yenidoğan konvulziyonları, Hipoglisemi, Postneonatal epilepsi

INTRODUCTION

Neonatal convulsions are one of the most common symptoms of acute neurological disorders in the neonates. While conflicting data existed in the literature on these seizures, that may be an early sign of brain injury and the presence of convulsions in the neonatal period reported that is has been associated with long-term sequelae and death (1, 2).

Population-based studies have shown that the incidence of neonatal seizures is 1.8-3.5 per 1000 live births (3). Moreover, post-neonatal epilepsy following neonatal seizures occurs at a rate varying between 1.8% and 41.3% and has an estimated incidence of 70/100.000 among children and adolescents in Europe (4-6). Studies evaluating in newborns without hypoxic-ischemic encephalopathy are limited. Frequent etiologies that were reported, differ from hypoxic-ischemic encephalopathy include focal hypoxia ischemia, intracranial hemorrhage, cerebral malformation, transient metabolic disturbance, perinatal infection, and inborn errors of metabolism (7). Malmqvist et al reported that, 40 newborns had seizures without hypoxic-ischemic encephalopathy and 9 of them had epilepsy (7).

Neonatal seizures are known to increase the risk of death, mental retardation and postnatal epilepsy in affected patients (8). These comorbidities become more prominent when patients develop epilepsy. The coexistence of mental retardation and

cerebral palsy was found in 87% of the patients who had neonatal convulsions and developed epilepsy in the follow-up (9).

Since the etiology of neonatal seizures has a treatable cause and convulsions might impair vital functions and lead to brain injury, it is crucial to recognize the seizure and it should be treated appropriately based on the identified etiology in the neonatal period (10).

In the present study, we aimed to determine associations of etiological factors with neurodevelopment and postneonatal epilepsy and evaluate the risk factors in newborns with neonatal convulsions that were not related to hypoxic-ischemic encephalopathy who were followed at our hospital.

MATERIALS and METHODS

This cross-sectional study included full-term infants who were born between January 2010 and December 2014, had neonatal convulsion history, had no history of hypoxic-ischemic encephalopathy and were followed for at least 1 year at our neurology clinic.

The institutional review board approved the study design and protocols (University of Health Sciences, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research

Hospital; No:73799008-799). Demographic characteristics, mode of delivery, age at the time of seizure, the type and etiology of seizure, anticonvulsant therapy and duration of treatment, neuroimaging findings, diagnostic laboratory studies, follow-up neurological findings and neuromotor and cognitive development levels (Bayley II) and occurrence of epilepsy during follow-up were retrieved from our hospital's electronic medical records and reviewed retrospectively for all patients.

In order to determine whether the time of seizure is a prognostic factor, four groups were formed based on the age of seizure onset: first 24 hours; 24-48 hours; from 48 hours to 1 week; >1 week. Due to the difficulty of obtaining information on the type of seizure from medical files, seizures were classified as subtle and others.

Patients with having clinical seizures in the postneonatal period or abnormal EEG findings were considered as having postneonatal epilepsy.

Neurological examination findings obtained on the last follow-up of patients were divided into two groups as normal/mild deficit and moderate/severe deficit. Patients with normal/mild neurological deficits were defined as those having mild changes in tonus or deep tendon reflex and minimal delays in developmental stages and patients with moderate/severe neurological deficits were defined as those with established cerebral palsy or significant delays in developmental stages.

Assessments performed using the "Bayley Mental Development Index-II/Bayles Scales of Infant Development" at 9 months of age and later were recorded for patients who were followed at the developmental pediatrics clinic up to at least 1 year of age. Scores lower than 70 (2 standard deviations below the mean) were considered as abnormal.

Electroencephalography (EEG); was performed with using the international 10-20 system for electrode placement that has been modified because of the smaller head size of the babies and relatively low EEG activity were noted in the frontopolar head regions and the widely accepted newborn montage system (9-10 electrodes) with anterior-posterior and transverse montage including central vertex (Cz) was used (11). EEG discharges were recorded as normal, focal or multifocal.

Neuroimaging data from transfontanel ultrasonography (TFUSG), computed tomography (CT) and magnetic resonance imaging (MRI) were reviewed and the results were classified as normal and abnormal. Imaging results showing developmental anomalies of brain, changes related to hypoglycemia and hypoxia, myelination defects and hemorrhage, thrombus and infarct findings associated with cerebrovascular events were considered as abnormal.

Statistical analyses were conducted using the IBM SPSS for Windows, Version 22.0 software package. Numerical variables were summarized as mean $\pm$ standard deviation and median [minimum – maximum] values. Categorical variables were

expressed as number and percentage. Chi-square test or Fisher's exact test was used to compare categorical variables. McNemar's test was used to check whether there were differences between neonatal EEG and follow-up EEG values. Statistical significance was set at $p < 0.05$.

RESULTS

In 49 pediatric patients, who were followed for neonatal convulsions and born at term with no history of hypoxic-ischemic encephalopathy, 35 (71.4%) were male. The mean duration of the follow-up was 19.8 months, with a minimum follow-up of 12 months. Twenty-eight (58.3%) patients were born via normal spontaneous vaginal delivery and 20 (41.7%) were born via Cesarean section. Information on mode of delivery could not be retrieved for only one patient. Patient ages at the seizure onset are shown in Table I.

Examinations at the initial presentation have identified an etiological factor in 27 (55.10%) patients through the laboratory studies. Among the identified etiologies at the initial presentation, hypoglycemia was the most common cause which was presented in 11 (40.74%) patients. Data on etiological factors identified at initial presentation are shown in Table I.

Overall, 36 patients were assessed using TFUSG, 7 patients using CT and 30 patients using brain MRI during follow-up. New etiologies were identified with follow-up magnetic resonance imaging in 4 patients in addition to the aforementioned etiological factors. Hypomyelination in 1 patient, hypoxic-ischemic changes in 1 patient and hemorrhagic sequelae findings in 2 patients were reported in MRI findings. Thus, a precise etiological factor had been identified by all of these diagnostic tests in a total of 31 patients (63.2%).

During the follow-up, 22.4% (n=11) of the patients developed postneonatal epilepsy (Table III). Among these patients, in 4 patients hypoglycemia was the etiological factor identified at presentation. Hyperinsulinemic hypoglycemia was diagnosed in 2 of these 4 hypoglycemic patients at follow-up. A patient with subarachnoid hemorrhage developed epilepsy during follow-up and showed abnormal findings on neurological examination. Also, 1 patient with West syndrome, 1 syndromic patient with holoprosencephaly, 1 patient with hypoxia related to cardiac arrest, 2 patients with hemorrhagic sequelae findings on MRI had postneonatal epilepsy. The etiological factor of one patient couldn't be identified.

One patient with meningoencephalitis and one patient with encephalitis had normal neurological examination findings and did not develop epilepsy during follow-up.

The seizure type distributions of patients were as follows, subtle type in 19 patients (38.8%), and the other types in 29 patients (59.2%). Seizure type information of 1 patient could not be reached.

Table I: Etiological factors identified at initial presentation in the terms of seizure onset age.

Age at the seizure onset	Etiological factors identified at initial presentation	Number of the patients	n:49 (%)
0-24 hours	Hypoglycemia	1	10 (20.4%)
	Pyridoxine dependent seizure	1	
	Sinus vein thrombosis	1	
	Unknown reason	7	
24-48 hours	Hypoglycemia	6	15 (30.6%)
	Encephalitis	1	
	Hypoglycemia and meningoencephalitis	1	
	Cerebral infarct and sepsis	1	
	West syndrome	1	
	Unknown reason	5	
48 hours-1 week	Hypertatremic dehydration	3	12 (24.5%)
	Hypoglycemia	1	
	Hypoxia related to cardiac arrest	1	
	Intracranial hemorrhage	1	
	Holoprosencephaly as a syndromic patient	1	
	Unknown reason	4	
>1 week	Hypocalcemia	2	11 (22.4%)
	Hypoxia following cardiac arrest, kernicterus	1	
	Hypertatremic dehydration	1	
	Subarachnoid hemorrhage	1	
	Unknown reason	6	
Unknown	Hypoglycemia	1	1 (2%)

Table II: The risk factors of the development of postneonatal epilepsy.

Patients	Epilepsy diagnosis n (%)	p
Moderate/severe deficits present in follow-up neurological examinations	5 (62.5%)	0.009
Being not benefited from acute treatment	6 (100%)	<0.000
Abnormal follow-up EEG findings present	5 (100%)	<0.000

Eight (16.3%) patients were not being given an antiepileptic therapy and 2 (4.1%) patients who were given an antiepileptic therapy were not regularly being given their medications by their parents. Of 39 patients initially being given an antiepileptic treatment, 33 (84.61%) patients were benefited from acute therapy and 6 (15.38%) patients diagnosed with postneonatal epilepsy did not receive any benefit from acute therapy.

EEG was performed in 47 patients in the neonatal period. When EEG findings of the patients were divided into three groups as focal, multifocal and normal, EEG abnormality was found in a total of 22 (46.8%) patients including 18 (38.3%) patients with focal abnormality and 4 (8.5%) patients with multifocal abnormalities. EEG findings were normal in 25 (53.2%) patients.

Examination of the follow-up EEG findings of patients showed that 2 (4.1%) patients did not being performed EEG monitoring during follow-up. A total of 5 (10.6%) patients had EEG abnormalities including 3 (6.4%) patients with focal EEG findings and 2 (4.3%) patients with multifocal EEG findings. Forty two (89.4%) patients had normal EEG results. Epilepsy was present in all of these 5 patients with abnormal follow-up

EEG results and epilepsy was absent in 38 (90.48%) out of 42 patients with normal follow-up EEG results ($p=0.000$).

Bayley II test results were normal in 49% ($n=24$) and abnormal in 14.3% ($n=7$) of the patients, and 36.7% ($n=18$) of the patients were not subjected to Bayley II test. Epilepsy developed in 4 of 7 patients with abnormal test results. In the remaining 3 patients who did not develop epilepsy, had focal EEG abnormalities at presentation however their last EEG data were normal.

Follow-up neurological examination findings showed that normal/mild neurological deficits were present in 41 (83.67%) patients and moderate/severe neurological deficits in 8 (16.32%) patients. The risk of developing epilepsy was significantly associated with neurological findings, being not benefited from acute treatment and abnormal EEG findings of the patients at follow-up. The characteristics of patients associated with the increased risk factors of developing epilepsy are shown in Table II.

Patient characteristics including gender ($p:0.254$), age at the seizure onset ($p:0.355$), type of the seizure ($p:0.732$),

Table III: The features of the patients developing postneonatal epilepsy.

Patient	Gender	Mode of delivery	Ages at the seizure onset	Etiology	EEG findings in neonatal period	EEG findings in follow-up	Bayley II results	Follow-up neurological examination
1	F	VD	48 hours-1 week	with holoprosencephaly as a syndromic patient	focal	focal	abnormal	moderate/severe neurological deficits
2	F	CS	48 hours-1 week	hemorrhagic sequelae findings in kranial MRI	focal	normal	abnormal	moderate/severe neurological deficits
3	F	CS	unknown	hypoglycemia	focal	multifocal	unknown	moderate/severe neurological deficits
4	M	CS	24-48 hours	hypoglycemia	normal	normal	normal	normal/mild neurological deficits
5	M	CS	24-48 hours	hemorrhagic sequelae findings in kranial MRI	focal	normal	normal	moderate/severe neurological deficits
6	M	CS	48 hours-1 week	hypoglycemia	focal	focal	abnormal	normal/mild neurological deficits
7	M	CS	48 hours-1 week	hypoxia related to cardiac arrest	focal	normal	normal	moderate/severe neurological deficits
8	F	CS	0-24 hours	unknown	normal	normal	normal	normal/mild neurological deficits
9	M	VD	24-48 hours	hypoglycemia	normal	normal	normal	normal/mild neurological deficits
10	F	VD	24-48 hours	west syndrome	multifocal	focal	normal	normal/mild neurological deficits
11	M	VD	>1 week	subarachnoid hemorrhage	multifocal	multifocal	abnormal	normal/mild neurological deficits

F: Female; **M:** Male; **VD:**Vaginal delivery; **CS:**Cesarean section

neuroimaging findings ($p:0.256$) and Bayley II test results ($p:0.17$) were not significantly associated with the development of epilepsy.

A statistically significant association was found between neonatal EEG findings and EEG findings during later follow-up ($p=0.000$). In addition, follow-up EEG findings were normal in 100% of the patients with normal neonatal EEG findings but 77.3% ($n=17$) of the patients with focal/multifocal abnormalities had normal follow-up EEG results.

Neonatal EEG findings were significantly associated with final neurological examination findings ($p=0.040$). Among 25 patients with normal EEG findings, 24 (96%) patients had normal and mild deficits on neurological examination.

A significant association was observed between final neurological examination findings and MRI findings of the patients. Among patients with normal MRI findings, 88.2% had normal and mild deficits on neurological examination ($p=0.049$).

DISCUSSION

In this study, 49 pediatric patients were included. The most common cause of neonatal convulsions was hypoglycemia which occurred in 11 patients. Epilepsy did not develop in 77.6% of the patients and the risk of developing epilepsy was significantly associated with neurological findings, not being

benefited from acute treatment and abnormal EEG findings at follow-up.

Newborns suffering convulsions in the first day or after the third day of life were reported to have poorer outcomes than patients developing convulsions in the second or third days of life (12). In our study, 20.4% ($n=11$) of the patients suffered a seizure in the first 0-24 hours of life, 30.6% ($n=15$) of the patients within a period of 24-48 hours after birth, 24.5% ($n=12$) within 48 hours and up to 1 week, and 22.4% ($n=11$) of the patients after the first week of life. Time of the seizure onset was not significantly associated with the risk of developing epilepsy and final neurological examination findings.

In the current study, no significant association was found between the type of seizure and epilepsy and this is compatible with the literature that did not show an association between the type of seizure and prognosis of patients (13,14). However, Garfinkle and Shevell found a significant association between the seizure type and neurodevelopmental outcome. They observed poor prognosis in 71% of the patients with a subtle, multifocal clonic, tonic or myoclonic seizure but only 23% of the patients had focal clonic seizures (12).

Several studies have demonstrated that seizure etiology is the major factor in determining the prognosis (13,15-18). In our study, among the identifiable etiologies, the most common cause of the seizures was hypoglycemia ($n=11$ patients) and postneonatal epilepsy developed in 4 of these patients.

One patient with meningoencephalitis and one patient with encephalitis had normal follow-up neurological examinations and did not develop epilepsy. A patient with subarachnoid hemorrhage developed epilepsy during follow-up and showed abnormal findings on neurological examination.

The risk of developing postneonatal epilepsy (68.5%) (about 3/4 of the patients) was higher in the first year of life and the remaining one-fourth of the cases occurred during in the first 5 years of life (19). Short follow-up period in our study as well as in many other studies precluded the ability to observe the occurrence of epilepsy and to examine the effects of neonatal convulsions on the developing brain in childhood and adolescence, which represents a limitation. The mean duration of follow-up was 19.8 months for our patients.

The prevalence of epilepsy following neonatal seizures was ranged between 16-56% and the rates vary depending on the chosen criteria and the duration of follow-up (20). In a meta-analysis including 44 studies (4 population-based and 40 hospital-based studies) between 1954-2013 showed that among 4538 infants with neonatal convulsion, 17.9% developed postneonatal epilepsy later on (19). Data were also reported separately for preterm infants and term infants with a postneonatal epilepsy prevalence of 17% and 30%, respectively (2). In our study, 22.4% of term infants developed postnatal epilepsy.

Severe neurological defects may occur in patients with neonatal convulsions including impairment of neurodevelopment, initiation of synaptic reorganization, altered plasticity, molecular reorganization of receptors and channels and development of epilepsy with increased brain injury (21). We identified an etiological factor in all of the patients with moderate/severe deficits in neurological examination. Additionally, we found that 85.4% of the patients with normal neurological findings or mild neurological deficit did not develop epilepsy but 62.5% of the patients with moderate/severe neurological deficit developed epilepsy. A statistically significant association was observed between neurological findings and the risk of developing epilepsy.

Patients with normal imaging results were reported to have a better prognosis than patients with imaging results showing severe deficits. Studies existed in the literature showed that diffuse abnormalities on MRI and CT scans are found to be 100% correlated with a poor prognosis and 66% of the patients with diffuse abnormalities were developed epilepsy (22,23). A retrospective review of the medical charts of our patients showed that 26.5% of the patients did not undergo ultrasound examination and MRI examination was not being performed in 38.8% of patients. Thus, no significant relation was found between the development of epilepsy and USG findings or MRI findings at follow-up.

Mortality and other poor outcomes were found in the majority of patients with moderate or severe EEG abnormalities. Moderate

or severe EEG abnormalities were reported to be an important prognostic factor for epilepsy, developmental delay and cerebral palsy (12-14,24). Ninety-six percent of the patients with normal neonatal EEG findings and 90.48% of patients with normal follow-up EEG findings had normal neurological examination or mild neurological deficit. Although there was no significant association between neonatal EEG findings and the occurrence of epilepsy, follow-up EEG findings were found to be significantly associated with the development of epilepsy. Epilepsy did not occur in 86.4% of the patients with normal follow-up EEG results. Demonstration of the electrical seizures that reflect most of the seizure start in newborns through continuous monitoring would be a value in future studies.

In clinical trials, patients who do not receive any benefit from antiepileptic treatment were found to develop epilepsy in later life as reported by clinical trials (9,19). In our study, 67.3% of the patients starting on antiepileptic therapy at presentation benefited from treatment. Consistent with literature, a low rate of epilepsy (15.2%) was found in the patients deriving benefit from initiation of treatment and all of the patients who did not receive any benefit from treatment developed epilepsy. Among patients who did not experience recurrent seizures and not deemed to require treatment, none of them developed epilepsy at follow-up.

In conclusion, neonatal convulsions are one of the most common symptoms of acute neurological disorders in the neonatal period. Several researchers have proposed a scoring system to be able to demonstrate the effects of neonatal seizures on epilepsy and neurodevelopmental outcomes. However, most of the studies were limited due to short follow-up periods. More information is needed on this issue.

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The Effect of Environmental Conditions of Schools on Student Success and Absenteeism

Okulların Çevresel Koşullarının Öğrenci Başarısı ve Devamsızlığı Üzerine Etkisi

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ABSTRACT

Objective: The purpose of this study is to reveal the characteristics of indoor physical environments of schools by means of measuring electromagnetic radiation, lighting, noise, temperature, and humidity and to evaluate the relationship between the physical characteristics with the success of students and absence.

Material and Methods: All schools in the Derince region of the city of Kocaeli (n=42) have been included in the survey without selection of a sample and the cross-sectional type of research technique has been employed. For the analysis of the data, correlation analysis (Spearman and Pearson), Mann-Whitney U, and Kruskal Wallis tests have been used.

Results: In schools, the electromagnetic field level was measured as 0.53 ± 0.27 mG, the noise level was 57.43 ± 7.77 dB (schoolyard), and the lighting level was 370.11 ± 95.15 lux. There has been a statistically significant difference detected between the grade point averages of the sixth grades of the schools that comply with the standards of classroom noise level and those that do not ($p=0.039$). A negatively significant correlation between the classroom lighting level and grade point averages has been detected (respectively; $r -0.498$ $p 0.011$; $r -0.548$ $p 0.021$; $r -0.563$ $p 0.004$). A negatively significant correlation between the building standards points of the schools and the rate of absence of the students has been detected ($r -0.371$ $p 0.011$).

Conclusion: A significant relationship between the indoor physical environment characteristics in schools and the school success has been found.

Key Words: Electromagnetic Fields, Noise, Lighting, School

ÖZ

Amaç: Bu çalışmanın amacı, elektromanyetik radyasyon, aydınlatma, gürültü, sıcaklık ve nemi ölçerek okulların kapalı fiziksel ortamlarının özellikleriyle öğrencilerin başarıları ve devamsızlığı ilişkisiyi değerlendirmektir.

Gereç ve Yöntemler: Kocaeli ili Derince bölgesindeki tüm okullar (n = 42) örneklem seçilmeden dahil edilmiş ve kesitsel araştırma tekniği uygulanmıştır. Verilerin analizi için korelasyon analizi (Spearman ve Pearson), Mann-Whitney U ve Kruskal Wallis testleri kullanılmıştır.

Bulgular: Okullarda elektromanyetik alan seviyesi 0.53 ± 0.27 mG, gürültü seviyesi 57.43 ± 7.77 dB (okul bahçesi) ve aydınlatma seviyesi 370.11 ± 95.15 lüks olarak ölçülmüştür. Sınıf gürültü düzeyi standartlarına uyan okulların altıncı sınıflarının not ortalamaları ile uymayanlar arasında istatistiksel olarak anlamlı farklılık tespit edilmiştir ($p = 0.039$). Sınıf



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Contribution of the Authors / Yazarların katkısı: **PALANBEK YAVAS S:** 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. **CAGLAYAN C:** 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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aydınlatma düzeyi ile not ortalamaları arasında negatif yönde anlamlı bir ilişki tespit edilmiştir (sırasıyla; $r = -0.498$ $p = 0.011$; $r = -0.548$ $p = 0.021$; $r = -0.563$ $p = 0.004$). Okulların bina standartları puanları ile öğrencilerin devamsızlık oranları arasında negatif yönde anlamlı bir ilişki tespit edilmiştir ($r = -0.371$ $p = 0.011$).

Sonuç: Okullardaki kapalı mekan fiziksel çevre özellikleri ile okul başarısı arasında anlamlı bir ilişki bulunmuştur.

Anahtar Sözcükler: Elektromanyetik alanlar, Gürültü, Aydınlatma, Okul

INTRODUCTION

Children spend approximately 9 months of the year and one third of their days at school. In this respect; among the environments the child spends time in, school is an important establishment that gets involved in his life for a long time and that influences his behaviours (1,2). School health services have an important function in protecting and improving children's health. WHO has defined "the school which promotes health"; as a school that constitutes a healthy environment for living, learning, and studying and maintains this capacity (3). American Academy of Paediatrics has emphasized "the healthy school environment" as a school environment which protects the students and the employees from injuries, illnesses, and disabilities, and in which behaviours and activities for preventing environmental risk factors are embraced (4). In fact, school environmental health practices involve everything at school and its surroundings; they are practices to prevent all sorts of pollution that may occur at the location of the school, in its building, indoor atmosphere, water and sanitation safety, lighting, the noise levels, the school yard and the school buses (1).

The biological risk factors resulting from the school and its surroundings consist of moulds, unsafe foods, diseases that are infected through vectors; the chemical risk factors consist of air and water pollution, pesticides, hazardous wastes, asbestos, paint, cleaning supplies; and the physical risk factors consist of transportation, violence, injuries, extreme hot and cold, and radiation (3).

The problems resulting from the school environment affect the learning capacity of children significantly as much as they affect their health. The studies carried out determined that bad school environment conditions cause a decrease in the general well-being and the learning capacity of children while causing an increase in the rates of absence (5,6). Moreover, it has been determined that exposure to noise within the school decreases the long-term memory, reading skills, and motivation of students; and the inconvenience of the lighting level cause a decrease of success in classes and a state of discomfort (7-9). As for temperature and humidity values, they have been accepted as a mixer in learning processes and it has been determined in the studies that the convenient temperature levels improve the cognitive performance; and that a relationship between exposure to electromagnetic field and childhood leukaemia has been found (10,11). Therefore, the school success rate is accepted as an indicator showing the health effects of the school environment (12).

Studies conducted in Turkey have shown that schools have significant deficiencies in compliance with environmental health standards (13-16). In this study, it was aimed to evaluate the effects of physical environment characteristics of schools on students' success and absenteeism.

MATERIAL and METHOD

Population and sample

The population of this cross-sectional study consists of total of 42 primary and secondary level schools located within the borders of the province of Derince in the city of Kocaeli in the school year of 2014-2015. A sample has not been selected for the research and all schools have been included in the research. The total number of classrooms in schools is 624, and in our study, measurements were made in 203 (32.5%) classrooms. The classroom selection criteria in schools has been made by investigating two classrooms from the right and left sides of each hall from each floor, starting from the top floor, for schools that have a single building; and for schools that have two separate buildings, by investigating one classroom that is closest to the end of the staircases from each hall in each floor, starting from the top floor, separately from each building (13). The study was obtained from the Kocaeli University Clinical Research Ethics Committee with the decision number 4/18, dated 27.11.2015.

Variables of the research

The dependent variables of the research are the school success rates. School success rates are calculated by dividing the total of success points of the students in each school to the number of students in the school. This data has been obtained from the records of Derince District Directorate of National Education.

Independent variables of the research consist of 2 different groups of variables.

- 1) School indoor environment physical characteristics: Electromagnetic field level in schoolyard (mG), noise level in schoolyard (dB), temperature in schoolyard (°C), and humidity levels (%), measurement parameters related to the electromagnetic field, lighting, noise, temperature, and humidity levels of the determined classrooms. In schools that had a library, the lighting level of the library was also measured.
- 1) Class properties: It consists of variables such as the hygiene of the classroom, type of the board, distance of the board from the desks, position of the windows, width of the door, space

of the classroom, capacity of the classroom. The data has been collected by means of questions and measurements composed based on TS 12014 School Environmental Health, TS 9518 General Physical Settlement Rules for Elementary Schools, developed by the Turkish Standards Institution for schools, and the literature information (17,18). It has been calculated by giving 1 point to the question and values in the data form that were compliant with the standards and adding them up. The maximum standard point that a school can obtain according to this scoring is 14 and more points show compliance with the standards.

Measurements

Electromagnetic field measurement; It has been performed in the form of 5 measurements in total as from 4 corners and from the middle with Traxial Elf Magnetic Field Meter Model 4190 device in the determined classrooms; as for the schoolyard, four corners of the yard and the entrance of the school building, 5 measurements in total. The limit value of ≤ 2 mG for electromagnetic radiation level, which is recommended by USA National Council of Radiation Protection and Measurements (NCRP) for schools and children playgrounds, has been accepted as the limit values in our research (19).

Noise measurement; Measurements that lasted 10 minutes were performed with a RION NL-31 brand noise measurement device, in classrooms as 1 meter away from the surface, 1.5 m away from significant sound permeation elements such as windows and with the conditions of having at least 0.7 m long distance between the 3 spots measured. The measurement in the schoolyard has been performed as 3.5 away from the school building, 3 m away from the road from where the traffic flows, and 1.5 m above the ground. The values of 35 dB when the class windows are open and 45 dB when the class windows are closed, which are in the Regulation of Evaluation and Management of Environmental Noise have been accepted as the limits (20). For the outdoor schoolyard noise level, 55 dB, determined by WHO, has been accepted as the limit value (21).

Lighting measurement; has been performed with a TES 1335A Digital Light –Meter luxmeter as 80 cm above the ground, 9 measurements from the front, middle, and back seats and 1 from the middle spot attached to the board, 10 measurement in total by pulling 1 m away from the device. The limit values

in classrooms for lighting was based on at least 200 lux light intensity, which is in TS 9518/ General Physical Settlement Rules for Elementary Schools, maximum 500 lux (in the literature), and as for the libraries, it is based on 500 lux (17,18,21-23).

Temperature and humidity measurement; has been performed from 5 different spots, 10 minutes after entering the determined classrooms, as 1 m above the ground. The in-class and schoolyard measurements were made with a ROHS Model AR 714 type XG6608 thermometer – hygrometer. Outdoor temperature and humidity values have been recorded by measuring once in the schoolyard, regardless of a particular place. The temperature values recommended by ASHRAE as 22.77°C.-26.66°C for summer; and humidity between 30-60% were accepted (24).

The in-class measurements from the determined classrooms (space of the classroom, window, door, distance of the board to the first desk, etc.) have been made with a 5 meter long tape measure.

Statistical Analysis

Data entry and analysis have been made by using the package software SPSS 20.0. The compliance of the continuous variables to the normal distribution has been tested via Kolmogorov-Smirnov test. For the data could not meet the parametric test estimates in the comparison of the average between groups, Mann-Whitney U test, Kruskal Wallis test and Spearman correlation analysis were employed.

RESULTS

The average of the score of conformity, 203 classrooms examined in the research have obtained with regards to their classroom physical properties is 9.56 ± 1.02 (min:7.75-max:12.00). It has been determined that in 30.1% of the classrooms, the air volume per student is 6 m^3 and above, thus conforming with the standards, and the average air volume per students is $3.21 \pm 0.96 \text{ m}^3$. It has been determined that, in 99.5% of the classroom, it is 1.2 m^2 and above per student, thus conforming with the standards. It has been determined that the space per student in the classrooms is minimum $1,12 \text{ m}^2$ maximum 3.20 m^2 per student and the average space per

Table I: Distribution of the Classroom Properties of the Schools, (n=203).

Classroom Properties of the Schools	Number(n)	Pct. (%)
Space per student $\geq 1.2 \text{ m}^2$ (conforming)	202	99.5
Air volume per student $\geq 6 \text{ m}^3$ (conforming)	61	30.1
Height of classroom from floor to ceiling $\geq 3.5 \text{ m}$ (conforming)	0	0.0
Total	203	100

Table II: Distribution of Schools According to Their State of Conformity with the Standards of Electromagnetic Field, Noise, Lighting, Temperature, and Humidity Levels.

	Number (n)	Pct. (%)
Conformance of School Electromagnetic Field Level to the Standards		
Schoolyard ≤ 2 mG (conforming)	42	100
Classroom ≤ 2 mG (conforming)	203	100
Conformance of School Noise Levels to the Standards		
schoolyard ≤ 55 dB (conforming)	20	47.6
Classroom with windows open ≤ 45 dB (conforming)	30	71.4
Classroom with windows closed ≤ 35 dB (conforming)	25	59.5
Conformance of School Lighting Levels to the Standards		
Classroom with Lights on windows closed 200 ≤ and ≤ 500 lux (conforming)	37	88.1
Classroom with lights off windows open 200 ≤ and ≤ 500 lux (conforming)	27	64.3
Library (n=23) ≥500 lux (conforming)	15	65.2
Conformance of School Temperature and Humidity Levels to the Standards		
Classroom Temperature 22.77 ≤ and ≤ 26.6 °C (conforming)	18	42.9
Classroom Humidity %30≤ and ≤%60 (conforming)	41	97.6
Total	42	100

student is $1.81 \pm 0.32 \text{ m}^2$. It has been determined that the height of none of the classrooms, from floor to ceiling, is 3.5 m and above. It has been determined that the height of the classrooms is minimum 2.80 m maximum 3.20 m and the average classroom height is $3.01 \pm 0.08 \text{ m}$. The classroom properties of schools are given in table I. The measurement results of the indoor physical characteristics of the schools within the scope of our research are given in table II.

The average of the electromagnetic field measurement while the electronic devices were on in the classrooms measured in our research, has been determined as $0.53 \pm 0.27 \text{ mG}$ (minimum 0.20 mG-maximum 1.20 mG). The average of the electromagnetic field measurement while the electronic devices were off has been determined as $0.47 \pm 0.26 \text{ mG}$ (minimum 0.17 mG - maximum 1.12 mG). The electromagnetic field level measured in the administrative units of schools has been determined as $0.74 \text{ mG} \pm 0.40 \text{ mG}$ in average. The electromagnetic field level of schoolyard has been determined as $0.63 \pm 0.26 \text{ mG}$ (minimum 0.34 mG - maximum 1.50 mG) in average. The electromagnetic field level in all of the schools in our research is conforming with the recommended limit values.

The noise level in the classroom has been determined as $37.60 \pm 7.09 \text{ dB}$ (minimum 24.60 dB - maximum 48.78 dB) in average when measured when the windows were open and as $35.23 \pm 6.76 \text{ dB}$ (minimum 22.25 dB - maximum 46.42 dB) when measured when the windows were closed. The average noise level of the schoolyards has been determined

as $57.43 \pm 7.77 \text{ dB}$ (minimum 45.00 dB- maximum 69.50 dB). It has been determined in our research that, the schoolyard noise level of 47.6% of the schools, the noise level of 71.4% in the classroom when the windows are open, and the noise level of 59.5% when the windows are closed, comply with the values determined in the standards.

The level of lighting measured in the classrooms when the lights are on and the curtains are closed has been determined as $370.11 \pm 95.15 \text{ lux}$ (minimum 213.66 lux - maximum 586.25 lux) and the level of lighting measured when the lights are off and the curtains are open as $446.62 \pm 164.41 \text{ lux}$ (minimum 150.66 lux - maximum 815.66 lux). The level of lighting in the libraries of the schools has been determined as $525.76 \pm 113.23 \text{ lux}$ (minimum 235.00 lux - maximum 717.00 lux). It has been determined in our research that, the level of lighting of 88.1% of the schools, when the classroom lights are on and the curtains are closed, the level of lighting of 64.3%, when the classroom lights are off and the curtains are open, comply with the standard values. It has been determined that the library lighting level of 65.2% of the schools that have libraries (n=23), complies with the standard values.

The temperature of the classrooms has been calculated as $26.83 \pm 2.12 \text{ }^\circ\text{C}$ (minimum 23.25 °C- maximum 33.66 °C) in average and the humidity level as $50.61 \pm 5.73\%$ (minimum %35.00 - maximum %60.33). According to the measurements made in the schoolyard, the temperature of the school environment has been determined as $28.08 \pm 3.06 \text{ }^\circ\text{C}$ (minimum

Table III: Relationship Between the State of Conformity of the Noise Levels of Schools to the Standards and Grades.

	Grade Average± SS	p
School Environment Noise Level*		
Conforming	79.03±1.24	0.042
Nonconforming	73.79±1.47	
Classroom Noise Level†		
Conforming	80.21±2.15	0.039
Nonconforming	76.62±1.05	

*7th Grades, † 6th Grades

Table IV: Relationship Between the Physical Parameter Measurement Values of Schools and The Grade Average of Students.

Correlation	Grade Average
	r (correlation coefficient)
Level of Lighting when lights are on and windows are closed	0.563
Level of Lighting when lights are off and windows are open	0.480
School environment temperature level	0.491
Total class scores of schools	0.528

23.00 °C- maximum 35.00 °C) and the school environment humidity level as 59.19±10.41% (minimum %32.00- maximum %74.00). In our research, it has been determined that, the classroom temperature values in 42.9% of the schools, and the classroom humidity values in 97.6% are conforming with the standards.

The student grade point average of elementary schools (n=19) has been determined as 81.26±4.86 (minimum 73.43- maximum 88.59). The student grade point average of middle schools (n=23) has been determined as 77.35±4.90 (minimum 69.39- maximum 86.02).

As for the statistical analyses conducted by means of categorising as schools conforming with the school environment noise level standards and those that do not, a statistically significant difference between the grade averages of the seventh grades of schools conforming with the noise standards and schools that do not (p=0.042) has been determined. Similarly, a statistically significant difference between the grade averages of the sixth grades of schools conforming with the in-class noise level standards and schools that do not has also been determined (p=0.039) (Table III).

A negatively significant correlation between the level of lighting in the classroom when the lights are on and the curtains are close and the grade averages of the fifth, sixth, and seventh grades has been determined (respectively; r -0.498 p 0.011; r -0.548 p 0.021; r -0.563 p 0.004). Similarly, a negatively significant correlation between the level of lighting in the classroom when the lights are off and the curtains are open and the grade average of the fifth, sixth, and seventh grades (respectively; r -0.480 p 0.015; r -0.416 p 0.039; r -0.409 p 0.047).

A negatively significant correlation between the school environment temperature level and the grade average of the 4th grades has been determined (r -0.491 p 0.020).

A positively significant correlation between the classroom scores of the schools and the grade averages of the fifth grades has been determined (r 0.528 p 0.007). A negatively significant correlation between the building scores of the schools and the rate of absence of the students has been determined (r -0.371 p 0.011). The correlation between the physical parameter measurement results of the schools and the grades has been given in Table IV.

DISCUSSION

The problems resulting from the school environment affect the learning capacity of children significantly as it does their health. In a study examining the effects of school environmental health conditions on students and teachers, the characteristics related to natural lighting, ventilation, acoustic design and thermal conditions of the school building are described as the main determinants affecting student health (12). The determinant of the students' health are the performance indicators such as the grades, graduation averages of students. The acquisition of values belonging to the variables of noise, lighting, electromagnetic field, temperature, and humidity, which determine the indoor physical environment of the schools in this research through measuring, is the strength of the research. However, the fact that the students' success was evaluated based on the school and there had been no individual measurement conducted is a constraint of the research.

Our findings support that the physical characteristics of classrooms have effect on the success of the students.

The air quality in the indoor volume of schools, in which children who are more defenceless against environmental risks spend a significant amount of their time, affects the health and success of the students negatively due to natural pollution

source (respiration/ CO_2), in case precautions are not taken. Therefore, it is important that enough space and air volume per student, which are indicated also in school environmental health standards, are provided (25,26). In our research, the determination of the conformity of space per student with the standards in nearly all of the classrooms, is positive. However, it has been determined that in only 30.1% of the classrooms, 6 m³ and above air volume per student is provided. In the study carried out by Heath et al, it was determined that the indoor air quality, the absence and the performance of the students result from the effects of the air pollutants on health (27). Bako- Birko et al. has determined in the study they have carried out that, when the speed of the clean air circulation is increased from 0.3-0.5 L/s to 13-16 L/s, the study rate of the students has increased 7% (28). In the study carried out by Shaughnessy similarly, a significant relationship between the increase of the speed of ventilation and the increase of the math scores has been determined (29).

The basis of noise's mechanism of disrupting learning is on the disrupting the student's relationship with pronunciation, reading, and perception during language learning. In the studies carried out, it has been detected that the students receiving education in schools which are exposed to environmental noise, have issues precepting and that their scores on the long-term memory test are low (8). A significant relationship between the school noise level and the grade average of the 6th and 7th grades, has been found. Similarly, in the study carried out by Pujol et al. average school noise level has been determined as 51.5 dB and the students' low scores in math and French classes has been associated with the school noise level ($p=0.02$) ($p=0.01$) (30). In the study carried out by Papanikolaou et al. the reading performance of the children in schools with low noise level (55-66 dB) has shown a statistically significant difference from the children with middle (67-77 dB) and high levels of noise (72-80 dB) ($p<0.001$) (31).

As a component of indoor environment, lighting affects the learning processes, memories, and the attention span of student directly (32). A negatively significant correlation between the lighting levels of the classrooms and the grade averages of the fifth, sixth, and seventh grades has been determined in our research. Similarly, it has been determined in the study carried out by Hescong Mahone Group that, high intensity of light affects vision negatively due to flashing and particularly has a negative effect on the success of the students in math class (33). In the study of Samani it has been detected that the improvement of the lighting conditions in classrooms motivates the students and increases their performance (34). Similarly, In the study carried out by Gilavand et al. (35) it has been shown that lighting affects learning and academic success significantly ($p<0.05$).

Inconvenient temperature and humidity values may disturb the students physically and thus affect their academic success negatively. It has been determined in our research that, the classroom temperature levels of the 42.9% schools, and the

classroom humidity levels of the 97.6% conform with the standards. In the study, Teli et al. (36) has carried out in England, it has been determined that the temperature in classrooms ranges between 19.2-28.9 °C and that the humidity levels are between 40-60%. In the study carried out by Haverinen-Shaughnessy et al. (37) it has been determined that, students who do not receive education under the conditions of a hot classroom have given 4% more correct answers in the test questions, in comparison to other students, and thus the high level of temperature has been associated with headache, having difficulty concentrating, and the increase of absence.

CONCLUSION

In this study, the effect of the environmental parameters of all schools in the Region of Derince, which has a relatively low socio-economic state, on the success and the absence of the students has been examined. It has been determined that the lighting and noise levels are effective on the success of the students and also the building scores of the schools affect the absence of students. In general, the environmental conditions of the schools may be evaluated as mediocre. The deficiencies of the school buildings located in the area we have worked needs to be eliminated and they need to have child-friendly school environment. For this purpose, solutions such as increasing the awareness of teachers and school administrators, re-evaluation of the in-school architectural services, for example; sound-proof insulation panels, adjustment of the amount of in-class natural and artificial light, may be suggested. Minimising the environmental risks resulting from the school environment, shall provide security for children, thus for the society. Should the studies, which shall be carried out with regards to this matter, get planned as intervention studies and focus on individual success, more in detail results might be obtained.

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Clinical and Demographic Characteristics of Pediatric Patients Diagnosed with Localized Scleroderma: A Retrospective Analysis

Lokalize Sklerodermalı Çocuk Hastalarda Klinik ve Demografik Özellikler: Bir Retrospektif Çalışma

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ABSTRACT

Objective: Localized scleroderma (LS), which is also called as morphea, is a rare skin disease with unknown etiology. LS is typically characterized by sclerosis in the dermis and the subcutaneous tissue. The number of retrospective studies examining the epidemiological, clinical and laboratory data of patients with juvenile LS in Turkey is very limited. The purpose of this study was to investigate the clinical and demographic characteristics of pediatric patients under the age of 18, who were followed up with a diagnosis LS, also to evaluate and compare these findings with available literature.

Material and Methods: The medical records of 39 patients, who had been clinically and histopathologically diagnosed with LS and followed up in our clinic between 2012-2018, were retrospectively reviewed. Demographic, clinical and laboratory findings, and treatment options of the patients were recorded.

Results: A total of 39 pediatric patients (8 boys, 31 girls, mean age 12.1 years) with LS were enrolled in the present study. The age at disease onset was 8.6 years. The mean duration of the disease was 3.6 years. The most common type was plaque type morphea. In two cases, there was movement restriction in the legs, and lichen sclerosus was concurrently present in another case. 12 patients had antinuclear antibody positivity, while 3 cases had positive Borrelia antibodies.

Conclusion: Morphea has lifelong complications for children. Early diagnosis and monitoring of morphea in the childhood period is important in order to avoid both physical and psychological sequelae that may occur in the future.

Key Words: Epidemiology, Localized scleroderma, Morphea, Pediatric patients

ÖZ

Amaç: Morfea olarak da bilinen lokalize skleroderma (LS), etyolojisi tam olarak aydınlatılamamış nadir bir deri hastalığıdır. LS tipik olarak dermis ve subkutan dokuda skleroz ile karakterizedir. Türkiye’de juvenil LS hastalarının epidemiyolojik, klinik ve laboratuvar özelliklerinin araştırıldığı retrospektif çalışma sayısı oldukça azdır. Bu çalışmanın amacı LS tanısı ile takip edilen 18 yaş altı pediatrik olgularda klinik ve demografik özelliklerin araştırılması ve bulguların mevcut literatür ile karşılaştırmalı gözden geçirilmesidir.

Gereç ve Yöntemler: 2012-2018 yılları arasında kliniğimizde klinik ve histopatolojik açıdan LS tanısı konulan 39 hastanın medikal kayıtları retrospektif olarak incelendi. Demografik, klinik ve laboratuvar bulguları, ayrıca tedavi modaliteleri kaydedildi.

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 approved by the, YBU Yenimahalle Education and Research Hospital Clinical Research Ethics Committee (IRB NO:17/10/2017-2017/08/09-2017/47).

Contribution of the Authors / Yazarların katkısı: **AKBAS A:** 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. **KILINC F:** 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, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Çalışmaya 39 LS tanısı olan pediatrik hasta (8 erkek, 31 kız, ortalama yaş 12.1 yıl) dahil edildi. Hastalığın başlangıç yaşı 8.6 yıl olarak bulundu. Ortalama hastalık süresi 3.6 yıldır. En sık görülen tip plak morfeaydı. İki vakada bacaklarda hareket kısıtlılığı varken, bir vakada eş zamanlı liken skleroz mevcuttu. 12 hastada antinükleer antikor pozitifliği varken, üç vakada *Borrelia* antikorları tespit edildi.

Sonuç: Morfea çocuk olgularda hayat boyu devam eden komplikasyonlara neden olabilir. İlerleyen yıllarda ortaya çıkabilecek hem fiziksel, hem de psikolojik sekellerin önlenmesi için çocuk yaş grubunda morfeanın erken teşhis ve takibi oldukça önemlidir.

Anahtar Sözcükler: Epidemiyoloji, Lokalize skleroderma, Morfea, Pediatrik olgular

INTRODUCTION

Localized scleroderma (LS), which is also known as morphea, is a rare inflammatory skin disease, that causes sclerosis in the dermis and subcutaneous tissue. Although the exact underlying mechanisms have not been fully understood yet, many factors have been implicated in the etiopathogenesis of morphea (1-3). Morphea is more frequent in females and the incidence has been reported to be 0.4 to 2.7 % (1,2,4-6). The prevalence of morphea is equal in adults and children (2,7). 90 % of children with morphea are aged between 2 and 14 years old. Morphea is well-known with the potential to cause functional and cosmetic problems. While the erythematous purple patches and plaques are observed in the inflammatory phase, they become white and sclerotic lesions and surrounded by a violet halo over time. These lesions generate post-inflammatory hyperpigmentation during improvement (1,4,5).

There have been many classifications related to morphea, while the most recent classification belongs to Laxer et al. (8). 20 % of morphea patients consist of children, and it is 10 times more common than systemic sclerosis (4,7,9,10). Although several studies are available worldwide on the epidemiological, clinical and laboratory data of patients with pediatric morphea, there is a shortage of these data in our country (11-13). The aim of the present study was to investigate the demographic, clinical, laboratory characteristics and treatment modalities of pediatric patients with morphea, also to compare our findings with the available literature.

MATERIAL and METHODS

This study was approved by the local ethics committee (IRB NO:17/10/2017-2017/08/09-2017/47). The files of 39 patients, who had been clinically and histopathologically diagnosed with morphea and followed up in our clinic between 2012-2018, have been retrospectively reviewed. Patients aged 18 and below have been included in the study. Demographic characteristics, physical examination and laboratory findings (hemogram, sedimentation rate, biochemistry analysis, *Borrelia* antibody, antinuclear antibody (ANA), antids- DNA (double stranded DNA antibody) etc.) of the patients were recorded. Age of disease onset, its duration, clinical type, involved anatomic site, accompanying systemic signs and symptoms, triggering factors, laboratory findings, family history of rheumatic disease,

and treatment options were recorded. The presence of accompanying diseases was also investigated.

The disease subtypes were classified as localized plaque, linear, generalized and mixed type according to the Laxer classification (8). One or several plaques that were placed in maximum 2 anatomic sites (head - neck, each extremity, trunk) in oval or rounded configuration were regarded as localized morphea and the type which involved at least 2 anatomical sites with 4 or more infiltrated plaques, each of which was larger than 3 cm, was considered as generalized morphea; sclerotic lesions with linear fibrotic banding (affecting extremities and head region - en coup de sabre (ECDS) were accepted as linear type; the type containing linear and plaque types was considered as mixed type; the type with the involvement of skin and deep layers of the connective tissue was regarded as pansclerotic morphea (8).

Patients have been divided into 4 groups depending on their age: age 0-2 (baby), age 3-5 (preschool), age 6-11 (school child) and age 12-18 (adolescent). 0-2 years of age consisted of 2.6 % (n=1) of cases, ages between 3-5 consisted of 7.7 % (n=3), ages between 6-11 years consisted of 30.8 % (n=12), and ages between 12-18 years consisted of 59 % (n=23) cases of the patients. Statistical analysis was performed using SPSS software, Version 20 (SPSS Inc., Chicago IL, USA). Frequencies were calculated for variables related to demographic and clinical patient characteristics. Qualitative variables were expressed in percentage. Quantitative variables were expressed in mean values.

RESULTS

A total of 39 pediatric patients (8 boys 31 girls, mean age 12.1 years, range: 2-18 years) with morphea were enrolled. 79.5 % of the patients (n=31) were girls, the female/male ratio was 3.9;1. The majority of patients were in the age group of 12-18 years (n=23). The mean duration of disease before diagnosis was 3.6 years. The age of disease onset was 1-16 with an average of 8.6. The most common morphea type was plaque type with 56.5 % (n=22); followed by linear type with 25.6 % (n=10) and generalized type with 10.2 % (n=4), and mix type with 7.7 % (n=3). There were no deep and pansclerotic types.

The most common site of anatomic involvement was the trunk. Only trunk involvement was 33.3% (n=13), while the involvement

Table I: Age, gender and clinical characteristics of the cases.

Patient Groups P.No -%	F/M	Mean age	The Age of Onset	Mean D.period	Patient numbers/ Lesion Type	Patient numbers/ Localization%
0-2 y (n=1 2.56%)	1/-	2 years	1 year	1 year	1-Plaque	On the left leg
3-5 y (n=3 7.69%)	2/1	4 years	2,6 years	1.3 years	1-Linear 2-Plaque	1-Face 1-Body 1-Face+trunk
6-11 y (n=12 30.76%)	10/2	8.25 years	6.8 years	1.8 years	6-Linear 5-Plaque 1-Mix	2-Face 4-Body 1-Face+trunk 5-Legs
12-18 y (n=23 58.9%)	18/5	15.1 years	11 years	14.6 years	14-Plaque 4-Generalized 3-Linear 2-Mix	5-Face 1-Nose 2-Forehead 2-Cheek 5-Legs 8-Trunk 5-More than one
TOTAL n=39 100%	31/8 3.9:1	12.1	7.0	3.56 years	22-Plaque (56.4%) 10-Linear (25.6%) 4-Generalized (10.2%) 3-Mix (7.69%)	8-Face- 20.5% 13-Trunk-33.3% 11-Legs-28.2% 7-More than one-17.9%

Table II: Comparison of laboratory findings, treatment and concomitant diseases by age groups.

Patient Groups P.No	Concomitant Diseases, Trauma story Family story	ANA, AntiDsDNA Positivity The other lab findings P.No	Treatments P.No
0-2 years (1)	Restriction of left leg motion -	-	Topical Steroid
3-5years (3)	-	1-ANA +	1-Topical steroid 2-Methotrexate 1-Hydroxychloroquine 2-Systemic Steroid 1-Calsipotriol
6-11y (12)	2-Vitamin D deficiency 1-Anemia (iron deficiency) 1-Genital Lichen sclerosis 1-Deformities of leg 1-Diabetes Mellitus 1-Trauma story +	5-ANA+ 1-Anti dsDNA + 1-CRP +	2-Topical steroid+2-Calsipotriol 6- Calcineurin inhibitors 2-Methotrexate 3-Colchicine 1-Systemic Steroid 2-UVA -1
12-18y (23)	6-Anemia (Iron deficiency) 5-VitaminB ₁₂ deficiency 1-Hashimoto tiroiditis 3-Trauma story +1-Arthritis story of his brother	6-ANA+ 1-Anti dsDNA + 1-CRP + 3-Borrelia antibodies 2-RF +	8-Topical steroid+Calsipotriol 6- Calcineurin inhibitors 7-Colchicine 2-Methotrexate 1-Systemic Steroid 1-Hydroxychloroquine 2-Narrow bandUVB, 1-Laser 2-Depigmentation therapy 1-Isotretinoin
Total % (39)	7-Anemia (iron deficiency), 17.9% 5-VitaminB ₁₂ deficiency, 12.8% 2-Vitamin D deficiency 5.1% 1-Genital LS, 2.5 % 1-Hashimoto tiroiditis, 2.5% 1-Diabetes mellitus, 2.5% 4-Trauma story +,10.2% 2-Deformities of leg, 5.1% 1-Arthritis story of his brother, 2.5%	12- ANA +, 30.7% 2 Anti ds DNA, 5.1% 3- Borrelia antibodies, 7.7% 2-RF +, 5.1% 2-CRP +, 5.1%	1-Topical steroid, 2.5 % 10-Topical steroid+Calsipotriol, 25.6 % 12- Calcineurin inhibitors, 30.7% 10-Colchicine, 25.6% 6-Methotrexate, 15.4% 2-Hydroxychloroquine, 5.1% 4-Systemic Steroid, 10.2 % 1-Isotretinoin, 2.5 % 2-Narrow band UVB, 5.1% 2-UVA-1, 5.1% 2-Depigmentation therapy, 5.1% 1-Laser, 2.5%

**Figure 1:** Plaque morphea.**Figure 2:** En coup de sabre lesion on forehead.**Figure 3:** Linear morphea on the leg.**Figure 4:** Generalized atrophic plaque lesions.

of extremities alone was 28.2 % (n=11), the involvement of more than one site was 17.9 % (n=7), and also there was head-neck involvement in 20.5 % (n=8) of patients. The plaque types were on the nose (n=1), forehead (n=1) and cheeks (n=1). The other plaque localization was trunk and legs. The others (n=5) belonged to linear-ECDS type (Figures 1-4). Five cases of linear morphea were on the legs. Only one patient had an association of autoimmune disease (Hashimoto's thyroiditis) and diabetes mellitus. There was a family history of autoimmune disease in one patient.

Twelve patients had ANA positivity (30.7%) and antids- DNA antibodies were found to be higher in 2 cases (5.2%), 2 patients had C reactive protein (CRP) and rheumatoid factor (RF) positivity, whereas antihistone antibodies and eosinophilia were not detected in any of the cases. In three cases, Borrelia-IgG antibodies were positive. 7 patients (17.9%) had iron deficiency; five patients (12.8%) had vitamin B12 (vitB12) deficiency. The age, gender and clinical characteristics of the patients were demonstrated in Tables I. Preferred treatment modalities of the patients were as follows: topical combination of calcipotriol and cortisone in 10 cases (25%), colchicine in 10 cases (25%), methotrexate (MTX) in 6 cases (15.3%), narrowband UVB and UVA-1 in 2 cases (each one, 5.1%), systemic steroid in 4 cases, hydroxychloroquine in 2 cases (5.1%) and systemic isotretinoin in one case (2.5%). One patient did not receive treatment. Laser treatment was applied to three patients, who had scars. Table II demonstrates comparison of laboratory findings, treatment and concomitant diseases by age groups. Treatment results could not be evaluated because the study was retrospective.

DISCUSSION

The rate of affected females is 2-4 times higher than affected males in morphea (2,4,5). The most comprehensive one of the multi-centered studies up to this date belongs to Zulian et al. (14) with 750 juvenile patients. Zulian (14) found the ratio of females/males as 2.4, Mertens et al. (16) as 2.8, Marzano (17) as 2.0, and Cristen Zaech (15) as 2.6, while Wu et al. (18) determined it as 3.5 and Leitenberger (19) as 3.7. Although the ratio of girls/boys was found to be between 2.4 and 1.2 in other studies performed in our country, we found it to be 3.9 in our 39 cases, which is comparable with the most available literature (11,12).

Age of disease onset has been reported as 2-14 years in various studies. We found that the mean age of onset was 8.6 years. The interval between the first clinical manifestations and the diagnosis of morphea ranges from 1 month to 8 years, with a mean of 0.93-2.3 years (14,20). In Zulian et al.'s (14) study, it was reported that the diagnosis of 20% of morphea patients took more than 2 years. This duration was found to be 3.6 years in our study. This may be due to the fact that primary care physicians and pediatricians might fail to recognize morphea adequately, and the arrival of patients to the dermatologists is delayed.

The incidence of linear morphea varies between 25%-70% (2,5,21). It is well-known that plaque type is seen more frequently in adults, and linear morphea is seen more frequently in children (2,5,6,14,19). Many researchers have made observations supporting this view (14-16,22,23). In a study from Turkey, Izol et al. (11) also stated that they encountered the linear type morphea more commonly. Marzano et al. (17) suggested that plaque type morphea is a more common subtype in children with a range of 48.4 %. Meanwhile according to results of our study, the incidence of plaque type was 56.4 %, while the linear type was 25.6 %. From this aspect, our study is similar to that of Marzano et al.'s (17). This rate was reported for plaque type by Christen Zaech (15) as 36 %, Mertens (16) as 28.6 %, Leitenberger (19) as 27.9 %, and Wu et al. (18) as 15 %. Mix type, which includes more than one type, is seen in 15 % of the children (2,21). Marzano et al. (17) reported that the rate of mix type was determined as 14.3 %, while Wu et al. (18) reported it as 20% and Zulian (14) as 23%. In our 39-case study, the rate of mix type was 7.7 %. In the generalized type morphea, there are four or more plaques in more than one anatomic site. It is observed in a range of 7-9 % (2,5). In our study, the rate of generalized type morphea was 10.2% (4 cases).

Some triggering factors such as vaccination, drugs, chemical substances, trauma, insect bites, sunburn, infections, radiation, autoimmunity and psychological stress may play a role in the etiopathogenesis of morphea (3,24). The presence of environmental factors was found in 13.3% (n=100) of the patients, 7.3% of which was traumatic (14). Only 4 of our patients (10.2 %) had an history off trauma and were compatible

with the literature. The role of *Borrelia burgdorferi* infection in the etiology of morphea has been questioned for many years. In recent years, the relationship with *Borrelia Burgdorferi* and morphea has been reported. Although there are reports describing clinical improvement of morphea with treatment of *Borrelia Burgdorferi*, some of the results are contradictory (25). In our study, we detected three cases, whom *Borrelia* IgG antibodies were positive. These patients had not previously received treatment for *Borrelia* infection.

In some studies, extracutaneous changes have been reported especially in the group of morphea starting in childhood (7,24). We, however, did not detect extracutaneous involvement in our patient group. This may be due to the inadequacy in the monitoring of the disease progression because of the retrospective nature of the study.

In juvenile morphea frequently autoimmune diseases can accompany the disease. This ratio can vary from 1% to 3% (20). In some studies, the association of autoimmune diseases with morphea has been reported as high as 17% (20). In a study conducted by Leitenberger et al. (19), 4.9 % of morphea cases showed an accompanying autoimmune or rheumatologic disease such as vitiligo, psoriasis, celiac disease, alopecia areata, autoimmune thyroiditis, etc, similar to what Ceylan et al. (26) reported from our country. In our study, there were only one case of autoimmune thyroiditis, diabetes mellitus and lichen sclerosis. However, among our patients, there were 7 cases with (17.9 %) iron deficiency anemia and 5 (12.8%) cases with vitamin B₁₂ deficiency, which are frequently found in this age group. This may be related to inadequate intake of iron and vit B₁₂ in the diet of children.

The presence of autoimmune disease in the family is 12%-25% higher in pediatric morphea than in adults (19,20). It has been reported that familial autoimmunity is more common in the generalized and mixed type (15). Zulian et al.(14) found this ratio to be 23.5% for generalized type, 12% for linear and plaque type, while Leitenberg determined it as 4.9% (19). One of our patients with plaque morphea had a sibling history with rheumatoid arthritis (2.6%).

Linear morphea is more frequent in the first two decades and causes deformation due to the fact that it may involve deep tissues affect the underlying tissue (4,6). Piram et al. (27) also stated that this type of morphea may be refractory to treatment, and that it needs long-term follow-up. Marzano et al.(17) reported that musculoskeletal anomalies such as limb contracture, limited range of motion and arthralgia etc. in children were normally 12%, while it was 45% children with linear morphea. In our study group, orthopedic complications were detected in only two patients with linear morphea, which were on the left side. This may support the view that orthopedic complications are more common in children with linear morphea.

Among the studies conducted, changes in various laboratory parameters were indicated in patients with morphea (5,28,29). Patients with extracutaneous involvement were found to have

increased levels of inflammatory parameters such as ESR and CRP (9). In those who have joint damage, the RF rate increases up to 25 %-40% (9). In terms of the inflammation parameters, only 2 cases (5.12%) had elevated CRP and RF in our patient group.

Autoantibody positivity is also seen very commonly in morphea (30,31). However, the clinical and prognostic significance of these autoantibodies is still not understood (9). The presence of extensive morphea in a patient who had an ANA positivity of 1/1000 titer may indicate that serology may be important in terms of progression. Woo et al. noted that ANA and RF positivity should be considered as sign in terms of extracutaneous involvement (30). Many autoantibody positivity, such as ANA, antids- DNA, anti-histone antibody, and anti-Scl 70 has been reported in morphea cases. Meanwhile, ANA positivity was found in 5.9%-73% of the cases on the literature (9,17,19). It has been reported that ANA positivity ratio is higher in generalized and mix types (19). These investigators reported that ANA positivity was 44%-53% in adults and 26%-53% in children, indicating a difference between the two groups. Parlak et al.(13) found in their study that ANA positivity was 26.1% for the generalized type and only 8.7% for the mixed type. Marzano et al. (17) detected a similar rate of ANA positivity (26%-53%), while other autoantibodies were detected in 7%, and it was higher in the generalized type. The rate of ANA positivity was 30.7% in our study (in 12 cases).

In addition to ANA; Scl-70, anti-centromere, anti-dsDNA, and anti-histone antibody positivity can be seen in patients. Zulian et al. (14) found antids-DNA at 4%. In a study performed by Sato et al. (29), anti-histone antibodies were found to be associated with the number of morphea lesions and it was suggested that it could be a serologic marker for generalized involvement. In our study, the antids-DNA antibodies were present in only 2 (5.1 %) cases, whereas no anti-histone antibody was detected in any case.

Since the cause of morphea is not known exactly, there is no effective specific treatment. The goal of the treatment is to reduce the progression of the disease in the early period in order to prevent functional and cosmetic complications. Treatment options are assessed according to the type and severity of the disease, and the presence of complications (1,2,5). For localized plaque type morphea, first-line treatment has been reported as topical steroids, tacrolimus, imiquimod, combination of calcipotriol and betamethasone, and lesion limited phototherapy [UVA, UVA1, narrowband UVB (nbUVB)] (31,32). Phototherapy, combination of systemic steroids and methotrexate (MTX), hydroxychloroquine, D penicillamine, cyclosporine, sulfasalazine, photopheresis, mycophenolate mofetil (MMF) are the treatment options in the generalized morphea (5,32,33).

In our study, MTX (15.3%) was given to each of the patients with generalized, mixed and ECDS. Systemic steroids were administered to 4 patients (10.2%). Although colchicine is not

mentioned in the morphea treatment guideline, inhibitory effect of this drug on fibroblast proliferation, the effect on elastic fibers, and its anti-inflammatory features have been shown "in vitro" (34). Colchicine is a preferred drug in our country, as well as in Korea (35). Some researchers in our country have reported the effectiveness of colchicine treatment in their patients (12,13). In this study, colchicine treatment was given to 10 patients (25.6%). Spontaneously regression within 3 to 5 years is a matter of fact for morphea, thus treatment for plaque type morphea is generally regarded as unnecessary (9,4,32). In one of our cases with widespread, plaque-like lesions on the back, the treatment was refused by the patient and parents. After 10 years, post inflammatory hyperpigmentation was present, but there was no progress in the disease.

In our study, 24 (61.5%) patients with limited plaque type lesions received topical corticosteroids, calcipotriol, calcipotriol+steroid combination, and tacrolimus and pimecrolimus. Preferred treatment modalities were systemic steroids in 4 cases (10.2 %), narrowband UVB, UVA 1 and hydroxychloroquine in two cases (5.1%) and isotretinoin in one case (2.5%). One patient did not receive any treatment. Two patients (5.1%) received scar treatment. It has been shown in various trials that MTX and MMF may be good treatment options in resistant cases (16,32,36). Zulian treated 37% of their patients with MTX, 2% with cyclosporine, 49% with steroids (14% topical steroids, 35% systemic steroids), 26% with D penicillamine, 4% with PUVA, 10% with vitamin D and 17 % with nonsteroidal anti-inflammatory drugs (NSAIDs). In our study, 15.4% of the patients were administered MTX. Treatment results could not be evaluated because the study was retrospective.

CONCLUSION

Although linear morphea was reported as the most common form of pediatric morphea, plaque type morphea was more frequently observed in our study. Due to the cosmetic and functional deformities that can develop in the linear type, early diagnosis and treatment are important. Patients should be carefully examined for extracutaneous symptoms, and further investigations should be performed when necessary. ANA should be followed in terms of systemic and extracutaneous involvement.

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Mycophenolate Mofetil Treatment in Childhood Steroid-Sensitive Nephrotic Syndrome: Single Center Experience

Çocukluk Çağı Steroid Duyarlı Nefrotik Sendromda Mikofenolat Mofetil Tedavisi: Tek Merkez Deneyimi

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ABSTRACT

Objective: We aimed to investigate the efficacy of mycophenolate mofetil (MMF) for maintaining remission and reduce the number of relapses in childhood steroid-sensitive nephrotic syndrome. The effects of MMF on growth and blood pressure parameters were also evaluated.

Material and Methods: This retrospective, single-center observational study included patients with steroid-sensitive nephrotic syndrome who were treated using MMF between 2009 and 2019 in the Department of Pediatric Nephrology in our hospital.

Results: Ten patients had steroid-dependent nephrotic syndrome; six patients frequently had relapsing nephrotic syndrome in this study. The mean duration of the disease was 93.3 ± 25.0 months and the mean duration of the MMF onset was 33.9 ± 16.7 months after diagnosis. Ten patients showed a 50% or greater reduction in the relapse rate and the prednisolone treatment was discontinued in eight patients for six months or more. Compared to the previous year, before the start of the MMF treatment, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. The height z score and the median office systolic blood pressure standard deviation scores of the patients improved after MMF treatment (respectively $p = 0.003$, $p = 0.01$).

Conclusion: The findings suggest that MMF may lead to decreased relapse rates and cumulative steroid dose, which has a positive effect on growth and blood pressure parameters in steroid-sensitive nephrotic syndrome.

Key Words: Blood pressure, Childhood, Growth, Mycophenolate mofetil

ÖZ

Amaç: Mikofenolat mofetilin çocukluk çağı steroide duyarlı nefrotik sendromda remisyonu sürdürme ve relaps sayısını azaltmadaki etkinliğinin belirlenmesi amaçlandı. Ayrıca MMF'in büyüme ve kan basıncı üzerindeki etkileri değerlendirildi.

Gereç ve Yöntemler: Bu retrospektif, tek merkezli gözlemsel çalışma, 2009-2019 yılları arasında hastanemiz çocuk nefroloji kliniğinde MMF ile tedavi edilen steroide duyarlı nefrotik sendromlu hastaları içermektedir.



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Contribution of the Authors / Yazarların katkısı: **GUNGOR T:** 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. **KARA EROGLU F:** 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. **KARGIN CAKICI E:** Organizing, supervising the course of progress and taking the responsibility of the research/study. **YAZILITAS F:** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. **CAN G:** Organizing, supervising the course of progress and taking the responsibility of the research/study. **KURT SUKUR ED:** Reviewing the article before submission scientifically besides spelling and grammar. **OZDEL S:** Reviewing the article before submission scientifically besides spelling and grammar. **CELIK KAYA E:** Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **KARAKAYA D:** Taking responsibility in necessary literature review for the study. **BULBUL M:** Constructing the hypothesis or idea of research and/or article.

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Bulgular: Çalışmamızdaki 10 hasta steroida bağımlı nefrotik sendrom, 6 hasta sık relaps nefrotik sendromdu. Ortalama hastalık süresi 93.3 ± 25.0 ay ve tanıdan sonra ortalama MMF başlangıç süresi 33.9 ± 16.7 aydı. On hastanın nüks oranında %50 veya daha fazla azalma görüldü ve prednizolon tedavisi 8 hastada 6 ay veya daha uzun süre kesildi. Bir önceki yıla kıyasla, 12 aylık MMF tedavisinden sonra nüks oranında %52.7 ve yıllık kümülatif steroid dozunda %36.6 azalma oldu. Mikofenolat mofetil tedavisi sonrası hastaların boy z skoru ve ortanca ofis sistolik kan basıncı standart sapma skorları iyileşti (sırasıyla $p = 0.003$, $p = 0.01$).

Sonuç: Mikofenolat mofetil, steroid duyarlı nefrotik sendromda nüks oranlarını, kümülatif steroid dozunu azaltarak büyüme ve kan basıncı ölçümleri üzerine olumlu etkilere neden olur.

Anahtar Sözcükler: Kan basıncı, Çocukluk çağı, Büyüme, Mikofenolat mofetil

INTRODUCTION

Idiopathic nephrotic syndrome (NS) is the most common chronic glomerular disease in children between 1.5 and 10 years of age (1,2). Approximately 80-90% of these children respond to oral steroids, and in these cases, it is called steroid-sensitive NS (SSNS). Approximately 60% of children with SSNS develop frequently relapsing NS (FRNS) or steroid-dependent NS (SDNS). However, 40-75% of all SSNS cases require long-term steroids and/or other immunosuppressive agents, such as cyclophosphamide, calcineurin inhibitors and mycophenolate mofetil (MMF), to maintain remission and prevent frequent relapses (2-4).

MMF is a prodrug of mycophenolic acid and classified as a reversible inhibitor of inosine monophosphate dehydrogenase. Mycophenolate is used in combination with other immunosuppressant drugs, such as cyclosporine and corticosteroids, to prevent organ rejection after hepatic, renal and cardiac transplants. In addition to the above uses, MMF has also been studied for the treatment of nephrotic syndrome, nephritis and other complications of autoimmune diseases. MMF has been evolving gradually as a new therapeutic agent for pediatric idiopathic NS, especially as a steroid-sparing agent for the prevention of relapses (5,6).

In this study, we aimed to investigate the efficacy of MMF for maintaining remission and reducing the number of relapses in childhood SSNS. Furthermore, the effects of MMF on growth and blood pressure (BP) parameters were evaluated.

MATERIALS and METHODS

This retrospective, single-center observational study included 16 patients with SSNS who were treated with MMF between 2009 and 2019 in the Department of Pediatric Nephrology. The inclusion criteria in this study were as follows: Patients who were 1-18 years of age at the start of the MMF treatment and they had a minimum follow-up time of 12 months after the start of the MMF treatment.

Patient medical records, including clinical and demographic characteristic like age, gender, weight, height, and BMI, physical examination findings, including BP at presentation and

each follow-up visit, and laboratory findings, such as serum creatinine, albumin, urinalysis, urinary protein creatinine ratio and 24-h protein excretion, were retrospectively reviewed.

Standard height, weight, and BMI scores were based on Turkish children's growth curves. BMI was calculated as $\text{kg/height (m}^2\text{)}$. Blood pressures of patients were measured in the out patient setting after a resting period for at least 10 minutes. Mean standard deviation scores (SDS) of three consecutive systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements by the auscultatory method were calculated (7).

Standard definitions were used for NS, remission and relapse (3). A frequent relapse was defined as two or more relapses within six months of the initial response or four or more relapses in any 12-month period. Steroid dependence was defined as two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy (1-4).

The MMF treatment was started after steroid remission was achieved and it was administered to the patients in two divided doses, with an average dose of $1000-1200 \text{ mg/m}^2/\text{day}$. All of the patients received cyclosporine or cyclosporine and cyclophosphamide as other immunosuppressive therapy for at least six months before being treated with the MMF. The frequency of relapse and duration of remission before and after MMF treatment were compared.

This study was approved by the Clinical Research Ethics Committee of Ankara Kecioren Training and Research Hospital (1963 / 11.09.2019).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables were shown as mean $\pm$ SD, and nonparametric variables were shown as median and IRQ. Categorical variables were presented as numbers and percentages. Student's t-test was used to compare parametric variables and the Mann-Whitney U test was used to compare nonparametric variables. The χ^2 test or Fisher's exact test was used to compare categorical variables. The level of statistical significance was set at $p < 0.05$.

RESULT

Sixteen patients who received MMF for FRNS and SDNS were included in this study. The mean follow-up duration was 7.7 ± 2.1 years. All of the patients received cyclosporine or cyclosporine and cyclophosphamide as other immunosuppressive therapy for at least six months before the MMF treatment. Five of the patients were treated using cyclosporine and cyclophosphamide, and 11 of the patients were treated using cyclosporine alone.

The mean age of the patients was 164.8 ± 24.1 months, and the mean age of diagnosis was 70.8 ± 34.1 months. The female to male ratio was 0.8. The mean duration of the disease was 93.3 ± 25.0 months, and the mean duration of the MMF onset was 33.9 ± 16.7 months after diagnosis. The mean dosage of MMF used was 1046.8 ± 78.4 mg/m²/day. Ten of the patients had SDNS; six patients had FRNS. The renal biopsies were consistent with minimal change disease in nine patients, focal segmental glomerulosclerosis in six patients, and mesangial proliferation in one patient.

The MMF treatment was started after steroid remission was achieved. The number of relapses after the MMF treatment decreased from 3.6/year to 1.7/year, which was significantly lower ($p = 0.000$). Ten of the patients showed a 50% or greater reduction in the relapse rate and the prednisolone treatment was discontinued in eight patients for six months or more. None of the patients had diarrhea, hematological abnormalities or impaired renal function.

Compared to the previous year, before the start of the MMF treatment, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. Relapse numbers of the SSNS patients before and after MMF treatment are given in Figure 1. The mean cumulative steroid dose was 232.5 ± 27.3 mg/kg/year for 0-12 months before MMF and the mean cumulative steroid dose 0-12 months post MMF decreased to 147.1 ± 94.3 mg/kg/year ($p = 0.004$).

The median BMI z-score decreased from 0.8 (IQR; -1.3 - 2.4) at the time MMF was initiated to 0.5 (IQR; -1.4 - 2.9) at the last follow-up visit ($p = 0.25$). However, no significant difference

was detected. The median height z-score at the time of MMF initiation was -0.8 (IQR; -3.2-0.9) and the median height z-score at the last follow-up visit was -0.7 (IQR; -2.4-1.3). The height z score in patients improved significantly after the MMF treatment ($p = 0.003$).

The median office SBP SDS at the time of MMF initiation was 0.5 (IQR; -0.8-2.3) and the median office SBP SDS at the last follow-up visit was -0.2 (IQR; -0.8-1.7) ($p = 0.01$). The median office DBP SDS at the time of MMF initiation was 0.3 (IQR; -0.3-2.3) and the median office DBP SDS at the last follow-up visit was 0.2 (IQR; -1-1.8) ($p = 0.08$). Office SBP SDS of the patients before MMF was significantly higher than after MMF. Office DBP SDS of patients before MMF did not differ significantly after MMF. Clinical and laboratory characteristics of patients before and after MMF treatment are given in Table I.

DISCUSSION

The present study aimed to investigate the effects of MMF on disease outcome, blood pressure levels and growth parameters in pediatric SSNS patients. MMF acts by inhibiting de novo purine synthesis by inhibiting the mofetil inosine monophosphate dehydrogenase enzyme. In particular, it inhibits T and B lymphocyte proliferation. These functions may be accountable for the amelioration of inflammation and/or the structural remodeling characteristics of the glomerular disease (6,8,9).

Steroid dependent NS and FRNS are clinical conditions with high morbidity due to the toxicity of the long-lasting steroid therapy with high doses of prednisone, as well as to the length of the disease (2,3). Over the past decade, there have been many studies on the benefits of MMF treatment in SDNS and FRNS. In most of the studies, the MMF was shown to result in a significant reduction in the frequency of relapses, as well as the cumulative dose of the steroid required, irrespective of the previous alternative drugs used (5,10,11). MMF also contributes to renal function by reducing the cyclosporine and/or steroid-induced effects. Previous studies have shown efficacy and protection for 12 months or more (5,11-13). Our study suggests that although the MMF was useful for preventing relapses and

Table I: Clinical and laboratory characteristics of patients before and after MMF treatment.

	Before MMF treatment (n=16)	After MMF treatment (n=16)	p
BMI z-score, median (IQR)	0.8 (IQR; -1.3 - 2.4)	0.5 (IQR; -1.4 - 2.9)	0.25
Height z-score, median (IQR)	-0.8 (IQR; -3.2 - 0.9)	-0.7 (IQR; -2.4 - 1.3)	0.003
Office SBP SDS, median (IQR)	0.5 (IQR; -0.8 - 2.3)	-0.2 (IQR; -0.8 - 1.7)	0.01
Office DBP SDS, median (IQR)	0.3 (IQR; -0.3 - 2.3)	0.2 (IQR; -1 - 1.8)	0.08
CSD, mg/kg/year, mean $\pm$ SD	232.5 ± 27.3	147.1 ± 94.3	0.004
Serum glucose level, mg/dL, mean $\pm$ SD	97.2 ± 18.9	98.1 ± 17.5	0.86

BMI: body mass index, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure, **CSD:** cumulative steroid dose

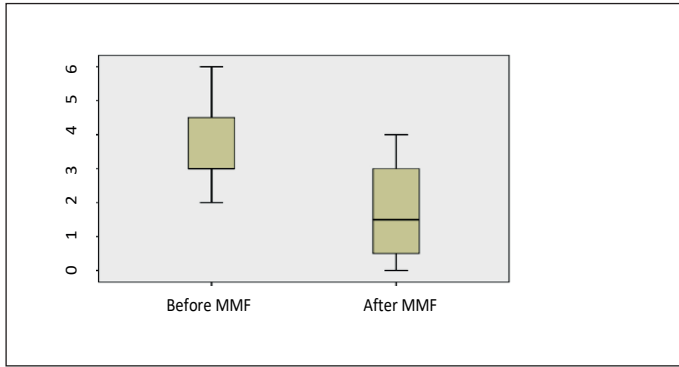


Figure 1: Relapse numbers of the SSNS patients before and after MMF treatment.

sparing steroids, it had no disruptive effect on the disease. The number of relapses after the MMF treatment decreased from 3.6/year to 1.7/year ($p = 0.000$) in our study. When compared to the previous year, before the start of the MMF therapy, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. Ten of the patients showed a 50% or greater reduction in the relapse rate, and the prednisolone treatment was discontinued in eight patients for six months or more. In all of the studies, the MMF showed the ability to decrease the relapse rate and the cumulative prednisone dose (5,8,14,15). Consistent with the literature, our study showed similar positive effects regarding steroid sparing.

It should be noted that there is considerable non-uniformity in both the MMF dosage and duration and in the other drugs used both before the MMF and with the MMF. The MMF dosage was calculated based on the body weight and the body surface area, and it varied from 600 mg/m²/day to 1200 mg/m²/day and from 25 mg/kg to 40 mg/kg, respectively. The mean dosage of MMF used was 1046.8±78.4 mg/m²/day in our study. In addition, there seems to be a wide variation in the therapy duration, from three months to seven years. The previous studies have not shown any significant variations in the outcomes regarding the efficacy and side effects based on the MMF dosage administered per day (5,9,16,17). However, the studies involving MMF for longer durations provide an indication that the MMF is more efficacious for maintaining remission if the therapy duration is increased from several months to several years. Some studies have concluded that administering MMF for more than 12 months is more efficacious than administering it for six months. Moreover, the treatment continuation beyond 12 months resulted in sustained steroid-sparing and reduced the need for alternative treatments while maintaining low relapse rates (14,17,18). The mean duration of the MMF onset was 33.9±16.7 months after diagnosis. This study included the use of MMF for more than 12 months for the benefit of maintaining remission.

The principal toxicities of MMF are gastrointestinal and hematological and they include leukopenia, diarrhea, and vomiting. MMF has an efficacy similar to that of cyclosporine,

but with fewer side effects, especially no risk of nephrotoxicity and no adverse cosmetic events. Digestive trouble, infectious events, anemia, lymphopenia and thrombocytopenia have been reported in several studies, but they were always mild and transient (4,18-20). None of the patients in our study required an MMF withdrawal due to unacceptable side effects.

There are few studies on the effects of other immunosuppressants on growth in children. In the present study, the height z score in 75% of the patients improved following MMF treatment, and the median height z score at the last follow-up visit was higher than at the time of initiation of MMF treatment ($p = 0.003$). MMF had a similarly positive effect on BMI in the SSNS patients in this study, but no significant difference was detected ($p = 0.25$). The median office SBP SDS of patients before the MMF treatment was significantly higher after MMF. The median office SBP SDS of patients improved after the MMF treatment ($p = 0.01$). These effects may arise from the decrease in cumulative steroid dose after MMF treatment. Although our patient group was relatively few, to our knowledge, this is the first study in the literature evaluating the effects of MMF on growth and blood pressure parameters in children with SSNS.

In conclusion, long-term treatment with MMF has been shown to reduce the relapse rates in patients with SSNS. MMF causes decreased cumulative steroid dose, which had a positive effect on growth, blood pressure parameters in SSNS. MMF seems to have a positive efficacy and side effect profile as a steroid protective agent in maintaining the remission in childhood SSNS. Although there appears to be general agreement on the efficacy of MMF in preventing relapses in NS, there is still no consensus on the optimal dosage and duration of MMF treatment. These data support the efficacy and safety of MMF treatment for longer than 12 months. The limitations of the present study are its retrospective design and the low number of cases.

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Çocukluk Çağı Plevral Efüzyon Nedenleri, Klinik Bulguları ve Yönetimi; Retrospektif Bir Analiz

A Retrospective Analysis; Etiological Evaluation of Pleural Effusion in Children, Clinical Presentation and Managemet

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ÖZ

Amaç: Plevral efüzyon çocukluk çağında ciddi morbidite ve mortalite nedenidir. Bu çalışmada plevral efüzyon tanısı ile hastanede yatırılan çocuklarda etyolojik sınıflama yapılarak hastaların izlem ve tedavilerini araştırmak amaçlanmıştır. Ayrıca, plevral efüzyonların en sık nedeni olan parapnömonik efüzyonların yıllar içerisindeki değişimi araştırılmıştır.

Gereç ve Yöntemler: Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Sağlık Uygulama ve Araştırma Hastanesi Pediatri Servisleri ve Yoğun Bakım Ünitesi'ne Ocak 2012- Aralık 2017 tarihleri arasında plevral efüzyon tanısı ile yatırılan çocuk hastalar değerlendirildi. Retrospektif tanımlayıcı özellikte olan bu çalışmada 0-18 yaş arası 135 hasta incelendi. Hastaların demografik ve klinik özellikleri, fizik muayene bulguları, altta yatan ek hastalık varlığı, laboratuvar verileri, görüntüleme yöntemleri, takip ve tedavileri incelendi.

Bulgular: Plevral efüzyon tanılı 135 hastanın 74'ü (%54.8) erkek olup ortalama yaş 8.4±5.3 saptandı. Hastaların 78'i (%57.8) parapnömonik efüzyon, 14'ü (% 10.4) sepsis, 10'u (%7.4) romatolojik hastalık tanısı almıştı. En sık başvuru semptomları ateş (%62.2), öksürük (%45.9) ve nefes darlığı (%32.6)'di. Fizik muayenede en sık saptanan bulgu takipne (%39.3)'dü. Hastaların yarısından fazlasında (%59.2) kronik hastalık olduğu tespit edildi. Bu ek hastalıklar içerisinde en sık nörolojik hastalıklar olduğu görüldü. Verilerine ulaşılabilen 127 hastanın 94'üne (%74) torasentez yapılmıştı; 70'ine (%55.5) göğüs tüpü takılmıştı. Parapnömonik efüzyon tanısı alan hastaların 42'si (%53.8) basit parapnömonik efüzyon, 36'sı (%46.2) komplike parapnömonik efüzyon (ampiyem) tanısı aldı. En çok izole edilen etken *Streptococcus pneumoniae*'di. Ampiyem tedavisinde en çok fibrinolitik tedavinin tercih edildiği görüldü. Plevra sıvısında 'pH ≤7.1' ve 'LDH ≥1000' saptanması ampiyem tanılı hastalarda basit parapnömonik efüzyon tanılı hastalara göre anlamlı bulundu (sırasıyla p:0.003 ve p:0.001). Parapnömonik efüzyonların yıllar içindeki dağılımına bakıldığında son yıllarda ampiyem sıklığında artış görülmektedir. Pnömonokok aşısı ile aşılamanın basit parapnömonik efüzyon ve ampiyem gelişiminde fark yaratmadığı görüldü (p:0.351).

Sonuç: Plevral efüzyon nedeniyle hastaneye yatırılan çocuk hastaların yarısından çoğunda parapnömonik efüzyon saptanmıştır. Ampiyem sıklığında son üç yılda artış görülmektedir. Bu durum aşılama ile önüne geçilemeyen invaziv suşların varlığını düşündürmektedir. Erken evrede tanı ve tedaviye yönelik daha fazla çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Ampiyem, Parapnömonik, Pediatrik, Plevral efüzyon

ABSTRACT

Objective: Pleural effusion is a serious cause of morbidity and mortality in childhood. In this study, it was aimed to investigate the follow-up and treatment of patients by performing etiological classification of children with hospitalization with pleural effusion diagnosis.

Çıkar Çatışması / Conflict of Interest: Tüm yazarlar adına, sorumlu yazar çıkar çatışması olmadığını belirtir.

Etik Kurul Onayı / Ethics Committee Approval: Bu çalışmada ulusal ve uluslararası etik kurallara uyulmuştur. Çalışma için Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu'nda 15.01.2018/2018-004 onay alınmıştır.

Yazarların katkısı / Contribution of the Authors: **KAPLAN G:** Araştırma ve/veya makalenin hipotezini veya fikrini oluşturan, Sonuçlara ulaşmak için planlama/metodoloji belirleme, Hasta takibinde sorumluluk almak, ilgili biyolojik malzemelerin toplanması, veri yönetimi ve raporlama, deneylerin yürütülmesi, Sonuçların mantıksal olarak yorumlanması ve sonuçlandırılması, Çalışma için gerekli literatür taramasında sorumluluk almak, Çalışmanın bütününe veya önemli bölümlerinin yazımında sorumluluk almak, Yazım ve dilbilgisi dışında bilimsel olarak gönderilmeden önce makaleyi gözden geçirme. **YAKUT Hİ:** Araştırma/çalışmanın sorumluluğunu üstlenmek, ilerlemenin seyrini denetlemek. **CİNEL G:** Sonuçlara ulaşmak için planlama/metodoloji belirleme, Yazım ve dilbilgisi dışında bilimsel olarak gönderilmeden önce makaleyi gözden geçirme

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Material and Methods: Pediatric patients who were admitted to the Pediatric Services and Intensive Care Unit of Health Sciences University Ankara Child Health and Diseases Hematology Oncology Education and Research Hospital between January 2012 and December 2017 were evaluated. In this retrospective descriptive study, 135 patients aged 0-18 years were examined. The demographic characteristics, clinical features, physical examination findings, underlying additional disease, laboratory data, imaging methods, follow-up and treatment methods of the patients were examined.

Results: 74 (54.8%) of 135 patients diagnosed with pleural effusion were male and the mean age was 8.4 ± 5.3 . 78 of the patients (57.8%) were diagnosed with parapneumonic effusion, 14 (10.4%) sepsis, 10 (7.4%) rheumatological disease. The most common presenting symptoms were fever (62.2%), cough (45.9%) and shortness of breath (32.6%). The most common finding on physical examination was tachypnea (39.3%). More than half of the patients (59.2%) had chronic disease. Among these diseases, the most common neurological diseases were found. Thoracentesis was performed in 94 (74%) of 127 patients whose data could be accessed; chest tube was inserted in 70 of them (55.5%). Of the patients diagnosed with parapneumonic effusion, 42 (53.8%) were diagnosed with simple parapneumonic effusion and 36 (46.2%) were diagnosed with complicated parapneumonic effusion (empyema). The most commonly isolated agent was *Streptococcus pneumoniae*. Fibrinolytic therapy was the most preferred treatment for empyema. Detection of ' $\text{pH} \leq 7.1$ ' and ' $\text{LDH} \geq 1000$ ' in pleural fluid was found to be significant in patients with empyema compared to patients with simple parapneumonic effusion, respectively ($p:0.003$) ($p:0.001$). Considering the distribution of parapneumonic effusions over the years, there has been an increase in the frequency of empyema in recent years. It was observed that vaccination with pneumococcal vaccine did not make any difference in the development of simple parapneumonic effusion and empyema ($p: 0.351$).

Conclusion: Parapneumonic effusion was detected in more than half of the pediatric patients who were hospitalized for pleural effusion. Empyema incidence has increased in the last three years. This suggests the presence of invasive strains which cannot be prevented by vaccination. Further studies are needed for diagnosis and treatment in early stage.

Key Words: Empyema, Parapneumonic, Pediatric, Pleural effusion

GİRİŞ

Plevra, pariteal ve visseral plevradan oluşur. Parietal ve visseral plevra arasında anormal sıvı bulunması plevral efüzyon olarak tanımlanır.

Çocukluk çağındaki plevral efüzyonların en sık nedeni %50-68 sıklıkla toplum kaynaklı pnömonilerdir (1). Parapnömonik efüzyonun steril olduğu ilk evre basit eksudatif evre; bakteriyel invazyon sonrası fibrin birikiminin olduğu evre ise komplike parapnömonik (ampiyem) evre olarak tanımlanır. Ampiyem evresinde plevral sıvıda $\text{pH} \leq 7.1$, glukoz ≤ 40 ve LDH ≥ 1000 saptanır.

Torasentez ile elde edilen plevral sıvı transuda ya da eksuda niteliğindedir. Light kriterlerine göre plevra sıvısı/serum protein > 0.5 , plevra sıvısı/serum LDH > 0.6 , plevra sıvısı LDH $>$ normalin üst sınırının $2/3$ 'ü kriterlerinden herhangi biri varsa plevral sıvı eksudatıdır. Transuda niteliğindeki efüzyonlarda kalp yetmezliği, nefrotik sendrom, hipalbuminemi gibi, sistemik hastalıklar ön plandayken eksuda niteliğindeki efüzyonlarda enfeksiyon ve malign hastalıklar daha çok düşünülmelidir (2,3).

Bu çalışmada plevral efüzyon tanısı ile hastanemizde yatırılarak izlenen 135 çocuk hastanın demografik, klinik, laboratuvar özellikleri incelenerek plevral efüzyonların etyolojisi, tanı ve tedavide uygulanan yöntemlerin araştırılması amaçlanmıştır. Ayrıca, plevral efüzyonların en sık nedeni olan parapnömonik efüzyonların yıllar içerisindeki değişimi araştırılmıştır.

GEREÇ ve YÖNTEMLER

Tek merkezli retrospektif tanımlayıcı nitelikte olan bu çalışmada Ocak 2012- Aralık 2017 tarihleri arasında Sağlık Bilimleri

Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Sağlık Uygulama ve Araştırma Hastanesi, Pediatri Servisleri ve Yoğun Bakım Ünitesi'nde plevral efüzyon tanısı ile yatırılarak izlenen 0-18 yaş arasındaki 135 hastanın özellikleri incelendi.

Hastane bilgi sistemi kullanılarak hastaların yatışı boyunca yazılan günlük klinik izlemleri incelendi ve ulaşılabilen veriler kaydedildi. Hastaların yaşı, cinsiyeti, başvuru tarihi, ek hastalık varlığı, kronik ilaç kullanımı, aşılanma durumu, başvuru semptomları, fizik muayene bulguları, görüntüleme (akciğer grafisi, ultrasonografi, bilgisayarlı tomografi) yöntemleri, torasentez bilgileri, plevral sıvı biyokimyasal ve mikrobiyolojik inceleme sonuçları, periferik kan sonuçları, hastalık etyolojileri ve tedavi yöntemleri değerlendirildi. Plevral efüzyon etyolojisinde yer alan hastalıklar pnömoni, sepsis, romatolojik hastalık, kardiyak hastalık, tüberküloz, malignite, kist hidatik, HLH (Hemofagositik Lenfositosis), nefrotik sendrom ve diğerleri olacak şekilde gruplandırıldı.

2012, 2013 ve 2014 yılları 1. grup; 2015, 2016 ve 2017 yılları 2. grup olarak sınıflandırılarak plevral efüzyon tanılarının yıllara göre artma ya da azalma ilişkisi araştırıldı. Plevral efüzyonların en sık nedeni olan parapnömonik efüzyonlar basit eksudatif parapnömonik efüzyon ve amp iyem olacak şekilde iki grupta karşılaştırılmalı olarak incelendi.

Çalışma için Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu'nda 15.01.2018/2018-004 onay alınmıştır.

Hastaların verileri 'SPSS for Windows 17.0' programı kullanılarak analiz edildi. Ki-kare, Fischer ve T testi kullanıldı; $p < 0.05$ anlamlı kabul edildi.

BULGULAR

Plevral efüzyon tanısı ile Ocak 2012- Aralık 2017 tarihleri arasında yatarak tedavi olan 135 hastanın %54.8'i erkek, %45.2'si kızdı. Hastaların ortalama yaş 8.4 ± 5.3 olup; 0-2 yaş arasında 23 (%17), 2-5 yaş arasında 26 (%19.2), 5 yaş üstü 86 (%63.8) hasta saptandı. Çalışmada yer alan hastaların %59.2 'sinde nörolojik hastalıklar başta olmak üzere ek hastalık olduğu görüldü. Başvuru semptomları sıklık sırasına göre ateş (%62.2), öksürük (%45.9), nefes darlığı (%32.6), göğüs ağrısı (%8.1), karın ağrısı (%6.7) ve yan ağrısı (%2.2)'di.

Hastaların fizik muayenesinde en sık saptanan bulgu takipne (%39.3) olup diğer bulgular ral-ronküs varlığı, solunum seslerinde azalma ve retraksiyondur. Çalışmada yer alan 135 hastanın 78'i (%57.8) pnömoni, 14'ü (%10.4) sepsis, 10'u (%7.4) romatolojik hastalık, 8'i (%5.9) kardiyak hastalık tanılarını aldı. Hastaların etyolojilerine göre sınıflandırılması Tablo I'de gösterilmiştir.

Hastaların tamamına akciğer grafisi çekilmiş olup; %98.3'üne ultrasonografi, %43.8'ine bilgisayarlı tomografi ile görüntüleme yapılmıştı. Plevral efüzyonun sıklıkla sağ taraftaydı (%37.5). Ultrasonografi ile yapılan ölçümlerde ortalama olarak sağda 34.5 mm solda 32 mm efüzyon saptandı.

135 hastanın içinde torasentez sonuçlarına ulaşılabilen 127 hastanın 94'üne (%74) torasentez yapılırken 70'ine (%55.5) göğüs tüpü takılmıştı. Torasentez ile elde edilen plevral sıvı Light kriterleri kullanılarak transuda ve eksuda olarak sınıflandırıldı. Torasentez ile yeterli sıvı alınabilen 80 hastanın 70'inde (%87.5) eksuda, 10'unda (%12.5) transuda vasıflı sıvı saptandığı görüldü. 1 hastada şilotoraks saptandı. 13 hastada ise yeterli örnek alınamadığı için plevral sıvı değerlendirmesi yapılamamıştı.

Eksuda vasıflı sıvıların %89'una, transuda vasıflı sıvıların %80'ine göğüs tüpü takılmıştı ve aralarında anlamlı fark saptanmadı ($p:0.600$). Plevral efüzyonu olan 135 hastanın 78'inde pnömoniyeye sekonder plevral efüzyon geliştiği görüldü.

Bu 78 hastanın 42'si (%53.8) basit parapnömonik efüzyon, 36'sı (%46.2) ampiyem tanılı hastalardan oluşmaktaydı. Başvuru semptomları incelendiğinde nefes darlığının ampiyemde basit parapnömonik efüzyona göre anlamlı olarak daha fazla görüldüğü saptandı ($p:0.047$).

Parapnömonik efüzyona sahip hastaların plevral sıvı verileri incelendiğinde ampiyemi olan olgularda plevra pH ≤ 7.1 ve plevra LDH ≥ 1000 olması basit parapnömonik gruba göre anlamlı saptandı ($p:0.003$) ($p:0.001$). Ultrasonografide septa oluşumunun da ampiyemde basit parapnömonik efüzyona göre istatistiksel olarak daha fazla olduğu görüldü ($p<0.01$).

Yıllara göre gelişen parapnömonik efüzyon sayısı Şekil 1' de gösterilmiştir. Bu verilere göre son 3 yılda ampiyem gelişen hastaların sayısı giderek artmaktadır. 2012, 2013 ve 2014 yılları 1.grup; 2015, 2016, 2017 yılları 2.grup olarak sınıflandırıldı. Parapnömonik efüzyonların ve diğer tüm tanıların yıl gruplarıyla anlamlı bir ilişkisi saptanmadı ($p:0.966$). İki yıl grubu arasında basit parapnömonik efüzyon ve ampiyem gelişiminin istatistiksel bir farkı saptanmadı ($p:0.759$).

Parapnömonik efüzyon tanılı hastaların aşılama verileri incelendi. Buna göre pnömokok aşısı ile aşılanmanın basit parapnömonik efüzyon ve ampiyem gelişiminde fark yaratmadığı görüldü ($p:0.351$). 7 bileşenli (PCV7) ve 13 bileşenli (PCV13) pnömokok aşılarının ampiyem gelişiminde ve ileri tedavi ihtiyacında anlamlı etkisi görülmedi ($p:0.577$).

Ampiyem tanısı alıp verisine ulaşılabilen 27 hastanın 8'inde gram boyama ile 5'inde ise kültür ile bakteri saptandı. Plevra kültürü sonuçlarında en sık saptanan etken *Streptococcus pneumoniae*'di (Tablo II).

Ampiyem tanılı 36 olgunun 16'sında (%44.4) fibrinolitik ajan, 2'sinde (%5.5) VATS, 1'inde (%2.7) dekortikasyon tedavisi uygulanmıştı. Çalışmada yer alan 135 hastanın 12'si kaybedildi. Bu hastaların 7'si sepsis, 2'si kardiyak hastalık, 2'si romatolojik hastalık ve 1 tanesi pnömoni tanılıydı.

Tablo I: Plevral efüzyon etyolojisi.

Tanı	Hasta (%)	Cinsiyet (erkek/kız)	Ortalama yaş	Torasentez	Göğüs tüpü	Eksuda/Transuda	Exitus
Pnömoni	78 (57.8)	45/33	6.5 ± 4.7	54	43	49/0	1
Sepsis	14 (10.4)	7/7	10.2 ± 5.4	10	8	6/2	7
Romatolojik hastalık	10 (7.4)	7/3	11.9 ± 5.1	8	3	2/3	2
Kardiyak hastalık	8 (5.9)	3/5	12.7 ± 4.4	5	3	1/3	2
Tüberküloz	7 (5.2)	3/4	14.4 ± 2.0	5	3	5/0	0
Malignite	5 (3.7)	2/3	10.8 ± 6.0	5	4	3/1	0
Kist hidatik	4 (3)	3/1	9.2 ± 6.2	3	3	2/0	0
HLH	2 (1.5)	0/2	10.5 ± 6.3	1	1	1/0	0
Nefrotik Sendrom	1 (0.7)	1/0	2	1	1	0/1	0
Diğer	6 (4.4)	3/3	8.3 ± 4.6	2	1	1/0	0
Toplam	135 (100)	74/61	8.4 ± 5.3	94	70	70/10	12

Tablo II: Ampiyemde plevra kültür sonuçları.

Plevra Kültür Sonucu	Hasta Sayısı	(%)
<i>Streptococcus pneumoniae</i>	3	11.1
MRSA	1	3.7
<i>Burkholderia cepacia</i>	1	3.7
Negatif	22	81.5
Toplam	27	100

TARTIŞMA

Retrospektif tanımlayıcı özellikte olan bu çalışmada plevral efüzyon tanısı ile hastanede yatırılan hasta verileri incelendiğinde olguların büyük çoğunluğu pnömoniydi. Mocelin ve ark'ın (3) yaptığı çalışmasında plevral efüzyonu olan 157 hastanın 150'sinde (%95.5); Utine ve ark'ın (4) yaptığı çalışmasında ise plevral efüzyonu olan 492 hastanın 381'inde (%77.4) parapnömonik efüzyon saptanmıştı.

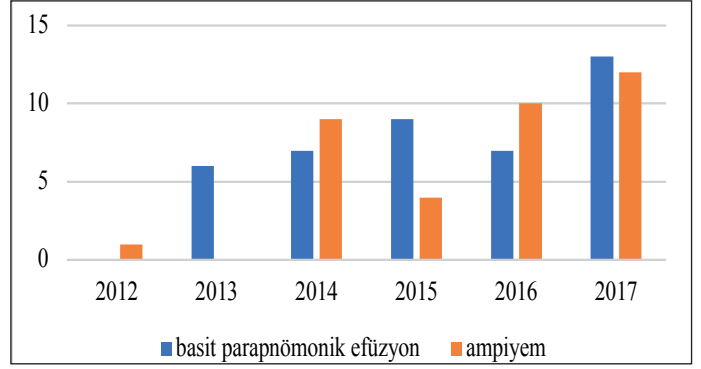
Altta yatan diğer hastalıklar ise sıklık sırasına göre sepsis, romatolojik hastalık, kardiyak hastalık tanıları aldı. Çalışmamıza yoğun bakım hastalarının da dahil edilmesi sepsis tanılı hasta sayısını arttırmıştır olabilir.

Plevral efüzyon tanısı alan 135 hastanın %59'unda ek hastalık mevcuttu. En çok görülen ek hastalık nörolojik hastalıklardı (serebral palsy, epilepsi ve kas hastalıkları gibi). Liese ve ark'ın (5) yaptığı parapnömonik efüzyon tanılı 1447 hastanın yer aldığı çalışmada altta yatan en sık hastalık nörolojik hastalık grubu olarak saptanmıştı. Aspirasyonun fazla olması, sekresyonun yeterli düzeyde atılamaması ve tekrarlayan mikrotravmalara bağlı hasarlı akciğer dokusunun olması nörolojik hastalığı olanlarda plevral efüzyonun daha ağır-komplike gelişeceğini düşündürmektedir.

Çalışmada yer alan 135 olgunun tamamı incelendiğinde en sık başvuru semptomu ateş, öksürük ve nefes darlığıydı. Utine ve ark'ın (4) yaptığı çalışmada da hastalar en sık ateş, öksürük ve nefes darlığı ile başvurmuştu.

Çalışmada ateş ve öksürük parapnömonik efüzyonu olan hastalarda daha fazla görüldü. Mocelin ve ark'ın (3) yaptığı çalışmada da parapnömonik efüzyon tanılı grupta ateş ve öksürük daha fazla görülmüştü. Bu durumun pnömonin temel bulguları arasında ateş ve öksürüğün yer almasına bağlı olduğu düşünüldü. Plevral efüzyonu olan hastalarda en sık görülen semptomlar öksürük, nefes darlığı ve göğüs ağrısı olmakla birlikte bu bulguların spesifite ve sensitivitesi düşüktür (6). Hastaların klinik seyri altta yatan nedene bağlı olarak değişkenlik gösterebilmektedir. Bu nedenle plevral efüzyon tedavisi için öncelikle altta yatan hastalığın tespit edilmesi gerekir.

Plevral efüzyon olgularında tercih edilen standart tanı yöntemi akciğer grafisidir (7). Bu çalışmada da en çok tercih edilen görüntüleme yöntemi hem ucuz hem kolay olması nedeni akciğer grafisi olmuştur. Özellikle lateral dekübit grafi ile daha



Şekil 1: Yıllara göre basit parapnömonik efüzyon ve ampiyem gelişimi.

iyi sonuç alınır fakat plevral sıvının karakterini ve miktarını belirlemede ultrasonografi daha duyarlıdır (8-10). Bu çalışmada yer alan plevral efüzyonların görüntülenmesinde ultrasonografi çok yaygın kullanılmıştır; hem seviye ölçülümünde hem de fibrin, septa gibi komplike yapıların değerlendirilmesinde yardımcı olmuştur. BT'nin parapnömonik efüzyonu olan çocuklarda rutin kullanımını önerilmemektedir fakat etyolojisi belirlenemeyen olgularda tercih edilebilmektedir (11,12).

Plevral efüzyon sıklıkla akciğerin sağ tarafında görüldü (%38). Hacimustafaoğlu ve ark'ın (13) yaptığı çalışmada parapnömonik efüzyon tanılı 80 hasta incelenmiş ve sağ tarafın daha çok tutulduğu saptanmıştı. Gayretli-Aydın ve ark'ın (14) yaptığı çalışmada parapnömonik efüzyon tanılı 116 hastada sağ taraftaki efüzyonların daha büyük çaplı olduğu saptanmıştı. Bu durum sağ ana bronşun daha yukarıda yer almasına bağlı olarak mikroaspirasyonların daha fazla olduğunu düşündürür ve bu da efüzyonun daha geniş ya da komplike olmasını açıklayabilir.

Hem tanıda hem tedavide önemli bir yeri olan torasentez işlemi ile plevral aralıktan sıvı örneği alınarak biyokimyasal, mikrobiyolojik, histolojik ve sitolojik incelemeler yapılabilir; ayrıca plevral sıvı drenajı ile klinik düzelme sağlanabilir (15).

Torasentez ile elde edilen plevral sıvı transuda ya da eksuda niteliğindedir. Light kriterlerine göre plevra sıvısı/serum protein > 0.5, plevra sıvısı/serum LDH > 0.6, plevra sıvısı LDH > normalin üst sınırının 2/3'ü kriterlerinden herhangi biri varsa plevral sıvı eksudadır (16). Çalışmamızda verilerine ulaşılabilen hastaların %74'üne torasentez yapıldığı ve plevral sıvının çoğunlukla eksuda vasıflı olduğu görüldü. Eksuda vasıflı plevral efüzyonların daha çok pnömoni, sepsis ve tüberküloz gibi enfeksiyon sonrası geliştiği saptandı. Transuda vasıflı efüzyonlar ise daha çok kardiyak ve romatolojik hastalık zemininde gelişmişti. Çalışmamızda geniş çaplı plevral efüzyon varlığında, solunum sıkıntısı gelişen olgularda ya da ampiyemde göğüs tüpü ile sıvı drenajı sağlanmıştır.

Plevral efüzyonların en sık nedeni olan parapnömonik efüzyonun steril olduğu ilk evre basit eksudatif evre; bakteriyel invazyon sonrası fibrin birikiminin olduğu evre ise komplike parapnömonik (ampiyem) evre olarak tanımlanır. Ampiyem evresinde plevral sıvıda pH ≤7.1, glukoz ≤40 ve LDH ≥1000 saptanır (16).

Ampiyem evresinde göğüs tüpü takılarak fibrinolitik ajan aracılığı ile ya da video aracılı torakoskopik inceleme (VATS) ile drenaj sağlanmalıdır. Bu iki yöntemin birbirine üstünlüğü tartışmalıdır, tercih edilecek yöntem kliniğin tecrübesine göre seçilmelidir (17,18). Bu çalışmanın incelendiği zaman aralığında hastanemizde izlenen ampiyem tanılı hastaların tedavisinde fibrinolitik ajanların daha çok tercih edildiği görüldü.

Torasentez yapılan parapnömonik plevral efüzyonu olan hastaların plevral sıvılarından gram boyama, kültür, *S.pneumoniae* için lateks aglütinasyonu, spesifik PCR çalışması önerilmektedir (12). Çalışmamızda gönderilen plevra kültür sonuçları büyük oranda negatif saptanması hastaneye başvuru öncesinde antibiyotik kullanımı ile ilişkili olabilir. Antibiyotik kullanım hikayesi ile ilgili yeterli veriye ulaşılammıştır. Bu çalışmada prapnömonik efüzyonların en sık nedeni literatürle uyumlu olarak *S.pneumoniae*'di (3,4,19).

Sonuç olarak; çalışmamızda yer alan plevral efüzyon olgularının büyük çoğunluğu parapnömonik efüzyon tanısı alan hastalardan oluşmaktaydı. Çalışmamızda ve tüm dünyada parapnömonik efüzyonların en sık nedeni *Streptococcus pneumoniae* pnömonisi olup ampiyem sıklığında yıllar içerisinde artış görülmektedir. Plevral efüzyondan alınan örnekte mikroorganizmanın üretilerek tiplendirilmesi ülke çapındaki sürveyans çalışmaları için çok önemli olacaktır.

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Evaluation of Clinical Symptoms and Clinical Course in Pediatric Patients with Tree Nut Allergy

Kuruyemiş Alerjisi Olan Çocuklarda Klinik Bulgular ve Doğal Seyrin Değerlendirilmesi

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ABSTRACT

Objective: Tree nut allergies (TNA) are an important health problem can cause severe reactions such as anaphylaxis and the frequency of improvement with age is low. This study aims to evaluate the clinical features and tolerance development of TNAs.

Material and Methods: In our study, the clinical characteristics, laboratory findings and tolerances of the patients who were followed with allergy to tree nuts between 2010-2017 in the Department of Pediatric Immunology and Allergy of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital were evaluated.

Results: A hundred and twenty eight (73.4% male) patients were included in the study with a median age of 61 (min-max:4-209) months. Of the patients, 109(85.2%) were hazelnuts, 60(46.8%) were allergic to walnuts, 47(36.7%) were allergic to pistachios, 37(28.9) were allergic to almonds, 22(17.2%) were allergic to cashew nuts. Presenting reaction was anaphylaxis in 47 (36,7%) patients. The median value of the follow-up period was 56.3 (16.3-134.2) months. Of the 128 patients, 37(29%) have overgrown all TNAs, 9 (7%) have outgrown some of TNAs and TNAs of 70(54.6%) patients persisted. Twelve patients (9.4%) couldn't evaluated. Forty-two percent of patients with single TNA, 31.5% of patients with multi-TNA has developed tolerance within follow-up period.

Conclusion: Tolerance development to TNA seems to be encouraging. Therefore, regular monitoring of these patients is important.

Key Words: Children, Prognosis, Symptoms, Tree nut allergy



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

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ÖZ

Amaç: Kuruyemiş alerjileri (KA), anafilaksi gibi ağır reaksiyonlara neden olabilmeleri ve yaşla düzelme sıklıklarının az olması nedeni ile önemli bir sağlık sorunudur. Çalışmamızda kuruyemiş alerjilerinin klinik özellikleri ve tolerans gelişiminin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamızda T.C. Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Alerji Kliniği'nde 2010-2017 yıllarında kuruyemiş alerjisi nedeni ile izlenen hastaların klinik özellikleri, laboratuvar bulguları ve prognozu değerlendirildi.

Bulgular: Çalışmaya ortalama yaşı 2.5 yıl (min-maks: 1-17) olan yüz yirmi sekiz (%73.4 erkek) hasta alındı. Hastaların 109'unda (%85.2) fındık, 60'ında (%46.8) ceviz 47'sinde (%36.7) antep fıstığı, 37'sinde (28.9) badem, 22'sinde (%17.2) kaju fıstığı alerjisi vardı. Kırk yedi (%36.7) hastada başvuru reaksiyonu anafilaksiydi. Takip süresi ortalama 56.3 (min-maks:16.3-134.2) aydı. Yüz yirmi sekiz hastanın 37'sinde (%29) tüm KA'leri düzelmişken, 9'unda (%7) bazı KA'leri düzelmiş 70 (%54.6) hastada ise KA devam etmiştir. On iki hasta (%9.4) değerlendirilemedi. Tekli KA'li hastaların %42'si, çoklu KA'li hastaların %31.5'i takip süresi içinde tolerans geliştirmiştir.

Sonuç: Kuruyemiş alerjilerine tolerans gelişimi cesaret verici görünüyor. Bu nedenle bu hastaların düzenli takibi önemlidir.

Anahtar Sözcükler: Çocuklar, Prognoz, Semptomlar, Kuruyemiş alerjisi

INTRODUCTION

Tree nut allergy(TNA) is an important health problem because it can cause severe reactions that can be lethal and also decreases the quality of life of children with allergies and their families. Tree nuts are the cause of 18-40% of all cases of anaphylaxis and with peanuts they account for the 70-90% of anaphylactic fatalities due to food allergy (1,2). The frequency of reactions with TN is reported to be increasing (3).

Current treatment of TNA is avoidance of the allergenic food, but children, especially at school age are at high risk of accidental exposure to TNs. Anxiety due to the possibility of anaphylactic reactions, efforts to avoid the allergen, disbelief of being ready to use adrenalin auto-injectors are burdens on the patient and the families (4). Parents can over protect their food allergic children and this may interfere with child's development of autonomy and social skills (5).

Tree nuts are reported to have beneficial effects for the health of children. They are widely available and accidental ingestion is common as they are included in many take-home foods (3). These points make the avoidance of TNs harder

Resolution rate of allergic reactions to tree nuts are considered to be low and they are presumed to continue until adulthood in most of the cases (3). However, the results of TNAs in the pediatric age group were obtained from a limited number of studies. In our study, we aimed to evaluate the clinical features of the patients who were followed with the diagnosis of TNA and to evaluate the clinical course of the patients.

MATERIALS and METHODS

The study included patients diagnosed with tree nut allergies between 2010 and 2017 at the Pediatric Immunology and Allergy Clinic of our hospital. Patients who had only sensitization according to skin prick test(SPT) and/or specific IgE(sIgE) and did not have a reaction with the culprit TN were not included in the study. Patients with symptom exacerbation upon exposure

or after open oral provocation test(OPT) and supporting allergy test results (positive results for SPT or sIgE tests) were diagnosed with TNA.

Patients' sociodemographic characteristics, complaints, type of allergic reactions, age of symptom development; mother's consumption of TNs in the period of pregnancy and lactation; maternal smoking during pregnancy; laboratory tests at the time of diagnosis, other TNs/ food /aeroallergen sensitivity, accompanying allergic/immunological disease; history of allergic disease in the family; follow-up period, clinical course information was recorded in standard form from patient records and interviews with patients. Patients whose last control has been more than 6 months ago were invited to the clinic and allergy tests (SPT and/or sIgE) were repeated if patient gave informed consent. Patients who consumed the culprit TN at home without any reaction were considered to develop tolerance and who developed reaction were considered to have ongoing TNA.OPT was planned to patients who did not have a reaction in the previous 6 months and who did not consume the culprit TN during this period when consent was taken from parents

Patients with primary immunodeficiency were excluded from the study.

The study was approved by the ethical review committee of the University of Health Sciences, Ankara Child Health and Diseases, Hematology, Oncology Training Research Hospital (EC number:2017-128).

Tree nuts are selected for SPT based on clinical history (suspected food-induced allergy symptoms on previous ingestion of the food or maternal dietary history if breastfed). Prior to SPT, vital signs of each child were measured, physical examinations were performed and recorded. Antihistamines were discontinued one week prior to tests. SPT was performed on the dorsal in younger children, and on the inner side of the forearm in older children. Histamine was used as a positive and saline was used as negative control. The test was accepted positive if the edema diameter that occurred after 15 minutes was greater than 3 mm larger from the negative control.

SPTs were performed using allergen extracts (ALK-Abello, Madrid, Spain) when available. Prick to-prick testing with raw food was done for hazelnut, walnut, pistachio, almonds and cashew nut.

Serum sIgE for hazelnuts, pistachios, cashews, walnuts, almonds and TN mix (peanuts, hazelnuts, Brazil nuts, almonds, coconut) was measured by the ImmunoCAP (PhadiaAB, Uppsala, Sweden) system. The IgE serum levels above 0.35 kU/l was considered positive.

The provocation tests and protocols were performed following the World Allergy Organization (WAO) Food Allergy Working Group and the European academy of allergy and clinical immunology (EAACI) Group Guidelines (6)

Open OPTs were performed using freshly prepared food by an experienced nurse under the supervision of a pediatric allergist. The dosing intervals were 15 minutes (7). Patients were followed for any allergic reaction and OPT was stopped and considered positive if any objective signs and symptoms were documented. Patients with negative results were observed for at least 2 hours after OPT and told to continue receiving the suspected food and admitting to the hospital in case of any reaction at home.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated by

Kolmogorov-Smirnov test. Numerical variables without normal distribution were shown as median (min-max). Categorical variables were expressed as numbers and percentages. Mann Whitney U test was used for comparison of numerical variables between two groups, and Kruskal Wallis H test (posthoc: Dunn tests test) was used for comparison between three groups.

RESULTS

Three patients with immunodeficiency were excluded from the study and 128 patients were included of which 73.4% (n=94) were male. The median age at the last follow-up was 61 (4-209) months. The median value of the follow-up period was 56,3 (16.3-134.2) months.

Symptom onset ages according to the types of tree nuts; 36 (4-213) months for hazelnut, 44 (5-214) months for walnut, 34 (5-197) months for pistachio, 36 (5-214) months for almond, and 35 (2-213) months for cashew.

A total of 275 tree nut allergy cases were observed in 128 patients (109 hazelnuts, 60 walnuts, 47 pistachio, 37 almond, 22 cashew allergy). Presenting reaction was urticaria in 124 (96.8%), angioedema in 54 (42.2%), anaphylaxis in 47 (36.7%) and atopic dermatitis in 51 (39.8%) patients. Eosinophilic esophagitis in 2 (%1.8) patients and FPIES in 2 (%1.8) patients. Detailed characteristics of each hypersensitivity reaction according to the type of nuts are given in Table I.

Table I: Clinical and demographic characteristics of patients according to tree nuts.

	All Patients n=128	Hazelnut n=109	Walnut n=60	Pistachio n=47	Almond n=37	Cashew n=22
Gender (n)						
female /male	34/94	32/77	15/45	14/33	11/26	4/18
Follow up period (months)						
median (min-max)	12.3(0.03-85.3)	58.5 (16 -104)	58.1 (16.3-102.8)	50.8 (16.4-99.9)	36.7 (16.8-100)	51 (20.7-97.8)
Age at diagnosis (months)						
median (min-max)	40.2(0.03-217.2)	34 (4-214)	38.6 (5-214)	33.6 (5-197)	39.0(5-214)	35.2 (2-214)
Initial skin prick test (mm)						
median (min-max)	7 (3-20)	7.3 (3-18)	6.5 (3-18)	8.3 (3-18)	9 (3-22.5)	6.5 (3-16.5)
Initial specific IgE (kU/l)						
median (min-max)	1.5 (0.1-157)	1.8 (0.4-157)	1.52 (0.35- 150)	-	3.91 (0.82-43.5)	10.76 (1.15-48.2)
Urticaria, *	124 (96.8)	102 (93.6)	58 (96.7)	45 (95.7)	36 (97.3)	22 (100)
Angioedema, *	54 (42.1)	43 (39.4)	31 (51.7)	27 (57.4)	20 (54.1)	14 (63.6)
Anaphylaxis, *	47 (36.7)	38 (34.9)	41 (68.3)	24 (51.1)	15 (40.5)	9 (40.9)
Atopic dermatitis, *	51 (39.8)	42 (38.5)	29 (48.3)	26 (55.3)	18 (48.6)	9 (40.9)
Eosinophilic esophagitis, *	2 (1.5)	2 (1.8)	2 (3.3)	2 (4.3)	2 (5.4)	1 (4.5)
FPIES, *	2 (1.5)	2 (1.8)	-	-	-	-
Accompanying non-TN food allergy, *	58 (71.6)	42 (38.5)	30 (50)	20 (42.6)	16 (43.2)	15 (68.2)
Aeroallergen sensitization, *	47 (36.7)	34 (31.2)	27 (45)	15 (31.9)	14 (37.8)	8 (36.4)
Tolerance development, *	46 (35.9)	38 (34.8)	18 (30)	8 (21.6)	12 (32)	1 (4.5)
Age of tolerance (months)						
median (min-max)	25.7(4.87-205)	49.2 (12.2-229)	67.9 (17.8-204.0)	69.7(18.5-102)	48.7 (12.1-156)	-

*:n (%), **FPIES**: Food Protein Induced Enterocolitis Sendrom, **TN**: Tree Nut

Table II: Comparison of Patients with One and More Tree Nut Allergy.

Variables	Population n=128	TN Allergy		p
		Single n=52	Multiple n=76	
Age at diagnosis (months) median (min-max)	33.8 (1.77-214)	28.6 (1.77-205)	35.8 (4.87-214)	0.985
Gender, *				
Female	34 (26.6)	12 (23.1)	22 (28.9)	0.543
Male	94 (73.4)	40 (76.9)	54 (71.1)	
Breastfeeding duration(month) median (min-max)	15 (0.3-42)	15 (2.5-24)	18 (0.3-42)	0.686
Onset of complementary food (month) median (min-max)	6 (2-24)	6 (2-12)	6 (3-24)	0.933
Onset of formula consumption (month) median (min-max)	9.5 (1-24)	7 (4-22)	10 (1-24)	0.260
Allergic disease in the family, *	58 (45.3)	21 (40.4)	37 (48.7)	0.372
Food allergy except tree nuts, *	90 (70.3)	27 (51.9)	63 (82.9)	<0.001*
Anaphylaxis, *	47 (36.7)	7 (13.5)	40 (52.6)	<0.001*
Eosinophil count median (min-max)	400 (100-4900)	300 (100-1400)	400 (100-4900)	0.147
Percentage of eosinophils (%) median (min-max)	4.1 (0.1-24)	3.4 (0.2-14)	4.5 (0.1-24)	0.077
Serum total IgE level (IU/mL) median (min-max)	205 (9.5-2454)	138 (9.5-1990)	258 (13.3-2454)	0.406
Aero-allergen sensitization, *	43 (33.6)	17 (32.7)	26 (34.2)	0.998
Tolerance status (tolerance to at least one TNA)	46 (36)	22 (42.3)	24 (31.5)	0.46
History of allergic disease, *	59 (46.1)	16 (30.8)	43 (56.6)	0.007*

*n (%)

Table III: Comparison of Patients presented with Anaphylaxis and Other Symptoms.

Variables	Initial symptom		p
	Anaphylaxis n=47	Others n=81	
Age of onset (month) median (min-max)	24.1 (5.7-209)	34 (2-213)	0.24
Gender			
Male	37 (78.7)	57 (70.4)	0.40
Female	10 (21.3)	24 (29.6)	
Breastfeeding duration(month) median (min-max)	15 (1.5-42)	16.5 (0.3-36)	0.97
Onset of complementary food (month) median (min-max)	6 (3-24)	6 (2-18)	0.71
Onset of formula (month) median (min-max)	10 (1-24)	9 (3-22)	0.57
Allergic disease in the family, *	22 (46.8)	36 (44.4)	0.85
Food allergy except TNs, *	37 (78.7)	53 (65.4)	0.16
Eosinophil count median (min-max)	300 (100-2200)	400 (100-4900)	0.60
Eosinophils percentage (%) median (min-max)	3.9 (0.1-20.2)	4.2 (0.3-24)	0.78
Serum total IgE level (IU/mL) median (min-max)	195 (13.3-1990)	290 (9.5-2454)	0.22
Aeroallergen sensitization, *	22 (46.8)	21 (25.9)	0.02†
TN consumption in pregnancy, * (once in a week or more frequent)	31 (66.0)	38 (46.9)	0.41
Concomitant of allergic disease, *	29 (61.7)	30 (37.0)	0.01†

*n (%), †p <0.05 shows statistical significance.

Table IV: Comparison of tolerance development of patients with tree nut allergy.

Variables	Tolerance to at least one TN n=46	No tolerance development n=68	p
Age of onset (month) median (min-max)	25.7 (4.87-205)	35.8 (2-214)	0.58
Gender, *			
female	9 (23.1)	21 (28.9)	0.543
male	37 (76.9)	47 (71.1)	
Breastfeeding Duration(month) median (min-max)	18 (2-36)	14 (0.3-42)	0.714
Onset of complementary food (month) median (min-max)	6 (3-24)	6 (2-18)	0.78
Onset of formula (month) median (min-max)	9 (1-24)	10 (2-21)	0.929
Food allergy except TNs, *	28 (60)	56 (82)	0.016*
Anaphylaxis, *	20 (43.4)	25 (36.7)	0.55
Eosinophil count median (min-max)	400 (100-2200)	400 (100-4900)	0.52
Eosinophils percentage median (min-max)	3.6 (0.1-16.2)	4.4 (0.2-24)	0.28
Serum Total IgE level(IU/mL) median (min-max)	138 (9.5-1600)	240 (21-2454)	0.160
Aero-allergen sensitization, *	18 (39)	22 (32)	0.54
Frequency of TN consumption in lactation: once in a week or more, *	22 (47.8)	34 (50)	0.57
Concomitant allergic disease, *	19 (41.3)	29 (42.6)	0.52

*n (%)

Of the patients, 90 (70.3%) had food allergy other than TNs: 53 (41.4%) egg allergy, 36 (28.1%) milk allergy, and 32 (25.0%) peanut allergy. Forty three patients (33.6%) had sensitization with aeroallergens: 38 (29.7%) pollen, 8 (6.3%) house dust mite, 7 (5.5%) animal dander, 5 (3.9%) mold, 4 (3.1%) cockroach sensitization.

Of the 128 patients with accompanying allergic diseases, 36 (28.1%) had asthma, 24 (18.8%) had allergic rhinitis, and 51 (39.8%) had atopic dermatitis .

The mean IgE value at the time of initial admission was 205 (14-2454) IU/mL. The median value of the eosinophil percentage was 4.1 (0.1-24) and the median eosinophil count was 400 mm³ (100-4900).

Fifty two (40.6%) of our patients had a single TNA (37 hazelnuts, 7 walnuts, 4 pistachios, 3 cashew nuts and 1 almonds); 76 (59.3%) had multiple TNA. Twenty-six patients (34.2%) had allergy to 2 TNs, 3 TNA were detected in 17 patients (22.4%), 4 TNA in 22 (28.9%), and 5 TNA in 11 patients (14.5%). When multiple TNA patients were compared to single TN allergic patients, frequency of other food allergy (82.9% vs 51.9%; $p<0.001$), presence of anaphylaxis (52.6% vs 13.5%; $p<0.001$) and presence of accompanying allergic disease (56.6% vs 30.8%; $p=0.007$) were higher in the multiple allergic group (Table II).

Of the 52 patients with single-TNA, 22 (42.3%) developed tolerance [18 (81.8%) hazelnuts, 3 (13.6%) walnuts, 1(4,6) pistachio]. Of 75 patients with multiple TNAs 24 (32%) developed tolerance to at least one of the TNs during follow-up period (20 (26.6%) hazelnuts, 11 (14.6%) almonds, 15 walnuts (20%), 7 (9.3%) pistachio and 1 (1.3%) cashew nuts). The ratio of tolerance development to at least one of the TNs did not differ between patients with multiple and single TN allergies ($p=0.46$) (Table II).

Anaphylaxis was defined in 36.7% of all patients (38 hazelnut allergy, 41 walnut allergy, 24 pistachio allergy, 15 almond allergy and 9 cashew nuts allergy). Frequency of aeroallergen sensitization (46.8% vs 25.9%; $p=0.02$) and accompanying allergic disease (61.7% vs 37%; $p = 0.01$) were more frequent in the anaphylaxis group (Table III).

Our 128 patients had 275 TNA cases. Of these cases, 123 had reaction with the culprit TN in the previous 6 months, so these were not evaluated and labeled as “did not develop tolerance”;63 had consumed the culprit TN at home without reaction and were labeled as “had developed tolerance”. Forty-eight TNA cases had anaphylaxis in the previous 12 months. We couldn't contact 8 patients. So, we couldn't evaluate these patients' tolerance status. Four parents refused OPT. Twenty OPTs were performed, 6 OPTs resulted positive and 14 OPTs resulted negative. Thus these 14 cases were also labeled as

“developed tolerance”. Consequently, 77 of 275 TNA cases (28%) ended with tolerance development. Of the 128 patients, 37 (29%) have overgrown all TNAs, 9 (7%) have outgrown some of TNAs and TNAs of 70 (54.6%) patients persisted. Twelve (9.4%) couldn't be evaluated.

When patients were compared according to tolerance development, frequency of food allergy except TNs was higher among patients who had not developed tolerance ($p=0.016$) (Table IV). Tolerance development was most frequently present in reactions to hazel nut (34%) and almond (32%). Median ages of children developing tolerance varied between 48.7 months for almond and 69.7 months for pistachio. Frequencies of and ages at tolerance development based on the type of TNAs are given in Table I.

When patients with hazel nut allergies were compared according to tolerance development, it was determined that presence of accompanying TNA ($p=0.012$) and food allergy other than TNs ($p=0.032$) were less frequent and initial sIgE levels were lower ($p=0.013$) among patients who had developed tolerance. When patients with walnut allergy were compared according to tolerance development, only initial sIgE level was lower among patients who had developed tolerance ($p<0.001$).

DISCUSSION

In the present study, the characteristics of 128 patients with 275 TNAs were presented. Hazel nut and walnut allergies were the most common. Leading presenting symptom was urticaria and anaphylaxis was defined in 36.7%. Accompanying food allergies and concurrent allergic diseases were common. Seventy-seven of 275 TNA cases (28%) ended with tolerance development. Of the 128 patients, 46 (36%) have outgrown at least one of TNAs they had.

Frequency of TNA and type of TNs causing sensitization differs from country to country, probably due to nutritional habits and genetic differences (5). In previous studies it has been reported that chest nut and cashew nut allergies were the most common type in USA and Brasilia while hazel nut and chest nut were common in European countries (8). In accordance with previous studies from our country and other countries hazel nut and chest nut allergies were the most common TNAs in our study (9,10).

Anaphylaxis is the most critical symptom of TNA. Couch et al.(11) reported that anaphylaxis was the first presenting symptom in 28% of patients with TNA. In our study, 47 patients (36.7%) were admitted with anaphylaxis symptoms and it was most common for chestnut allergic patients (68.3%). Among patients whose first symptom was anaphylaxis, concomitant allergic disease ($p=0.01$) and aeroallergen sensitization ($p=0.02$) were higher than patients presenting with other symptoms. In a recent study from our country, 48.9% of 184 children with TNA

were reported to have anaphylaxis as presenting symptom and female gender, having concomitant egg allergy and asthma were defined as risk factors (12). When patients have accompanying food allergies and allergic diseases, higher risk of anaphylaxis should be kept in mind.

Patients with TNA commonly have reactions with more than one type of TNs. In a retrospective multicenter study evaluating 109 patients who underwent OPT for TN sensitization, 54 (49.5%) patients had other TNA (11). In our study, 76 (59.3%) of our patients were observed to have multiple TNA and presence of other food allergies, accompanying allergic diseases and frequency of anaphylaxis as a presenting symptom were more common among patients who had multiple TNA. Sufficient data were not found in the literature regarding the risk factors for multiple TNA.

Reactions with food other than TNs are also common among patients with TNA. The incidence of non-TN food allergy was reported as 66.4-78% in two previous studies and peanut (60%), egg (42%) and milk (9%) were the most common accompanying non-TNAs (11,13). In our study, 90 (59.3%) of our patients had non-TN food allergy; the most common allergens were egg (41.4%), milk (28.1%) and legumes (41.4%). Other allergic diseases are also, common in patients with TNA (11,13). In our study, 28% of our patients had accompanying asthma, 39.8% atopic dermatitis and 18.8% allergic rhinitis. Also one third of our patients had aeroallergen sensitization.

Tolerance development is considered to be low for TNAs. However, as far as we could reach, there is scarce data about the frequency of tolerance development. The only study we could find is by Fleischer et al. (13) They have examined 278 patients aged between 3-21.6 years, 101 of them had reactions and skin test and/or sIgE positivity. These patients had 115 allergic reactions with TNs, cashew was the most frequent allergen. Of these patients, only 20 had undergone OPT and 9 had passed. Thus, they have reported that at least 8.9% of their patients had developed tolerance. Tolerance to at least one TNA was much higher, 36% in our study and tolerance rate ranged between 34.8% for hazel nut and 4.5% for cashew. In the study by Fleischer et al. (13), 81 of 101 patients could not be examined for tolerance development and this may have affected their results. Also, frequency of TNs causing reactions was very different from our study in their population. Hazel nut and walnut allergies were rare while cashew allergy was the most frequent (30%). For cashew allergy, tolerance development was less frequent and age of tolerance development was the highest in our study.

In the study conducted by Fleischer et al. (13), it was reported that there was lesser improvement in patients with additional tree nut allergy and additional food allergy. Accordingly, children who had developed tolerance to hazel nuts, less frequently had concurrent TNAs and other food allergies in our study. Furthermore, accompanying allergic diseases were less

frequent and initial sIgE levels were lower among these patients. Therefore, in patients with accompanying TNAs with additional food allergy and allergic diseases, the likelihood that the allergy may continue for a longer period should be considered during the follow-up period.

Our study was a observational study and this may have limited its results. Some of our patients were younger and had lower follow up periods, may be too low for tolerance development. A prospective study, with a detailed follow-up may give better results and we are hoping to share the results of our ongoing prospective study soon. But we think that the data gathered by this study is valuable as a large group of proven TNA patients were examined and detailed clinical and laboratory characteristics as well as tolerance status was determined.

According to our data we suggest that at least one third of TNA cases can develop tolerance at a mean age of 4-5 years, and thus children with TNAs should be followed-up for tolerance development. Additional TNAs, accompanying allergic diseases and other food allergies are common so patients should also be evaluated for these conditions.

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Clinical Spectrum of Acute Chlorine Poisoning in Children

Çocuklarda Akut Klor Zehirlenmesinin Klinik Spektrumu

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ABSTRACT

Objective: Chlorine gas (Cl₂) is a common substance used in industry, which causes toxic inhalation as a potent pulmonary irritant. Herein, we aimed to investigate the findings of pediatric cases accidentally exposed to Cl₂ gas.

Material and Methods: In October 2017, an accident involving Cl₂ gas exposure occurred in a school where 650 students were trained.

Results: Fifty students breathed in the steam generated in the school hallway as a result of an accident during cleaning. The mean age of the patients was 11.2±1.5 years (range 2–18 years); 62% of the children were male. Among patients evaluated at the emergency department, 21 (42%) patients were discharged within 4-6 hours after the initial examination and symptomatic treatment. The remaining 29 patients were hospitalized. The presenting symptoms were mostly associated with one another, which included cough and dyspnea (n=30, 60%), nausea and vomiting (n=6, 12%), headache (n=7, 14%), and sore throat (n=3, 6%). Thirty patients had elevated creatine kinase-MB (CK-MB) (mean 54.9±50.1 U/L). Five patients had sinus tachycardia on electrocardiogram. During the follow-up period, cardiac enzymes of all patients returned to normal levels. Seven patients were treated with steroids, bronchodilators, and humidified oxygen; 11 patients were treated with oxygen and bronchodilators; the remainders took oxygen alone.

Conclusion: We suggest that this study will contribute to raising awareness about chemicals that can produce toxic substances, as in our cases.

Key Words: Bleach, Chlorine gas, Hydrochloric acid, Pediatric

ÖZ

Amaç: Klor gazı endüstride yaygın olarak kullanılan ve akciğerlerde güçlü bir tahriş edici olarak inhalasyon toksisitesine neden olan bir maddedir. Bu çalışmada kaza ile klor gazına maruz kalan çocuk olgularının bulgularını incelemeyi amaçladık.

Gereç ve Yöntemler: Ekim 2017’de, 650 öğrencinin eğitim aldığı bir okulda Cl₂ gazına maruz kalmayı içeren bir kaza meydana geldi.

Bulgular: Elli öğrenci temizlik sırasında meydana gelen bir kaza sonucu okul koridorunda oluşan buharı teneffüs etti. Ortalama yaşları 11.2±1.5 yıl (dağılım 2-18 yıl) olan çocukların %62’si erkekti. Acil serviste değerlendirilen hastalardan 21’i (%42) ilk muayene ve semptomatik tedaviden sonra 4-6 saat içinde taburcu edildi. Kalan 29 hasta hastaneye yatırıldı. Çoğunlukla birbirleriyle benzer olan başvuru semptomları; öksürük ve nefes darlığı (n=30, %60), bulantı ve kusma (n=6, %12), baş ağrısı (n=7, %14) ve boğaz ağrısı (n=3, %6)’di. Otuz hastada yüksek kreatin kinaz-MB (CK-MB) vardı (ortalama 54.9±50.1 U/L); beş hastanın elektrokardiografisinde sinüs taşikardisi vardı. Takip süresi boyunca tüm hastaların kardiyak enzimleri normale döndü. Yedi hasta steroid, bronkodilatör ve nemlendirilmiş oksijen ile tedavi edildi; 11 hasta oksijen ve bronkodilatör ile tedavi edildi; kalanlar yalnızca oksijen aldı.



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Sonuç: Bu çalışmanın, bizim vakalarımızdaki gibi toksik maddeler üretebilecek kimyasallar hakkında farkındalığının artırılmasına katkı sağlayacağını düşünüyoruz.

Anahtar Sözcükler: Çamaşır suyu, Klor gazı, Hidroklorik asit, Pediatrik

INTRODUCTION

Chlorine gas (Cl_2) is a common substance used in society and industry. It is potentially toxic, particularly in children. Swimming pools, school chemistry experiments, and chemical vehicle accidents are the sources of pediatric toxicities, resulting in respiratory and cardiovascular morbidity (1). The respiratory system is the most commonly affected organ system by chlorine gas exposure (2). Accidental mixing of sodium hypochlorite and hypochlorous acid is one of the reasons for Cl_2 intoxication (3). To date, several accidental exposures have been reported. Herein, we aimed to investigate the findings of pediatric cases accidentally exposed to Cl_2 gas.

MATERIAL and METHODS

In October 2017, an accident involving Cl_2 gas exposure occurred in an elementary school housing 650 students. Fifty students inhaled the vapor formed in the school corridor after a cleaning staff mixed bleach and hydrochloric acid. We retrospectively reviewed the medical records of those who were admitted to our hospital. All patients admitted with acute chlorine poisoning after accidental exposure to the agent were included in the study. Hospitalization decisions were made by the pediatrician on duty. Criteria for admission included: potentially lethal exposure, respiratory distress (low oxygen saturation), persistent cough affecting the quality of life, and symptoms persisting for more than 6 hours after exposure. All medical records including signs and symptoms, physical examination, and laboratory results ECG, chest radiography and blood gas were evaluated.

Ethics committee approval of the study was obtained from Kırıkkale University Clinical Research Ethics Committee (Date: 08.07.2020, No: 2020/09).

Statistical Analyses

The IBM SPSS 25.0 software package was used for all statistical analyses. Independent samples t-test, Mann Whitney-U test, and Chi-square test were performed for comparison of two independent groups. The significance level was taken as $p < 0.05$ in all statistical analyses.

RESULTS

The mean age of the patients was 11.2 ± 1.5 years (range 2–18 years); 62% of the children were male. Among patients evaluated at the emergency department, 21 (42%) patients

were discharged within 4-6 hours after the initial examination; symptomatic treatment was administered to relieve upper respiratory tract symptoms mimicking a mild croup attack. These patients were treated with humidified oxygen via a mask. The remaining 29 patients were hospitalized. The presenting symptoms of the participant were only cough ($n=23$, 46%), cough plus dyspnea ($n=30$, 60%), nausea plus vomiting ($n=6$, 12%), headache ($n=7$, 14%), and sore throat ($n=3$, 6%). None of the patients was diagnosed with respiratory failure or acute pulmonary edema. Invasive or non-invasive airway support was not required. Seven patients were discharged on day 1, 21 patients on day 2, and 1 patient on day 3.

Regarding investigations performed at the hospital, 19 (38%) patients with respiratory distress were evaluated with a chest X-ray (CXR) which showed no pathology. They were also evaluated with an electrocardiogram (ECG) and arterial blood gas (ABG) analysis. Five patients ($M/F = 1/4$) had sinus tachycardia on ECG. CK-MB levels of these patients were above normal range (mean: 78 U/L , range: $46\text{--}278$). The presenting symptoms of these patients were only cough ($n=1$), cough plus dyspnea ($n=3$) and sore throat ($n=2$). During the follow-up period, CK-MB levels returned to normal levels.

Six patients had hypercarbia and respiratory acidosis; 2 had metabolic acidosis; 2 had metabolic alkalosis; and 2 had respiratory alkalosis. Troponin levels were analysed at time of admission. All of the patients levels were in normal range. Thirty patients had elevated creatine kinase-MB (CK-MB) (mean: $54.9 \pm 50.1 \text{ U/L}$) (Normal range: $0\text{--}25 \text{ U/L}$). During the follow-up period, sinus tachycardia disappeared and the CK-MB levels normalized. There was no abnormal result in complete blood count (CBC), transaminases, urea, and creatinine testing. During the follow-up period, cardiac enzymes of all patients returned to normal levels.

The proportion of asymptomatic female patients was significantly greater than that of the males ($52.6\% \text{ vs } 25.8\%$; $p=0.04$). There was no significant difference between the mean ages ($10.9 \pm 1.4 \text{ vs } 11.5 \pm 1.6$ years; $p=0.289$, for males and females, respectively) and CK MB levels ($63.6 \pm 16.5 \text{ vs } 47.1 \pm 29.8 \text{ U/L}$; $p=0.369$, for males and females, respectively) of the two sexes.

Seven patients who had signs and symptoms associated with upper or lower airway problems were treated with inhaled epinephrine, intravenous steroid (Dexametazon: 0.6 mg/kg), inhaled bronchodilators, and humidified oxygen; 11 patients were treated with oxygen and bronchodilators; the remainders took oxygen alone.

DISCUSSION

Sources of Cl_2 gas such as household disinfectants and swimming pool chlorinators make this agent potentially dangerous for children (3,4). There are some clinical reports in the pediatric age (5,6). Many reports have shown that the most prevalent complaints were pruritus, excessive lacrimation, rhinorrhea, conjunctival irritation, oropharyngeal pruritus, cough, sore throat, laryngeal stridor, and dyspnea (4,7,8). In our series, the most prevalent symptoms were cough and dyspnea.

After its inhalation, Cl_2 is transformed into hypochlorous acid (HOCl) and hydrochloric acid (HCl) through chemical reactions in human body (9). These products react with cellular proteins, nucleic acids, and lipids of the cells that line the airway epithelium, causing an inflammatory reaction in the alveolar space (10-11). This is why steroids are indicated in moderate-to-severe airway exposure. Seven of our patients with moderate exposure were treated with intravenous steroids. We did not know how much Cl_2 was released into the air. Evans reported that doses below 0.5 ppm can cause tickling of the nose and the throat, itching of the nose, coughing, burning of the eyes, and dryness of the throat (12). The fatal dose ranges from 50 to 2.000 ppm. So, it is obvious that a fatal dose was not released in our series.

There is no specific antidote for the treatment of Cl_2 exposure and the management is largely supportive (13). Guloglu et al. (4) recommended a combination of humidified O_2 and β agonist as supportive therapy in their study group because trachea-bronchitis and bronchoconstriction and/or pulmonary edema may develop in these cases. Moreover, Agabiti et al. (5) suggested the use of intravenous cortisone and humidified O_2 in hospitalized moderate and severe cases. Seven of our patients had signs and symptoms of tracheobronchitis. Thus, they were treated with intravenous steroids, humidified oxygen, and bronchodilator.

A baseline CXR should be obtained if a patient is symptomatic; additionally, respiratory functions should be monitored with ABG and pulse oximetry (14). Chest radiograms can show diffuse nodular opacities, patchy consolidation, pulmonary edema, and signs of vascular congestion. Radiologically, air

trapping can be seen in cases with persistent hyper reactivity and airflow obstruction. Our patients had no pathological sign on CXR. Cardiotoxicity is another important complication of Cl_2 toxicity. Chlorine inhalation attenuates myocardial contractile force, reduces systolic and diastolic blood pressures, and may cause cardiac failure and even death. The most common electrocardiographic finding is sinus tachycardia (15). Guloglu et al. (4) detected ST depression and sinus tachycardia in one patient and premature beats in another (only a total of 2 patients with ECG abnormalities were reported) among 18 cases. In our study, five patients had sinus tachycardia, however their troponin levels were normal at the time of admission. During the follow-up period, sinus tachycardia disappeared.

Girls were more severely affected than boys in our study. Considering that the severity of symptoms increase with the duration of exposure, it is thought that girls' departure from the accident area may be slower than boys and therefore they may have been exposed to Cl_2 for a longer time. In addition, considering that a significant part of the symptoms are related to anxiety (panic attack), it seems compatible with the high rate of these conditions in girls (16). The effect of a fear-panic state experienced collectively in mass incidents cannot be ignored, either. An observation and supportive approach should be applied for a final decision.

Twelve patients had different types of metabolic acid-base disturbances. Chlorine gas inhalation is usually accompanied by metabolic acidosis that has been attributed to lactic acidosis (17). On the other way, the presence of hypercarbia can lead to respiratory acidosis (18). Hyperventilation leads to respiratory alkalosis (19). However, two patients had metabolic alkalosis that we did not expect to encounter in chlorine intoxication. It may be a laboratory error.

Moreover we applied Haddon matrix to chlorine toxicity (Table I). A matrix looks at factors related to personal, agent and environmental attributes; before, during and after an injury (20). In this way, we aimed to ensure that such events do not recur.

The present study has a retrospective nature and is thus limited by several limitations. Firstly, the review of medical records mainly focused on common, recognizable symptoms. Subtle

Table I: Haddon matrix applied to acute chlorine poisoning.

	Victims	Agent Toxic substance	Environment Factors
Pre injury	Teach children not to play with unknown substances especially hazardous chemicals	Teach cleaning staff no to mix bleach and hydrochloric acid	Schools should establish a chemical storage and handling policy that addresses how chemicals should be properly stored, labeled, and secured.
Injury	Teach children how to respond to gas toxicity	Prevent gas contact with the students	Emptying the room, open the windows
Postinjury (after child injured)	Provide first aid	Put chemicals away from children	Put a warning note

toxicity was not evident in the review of medical records. Secondly, there was no measurable method for the correlation of the severity of Cl intoxication and symptoms.

In conclusion, serious undesirable situations including intoxication may develop after negligent and careless use of simple household chemicals. Accidental mass intoxication incidents, albeit rare, are important acute situations for which healthcare providers should be prepared. A good infrastructure should be available for rapid organization, medical treatment, and access to drugs and material. A similar one has been experienced during the more serious pandemic process. We are of the opinion that physicians should increase their interest in chemical reactions that may produce toxic substances such as in our cases.

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Kistik Fibrozis Hastalarında Akciğer Tutulumunun Manyetik Rezonans Görüntüleme ile Değerlendirilmesi

The Evaluation of Lung Involvement in Patients with Cystic Fibrosis By Using Mediastinal Magnetic Resonance Imaging

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ÖZ

Amaç: Kistik Fibrozis (KF) hastalığında pulmoner yapısal değişikliklerin erken dönemde noninvaziv olarak gösterilmesi ile tedaviye daha erken başlanarak ve mevcut tedavi gözden geçirilerek komplikasyonların önüne geçilebilir. Erken dönem pulmoner yapısal değişiklikleri, pulmoner alevlenme öncesi ve sonrası tedavi yanıtını göstermede bilgisayarlı toraks tomografisi (BT) ile beraber mediastinal manyetik rezonans görüntüleme (MRG) kullanılmaya başlanmıştır. Bu çalışmanın amacı, kliniğimizde KF ile takip edilen ve kliniği stabil hastalarda eş zamanlı olarak toraks BT ve MRG çekilen hastalardaki radyolojik bulguların birbirleri ile karşılaştırılması ve hastaların bazı klinik ve laboratuvar bulguları ile korelasyon yapılarak; takiplerinde uygun yöntemle görüntüleme yapmaktır.

Gereç ve Yöntemler: Ağustos 2018 - Şubat 2019 tarihleri arasında, hastanemiz Çocuk Göğüs Hastalıkları Kliniği'nde KF tanısı ile takip edilmekte olan, klinik olarak stabil 14 hastanın aynı gün çekilen BT ve MRG'leri geriye dönük olarak Helbich ve Eichinger skorlama sistemine göre incelendi. Hastaların demografik verileri, klinik ve laboratuvar bulguları kronik kolonizasyon durumu ve genetik mutasyonları kaydedildi.

Bulgular: KF tanısı ile takip edilmekte olan, pulmoner alevlenme şikayeti olmayan 14 hastanın aynı gün çekilen BT ve MRG'leri geriye dönük olarak değerlendirildi. BT ve MRG bulguları karşılaştırıldığında Helbich skorlama sistemine göre sadece mozaik atenüasyon paterninde BT ile daha iyi tanımlandığı gösterildi ($p = 0.003$). Helbich skorlama sistemine göre BT için ortalama skor 6.6 (1-17), MRG için 4.7 (0-15)'di. Eichinger skorlamasına göre MRG için ortalama skor 3 (0-16)'dı. Hastaların klinik ve demografik bulguları karşılaştırıldığında Phe508del homozigot mutasyonu olup *Paeruginosa* ile kronik kolonize olan hastaların BT ve MRG skorları diğer hastalara göre anlamlı olarak daha yüksekti ($p = 0.002$).

Sonuç: KF hastalarında pulmoner etkilenmeyi göstermek için mediastinal MRG toraks BT kadar güvenilir; radyasyon içermediği için de tercih edilebilir bir yöntemdir. Mozaik atenüasyon gibi erken dönem akciğer bulgularının değerlendirilmesinde ise BT ile beraber kullanılabilir. Yakın zamanda KF hastalarındaki akciğer bulgularını göstermede deneyimli personel ve yeni çekim teknikleri ile MRG altın standart haline gelebilir.

Anahtar Sözcükler: Kistik fibrozis, Bilgisayarlı tomografi, Manyetik rezonans görüntüleme, Pulmoner tutulum



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ABSTRACT

Objective: In Cystic Fibrosis (CF) disease, complications can be avoided by noninvasively demonstrating pulmonary structural changes in the early period by starting treatment earlier and reviewing the current treatment. Computed thoracic tomography (CT) and mediastinal magnetic resonance imaging (MRI) have been used to show early pulmonary structural changes and treatment response before and after pulmonary exacerbation. The aim of this study is to compare the CT and MRI findings of CF patients with some clinical and laboratory findings, and to perform imaging with an appropriate method in their follow-up.

Material and Methods: CT and MRIs of 14 clinically stable CF patients August 2018 and February 2019 were retrospectively analyzed according to the Helbich and Eichinger scoring system. Patient's laboratory findings, chronic colonization status and genetic mutations were recorded.

Results: According to Helbich scoring, the mean score in CT was 6.6 (score range 1-17), while MRI was 4.7 (score range 0-15). The mean score in the MRI was 3 (score range 0-16) according to the Eichinger score. There was a statistically significant difference between CT and MRI findings according to Helbich scoring ($p=0.003$). CT was superior to MRI in demonstrating mosaic attenuation. Four patients who had Phe508del homozygous mutation chronic colonised with *p.aeruginosa* and had higher CT and MRI scores than rest of them ($p=0.002$).

Conclusion: Mediastinal MRI is as reliable as thoracic CT; to show pulmonary involvement in CF patients and can be preferred to reduce radiation damage. MRI can be used together with CT in the evaluation of early lung findings such as mosaic attenuation. Recently, MRI may become the gold standard with experienced staff and new imaging techniques in demonstrating lung findings in CF patients.

Key Words: Cystic Fibrosis, Computed Tomography, Magnetic Resonance Imaging, Lung Involvement

GİRİŞ

Kistik Fibrozis (KF), 2500 canlı doğumda bir görülen, çocukluk çağıının en sık görülen genetik hastalıklarından biridir. Kistik Fibrozis Transmembran Regülatör (KFTTR) geninde görülen mutasyonlar ile ekzokrin sekresyonların akışkanlığı azalır, uzun süreli bronşiyal obstrüksiyon, enfeksiyon ve inflamasyon, skar (fibrozis) ve bronşektazi ile karakterize kalıcı akciğer hasarı oluşur (1-3). KF'de safra kesesi, karaciğer ve pankreasta da tutulum olmakla birlikte, pulmoner komplikasyonlar morbidite ve mortalitenin %95'inden sorumludur (1-4). Yenidoğan tarama programları ile daha erken dönemde tanı konulabilmektedir. Pulmoner yapısal değişikliklerin erken dönemde noninvaziv olarak gösterilmesi ile tedaviye daha erken başlanarak ve mevcut tedavi gözden geçirilerek komplikasyonların önüne geçilmesi ile bu hastaların morbidite ve mortalitesi azaltılabilir. Bu nedenle, İngiltere ve Avustralya KF takip yönergelerinde ilk 2 yaşta asemptomatik dönemde ve ilk 6 yaşta düzelmeyen pulmoner bulguları olan hastalarda, daha önce yapılmadıysa ileri görüntüleme yöntemleri önerilmektedir (5,6). Seçilen görüntüleme yöntemlerinin kolay uygulanabilir, radyasyon içermeyen, aynı zamanda pulmoner bulguları göstermede hassas olması gerekmektedir.

BT'nin KF hastalarında pulmoner bulguları ayrıntılı olarak gösterdiği, küçük çocuklarda çok erken dönemde bile hava hapsini gösterebildiği uzun zamandır bilinmektedir (7,8). Uzayan yaşam süreleri ve izlemde sık BT çekilmesi ile beraber hastaların maruz kaldığı kümülatif radyasyon dozu artabilmektedir. Bilindiği üzere; Helbich skorlama sistemi uzun yıllardır BT'de akciğer patolojilerinin (amfizem, bronşektazi, bronşial kalınlaşma vb.) skorlanması (maksimum puan=27) için kullanılmaktadır. Son yıllarda mediastinal MRG için de modifiye edilmiştir (Tablo I.) Eichinger skorlama sistemi (maksimum puan=60) ise Helbich skorlama sistemine bazı bulgular tam uyarlanamadığı için son 10 yılda geliştirilmiştir. Eichinger skorlama sistemi

Tablo I: BT ve MRG için Helbich skorlama sistemi.

	BT*	MRG*
Bronşektazi	0-3	0-3
Bronşiyal duvarda kalınlaşma	0-3	0-3
Bronşektazi yaygınlığı	0-3	0-3
Mukus plağı yaygınlığı	0-3	0-3
Apse ve sakkulasyon yaygınlığı	0-3	0-3
Bronşiyal bölge tutulumu	0-3	0-3
Bül ciddiyeti	0-3	0-3
Amfizem ciddiyeti	0-2	0-2
Mozaik perfüzyon ciddiyeti	0-2	0-2
Kollaps/konsolidasyon ciddiyeti	0-2	0-2

* (maksimum skor = 27)

Tablo II: MRG için Eichinger skorlama sistemi.

	MRG*
Bronşektazi/bronşiyal duvar kalınlaşması	12
Mukus tıkaçı	12
Apse/sakkulasyon	12
Konsolidasyon	12
Spesifik bulgular (plevral efüzyon, plörezi, pnömotoraks)	12

* (maksimum skor = 60)

akciğer patolojilerinin mediastinal MRG'de yorumlanması için geliştirilmiştir (Tablo II). Son yıllarda mediastinal manyetik rezonans görüntüleme (MRG)'nin KF hastalarında erken dönem pulmoner yapısal değişiklikleri, pulmoner alevlenme öncesi ve sonrası tedavi yanıtını göstermede etkin olarak kullanılabileceğini bildiren az sayıda çalışma mevcuttur (9-12). Radyasyon içermeyen görüntüleme yöntemleri özellikle çocuklarda daha sık tercih edilmektedir. KF hastalarında da pulmoner tutulumu göstermekte altın standart kabul edilen BT yerine yeni çekim

teknikleri ile MRG de tercih edilmeye başlanmıştır. MRG ile BT'de saptanan bronşektazi ve mukus tıkaçı gibi pulmoner parankim bulgularının saptanabileceği bildirilmiştir (7,9-12).

GEREÇ ve YÖNTEMLER

Çalışmamızda klinik olarak stabil dönemde olan ve akciğer grafilerinde önceki akciğer grafilerine göre değişiklik olmayan hastaların BT ve MRG ile görüntülenmesi yapılmış ve bundan sonraki takiplerinde akut pulmoner alevlenme gibi klinik gereklilik halinde veya 5 yılda bir tekrarlanan rutin görüntülemeleri esnasında en uygun yöntem ile görüntüleme yapılması amaçlanmıştır. Ayrıca, toraks BT ve MRG çekilen hastalardaki radyolojik bulguların birbirleri ile karşılaştırılması ve bu bulguların kronik kolonizasyon durumu ve KFTR mutasyon analizi sonucu vb. klinik bulgular ile korelasyonunu değerlendirmek amaçlanmıştır.

Çalışmada KF hastalarında akciğer tutulumu bulgularının izleminde MRG ile takip planlanır ise; gelecekte de daha sık kullanılabileceğinden MRG için spesifik skorlama sistemi olan Eichinger sisteminin de kullanılması uygun bulunmuştur. Bu nedenle; hastaların BT ve MRG'leri Helbich skorlama sistemi ile skorlanmış; MRG'ler Helbich skorlama sistemine ek olarak Eichinger skorlama sistemi ile de skorlanmıştır. Sonuçlarda her 2 skorlama sistemini bulguları karşılaştırılmıştır.

Çalışmamız için Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu'ndan 16.04.2019 tarih ve 2019-090 karar numarası ile onay alınmıştır.

Ağustos 2018 ile Şubat 2019 tarihleri arasında, hastanemiz Çocuk Göğüs Hastalıkları Kliniği'nde KF tanısı ile takip edilen, klinik olarak stabil, 18 yaş altındaki, toraks BT ve mediastinal MRG görüntülenmesi yapılmış hastalar geriye dönük olarak tarandı. Hastaların yaşı, cinsiyeti, klinik ve laboratuvar bulguları, kronik kolonizasyon durumu KFTR DNA sekans analizi sonuçları çocuk göğüs hastalıkları doktorları tarafından değerlendirildi.

Hastaların BT ve MRG görüntüleri, hastaların kliniği hakkında bilgisi olmayan bir pediatrik radyolog tarafından Helbich ve Eichinger skorları kullanılarak yeniden değerlendirildi (Tablo I ve II). Deneyimli pediatrik radyolog önce hastaların BT ve MRG görüntülerini Helbich skorlama sistemine göre karşılaştırmış; daha sonra MRG görüntülerini Eichinger skorlama sistemi ile değerlendirmiştir. Değerlendirme sonucunda, kontrolleri sırasında pulmoner alevlenme döneminde olan hastalar çalışma dışında bırakılmıştır.

Tüm BT görüntülenmesi, 16 kesitli cihaz ile (Toshiba America Medical Systems), (100–120 kV; kesit kalınlığı ≤ 2 mm; matriks 512×512 piksel; gantry açısı 0°) intravenöz kontrast madde kullanılmadan, hasta yaşına uygun kV (<2 yaş: 100 kV, >2 yaş: 120 kV) seçilerek gerçekleştirildi. Tüm MR görüntülemeleri 1.5T cihaz ile (GE Healthcare, Milwaukee, WI) çok kanallı

sarmal kullanılarak, aksiyel ve koronal T2 ağırlıklı (TR/TE:4500–6000/90–110 ms) sekansları kullanılarak solunum tetiklemeli olarak elde edildi. Görüntülerin kesit kalınlığı 3–4 mm, ortalama çekim süresi 7 dakikadır. MR görüntülemeler, küçük çocuklarda yüzeyel sedasyonlu (klorohidrat) veya sedasyon kullanılmadan kendi uykusu altında gerçekleştirildi.

İstatistiksel Analiz

Kategorik değişkenler, sayı ve yüzde ile sayısal değişkenler ortalama±standart sapma (SD) şeklinde verildi. Tüm analizler SPSS ile (versiyon 22.0, SPSS Inc., Chicago, IL) yapıldı ve $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya KF tanısı ile takip edilmekte olan pulmoner alevlenme şikayeti olmayan 14 hasta dahil edildi. Hastaların 10'u (%71.4) erkek, 4'ü (%28.6) kızdı; yaş ortancası 3.9 yıl (1 en küçük-18 en büyük)'dü (Tablo III). Çalışmaya dahil edilen klinik olarak stabil 14 KF hastasına aynı gün veya yakın tarihlerde BT ve MRG çekilmişti (BT=14, MRG=14). Akut pulmoner alevlenme döneminde olan 3 hasta çalışma dışı bırakılmıştı. Noninvaziv mekanik ventilasyon (NIMV) ile izlenen bir (%7.1) hasta dışında kronik solunum yetmezliği nedeniyle tedavi alan hastamız yoktu. Bir hasta dışında tüm hastalarımız (%92.8) inhale dornaz alfa tedavisini düzenli kullanmaktaydı. Beş (%35.7) hasta *P. aeruginosa* ile kronik kolonizeydi. *S.aureus* ile kronik kolonize

Tablo III: Hastaların klinik ve laboratuvar bulguları.

	n=14	%
Yaş ortancası	3.9 (1-18 yaş)	
E/K	10/4	71.4/28.6
Malnütrisyon	2	14.2
Yenidoğan tarama programı ile tanı	2	14.2
Dornaz Alfa kullanımı	13	92.8
<i>P. aeruginosa</i> ile kronik kolonizasyon	5	35.7
Normal spirometri ^a	3/4	75
NIMV	1	7.1
KFTR DNA Sekans Analizi	14	100
F508del homozigot	4	28.5
Q220X / 2789+5G->A	1	7.1
R334Q / p.Phe152	1	7.1
R1070Q Homozigot	1	7.1
457TAT->G Homozigot	1	7.1
S466X Homozigot	1	7.1
G314E Homozigot	1	7.1
2184delA / 3878 delG	1	7.1
G542 / D58N	1	7.1
G85E Homozigot	1	7.1
c.2657+5G>A Homozigot	1	7.1

E: erkek; **K:** kadın; **NIMV:** non invaziv mekanik ventilasyon; **KFTR:** kistik fibrozis transmembran regülatör; **min:** minimum; **max:** maksimum. ^a:(FEV1>%80, FVC>%80, FEF 25-75>%70, FEV1/FVC>80)

Tablo IV: KF hastalarının BT ve MRG bulgularının karşılaştırılması.

Parankimal Bulgular	BT		MRG		p
	n=14	%	n=14	%	
Bronşektazi/peribronşial kalınlaşma	10	71.4	10	71.4	>0.05
Tomurcuklanmış ağaç manzarası	8	57.1	8	57.1	>0.05
Mozaik atenüasyon	7	50	1	7.1	*0.003
Mukus tıkaçı	4	28.5	4	28.5	>0.05
Lineer-subsegmental atelektazi	4	28.5	4	28.5	>0.05
Skorlama					
Helbich Skoru, ortalama skor ± standart sapma	6.6 ± 2.2 (skor aralığı, 1-17)		4.7± 2.3 (skor aralığı, 0-15)		>0.05
Eichinger Skoru, ortalama skor ± standart sapma	-		3± 2.2 (skor aralığı, 0-16)		

olan hastamız yoktu. KFTR DNA sekans analizi sonuçları ile 4 (%28.5) hastada Phe508del homozigot mutasyonu olduğu gösterildi (Tablo III). Spirometre de koopere olabilen 4 (%28.5) hastadan *P. aeruginosa* ile kronik kolonize, Phe508del homozigot mutasyonu olan NIMV ile izlenen bir hastamızın ağır restriksiyonu mevcuttu. Diğer üç (%75) hastanın ise spirometre değerleri normaldi (FEV1>%80, FVC>%80, FEF 25-75>%70, FEV1/FVC>80) (Tablo III).

BT'de hastaların %71.4'ünde (10/14) bronşektazi ve peribronşial kalınlaşma, %57.1'inde (8/14) tomurcuklanmış ağaç manzarası, %50'sinde (7/14) mozaik atenüasyon, %28.5'inde (4/14) mukus tıkaçı, %28.5'inde (4/14) lineer-subsegmental atelektazi saptandı (Tablo III).

Helbich skorlama sistemine göre BT'de ortalama skor 6.6 $\pm$ 2.2 (skor aralığı, 1-17), MRG'de 4.7 $\pm$ 2.3 (skor aralığı, 0-15)'di. Eichinger skorlamasına göre MRG için ortalama skor 3 $\pm$ 2.2 (skor aralığı 0-16)'di. BT ve MRG bulguları karşılaştırıldığında, Helbich skorlama sisteminde değerlendirilen kriterler arasında sadece mozaik atenüasyon paterninde istatistiksel olarak anlamlı fark saptandı (p = 0.003). Diğer kriterlerde anlamlı fark görülmedi (p>0.05) (Tablo IV) (Şekil 1).

Hastaların klinik ve demografik bulguları karşılaştırıldığında F508 delesyonu homozigot mutasyonu olup *P. aeruginosa* ile kronik kolonize olan dört (%28.5) hastanın yaş ortancası 8.9 (6.5 en küçük-20 en büyük)'tü. Bu hastaların BT ve MRG skorları, yaş ortancası 3.9 (1-20 yaş) olan diğer hastalara göre anlamlı olarak daha yüksekti (p = 0.002).

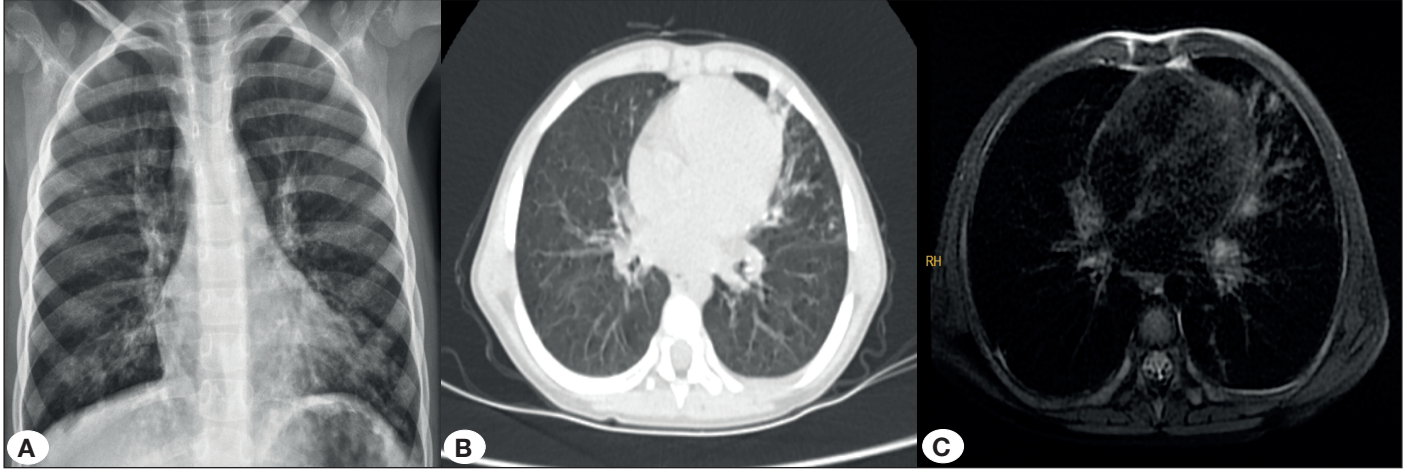
TARTIŞMA

Bu retrospektif kesitsel çalışmada klinik olarak stabil iken çekilen BT ve MRG'de mozaik atenüasyon dışındaki akciğer bulgularında istatistiksel olarak anlamlı fark olmadığı saptandı. KF'de erken dönemde periferik hava yolu inflamasyonu, enfeksiyonlar ve bozulmuş mukosilyer klirens ile başlayan akciğer hasarı, geri dönüşümsüz yaygın bronşektaziler ve son dönemde kronik solunum yetmezliği nedeni olabilir (13,14). Akut pulmoner alevlenmede solunum fonksiyon testleri etkilenmeden

önce BT'de de klinik ile korele değişiklikler görüldüğü, uzun dönem izlemde de pulmoner alevlenme sayısı arttıkça BT bulgularının da belirginleştiği gösterilmiştir (8,15).

Merkezimizde de KF hastalarımız için rutin BT çekimi yapılmamakta, gereklilik halinde kontrast madde kullanılarak BT çekilmektedir. Şikayet olması halinde veya yıllık kontroller sırasında rutin akciğer grafisi çekilmektedir. Çalışmamızda klinik olarak stabil dönemde olan ve akciğer grafilerinde önceki akciğer grafilerine göre değişiklik olmayan hastaların BT ve MRG ile görüntülenmesi yapılmıştır. Akciğer grafisi ucuz, hızlı ve yaygın kullanılan bir yöntemdir; bu nedenle yılda bir kontrol amaçlı ve gereklilik halinde daha erken çekilmesi önerilmektedir (13). Grafiler atelektazi, konsolidasyon, plevral efüzyon gibi anormalliklerin tanısında yararlıdır; ancak bronşektazi tanısında hassasiyeti düşüktür (16). KF hastalarında erken dönemde önce geri dönüşümlü küçük hava yolu hastalığı, zamanla bronşektazi gelişimi ile kalıcı akciğer hasarına yol açarak yaşam kalitesini düşürmekte; morbidite ve mortaliteyi arttırmaktadır (17-20). Küçük hava yolu hastalığının erken dönemde tespiti mümkün olduğunda; etkin fizyoterapi ve postural drenaj, enfeksiyonlardan korunma ve gerektiğinde dornaz alfa tedavisi ile bulgulara bir miktar düzelme sağlanabilir (21). BT ile tüm akciğer parankimi ayrıntılı değerlendirilip, bronşektazi tanısı konulabilmektedir (22-24). Küçük hava yolu hastalığının gösterilmesinde en çok bilinen ve sık kullanılan yöntem BT'dir (25). BT çekim sıklığı ve endikasyonları ile ilgili klinikte bazı görüş ayrılıkları görülmektedir. Bazı merkezler, ilk bir yıldan başlayarak en az 2 yılda bir kontrol BT çekilmesini önermekte iken; bazı merkezler ise BT'nin rutin kullanımını önermemektedir (17,24). İngiltere'de 27 merkezli 3.basamak KF takip ve tedavi merkezinde yapılan bir anket çalışmasında klinisyenlerin %93'ü BT'yi hastalık progresyonunda (en sık nontüberküloz mikobakteriler ve allerjik bronkopulmoner aspergillozis) kullanmış ve %70'i de BT sonuçlarının tedaviyi yönlendirdiğini belirtmiştir, ancak sadece %17'si yıllık rutin BT önermiştir (25). Klinisyenlerin %14'ü ekspiratuar fazda, %5'i de intravenöz kontrast ile BT kullanmıştır (25). BT ile hastalığın çok erken döneminde bile hafif pulmoner değişiklikler saptanabilir; bu nedenle değişken endikasyonlarda sıklıkla kullanılmaktadır.

Çalışmamızda da BT ve MRG bulguları benzerlik göstermiştir. Yaşı küçük olan çocuk hastalarda kooperasyonun az olması



Şekil 1: KF hastasında akciğer grafisi, BT ve MRG Görüntüleme Bulguları KF nedeniyle takipte, Phe508del mutasyonu olan yaygın sol akciğerde daha bronşektazileri olan 5 yaşında bir hastanın; **(A)** Akciğer Grafisi: Bilateral sol akciğerde daha belirgin parakardiyak peribronşiyal kalınlaşma ve atelektazi mevcut; **(B)** BT: sol lingüler bronşektazi ve atelektazi, bilateral peribronşiyal kalınlaşma ve mozaik atenüasyon mevcut; **(C)** MRG: BT ile benzer bulgular mevcut ancak mozaik atenüasyon gösterilemedi.

nedeniyle çalışmamıza dahil edilen hastalarda ekspiratuar fazda BT çekimi yapılmamıştır. Mozaik atenüasyon, ekspiratuar fazda elde edilen BT'lerde daha belirgin olarak seçilebilse de, inspirasyon fazında elde edilen BT'lerde de görülebilmektedir. BT'nin iyonizan radyasyon içeren bir görüntüleme yöntemi olması nedeniyle son yıllarda rutin kullanımı tartışılmaya başlanmıştır (26,27). Radyasyon maruziyetinin olmaması nedeniyle KF hastaları için MRG'nin akciğer hasarını gösterme başansı ile çalışmalar artmıştır. MRG'deki tetkik sürelerinin hızlı görüntülemeye imkan sağlayan sekanslar (Ultra-short TR/TE 2D Steady State Free Precession ile Sequence) ile kısalması, görüntülerin solunum ile senkron elde edilebilmesi ile akciğer parankimini değerlendirmek mümkün olabilmektedir (28). Ayrıca, KF olan çocuk hastalarda da erişkinlerde olduğu gibi; inhale ^3He ve ^{129}Xe ile MRG çekiminin tolere edilebilir olduğu ve ilk 1 yaşta bile küçük hava yollarındaki hafif değişikliklerin ve bölgesel ventilasyon bozukluklarının görüntülediği bildirilmiştir (29,30). MR görüntülemeye çocuk hastalarda karşılaşılan en büyük problem hasta ile olan kooperasyondur. Özellikle küçük yaşta çocuklarda yüzeyel veya genel sedasyon ihtiyacı olabilmektedir. Literatürde KF hastalarında MR görüntüleme kullanımı ile ilgili birkaç çalışma bulunmaktadır. 2014'te Sileo ve ark. (33), yaş ortalaması 12.5 yıl olan 17 KF hastasının rutin BT çekimi esnasında MRG'lerini çekmiş, Eisenger ve Helbich skorları ile BT ve MRG bulgularını karşılaştırmıştır. Her iki skorlama sisteminin birbiri ile korelasyon gösterdiği; mukus tıkaçı, bronşektazi, peribronşiyal kalınlaşma skorlarının BT ve MRG de benzer olduğu ve en önemlisi ekspiratuar fazda çekilen MRG'de T2 ağırlıklı görüntülerde mozaik atenüasyonun gösterilebildiği bildirilmiştir (31). Almanya'da 0-6 yaş arası 50 KF hastasına stabil dönemde MRG çekilmiş; ilk 1 yıl dahil olmak üzere, bronşiyal duvar kalınlaşması, mukus tıkaçı, bronşektazi ve perfüzyon bozuklukları gösterilebilmiştir (9). Bu çalışmada ayrıca akut pulmoner alevlenmede MRG skorlarının yükseldiği

ve tedaviden 1 ay sonra anlamlı olarak düştüğü de gösterilmiştir (9).

Çalışmamızda BT'de mozaik atenüasyon saptanan 7 hastadan sadece 1'inde MRG'de mozaik atenüasyon saptanabilmiştir. Çalışmamızda elde edilen MR görüntülerde daha önceki çalışmalardan farklı olarak mozaik atenüasyonun BT'den daha az saptanabildiği görülmüştür. MRG'de normalde havaya ait sinyal kaydı bulunmamakta olup akciğer parankiminde havalanma artışı gösteren parankim alanında da sinyal farklılığı saptanamamaktadır. Akciğerlerde hava hapsi alanları gösteren parankim ile normal parankim arasındaki sinyal farkının saptanabilirliğinin, ekspiratuar ve inspiratuar fazlarda alınan görüntülerin karşılaştırılması ile mümkün olabileceği bildirilmiştir (32).

Çalışmamızda da *P. aeruginosa* ile kronik kolonize olan ve Phe508del homozigot mutasyonu olan hastalarımızın BT ve MRG skorları birbiriyle korele olarak daha yüksekti. Bu durum, KF hastalarında genetik faktörlerin etkisi ve sık pulmoner alevlenmeler ile akciğer tutulumunun yaşla artması ile ilişkilendirildi.

Bronşektazi (BE) ile ilgili yapısal değişikliklerin yenidoğan ve erken infantil dönemde BT'de hafif hava hapsi bulguları ile başladığı ve inflamasyon ile ilerleme gösterdiği saptanmıştır (12,33-35). BT bulguları ile yapılan klinik korelasyonlarda bronşektazi gelişiminde, *P. aeruginosa* enfeksiyonu ve kolonizasyonunun inflamasyonu ve akciğer hasarını arttıran en önemli faktörlerden biri olduğu gösterilmiştir (18,20,35). *P. aeruginosa* bronşektazi gelişimi ile yaşam kalitesini düşürmekte ve son dönem akciğer hastalığında mortalitenin en önemli komponentlerinden biri olmaktadır (14,20). Bu nedenle; akciğer hasarının erken dönemde gösterilmesi ve enfeksiyonların önlenmesi ile bronşektazi ilişkili akciğer hasarının yavaşlatılması amaçlanmaktadır.

Çalışmamızda solunum fonksiyon testlerinden spirometreye koopere olan hasta sayımız radyolojik bulgular ile klinik korelasyon yapmak için yetersizdi. Her ikisi de iyonizan radyasyon içermeyen, noninvaziv ve küçük çocuklarda da uygulanabilen solunum fonksiyon testlerinden lung clearance index (LCI) ve MRG'nin koordine kullanımı son dekatta giderek artmaktadır (36). Bilindiği üzere spirometre FEV1 yüzdeleri düşmeden önce Nitrojen Multiple Breath Washout (MBW) tekniği ile LCI de ventilasyon heterojenitesi saptanabilmektedir. İlk olarak, spirometride FEV1 yüzdeleri normal olan KF hastalarında da hafif değişikliklerin 129Xse MRG ile erken dönemde saptandığı bildirilmiştir (36). LCI'nin kullanımının sıklaşması ile; MRG'de erken parankimal bulguların LCI ile korelasyonunu gösteren çalışmalar artış göstermektedir. Stahl ve ark. (37) 2017'de yaptığı bir çalışmada, KF hastalarında stabil dönemde LCI yüksekliği ile görülen ventilasyon heterojenitesinin (VH), MRG' de bölgesel mukus plağı ve hipoperfüzyon ile yükselen ventilasyon defekti yüzdesi (VDY) ile lokalize edilebildiğini bildirmiştir. Ayrıca bu hastalarda akut pulmoner alevlenme esnasında LCI ve MRG global skorlarının birbirleri ile korele olarak yükseldiği; uygun tedavi sonrasında düştüğü de gösterilmiştir (37). 2020'de Couch MJ ve ark.(38) stabil dönemde ve akut pulmoner alevlenme döneminde solunum fonksiyon testlerinden FEV1, LCI ile görüntüleme yöntemlerinden PREFUL ve 129Xse MRG bulgularını karşılaştırılmıştır. KF hastalarında stabil dönemde FEV1 yüzdeleri normal, LCI VH'ni gösterecek şekilde yüksek iken; hem 129Xse MRG hem de PREFUL MRG'de VDY benzer oranda gösterilebilmiştir (39,40). Akut pulmoner alevlenmede ise; FEV1 düşük ve LCI yüksek iken 129Xse MRG ve PREFUL MRG'de VDY'nin arttığı; uygun tedavi ile FEV1 ve LCI düzelirken gene her iki MRG'de de düzelmeye gösterilmiştir (41). Bu yöntemlerden normal tidal ventilasyon esnasında daha az aplikasyon ile çekilebilen PREFUL MRG'nini kullanımının teknik olarak daha kolay olduğu bildirilmiştir (41).

Çalışmamızın kısıtlılıklarından birisi solunum fonksiyon testlerinden spirometre dışında pletismografi, LCI yapılamaması ve bu nedenle 6 yaş altı hastalarımız için görüntüleme yöntemleri ile korelasyon yapılamamasıdır.

Bir diğer kısıtlılık ise teknik şartlar nedeniyle tüm hastalarda ekspiratuar fazda MRG çekilememesidir, ancak mevcut MRG tekniği ile mozaik atenüasyon dışındaki parankimal bulgular BT ile karşılaştırılabilmiştir

Daha çok hastanın dahil olduğu; KF hastalarının 1 yaştan itibaren izlendiği, prospektif, randomize kontrollü çalışmalara ihtiyaç vardır.

SONUÇ

KF hastalarında pulmoner etkilenmeyi erken dönemde göstermek için MRG güvenilir; radyasyon içermediği için de tercih edilebilir bir yöntemdir. Yakın zamanda KF hastalarındaki akciğer bulgularını göstermede yapılacak daha büyük çaplı çalışmalar ile MRG altın standart haline gelebilir.

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Inguinal Hernia Repair with Laparoscopic-Supported Percutaneous Internal Ring Suturing Technique in Children - One Center Experience

Çocuklarda Laparoskopik Destekli Perkütan İç Halka Kapatılması Tekniği ile Kasık Fıtığı Onarımı – Tek Merkez Deneyimi

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ABSTRACT

Objective: High ligation of the hernia sac is applied as the basic principle in inguinal hernia surgery. Nowadays, it is possible to perform inguinal hernia surgeries with minimally invasive methods and with the help of technological developments with the same success rates. One of these minimally invasive methods is the percutaneous internal ring suturing method, assisted by laparoscopy.

In this study, we aimed to present the case series that we treated with a laparoscopy-assisted percutaneous internal ring suturing and its results up to six months after surgery.

Material and Methods: Pediatric patients admitted to the Pediatric Surgery Clinic of Our Hospital with indirect inguinal hernia between November 01, 2019, and February 29, 2020, were included in the study. Patients with clinical features of incarcerated inguinal hernia were excluded from the study.

Inguinal hernia repair was performed by the percutaneous internal ring suturing method supported by laparoscopy.

Results: During the study period, 36 inguinal hernia repairs were performed in 27 patients. The distribution of age groups is over 24 months (8/27), 2-6 months (5/27), 6-12 months (4/27), and 12-24 months (1/27). No patient required open surgical technique or the use of additional trocars. The mean operation time was 24.3±1.77 minutes. The mean hospitalization period of the patients was 2.15±0.12 days.

During the follow-up of the patients, no recurrence, intra-abdominal complication, or inguinal complication was detected.

Conclusion: We found that the percutaneous internal ring closure method applied under laparoscopic support in childhood is an easy and safe method for indirect inguinal hernia repair.

Key Words: Inguinal hernia, Laparoscopic surgery, Minimally invasive surgery

ÖZ

Amaç: Kasık fıtığı cerrahisinde, fıtık kesesinin yüksek ligasyonu temel prensip olarak uygulanmaktadır. Günümüzde kasık fıtığı ameliyatlarının minimal invaziv yöntemlerle ve teknolojiye gelişmelerin yardımıyla aynı başarı oranları ile yapılması mümkün olmaktadır. Bu minimal invaziv yöntemlerden biri de laparoskopik destekli perkütan iç halka kapatılması yöntemidir.



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Contribution of the Authors / Yazarların katkısı: **NARSAT MA:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, 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. **YILMAZ A:** 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, Reviewing the article before submission scientifically besides spelling and grammar. **YILDIZ E:** 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, Reviewing the article before submission scientifically besides spelling and grammar.

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Bu çalışmada, laparoskopik destekli perkütan iç halka kapatılması yöntemi ile tedavi ettiğimiz olgu serimizi ve ameliyat sonrası altı aya kadar olan sonuçlarını sunmayı amaçladık.

Gereç ve Yöntemler: Hastanemiz Çocuk Cerrahisi Kliniğine 01 Kasım 2019- 29 Şubat 2020 tarihleri arasında endirekt kasık fıtığı ile başvuran çocuk hastalar çalışmaya dahil edildi. İnkarere kasık fıtığına ait klinik özellikleri taşıyan hastalar çalışma dışı bırakıldı.

Laparoskopik destekli perkütan iç halka kapatılması yöntemi ile kasık fıtığı onarımı yapıldı.

Bulgular: Çalışmanın yapıldığı süre içerisinde 27 hastada 36 kasık fıtığı onarımı yapıldı. Yaş gruplarının dağılımı 24 ay üstü (8/27), 2-6 ay arası (5/27), 6-12 ay arası (4/27) ve 12-24 ay arası (1/27)'dir. Hiçbir hastada açık cerrahi tekniğe ya da ek trokar kullanılmasına gerek olmadı. Ortalama ameliyat süresi 24.3 ± 1.77 dakikaydı. Hastaların hastanede ortalama yatış süresi 2.15 ± 0.12 gündü.

Hastaların takiplerinde rekürrens, karın içi komplikasyon ya da kasık bölgesinde komplikasyon saptanmadı.

Sonuç: Çocukluk çağında laparoskopik desteğinde uygulanan perkütan iç halka kapatma yönteminin endirekt kasık fıtığı onarımı için kolay ve güvenli olarak uygulanabilen bir yöntem olduğunu saptadık.

Anahtar Sözcükler: Inguinal herni, Laparoskopik cerrahi, Minimal invaziv cerrahi

INTRODUCTION

In inguinal hernia surgery, high ligation of the hernia sac has been used as the basic principle since the 19th century (1). This method, which is inadequate due to high recurrence rates in adults, has been used successfully for years of indirect inguinal hernia seen in childhood (2). Nowadays, it is possible to perform inguinal hernia operations with minimally invasive methods and with the same success rates with the help of technological developments (3). One of these minimally invasive methods is the laparoscopy-assisted percutaneous internal ring suturing (PIRS) method described by Patkowski et al. (4) in 2006. In this method, which can be applied without the need for any additional materials in clinics where pediatric laparoscopic surgeries are performed, inguinal hernia repair is performed percutaneously from the groin with the support of laparoscopy made from only one trocar incision.

In this study, we aimed to present the case series that we treated with the PIRS method supported by laparoscopy and its results up to six months after surgery.

MATERIAL and METHOD

After the approval of the local ethics committee, dated 26.11.2020 and numbered 2020-KAEK-143-02.01, the data of pediatric patients who applied to the Pediatric Surgery Clinic of our hospital between 01 November 2019 and 29 February 2020 were retrospectively evaluated and included in the study. Patients with clinical features of incarcerated inguinal hernia were excluded from the study.

Inguinal hernia repair was performed using the PIRS method supported by laparoscopy (4-5).

Operation steps

Under general anesthesia, 5 mm and 30° laparoscopy optic was advanced through the umbilical incision with the aid of a reusable trocar under 5 mmHg intraabdominal pressure setting. The appearance of the inguinal canals and their openness were evaluated (Figure 1-A). The 21G injection needle, used as a

guide, was advanced from the lateral of the inguinal canal to the preperitoneal area carrying the carrier loop suture material (Figure 1-B, C). The guide needle was advanced between the carrier loop suture material, taking care not to take it into the spermatic cord from the medial of the inguinal canal, and the carrier loop suture material was placed on the guide needle (Figure 1-D). The ligature suture material, which was advanced through the guide needle, was released and was taken out of the body with the help of loop suture material (Figure 1-E, F). As the binding material, 3/0 non-absorbable mono-fiber suture material was used in children under the age of three, and 2/0 non-absorbable monofilament suture material was used in children over the age of three. The closure of the internal inguinal ring was checked and the intervention in the groin area was terminated when it was observed that it was closed (Figure 1-G). In the case of accompanying umbilical hernias, umbilical hernia repair was also performed.

The patients were followed up in the sixth month after the operation. During this control, the relatives of the patients were asked to visually evaluate the umbilical incision between “1 worst view” and “5 best views” and it was recorded in the file. Apart from the surgeon who performed a similar evaluation, another doctor was made and recorded in the file.

The demographic characteristics of the patients, preoperative and postoperative findings, operation time, treatment costs, and surgical complications were collected and recorded.

RESULTS

During the study period, 36 inguinal hernia repairs were performed in 27 patients. In our patient series, the most operated age group was under 2 months (9/27). The distribution of other age groups in order of frequency is over 24 months (8/27), 2-6 months (5/27), 6-12 months (4/27), and 12-24 months (1/27). The mean age of the patients was calculated as 2.78 ± 4.53 years, 2.00 ± 4.74 for males and 4.10 ± 4.04 for females.

In the preoperative examination, an inguinal hernia was most frequently detected on the right side (15/27). The distribution of

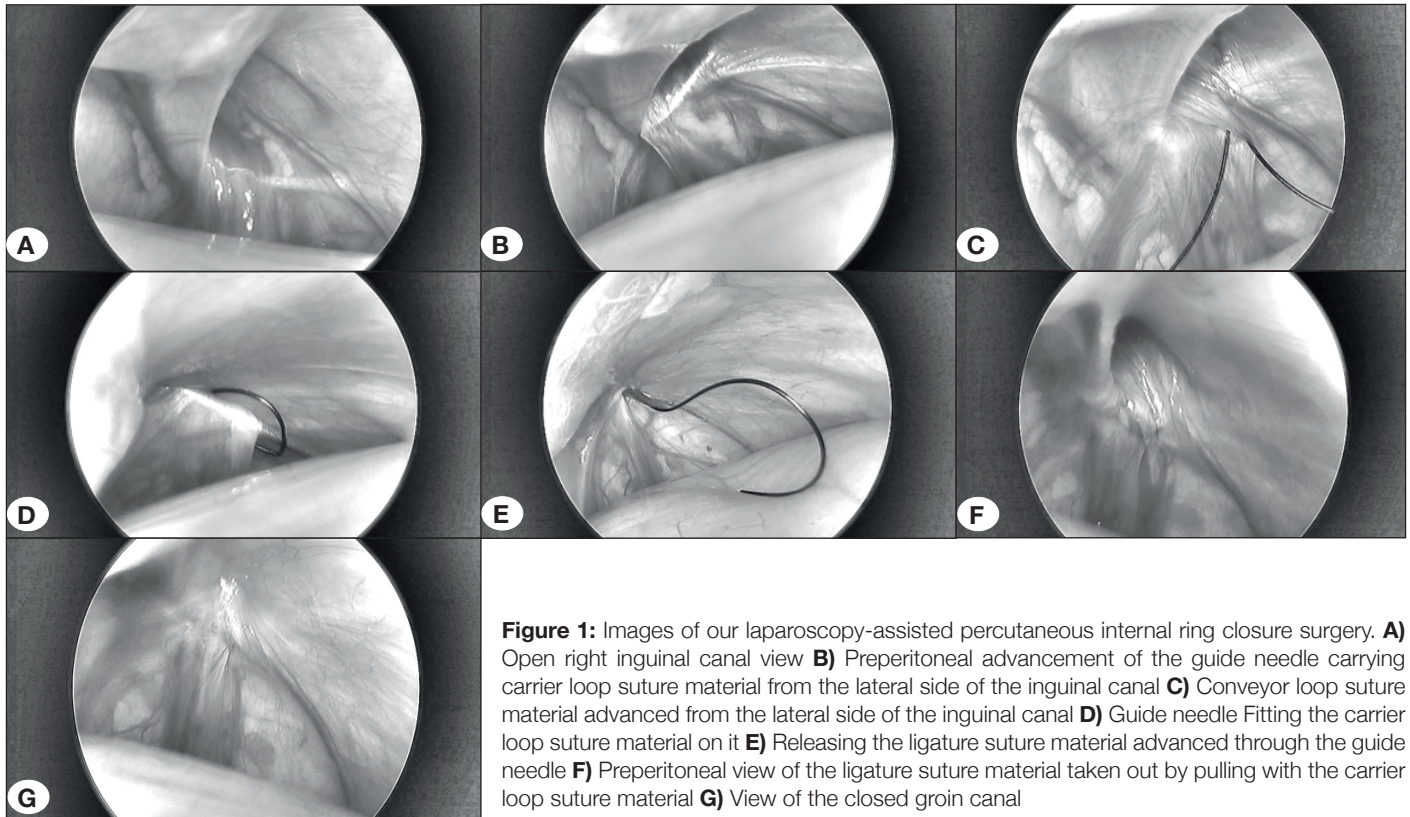


Figure 1: Images of our laparoscopy-assisted percutaneous internal ring closure surgery. **A)** Open right inguinal canal **B)** Preperitoneal advancement of the guide needle carrying carrier loop suture material from the lateral side of the inguinal canal **C)** Conveyor loop suture material advanced from the lateral side of the inguinal canal **D)** Guide needle fitting the carrier loop suture material on it **E)** Releasing the ligature suture material advanced through the guide needle **F)** Preperitoneal view of the ligature suture material taken out by pulling with the carrier loop suture material **G)** View of the closed groin canal

the side of the hernia by gender in patients is shown in Table I. There were four patients with contralateral inguinal hernia when the abdomen was inflated with pressure during the operation. Three of these patients had preoperative left inguinal hernia findings. Patent processus vaginalis openings in patients without swelling in the inguinal region in pressure inflation were not recorded.

Surgery was completed with 5mmHg intraabdominal pressure in 10 patients. Considering all patients, the mean intra-abdominal pressure value used was found to be 8.07 ± 0.52 mmHg. Preperitoneal bleeding developed in one patient during the operation. After the bleeding was controlled with tampon application, the repair was completed. No patient required open surgical technique or the use of additional trocars. The mean operation time was 24.3 ± 1.77 minutes (male 23.59 ± 7.55 and female 25.50 ± 11.91). The average length of stay of the patients in the hospital was 2.15 ± 0.12 days. The average treatment cost per patient was calculated as 1799 ± 92 Turkish Lira.

During the follow-up of the patients, no recurrence, intraabdominal complication, or inguinal complication was detected. Skin infection developed in the umbilical incision in one patient. None of the patients had skin scar in the groin area in the control examination performed in the sixth month. In six patients, it was found that the prolene knot material could be palpated subcutaneously. In the examination of the male patients, the testicles were in an age-appropriate size and the scrotum. The visual assessment of the umbilical incision was

Table I: Distribution of the side with the hernia by gender (n = 27).

	Right	Left	Bilateral	Total
Male	12	2	3	17
Female	3	5	2	10
Total	15	7	5	27

scored as an average of 4.74 ± 0.12 by the patient's relative and 4.0 ± 0.12 by the doctor whose opinion was taken.

DISCUSSION

In the laparoscopy-assisted PIRS attempt performed in 36 inguinal hernias in 27 cases we performed in our hospital for a period of four months, the preperitoneal bleeding that occurred in one patient during the surgery was a complication other than the skin infection occurring in the umbilical incision in one patient and especially hernia recurrence not observed. With these results, our intraoperative and postoperative 3.7% minor complication rate and recurrence results are similar to previous studies (4, 5).

The inguinal hernia has traditionally been performed with open technique and high ligation for years. However, laparoscopic methods, which have been used primarily for recurrence and bilateral hernia surgeries, have been used more frequently in parallel with the increase in the number and experience of the surgeons performing (6). However, in laparoscopic repairs

performed using three ports as previously described, the difficulty of knot application for closing the inguinal canal and the fact that the total size of the incisions made for the port reached the size of the open technique prevented its spread (7).

The use of a single port of 5mm or even 3mm in the PIRS technique and the easy application of the node used to close the internal ring eliminated the negative aspects of laparoscopic methods previously described and used for hernia repair (4, 5, 8, 9). In our series of 27 patients with nine patients younger than two months, we did not experience any difficulties or negativities in using this method.

Another advantage of the PIRS method is that the inguinal hernias on the contralateral side that do not show any symptoms before surgery, and even if the patient has an accompanying umbilical hernia, can be repaired simultaneously using a single incision. In the recent publications of Miyake et al. (10) And also Dreuning et al. (7), It is suggested that the ongoing discussions about the exploration of the opposite side in repairs performed with the open technique will disappear with the widespread use of the PIRS method. In our series, hernia repair was performed on the contralateral side simultaneously in four patients who were not detected in the preoperative examination but were found to have an inguinal hernia on the contralateral side during surgery. Also, an umbilical hernia detected in three patients was simultaneously repaired in the same session and using the same incision.

No significant intra-abdominal complications associated with the PIRS method have been reported in the literature (7). We did not observe any intraabdominal complications during the surgery. In our series, prolene suture material is palpated subcutaneously in six patients during follow-up. In a study in 2020, in who Patkowski was also one of its authors, it was reported that both non-absorbable monofilament and non-absorbable polyfilament suture materials were used (11). This situation made us think that the authors faced similar problems. In this study of the authors, granuloma occurred in a patient in which they used nonabsorbable polyfilament suture material, and reoperation was required for the granuloma. In our series, palpation of the stitches did not cause any problem for any patient or parents. However, it was seen that the method should be evaluated and developed in this respect.

After the previously described and applied laparoscopic inguinal hernia repair method, the average length of stay stated in the studies is higher than the open method; however, there was no difference in operative time between the two methods (12, 13). We did not compare the operation time, length of stay, and treatment cost with any other laparoscopic or open method that we determined in our series. However, both the operation time, the duration of stay, and the treatment cost were within acceptable limits and the morbidity rate did not increase significantly. Since the average length of stay of the

patients in the hospital is calculated as days, the hospital stay of the patients who are followed up overnight appears to be two days. The follow-up of pediatric patients operated under general anesthesia by staying in the hospital for 24 hours is a routine approach in our hospital. Even if we do not apply it, patients who are operated under general anesthesia can be discharged on the same day. If this method is preferred, the duration of hospital stay will be shorter.

When the open method is applied, there is no obstacle to using the recurrence open method. Recurrence of hernia beyond the age of six years was detected after the series. However, the small sample size of our case series does not allow us to generalize. In their study published by Thomas et al. In Istanbul (8), they predict that the complication and recurrence rates will decrease as the method continues to be used and one experience is gained.

Although evaluations regarding the damage of testicular tissue and the spermatic cord in male patients are dangers that need to be considered, no scrotal complications were found in our study, and no reduction in testicular size was observed in the six months (14, 15).

Even within a period of six months, the skin incision made for the umbilical port entry has almost regained its normal appearance and reached a cosmetically perfect result as determined by the scoring of both the patient's parents and an independent physician. This result we obtained in our series is in line with the results of the research published by Chen et al.(16) regarding this method in 2020.

In addition to the limitations of all retrospective studies, our study does not offer the opportunity to compare the results within itself, since it was conducted with a single patient group. According to what Wolak mentioned in his publication, the technique is easier to apply in female patients (5). However, in our study, the mean duration of operation was longer in female patients. Another limitation of the article is that the factors affecting the operation time are not recorded. However, in the light of the evaluated literature and the results of our own series, it is seen that the PIRS technique is a safe method, despite minor complications.

CONCLUSION

We found that the PIRS method applied under laparoscopic support in childhood is an easy and safe method for indirect inguinal hernia repair. In our small case series, we did not observe any significant complications related to hernia or scrotum both during the operation and in the six-month postoperative period. These results suggest that this method can be a candidate to replace the open method because it is reliable and applicable. However, long-term studies with large series are required to

investigate the results of laparoscopy-assisted percutaneous internal ring repair as much as the open method applied for more than a century and to reveal the problems that may occur.

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Upper Gastrointestinal Endoscopy in Pediatric Surgical Practice

Pediatric Cerrahi Pratiğinde Üst Gastrointestinal Endoskopi

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ABSTRACT

Objective: We aimed to focus descriptively and comparatively on the children with esophageal disorders requiring endoscopy: demographics, indications, methods, complications and outcomes.

Material and Methods: The records of the children with esophageal disorders indicative of endoscopy between January 2005 and February 2020 at the department of pediatric surgery of a tertiary health care center were reviewed in terms of demographic, etiological, technical aspects; including the comparison of flexible endoscopy (FE) and rigid endoscopy (RE).

Results: Endoscopy was indicated in a total of 242 children for foreign body ingestion (n=70, 28.9%), caustic ingestion (n=89, 36.8%), esophageal stricture (n=52, 21.5%) and other rare conditions (n=31, 12.8%). Forty two of them did not undergo endoscopy, because their caregivers did not consent. Of the rest; 102 (42.1%) underwent RE, and 98 (40.5%) underwent FE. The mean age was 36.4±35.7 months. No statistically significant difference was detected between the mean ages of RE and FE groups (33.3±32.1 vs. 33.7±24.9 months, p=0.918). Most of the patients who underwent FE were significantly males (52% in FE group, 39.2% in RE group, p=0.046). Complication rate was 6.9% in RE group and no complication was detected in FE group (p=0.008). The difference of failure rates of the groups was statistically insignificant (3.9% in RE vs 0 in FE, p=0.066).

Conclusion: Both rigid and flexible endoscopy techniques are effective and safe for diagnostic or therapeutic esophageal interventions. Although each has its own advantages and disadvantages, performing rigid endoscopy takes a slightly but significantly higher risk of complication.

Key Words: Children, Endoscopy, Esophagus

ÖZ

Amaç: Çalışmamızda endoskopi gerektiren özofagus bozukluğu olan çocuk hastaların demografik özelliklerini, bu hastalarda rijid ve bükülebilir endoskopi endikasyonlarını, işlem komplikasyonlarını ve sonuçlarını değerlendirdik.

Gereç ve Yöntemler: Ocak 2005 - Şubat 2020 tarihleri arasında endoskopi planlanan çocukların kayıtları incelendi. Klinik veriler, endoskopi yöntemleri, sonuç ve komplikasyonlar araştırıldı. Bükülebilir endoskopi (BE) ve rijid endoskopi (RE) grupları karşılaştırıldı.

Bulgular: Toplam 242 olgu saptandı. Yetmiş yabancı cisim yutma (%28.9), 89'u kostik madde içme (%36.8), 52'si özofagus darlığı (%21.5) ve 31'i diğer nadir durum (%12.8) olgularıydı. Kırk iki hastaya, onam verilmediği için endoskopi yapılmadı. Ortalama yaş 36.4±35.7 aydı. Olguların 102'sine (%42.1) RE, 98'ine (%40.5) BE uygulandı. İki grubun ortalama



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Contribution of the Authors / Yazarların katkısı: **GUNEY LH:** 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 necessary literature review for the study. **FAKIOĞLU E:** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. **ACER DEMİR T:** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments.

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yaşları arasında istatistiksel olarak anlamlı fark yoktu (33.3 ± 32.1 ve 33.7 ± 24.9 ay, $p=0.918$). BE yapılan hastaların çoğunlukla erkek olduğu (BE grubunda %2, RE grubunda %39.2, $p=0.046$). RE grubunda komplikasyon oranı %6.9'di ve BE grubunda ise komplikasyon yoktu ($p=0.008$). Gruplar arasında başarısızlık oranı açısından anlamlı bir fark yoktu (RE'de %3.9 ve BE'de 0, $p=0.066$).

Sonuç: Hem rijid hem de bükülebilir endoskopi teknikleri, özofagus hastalıklarında tanısal veya terapötik olarak etkili ve güvenli olarak kullanılabilir. Her birine özgü avantaj ve kısıtlılıklarla birlikte, rijid endoskopinin komplikasyon riski daha yüksektir.

Anahtar Sözcükler: Çocuk, Endoskopi, Özofagus

INTRODUCTION

In pediatric surgical practice; acquired, congenital or functional esophageal disorders compose a remarkable group of diseases to be managed; with their potential of becoming highly complicated, chronic, morbid problems such as persistent strictures, inefficient motility. The crucial functions of the esophagus, with its unique anatomical and physiological properties make it indispensable for an optimum quality of life. Therefore, esophageal diseases are critical, both in terms of timely diagnosis and proper treatment.

Foreign body (FB) ingestion is one of the most common and serious conditions in children who are consulted to the pediatric surgeons by emergency clinicians. For management, endoscopic FB removal under direct visualization remains the overwhelmingly accepted technique among others using bougies, Foley catheter, or magnetic nasogastric tubes (1,2). Ingestion of caustic substances is an important public health problem associated with significant morbidity and mortality. For children with only vomiting or drooling and those who refuse to drink, overnight observation is routine, and endoscopy is performed only if symptoms persist and/or the child remains unable to take oral fluids. Endoscopy should be performed no later than the first 24 – 48 hours after ingestion, since wound softening later increases the risk of perforation. Injuries should be graded with the use of standardized terminology (3).

Post-operative or post-inflammatory strictures, anatomic abnormalities, gastroesophageal reflux and achalasia comprise the other indications for endoscopy in children.

Endoscopic examination and treatment of disorders of the esophagus have taken its crucial place in surgical specialty since the introduction of the rigid endoscope (RE) by Kussmaul in 1868. The RE enabled direct visualization of the esophagus and made advanced instrumentation possible. Until the invention of the flexible endoscope (FE) in the mid-1950s, RE was the dominant modality for diagnosis and treatment of the esophageal pathologies. Today, both types of endoscopy are used with overlapping indications. However, there is no uniformly agreed or contradicted method amongst pediatric surgeons. Both procedures are accepted to be safe and effective in experienced hands. Generally the method chosen depends on the surgeon's preference. The purpose of our study is to present the demographics, indications, complications

and outcomes of children who have undergone rigid or flexible endoscopy in our clinic. We aimed by sharing our institutional experience of pediatric upper gastrointestinal endoscopy with a wide diagnostic spectrum, including the technical aspects; to contribute improving outcomes.

MATERIAL and METHOD

The present study was approved by the Local Ethics Committee of Başkent University Hospital, Ankara, Turkey (Project no: KA 15/49).

A retrospective review of all children admitted with diagnosis of an esophageal disorder which required rigid or flexible endoscopy between January 2005 and February 2020 in the department of pediatric surgery of a single tertiary health care center was made.

The records of the 242 children who underwent diagnostic or therapeutic FE or RE or both were reviewed.

Inclusion criterias; we included all the patients who were performed FE or RE during the mentioned period. The patients with foreign body or caustic ingestion whose caregivers did not consent the recommended endoscopy were included only for appropriate demographical analysis. Exclusion criterias; we excluded the patients on whom, other techniques (Foley catheter) were applied for esophageal FB removal.

An Olympus XP 240, 2030294 (Olympus, Japan) was used for FE. A STORZ Esophagoscope (Germany) and STORZ Optics (0°, 4 mm, 27005A abd 30°, 2.9 mm) were used for RE. The patient records were initially reviewed according to the diagnosis. The patients were divided into two groups according to the endoscopy technique (RE or FE). Data regarding success or failure of the procedure and complications, were examined. A failure was defined as the need to conversion of endoscopic method to the other modality to successfully achieve the esophageal diagnostic or therapeutic goal.

Demographic and clinical characteristics of the RE and FE groups were compared, using Chi-square test and Fischer's exact test where appropriate, and a t test, for categorical and continuous variables, respectively. All the analysis was computed using SPSS 24, and a p value < 0.05 was considered statistically significant.

RESULTS

Over the 15-year period, 242 children were admitted with esophageal conditions requiring endoscopy. Forty two (17%) of them were not noted to have endoscopy because their caregivers did not consent the interventions. Although we used their data to a certain extent of demographic review, we excluded them from further analysis. The demographic data of the patients who underwent upper gastrointestinal endoscopy are listed in table I.

The mean age of the group was 36.4 ± 35.7 months. Children younger than three years accounted for the majority (69.8%). Females constituted 54.5% of the population with a majority of caustic ingestion (37.2%). The 42 patients who did not undergo endoscopy were composed of 29 (69%) FB ingestion, 13 (31%) suspected corrosive ingestion cases. In total; 102 (42.1%) patients underwent RE, and 98 (40.5%) underwent FE. In four patients, conversion from RE to FE was needed. Two of those were FB, and the other two were corrosive ingestion cases. Three patients had minor complications, which were dental injury and mucosal hemorrhage.

Endoscopy for Foreign body ingestion:

The types and locations of esophageal foreign bodies are detailed in table II. A total of 70 children (37 males) ingested foreign bodies. The most commonly ingested FB was a coin ($n=23$, 32.8%). Other FBs impacted in the esophagus included needle, battery, plastic toy, magnet, paper clip, pebble, button and gold. Seven patients had a history of esophageal atresia and tracheoesophageal fistula (EA/TEF) repair that predisposed retention of the foreign body. Successful foreign body removal was accomplished in all of the patients.

Endoscopy for Caustic Agents Ingestion:

Out of 89 children with caustic ingestion, 55.1% (49) were females and 44.9% (40), males. The age group who most commonly ingested a caustic agent corresponded to children younger than 3 years, who accounted for 77.5% (69) of cases (mean age 30.4 ± 27.5 months). Thirty five (39.31%) patients underwent RE, 41 (46.1%) underwent FE in the first

Table II: Type and location of esophageal foreign bodies.

Type of foreign body n= 70 (%)	
Coin	23 (32.9)
Needle	13 (18.6)
Battery	9 (12.8)
Plastic toy	9 (12.8)
Magnet	5 (7.2)
Other	11 (15.7)
Type of endoscopy for FB (%)	
Rigid E.	17 (24.3)
Flexible E.	24 (34.3)
No Endoscopy	29 (41.4)
Location of removed FB (%)	
Proximal 1/3	23 (56)
Middle 1/3	7 (17)
Distal 1/3	9 (22.9)
Stomach / distal	2 (4.1)

24 to 48 hours after ingestion and 13 (14.6%) patients were observed conservatively. The ingested corrosives were alkaline substances in 60 cases (67.5%) and acidic substances in 29 (32.5%). Sodium hypochloride was the most commonly ingested alkaline agent; while hydrochloric acid was the most common acidic substance ingested. Figure 1 demonstrates an example for the chemical esophageal injury via FE.

Endoscopy for dilatation of the esophageal strictures:

In the study period, a total of 52 patients (33, 63.5% females) underwent endoscopy for dilatation of esophageal strictures with a mean age of 40.1 ± 35.8 months. The stricture causes were; operated esophageal atresia in 35 cases, chemical burns in 16 cases, epidermolysis bullosa in one case. Dilatations were performed via RE in 29 (55.7%), via FE in 23 (44.3%) patients. Rigid over-the-guidewire dilators were used in all of the RE (29), and three of the FE cases. Balloon dilators were used in the remaining 20 FE cases.

Endoscopy for rare esophageal conditions:

This group included 31 patients (21 RE, 10 FE). The indications for endoscopy include suspected traumatic esophageal perforation in one, suspected congenital esophageal stenosis in six, dysphagia in 10, achalasia in four, gastroesophageal reflux (GER) and suspected mucosal changes in 10 patients.

Depending upon preference of the surgeon and clinical variables of each case, either RE or FE was performed. No statistically significant difference was detected between the two groups in terms of mean age (33.3 ± 32.1 vs. 33.7 ± 24.9 months, $p=0.918$). We found that most of the patients who underwent FE were significantly males (52% of RE group, 39.2% of FE group, $p=0.046$). Complication rate was significantly higher (6.9%) in RE group, as no complication was recorded for FE group ($p=0.008$). There was no significant difference of failure rate between endoscopic techniques (3.9% in RE, 0 in FE, $p=0.066$). Our institution's complication rate was 3.5%. There was neither major complications requiring surgery, nor mortality in our study group due to endoscopy. The reasons

Table I: Demographics of the study group.

Characteristics	n(%)
Age*	36.4 ± 35.7 (2- 207)
0-3 years †	169 (69.8)
4-10 years †	66 (27.3)
Above 11 years †	7 (2.9)
Male gender †	110 (45.5)
Esophageal conditions †	
Foreign Body Ingestion †	70 (28.9)
Caustic Ingestion †	89 (36.8)
Esophageal Stricture †	52 (21.5)
Other †	31 (12.8)

*: Mean $\pm$ SD (min.- max. months), †: n(%)

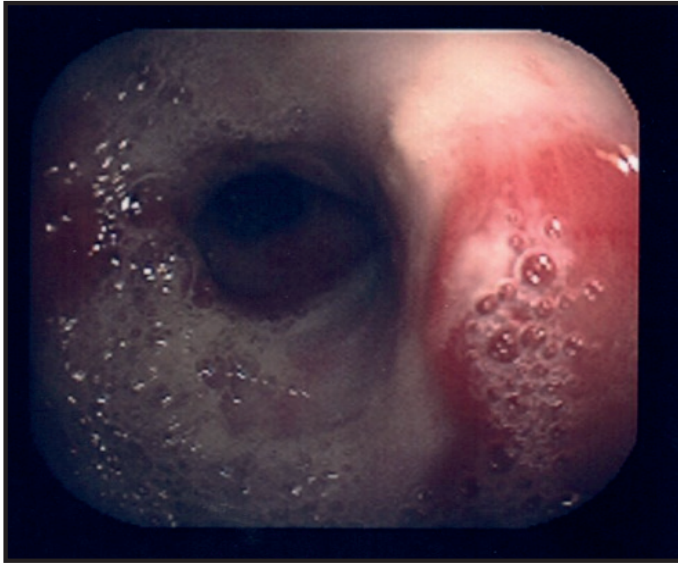


Figure 1: Chemical esophagitis.

for conversion to the other modality were most often related to difficulty of visualization with one modality, need for alternative grasping devices, and location change of the foreign body, making alternative modality more useful.

DISCUSSION

This study provides a brief overview of the conditions requiring endoscopy in pediatric surgical practice. Indications include suspected GER, dysphagia, corrosive injury, upper gastrointestinal bleeding, trauma, tracheo-esophageal fistula, strictures, percutaneous endoscopic gastrostomy, foreign body, endoscopic sclerotherapy, variceal band ligation and anatomic abnormalities like congenital stenoses, cartilaginous rings, leiomyomas, duplications. These anatomical abnormalities are usually first identified radiographically and then confirmed endoscopically.

Most frequent indication of endoscopy in our study is corrosive substance ingestion. Accidental ingestion of corrosive compounds is reported to be more frequently observed in young children, especially those younger than the age of five (4). Our results are consistent with that, with the far lower mean age detected (30 months). Early esophageal endoscopy (during the first 24 to 48 hours) is considered a safe procedure (5). Bıçakçı et al.(6) state that they avoid from early esophagoscopy as the early esophagoscopy requires unnecessarily general anesthesia administration and this is the most fragile period of esophagus. In our clinic endoscopy is performed only if symptoms persist. Eighty five percent of our patients underwent the procedure. Thirty five patients underwent RE. We converted the RE procedure to flexible in two patients because of the insufficient visualisation of both esophagus and

the stomach mucosa. Most of patients (n=41) were evaluated with FE without any complications but the patients who were evaluated with RE had minor complications (two of them were dental injuries one of them was mucosal bleeding that caused insufficient visualisation). Niedzielski et al.(7) presented their study including 150 patients who were evaluated due to caustic ingestion between 1967 -2018. They performed FE for all of their patients without any complication. They suggest performing endoscopy for all patients and point out 'endoscopy is the most effective and widely used method for determining the degree of injury and planning treatment'. Similarly Balderas et al. (8) report in their retrospective study with 133 patients that all of their patients underwent fiberoptic endoscopy with no complications.

More than 98% of FB the ingestions in children are accidental (9). The ingested objects usually pass through the gastrointestinal tract without complication; however, about 20% of those were reported to require an intervention (10). When retained, esophageal FB may cause stricture, esophageal perforation, tracheoesophageal fistula, aortoesophageal fistula. Those can be mortal if the diagnosis is delayed (11,12).

The treatment option is conservative in asymptomatic cases who swallowed a foreign body that goes beyond the esophagogastric junction, and the size, position, nature of swallowed foreign body and the time passed upon swallowing are also important in treatment and follow-up (13).

Russel et al. (14) studied 12 year retrospective data including 657 children: Foreign bodies were removed by FE in 56% patients. They reported that there were no statistically significant differences between RE and FE in terms of complications, procedure length and success rate. Popel et al. (2) reported a total of 140 children with FB ingestion, 89 of which were removed via FE. They noted that both rigid and flexible endoscopy techniques are safe and effective in esophageal FB extraction. However, they remarked FE takes a substantial shorter duration compared to RE. Sink et al. (15) reported only 16% of patients underwent FE in their retrospective study group (543 children) and two patients required open surgical procedures for FB removal (15). Yan et al.(16) compared the effectiveness of RE and FE in the management of esophageal FB impactions in adults. The perforation rate and the need for general anesthesia were found higher in RE-associated extraction. Although FE is generally presented to be superior with higher-technology; RE still is reported to play an important therapeutic role in cases of FB impaction at upper esophagus, especially when the FB is sharp-pointed. The patient-related factors (age, clinical condition, compliance), size and sort of the FB, the impaction site, timing of impaction, and physicians' expertise are the determinants of the most appropriate management. Both FE and RE are emphasized to be effective and safe, with similar success and overall complication rates (17).

However, the two methods have distinct advantages related to the procedure needed and the underlying pathology. The primary advantage of RE is the direct access to the area of interest. The large lumen allows for the use of a wide variety of instruments, which in turn allows for the handling and removal of larger objects under direct visualization. The direct line of instrumentation is helpful when manipulating foreign bodies.

During RE, the lumen of the esophagus is maintained by the instrument and visualization of narrow segments, the postcricoid area in particular, is made possible. RE can be performed only with general anaesthesia. The most obvious advantage of FE is superior visualization of the mucosa. The fiber technology allows for picture enhancement and offers multiple connective options such as narrow band imaging and video output. The FE has a far greater range of motion and flexibility and allows the physician to reach much further into the gastrointestinal canal, than does the rigid endoscope. FE can be performed with general anesthesia or sedo-analgesia.

Although both procedures can lead to complications such as pain, mucosal lesions, bleeding, dental injury and perforation with subsequent mediastinitis, it is well documented that the RE carries a greater risk than FE does (18,19).

Recently non-invasive tools are started to be used for diagnosis in esophageal conditions. Gu et al. first reported a study of magnetically controlled capsule endoscopy (MCE) examination in children. They showed that MCE is feasible and safe in children older than 6 years (20). Randomized prospective studies are needed to further investigate the efficacy of endoscopy types in children. The heterogeneity of our patient population, with different diagnoses, limited us to make comparisons of other variables as duration of hospitalization, operation length and the type of anesthesia. The retrospective nature of this single center study is another limitation.

CONCLUSIONS

Both rigid and flexible endoscopy techniques are effective and safe for diagnostic or therapeutic esophageal interventions. However, performing rigid endoscopy takes a slightly but significantly higher risk of complication.

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Rapid Resolution of Multiple Liver Abscesses in a Chronic Granulomatous Disease Patient with Granulocyte Transfusions

Çoklu Karaciğer Apsesi Olan Bir Kronik Granülomatöz Hastasının Granülosit Transfüzyonu ile Hızlı Tedavisi

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ABSTRACT

Chronic granulomatous disease (CGD) is a genetically heterogeneous primary immune deficiency of phagocyte function characterized by recurrent, life-threatening bacterial and fungal infections that lead to granuloma formation. Early diagnosis is possible by the awareness of the clinician about early infectious clues of the disease. Aggressive treatment of infectious complications is very important in CGD patients and subsequently antimicrobial (antibiotic and antifungal) and immunomodulatory (interferon-gamma) prophylaxis until hematopoietic stem cell transplantation. Despite improved mortality, morbidities due to complications associated with CGD remain significant. One of these is a hepatic abscess in CGD patients which is seen in more than one-quarter of patients and also very refractory and frequently requires multiple surgeries with frequent morbidities. Therefore, the most optimal and beneficial treatments are still being investigated in the world. We present a 3 y old CGD patient with multiple liver abscesses due to *S.aureus* and *Aspergillus spp* who treated by several percutaneous liver-directed interventional radiological treatment along with granulocyte transfusions.

Key Words: Child, Granulomatous disease, Liver abscess

ÖZ

Kronik granülomatöz hastalık (CGD), tekrarlayan, yaşamı tehdit eden bakteri ve mantar enfeksiyonları ile karakterize olan, granülom oluşumuna yol açan genetik olarak heterojen bir primer immün yetmezlik olan fagosit fonksiyon yetersizliğidir. Erken teşhis, klinisyenin hastalığın erken enfeksiyon ipuçları konusunda bilinçlenmesi ile mümkündür. CGD hastalarında Enfeksiyöz komplikasyonların agresif tedavisi çok önemlidir ve hematopoietik kök hücre nakline kadar antimikrobiyal (antibiyotik ve antifungal) ve immünomodülatör (interferon-gama) profilaksileri de çok önemlidir. Mortalitenin azalmasına rağmen, CGD ile ilişkili komplikasyonlara bağlı morbiditeler önemini korumaktadır. Bunlardan biri, CGD hastasında, hastaların dörtte birinden fazlasında görülen ve aynı zamanda çok dirençli ve sıklıkla sık morbiditeli birden fazla ameliyat gerektiren karaciğer apsesidir. Bu nedenle dünyada halen en uygun ve faydalı tedaviler araştırılmaktadır. Granülosit transfüzyonları ile birlikte perkütan karaciğere yönelik girişimsel radyolojik tedavi ile tedavi edilen *S.aureus* ve *Aspergillus spp*'ye bağlı çoklu karaciğer apsesi olan 3 yaşında bir CGD hastasını sunuyoruz.

Anahtar Kelimeler: Çocuk, Granulomatöz hastalık, Karaciğer absesi



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INTRODUCTION

Chronic granulomatous disease (CGD) is caused by mutations leading to defects in subunits of the phagocyte NADPH-oxidase (gp91phox in X-linked; p22phox, p47phox, p67phox, and p40 in autosomal recessive-CGD) (1). The NADPH-oxidase-myeloperoxidase system generates microbicidal, reactive oxygen species required for host defense and control of inflammation (1).

CGD affects ~1:200 000 live births (2). X-linked-CGD accounts for approximately two-thirds of patients in Europe but in countries where consanguineous marriages are prevalent AR-CGD patients predominate (3-7). Symptoms comprise invasive infections and chronic autoinflammatory diseases (complications) leading to aggressive medical interventions, long hospitalizations, impaired quality of life, and increased morbidity/mortality (3-6) (Table I).

Infections typically affect organs in contact with the outside world like skin, gastrointestinal tract, and lungs as well as lymph nodes that drain these organs. Because of adjacent tissue and hematogeneous spread of the infection other organs can be affected especially the liver, bones, kidneys, and brain. Pathogens responsible for these clinical presentations are catalase-positive microorganisms as seen in Table I.

The use of life-long antibacterial prophylaxis with trimethoprim-sulfamethoxazole is recommended. Pulmonary *Aspergillus* infections are the leading cause of mortality. Anti-fungal

prophylaxis mainly with itraconazole can reduce the incidence of fungal infections (1-3). One of the most serious errors in the management of CGD patients is the failure to treat potentially serious infections early and to continue therapy long enough to eradicate them.

Although neutrophil absolute numbers are normal in CGD patients, it can be considered functional neutropenia because the killing function is impaired. Granulocyte transfusions have been used to treat infections in neutropenic patients for nearly 30 years (8-10) (Table II). The data from recent systematic reviews suggest that properly collected and promptly infused granulocytes are active against bacterial and fungal infections in the patient. The most important question is in which patients the administration of granulocytes will be necessary. Prominent evidence suggests that granulocyte transfusions should be used in selected cases, as a final measure to control an infection that is expected to be refractory to optimal antimicrobial treatment. In this regard, CGD patients who do not have their neutrophil response to the infection are good candidates for granulocyte transfusions (Table II).

It was planned to present our CGD patient with multiple liver abscesses to emphasize the characteristics of the use of granulocyte transfusion, which is a rare treatment method, the infection in CGD patients is usually due to resistant microorganisms, which are not common in the society, and its proven benefit in organ abscesses and rapidly spreading skin infections.

Table I: Infections, chronic complications, and organisms responsible in CGD patients in order of frequency.

INFECTIONS	CHRONIC COMPLICATIONS	INFECTING ORGANISMS
Pneumonia	Lymphadenopathy	<i>Staphylococcus aureus</i>
Lymphadenitis	Hypergammaglobulinemia	<i>Escherichia coli</i>
Cutaneous infection-impetigo	Hepatosplenomegaly	<i>Aspergillus species</i>
Hepatic-perihepatic abscess	splenomegaly	<i>Salmonella species</i>
Osteomyelitis	Anemia of chronic infection	<i>Klebsiella species</i>
Septicemia	Underweight	<i>Burkholderia cepacia</i>
Otitis media	Short stature	<i>Staphylococcus epidermidis</i>
Conjunctivitis	Chronic diarrhea(Crohn-like)	<i>Serratia marcescens</i>
Enteric infections	Gingivitis	<i>Enterobacter species</i>
Urinary tract infections	Dermatitis	<i>Streptococcus species</i>
Sinusitis	Chorioretinitis	<i>Proteus species</i>
Renal-perinephric abscess	Hydronephrosis	<i>Candida species</i>
Brain abscess	Ulcerative stomatitis	<i>Nocardia species</i>
Pericarditis	Pulmonary fibrosis	<i>Bacillus Calmette-Guérin</i>
Meningitis	Esophagitis	<i>Mycobacterium species</i>
	Gastric antral narrowing	<i>Chromobacterium violaceum</i>
	Granulomatous ileocolitis	<i>Candida glabrata</i>
	Granulomatous cystitis	<i>Actinomyces</i>
	Discoid lupus erythematosus	<i>Granulibacter bethesdensis</i>

Table II. Indications of granulocyte transfusions.**Minimal criteria:**

Absolute neutrophil count < 500/mm ³
Evidence of bacterial or fungal infection
Unresponsiveness to antimicrobial treatment for at least 48 hours
Cancer patients with severe neutropenia and fatal infections
Chemotherapy or HSCT-induced neutropenia
Aplastic Anemia
Congenital disorders of neutrophil function (Leucocyte Adhesion Deficiencies, Congenital Severe Neutropenia syndromes, Chronic Granulomatous Disease)

CASE REPORT

A 3 y old male patient from a Syrian immigrant family, admitted first when he was 18 mo old, to the Republic of Turkey, Ministry of Health, Ankara City Hospital, Children's Hospital, Emergency Department with a complaint of scrotal swelling. On admission, there was a left apical cervical, 1.5x1.5 cm diameter lymphadenopathy, submandibular pigmented scars left due to previous suppurative lymphadenitis, hepatomegaly 1 cm below the costal margin, palpable left inguinal lymphadenopathy, multiple micro epididymal, and scrotal abscess. His weight was 10 kg. The patient consulted the Pediatric Immunology Unit for primary immunodeficiency diseases and especially for congenital defects of phagocyte number and functional defects due to the skin and soft tissue infections of the patient. Parents were first-degree relatives (cousins). The patient was the 1st child of the family, and 2nd child was 7 mo old and healthy. There was a perianal abscess in the newborn period in his history. He was hospitalized and the biopsy of the cervical lymph node was reported as necrotizing granulomatous inflammation by the pathologist. The patient was evaluated with the immunological screening tests as seen in Table III. Nitroblue tetrazolium test showed the killing defect of the neutrophils of the patient and the Dihydro-rhodamine 123 test showed that the patient's probable mutant NADPH-oxidase component is p67 phox protein according to the stimulation index found. Mutation analysis results are pending for the precise diagnosis. After antimicrobial treatment, he was given the drug reports and prescriptions of prophylactic TMP-SMX 5mg/kg/d, 3 days/week, per oral.; itraconazole 5mg/kg/d, every day, per oral., and interferon-gamma (Imukin® -1b 100mcg flacon) 3 days/week, sc. and called for Pediatric Immunology outpatient clinic controls. Since the patient had a routine BCG vaccine, no history of BCGitis, a PPD test was applied. Since the result was 18 mm, chest radiography and CT were taken due to the possibility of active TB infection. It was normal; prophylactic Isoniazid and Rifampicin treatments (both 10 mg/kg/d dose) were started for latent TB. The family belonged to a low socio-cultural level and

could bring the child 12 months later for the new complaints of the child. They stated that they could not give the TMP-SMX, itraconazole continuously and regularly, except prophylactic TB drugs. Since the family was a Sirian immigrant, we contacted Sirian Social Aid Organisations in Turkey but Imukin could not be provided. His current complaints were >38° C fever of 5 days, abdominal pain, severe weakness, and pallor. The patient was hospitalized again in 2020 October. Physical examination revealed oral moniliasis, abdominal distention, bilateral suppurative cervical lymphadenitis with 3x3 cm diameter. Laboratory tests were given in Table III. Abdominal USG and abdominal MRI revealed multiple (nearly 8-9) subcapsular and scattered abscesses the biggest ones sized 42x48, 28x20, and 34x27 mm diameter at the right lobe of the liver. There were another abscess sized 23x17 adjacent to the upper part of the right kidney with an undetectable capsular border. There were also multiple reactive mesentery lymphadenopathies and minimal free liquid collection. Computed tomography of the thorax showed no appearance in favor of pulmonary TB and Aspergillus pneumonia when compared with previous MR, but 18 mm right pleural effusion. Cranial MRI was normal. Treatment began with meropenem, vancomycin, teicoplanin, amikacin, and caspofungin. IVIG was added as a single dose to support the treatment in a 0.5g/kg/dose. Subcapsular hepatic abscesses drained percutaneously. Despite these treatments, fever, blood, and abscess culture yields of *S.capitis* in the blood; *Aspergillus spp.* and *Staphylococcus spp.* in the hepatic abscess respectively, and the high number of the abscesses led us to decide to give granulocyte transfusion (GTX) to the patient. After the 14th day, vancomycin and caspofungin stopped and voriconazole was begun. After GTXs and multiple (3 times) interventional abscess drainages until they solidify, he remained afebrile, imaging showed improvement of all the abscesses, and the return of the erythrocyte sedimentation rate to its normal baseline (<20mm/h), the patient could be discharged after 1.5 months of antibiotic and antifungal treatment, returning to the routine CGD prophylaxis and increasing the awareness of the family about CGD, the decision was made to prepare for bone marrow transplantation. The patient was also discharged with continuing voriconazole treatment.

DISCUSSION

Recurrent cutaneous abscesses and lymphadenitis represent the earliest and common types of infection in CGD as seen in our patient. Impetigo, furuncles frequently in the perianal area due to feces contamination as well as recurrent perirectal abscess are seen (Table I). These require prolonged courses of oral and topical antibiotics to clear and once formed can persist for years despite aggressive antimicrobial treatment. Hepatic and perihepatic abscesses were also quite common in CGD as seen in our patient, mostly caused by the hematogenous spread of *S.aureus* in patients who are incompatible with

Table III: Immunological screening tests and other laboratory parameters of the patient on the two admissions.

	First admission	Second admission
CBC		
WBC	3930	18770
ANC	2000	12770
ALC	1100	4830
Plt	728 000	774 000
Hb/Hct	12.5/36	9/27
Eosinophil(%/Absolute)	12 (471)	1(200)
Serum immunoglobulins(mg/dl)		
IgG	1550	
IgM	250	
IgA	155	
IgE (U/ml)	500	
Lymphocyte subpopulations		
CD3+ Total Tcell(%/Absolute)	65	
CD4+Helper T cell (%/Absolute)	37	
CD8+ supressor T cell(%/Absolute)	25	
CD19+ B cell(%/Absolute)	26	
CD16+56 NK cell (%)	9	
Nitroblue Tetrazolium Test (NBT)	0%	
Dihidro-rhodamine 123 test	P67phox mutation is possible according to the pattern.	
Complement (mg/dl)		
C3	100	
C4	30	
CRP/Sedimentation on admission	3 mg/dl; 75mm/h	12,7 mg/dl; 100mm/h
The isolated pathogen in culture	<i>S. aureus</i>	<i>S. aureus</i> + <i>Aspergillus spp</i>
Liver/ Renal function tests	Normal limits	Normal limits
Coagulation tests(PT, PTT, D-dimer, Fibrinogen, Ferritin)	Normal	High

the prophylactic treatment. Spontaneous rupture can be seen, again as seen in our patient. Liver function tests are often normal. Hepatic abscesses in CGD are phenotypically distinct from the pyogenic liver abscesses associated with other conditions. They present as septate masses surrounded by a thick pseudocapsule containing amorphous cell debris in it which is difficult to drain. The resolution requires open surgical drainage or excision of the lesion (other surgical procedures may also be necessary such as liver resection, segmentectomy, or lobectomy); percutaneous interventional radiological procedures, and high dose corticosteroid use together with several months of targetted parenteral antibiotics (8,9). It is hypothesized that steroid-induced reduction of systemic inflammation reduces immune cell infiltration in the liver microenvironment and so reduces the need for procedural intervention and prevents complications. Corticosteroids (prednisone or methylprednisolone) as immunomodulatory management are used in a median dose of 1 mg/kg/day and subsequently tapered over a median of 5 months (8,9).

In recent years the prognosis of these organ abscesses has dramatically improved with the use of GTX. In cases of severe fungal and bacterial infections that fail to respond to medical

and surgical approaches, GTX is necessary to shorten the healing process.

We have experience with GTX in our hospital in severe necrotizing pneumonia, *Aspergillus* pneumonia, cerebral and cerebellum abscesses, osteomyelitis, and liver abscess in at least ten X- and AR-CGD patients to date. We observed its effectiveness in curing infections in CGD patients. We gave GTX also to this patient once in three days, from 4 unrelated donors with only one transfusion reaction of fever in the last infusion. Due to this reaction, the last GTX had to be cut in the half. He received high-dose granulocyte per body weight (Weight: 10 kg) since each granulocyte products contained 2.9 x10¹⁰, 1.4 x10¹⁰, 1.2 x10¹⁰ and 1.5 x10¹⁰ neutrophils respectively. We did not prefer steroid use in this patient because the patient's cultures obtained from drainage procedures were positive for *Aspergillus spp* and the danger of spread could be increased with steroids.

The Apheresis Unit of our hospital has a well-established granulocyte donor and patient preparation protocol for donor selection, viral screening, time and amount of G-CSF and dexamethasone doses are given to the donor, apheresis procedure (time to obtain the largest amount of granulocytes),

premedications given to the patient, and infusion rates (transfusing the product within 8 hours). We did not see any severe adverse reaction after GTX in our CGD patients, while some patients develop hypoxemia and pulmonary infiltrates after GTX with a frequency of 10% in some CGD patient trials (10,11).

There is another issue to be considered in CGD. Special attention must be given to CGD patients' transfusions, whether they be GTX, erythrocytes, or platelets (1,2). Some X-CGD patients have McLeod syndrome. Since the Kx protein is absent and other Kell antigens are weakly expressed on erythrocytes of X-CGD patients, they will become quickly sensitized to the Kell antigens if they are not transfused with Kx-negative McLeod blood products. If the molecular genetic basis of the CGD patient is not known erythrocyte antigen phenotyping should be studied before the first transfusion of the CGD patient because it is not possible to prevent red blood cell contamination during the apheresis procedure. Our patient's Kell blood group phenotyping was negative.

However, GTX often leads to alloimmunization which may significantly impair the likelihood of successful hematopoietic stem cell transplantation later on. Thus because of the increasing desire for HSCT in CGD, we reserve GTX for severe complications and use unrelated donors only in our patients. HLA and neutrophil alloimmunization in CGD patients who received frequent GTX in a study was 70% (14/18) (12).

To conclude, hepatic abscesses occurring in patients with CGD represent a clinically significant and life-threatening complication. GTX's may be life-saving and time-saving for the patient since evidence reveals that these lesions respond quickly to viable granulocytes to overcome the immunodeficient immune system of the CGD patients.

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Kafa İçi Basınç Artışı Sendromundan Beyin Ölümü ve Organ Donasyonuna Giden Bir Adölesan Olgu Sunumu

Organ Donation Following Brain Death Due to Increased Intracranial Pressure: An Adolescent Case Report

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ÖZ

Beyin, beyin sapı ve serebellum fonksiyonlarının geri dönüşümsüz kaybı beyin ölümü olarak tanımlanmaktadır. Geri dönüşümsüz beyin hasarı saptanan, tıbben beyin dışındaki organları sağlıklı olan donörler uygun organ donörü olabilirler. Son yıllarda organ naklindeki büyük gelişmelere rağmen, organ naklinin en önemli sorunu organ bağışındaki yetersizliktir. Bu nedenle organ donörü sağlanması açısından çocuk yoğun bakım ünitelerinde beyin ölümü tanısı koymak oldukça önemlidir. Burada 17 yaşında kafa içi basınç artışı sendromuna (KİBAS) bağlı beyin herniasyonu olan ve sonrasında beyin ölümü tanısı alan, böbrek, kornea ve akciğer nakli için donör olan bir olgu sunulmuştur.

Anahtar Sözcükler: Adölesan, Akciğer Nakli, Beyin Ölümü, Kafa içi Basınç Artış Sendromu, Doku ve Organ Bağışı

ABSTRACT

Brain death is defined as the irreversible loss of all functions of the brain, the brainstem and cerebellum. Donors with irreversible brain damage and medically healthy organs other than the brain may be suitable organ donors. Despite the great progress on organ transplantation in recent years, the most important problem of organ transplantation is the insufficiency in organ donation. Therefore, it is very important to diagnose brain death in pediatric intensive care units to provide organ donors. Herein, we report a 17-year-old patient who had brain herniation due to increased intracranial pressure and was subsequently diagnosed with brain death. The patient's organs including the lungs, both kidneys and both corneas were retrieved for donation.

Key Words: Adolescent, Lung Transplantation, Brain Death, Intracranial Hypertension Increase Syndrome, Tissue and Organ Procurement

GİRİŞ

Kafa içi basınç artışı sendromu (KİBAS), intrakranial yer kaplayan bir kitlenin (tümör, hematoma, abse gibi) gelişmesi; ekstra veya intrasellüler sıvı miktarının artması (beyin ödemi); beyin kan akımının artması, beyin omurilik sıvı miktarının artması nedeniyle oluşabilir (1). Hayatı tehdit eden, hızlı değerlendirme ve tedavi

gerektiren acil bir durumdur. Çocuklarda KİBAS'ın erken tanı ve doğru yönetimi ile kalıcı beyin hasarı gelişimi engellenebilir.

Beyin, beyin sapı ve serebellum fonksiyonlarının ve asendan retiküler aktive edici sistemin geri dönüşümsüz kaybı beyin ölümü olarak tanımlanmaktadır (2). Son yıllarda organ naklindeki büyük gelişmelere rağmen, organ naklinin en önemli sorunu organ bağışındaki yetersizliklerdir. Ülkemizde beyin ölümü



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sonrası organ bağışı oranları düşüktür (3,4). Organ donörü sağlanması için çocuk yoğun bakım ünitelerinde beyin ölümü tanısı koymak ve iyi bir donör bakımı yapmak oldukça önemlidir.

Bu yazıda KİBAS olan bir olguda beyin ölümü, potansiyel donör bakımı ve organ donasyonu tartışılmıştır.

OLGU

Daha öncesinden şikâyeti olmayan 17 yaşında erkek hasta aniden başlayan şiddetli baş ağrısı, bulantı ve kusma nedeniyle yaşadığı ildeki sağlık merkezine başvurmuş. Hastaya metoklopramid ve diklofenak sodyum intramusküler tedavileri uygulanmış ve eve gönderilmiş. Hastanın eve gittikten 2 saat sonra jenaralize tonik klonik nöbetleri başlamış. 112 aracılığıyla son başvurduğu hastaneye getirilen hastanın glaskow koma skalası (GKS) 9 olarak değerlendirilmiş. Tetkiklerinde c-reaktif protein (CRP) değerinde 4 kat artış gözlenmiş ve ateşi 39 °C ölçülmüş. Tek doz seftriakson yapılmış. Hastanın çekilen Kranial BT'si normal olarak değerlendirilmiş. Nöbetleri midazolam, fenitoin ve levatiresetam ile kontrol altına alınamayan hasta ensefalit, status epileptikus (SE) tanıları ile yoğun bakım ünitesi olan başka bir hastaneye sevk edilmiş. Transport sırasında ambulans içinde saturasyonu düşen ve bradikardisi olan hastaya 3 dakika kardiyopulmoner resüsitasyon uygulanmış ve hasta entübe edilmiş. Hastanın ikinci kabul edildiği hastanede genel durumu kötü, GKS 3 ve pupilleri fix dilateymiş. Hastaya seftriakson, vankomisin, asiklovir, klaritromisin ve oseltamivir tedavisi başlanmış. Kranial BT normal olarak değerlendirilmiş. Hasta 112 aracılığıyla ileri tetkik ve tedavi amacıyla hastanemiz çocuk yoğun bakım ünitesine (ÇYBÜ) kabul edildi.

Hastanın öyküsünden 1 yıl önce araç dışı trafik kazası geçirdiği, trafik kazası sonrasında kafa tabanı kırığı ve pnömosefalisi olduğu ve nöbet geçirdiği, bu nedenle fenitoin başlandığı öğrenildi. Ancak hasta kendi isteği ile ilaçlarını 2 yıldır kullanmıyormuş.

Geliş fizik muayenesinde; genel durumu kötü, bilinç kapalı, GKS 3, tansiyon 76/43 mmHg, kalp tepe atımı 85/dk, oksijen

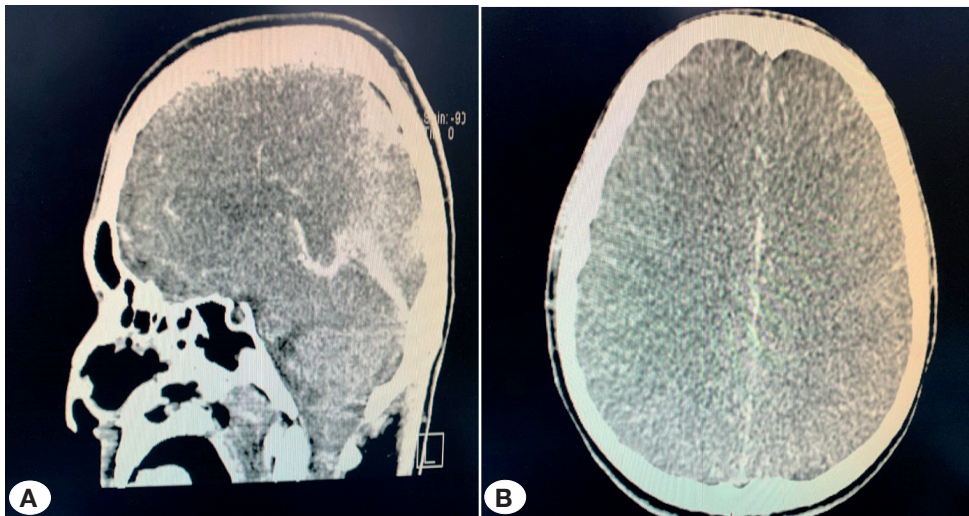
saturasyonu %90'dı. Bilateral ışık refleksi ve beyin sapı refleksleri alınamadı, pupilleri sabit dilateydi, spontan solunumu yoktu. Hastanın ense sertliği vardı. Diğer sistem muayeneleri normaldi. Hastanın başvurduğu merkezde sevk edilmeden önce GKS'sı 9 ve kranial BT'sinin normal olduğu öğrenilmişti. Fakat hastanın merkezimize başvurusunda GKS'sı 3'dü ve beyin ölümü bulguları (derin koma durumu, beyin sapı areflexisi) mevcuttu.

Hastanın tetkiklerinde: hemogloblin: 15.8 gr/dl, beyaz küre: 8450/mm³ (%87.9 nötrofil), trombosit: 105000/mm³, CRP: 234,5 mg/L, kreatinin: 1.01 mg/dL, kreatin kinaz: 1656 IU/L, troponin I: 2.55 ng/mL, kan gazı; pH: 7.29, pCO₂: 31 mmHg, pO₂: 70 mmHg, HCO₃: 15 mmol/Lt, BE: -10 mmol/Lt, laktat: 20 mg/dL olarak saptandı. Elektrolit dengesizliği yoktu ve karaciğer fonksiyon testleri normaldi. Olası intoksikasyon açısından serum ve idrardan ilaç düzeyleri gönderildi.

Geldiği hastanede ensefalit düşünülerek başlanılan seftriakson, oseltamivir, klaritromisin ve vankomisin tedavilerine devam edildi. Basınç kontrollü SIMV modda izleme alındı. Hipotansif olan hastaya adrenalin ve dopamin infuzyonu başlandı ve dozları titre edildi. Levatiresetam (20 mg/kg) bir kez daha yüklenerek idame tedaviye geçildi. Çekilen EEG'sinde her iki hemisferde de izoelektrik serebral aktivitenin izlendiği epileptik aktivite izlenmediği görüldü.

İkinci hastanede çekilen Kranial BT hastanemiz radyoloji bölümü tarafından tekrar değerlendirildi. Yaygın beyin ödemi ve tonsiller herniasyon görüldü (Resim 1). Lomber ponksiyon kontraendike olduğu için yapılmadı. Antiödem tedavi hipertonic (%3 NaCl) salin verildi. İnotrop adrenalin 1 mcq/kg/dk, noradrenalin 1.5 mcq/kg/dk ve dopamin 20 mcq/kg/dk dozlarına kadar çıkıldı. Hastanın serum ve idrarında ilaç düzeyi saptanmadı. Zehirlenme düşünülmeydi. Hastadan etiyolojiye yönelik gönderilen kan kültüründe ve idrar kültüründe üreme olmadı. Gönderilen geniş kapsamlı viral seroloji negatif saptandı.

Yatışının ilk günü ve ikinci günü, 24 saat arayla yapılan iki nörolojik muayenesinin beyin ölümü ile uyumlu olması üzerine hastaya apne testi yapıldı ve test pozitif saptandı. Kranial BT



Resim 1: Vakanın kranial BT'sinde; **A**'da sagittal kesitte serebellar tonsillerin foramen magnumdan herniye olduğu ve **B**'de transverse kesitte beyin ödemi görülmektedir.

Anjiyografi çekilerek beyin ölümü tanısı doğrulandı. Hastanın almakta olduğu asiklovir tedavisi nefrotoksik olduğu için kesildi. Hastanın kreatinin değerlerinde yükseklik olduğu için sürekli renal replasman tedavisi (SRTT) başlandı.

Beyin ölümü tanısı aileye deklare edildikten sonra organ nakil koordinasyonu tarafından donasyon teklifinde bulunuldu. Aile organ donörü olmayı kabul etti. Hastanın her iki böbreği, korneası ve akciğerleri transplant edildi.

TARTIŞMA

Burada 17 yaşında KİBAS'a bağlı beyin herniasyonu olan ve sonrasında beyin ölümüne giden bir olgu tartışılmıştır. Olgu beyin ölümü tanısı aldıktan sonra organ donörü olmuştur.

Çocuklarda KİBAS'a en çok kafa travması, intrakraniyal enfeksiyonlar veya kafa içi kitleler sebep olmaktadır (1). KİBAS, altta yatan nedeni tersine çevirmeye yönelik hızlı tanıma ve tedavi gerektirir. KİBAS olan hastaların hava yolu yönetimi acildir. KİBAS'tan şüphelenilen hastalarda hızlı ardışık entübasyonun (HAE) hava yolunun güvenliğini sağlamak için tercih edilmelidir. Bu öneri, HAE'nin yüksek başarı oranına ve düşük komplikasyon insidansına dayanmaktadır (5,6). GSK'sı 9 iken ambulansa alınan hastanın sevk olduğu hastanedeki GSK'nın 3 olması, hastada KİBAS'a bağlı herniasyon geliştiğini düşündürmektedir.

Beyin ölümü, beyin fonksiyonlarının geri dönüşümsüz kaybı olarak tanımlanır. Ülkemizde, beyin ölümü tanısı biri nörolog veya beyin cerrahi, biri de anesteziyoloji ve reanimasyon veya yoğun bakım uzmanından oluşan iki hekim tarafından oy birliği ile konulur. Beyin ölümü klinik tanısının 3 temel bulgusu derin koma durumu, beyin sapı arefleksisi ve pozitif apne testidir. Beyin ölümü temel bulgularının saptandıktan sonra geri dönüşümsüzlük kriterinin sağlanması için beyin ölümü bulgularının belirlenen sürede değişmediği gösterilmelidir (2). Beyin ölümü klinik tanısı serebral kan dolaşımı veya beyin elektriksel aktivitesi hakkında bilgi veren testler ile desteklenmelidir. Elektroensefalografi, duyusal uyarılmış potansiyeller, transkraniyal doppler ultrasonografi, radyonüklid serebral sintigrafi (SPECT), BT anjiyografi ve kateter serebral anjiyografiye destekleyici testlerdir (2).

Ülkemiz beyin ölümü teşhisi konan donörlerden organ nakli yapılmasına izin veren ilk ülkelerden olmasına (7) ve gerekli olanaklara sahip olmasına rağmen, beyin ölüm bildirimlerinin sayısı ve organ nakli oranı düşüktür (4,8). Ülkemizde 2019 verilerine göre; 28 bin 272 hasta nakil için sıradadır (8). Türkiye'de 1975'ten beri böbrek nakli yapılmaktadır ve ülkemizde en çok nakil yapılan organ da böbrektir (9). Akciğer nakli, tüm organ nakilleri içinde en komplike organ naklidir. Ülkemizde ise ilk başarılı akciğer nakli 2009 yılında yapılmıştır (10). Ülkemizde organ nakli bekleyen hasta sayısı her yıl yaklaşık %20 civarında artmaktadır ve organ bekleyen hastaların %10 undan fazlasının bu süreçte hayatını kaybetmektedir. Organ nakli bekleyen hasta sayısı her yıl yaklaşık yüzde 20 civarında artmaktadır ve

hastaların yüzde 10'undan fazlasının organ beklerken hayatını kaybetmektedir. 2019 verilerine göre; 2 bin 309 beyin ölümü bildiriminden 256'sı 0-19 yaş arasındadır ve bu hastalardan yalnızca 52 hasta organ donörü olmuştur (8). Bu nedenle, beyin ölümü erken tanısı ve donör organların bakımı son derece önemlidir.

Hastamızın gelişindeki nörolojik muayenesinde beyin ölümü kliniği hızlıca tanındı. Yapılan apne testi ve çekilen BT anjiyografisi beyin ölümü tanısı doğrulandı. Hastamıza beyin ölümü tanısı konulduktan sonra organların işlevlerinin korunması hedeflendi. Transplantasyonu yapılacak organlar travma, hipoksi, şok, anemi, kan ürünlerine maruziyet ve enfeksiyon sebebiyle hasar görebilir (11,12). Potansiyel organ bakımının amacı yeterli organ perfüzyonu ve yeterli doku oksijenasyonunu sağlamaktır. Bunun için vücut sıcaklığının korunması (35-37°C), kalp debisinin optimal düzeyde tutulması, yeterli ventilasyon sağlanması (oksijen saturasyon>%95, pH: 7.35-7.45) idrar çıkışının 1-2 ml/kg/sa tutulması gibi hedefler belirlenmiştir (12,13). Hastamızda organ bakımı amacıyla; elektrolit dengesini sağlandı, kan basıncının stabilizasyonu için aşamalı çoklu inotrop tedavisi başlandı, akciğer koruyucu mekanik ventilatör stratejisi uygulandı. Yapılan çalışmalar beyin ölümünde akut renal hasarın erken döneminde yapılan renal replasman tedavilerinin böbrek nakil ihtimalini artırdığını göstermiştir (14,15). Biz de hastamıza böbrek fonksiyon testlerinde bozukluk ve idrar çıkışında azalma olması nedeniyle SRRT tedavisi uyguladık. Hastanın ünitemizde hızla konulan beyin ölümü tanısı ve organların korunmasına yönelik uygun yoğun bakım hizmeti sayesinde nadir bir transplantasyon işlemi olan akciğer nakline gidişi sağlandı. Aynı zamanda her iki böbreği de iki ayrı hastada kullanılabilirdi.

Bu vaka, beyin ölümü tanısının hızlı konulması ve organların uygun şekilde korunmasının önemini vurgulamak amacı ile sunulmuştur.

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COVID-19 ve Nörolojik Bulgular

Neurologic Manifestations of COVID-19

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ÖZ

Yeni bir koronavirüs olan SARS-CoV-2'nin neden olduğu koronavirüs hastalığı (COVID-19) dünya genelinde ciddi bir sağlık sorunu haline gelmiştir. COVID-19 öncelikle akut solunum yolu enfeksiyonu şeklinde kendini gösterse de hastalarda pek çok nörolojik bulgu da tanımlanmıştır. Nörolojik bulgular santral, periferik sinir sistemi ve kas-iskelet sistemi olarak üç grupta sınıflandırılır. En sık görülen santral sinir sistemi bulgusu baş ağrısıdır. Ensefalit, ensefalopati, nöbet, akut iskemik inme de görülmektedir. Periferik sinir sisteminde en sık görülen bulgular koku ve tat kaybı iken kas-iskelet sistemi tutulumunda miyalji, miyozit, rabdomiyoliz görülebilir. Nörolojik bulguların hekimler tarafından bilinmesi hastalığın erken tanı ve tedavisinde fayda sağlayacaktır.

Anahtar Sözcükler: Baş ağrısı, COVID-19, Çocuk, Nörolojik bulgu

ABSTRACT

Coronavirus disease (COVID-19) caused by a new coronavirus, SARS-CoV-2, has become a serious health problem throughout the world. Although COVID-19 primarily presents as an acute respiratory tract infection, many neurological findings have also been described in patients. Neurological findings are classified into three groups as central, peripheral nervous system and musculoskeletal system. The most common central nervous system symptom is headache. Encephalitis, encephalopathy, seizures, acute ischemic stroke are also seen. The most common symptoms in the peripheral nervous system are loss of smell and taste. Myalgia, myositis and rhabdomyolysis also can be seen in musculoskeletal system involvement. Awareness of the neurological symptoms by physicians will be beneficial in early diagnosis and treatment of the disease.

Key Words: Headache, COVID-19, Child, Neurological findings

GİRİŞ

Yeni bir koronavirüs olan SARS-CoV-2'nin neden olduğu hastalık, koronavirüs hastalığı 2019 (COVID-19) olarak isimlendirilmiştir (1). COVID-19 ilk olarak Aralık 2019'da Çin'in Wuhan eyaletinden bildirilmiş ve dünya genelinde çok ciddi bir sağlık sorunu haline gelmiştir. Dünya Sağlık Örgütü tarafından da küresel bir salgın ilan edilmiştir.

Koronavirüs, esas olarak insan solunum sistemini hedef alan, üst ve alt solunum yolu enfeksiyonuna neden olan büyük,

zarflı bir RNA virüsüdür (1). SARS-CoV-2, öncelikle damlacık yoluyla bulaşır. COVID-19 hastalarının çoğu akut solunum yolu enfeksiyonu ile başvurur, ancak hastaların çoğunda semptomlar hafiftir. En sık görülen bulgular ateş, öksürük ve boğaz ağrısıdır. Solunum sistemi yanında diğer organ sistemleri de COVID-19'dan etkilenebilir. İshal, karın ağrısı, bulantı gibi gastrointestinal belirtiler ve baş ağrısı, mental durum değişikliği, ensefalit, miyozit, koku ve tat kaybı gibi nörolojik semptomlar görülebilir (1-2).

COVID-19'un nörolojik belirtileriyle ilgili erişkin hastaları içeren yayınlar her geçen gün artmaktadır. Wuhan'dan yayınlanan ilk



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vaka serisinde hastaların % 36.4'ünde nörolojik semptomlar tespit edilmiştir (2). Nörolojik bulgu oranı farklı çalışmalarda % 7.7 ile % 57.4 arasında değişmektedir (3-4). Hastalarının %4.2'sinde de nörolojik semptomlar başlangıç semptomu olarak görülebilir (5). Nörolojik semptomlar santral sinir sistemi (SSS), periferik sinir sistemi ve kas-iskelet sistemi olarak 3 gruba ayrılarak değerlendirilebilir (Tablo I).

Santral Sinir Sistemi ile ilişkili Bulgular

Santral sinir sistemi (SSS) bulguları arasında baş ağrısı, bilinç bozukluğu, ensefalit, ensefalopati, akut hemorajik nekrotizan ensefalopati, ataksi, nöbet ve akut serebrovasküler hastalık yer alır (6). Baş ağrısı, COVID-19 hastalarında en sık görülen başlangıç semptomlarından biridir. Baş ağrısı prevalansı farklı çalışmalarda %13.8 ile %66 arasında değişmektedir (2,6,7). Baş ağrısı hafif veya orta şiddette hastalığı geçirenlerde ağır geçirenlere göre daha sık bildirilmiştir (7). COVID-19 hastalarında bilinç değişikliği de %1.4 ile %69 arasında değişen oranlarda görülmektedir. Ağır ve yoğun bakım hastalarında daha sık görülmüştür (7-9). Nöbet ise olgu sunumları şeklinde bildirilmiştir (10). COVID-19 ile ilişkili menenjit /ensefaliti içeren vaka raporları da yayınlanmıştır (10-12). Japonya'dan bildirilen ilk ensefalit olgusu 24 yaşında olup, bilinç değişikliği ve jeneralize nöbet ile başvurmuştur. Beyin omurilik sıvısı (BOS) incelemesinde SARSCoV-2 PCR testi pozitif saptanmış, beyin manyetik rezonans görüntülemesinde (MRG) patolojik serebral lezyonlar görülmüştür (10). ABD'den de bir akut hemorajik nekrotizan ensefalopati vakası bildirilmiştir. Bu hastanın da beyin MRG incelemesinde bilateral talamus, medial temporal loblar ve subinsüler bölgelerde hemorajik, çevresinde kontrast tutulumu bulunan lezyonlar mevcuttur (13). Akut serebrovasküler olaylar ise hastalığı ağır seyreden, hipertansiyon, diyabet ve kardiyovasküler hastalıklar gibi komorbiditeleri olan COVID-19 hastalarında daha sıklıkla görülmektedir (7,14).

Tablo I: COVID-19 enfeksiyonunda görülen nörolojik bulgular.

Santral Sinir Sistemi
Baş ağrısı
Baş dönmesi
Bilinç bozukluğu
Ensefalit
Ensefalopati
Akut hemorajik nekrotizan ensefalopati
Ataksi
Nöbet
Akut serebrovasküler hastalık
Periferik Sinir Sistemi
Anosmi/hiposmi
Aguzi/hipoguzi
Guillain Barre syndrome
Miller Fisher sendromu
Kranial sinir felci
Kas-İskelet Sistemi
Miyalji
Miyozit
Rabdomiyoliz

Periferik Sinir Sistemi ile ilişkili Bulgular

Periferik sinir sistemi belirtileri arasında tat, koku kaybı, Guillain Barre sendromu ve Miller Fisher sendromu yer alır (15). Koku veya tat almada azalma veya tamamen kaybı baş ağrısından sonra en sık görülen semptomlardır. Bu semptomların bildirilen sıklıkları çalışmalarda değişkenlik göstermektedir. Wuhan'dan yapılan bir erişkin çalışmada, hastaların %5.1'inde koku almada, %5.6'sında tat almada bozulma bildirilmiştir (2). Ancak Avrupa'dan yapılan çalışmalarda bu oran daha yüksek saptanmıştır. Hafif ila orta dereceli COVID-19 hastalarını içeren bir çalışmada, koku ve tat almada bozulma, sırasıyla %85.6 ve %88.8 oranında görülmüştür (16). COVID-19 hastalarında Guillain Barre sendromu ise vaka serileri veya vaka raporlarında bildirilmektedir (7,17,18). Guillain Barre sendromu tanısı alan hastanın ilk semptomu, viral enfeksiyonun başlamasından sonraki 5-10 gün içinde ortaya çıkmıştır. Bu hastada BOS'ta SARS-CoV-2 PCR testi negatif saptanmıştır (17). COVID-19 hastalarında ayrıca GBS varyantları olan Miller Fisher sendromu ve polinöritis cranialis de bildirilmiştir (19). Fasial sinir ve okülomotor sinir felci gibi izole kranial sinir tutulumları da COVID-19 hastalarında görülebilmektedir (20,21).

Kas-İskelet Sistemi ile ilişkili Bulgular

Kas-iskelet sistemi belirtileri arasında ise miyalji, miyozit ve rabdomiyoliz yer alır. Miyalji, COVID-19 hastalığının sık görülen semptomlarından biridir ve hastaların %26-%51'inde görülmüştür (18,22). İki hastada da rabdomiyoliz bildirilmiştir (23).

Çocuklarda Görülen Nörolojik Bulgular

Çocuklarda ve yenidoğanlarda nörolojik tutulumla ilgili yayınlar oldukça kısıtlıdır. Bunun nedeninin hastalığın çocuklarda daha az oranda görülmesi ve daha hafif seyirli olması ile ilişkili olduğu düşünülmektedir. Çocuklar COVID-19'dan daha az etkilenmektedir (24). COVID-19 hastalarının yaklaşık % 2-5'i çocuktur (25). Çocukların çoğu hastalığı asemptomatik olarak geçirmekte, semptomatik olsa bile daha hafif atlatmaktadır. Ancak yetişkinlerde COVID-19 hastalığı genellikle daha şiddetli ve daha uzun bir seyir gösterir. Özellikle ağır hastalarda nörolojik semptomlar daha sık görülebilmektedir. Çocuk hastalarda yapılan gözlemsel bir çalışmada, hastalarda görülen tek nörolojik semptom baş ağrısı olarak belirtilmiş ve bu da hastaların % 3'ünde görülmüştür (26). COVID-19'lu 171 çocukla yapılan başka bir çalışmada nörolojik tutulum bildirilmemiştir (27). Son dönemde yayınlanan bir meta-analizde ise pediatrik COVID-19 hastalarında baş ağrısı, miyalji ve yorgunluk gibi nörolojik bulguların % 16.7 oranında görüldüğü saptanmıştır (28). Febril, afebril nöbet geçiren hastalar ve ensefalit olguları da yayınlarda bildirilmektedir (29,30). Tat ve koku kaybı ise çocuk hastalarda %6 oranında görülmüştür (31).

Son yayınlarda, COVID-19 enfeksiyonu ile ilişkili çocuklarda multisistem inflamasyon sendromu (MIS-C) tanımlanmıştır. Bu sendrom, toksik şok sendromu ve atipik Kawasaki hastalığı ile

ortak özelliklere sahiptir. Asemptomatik veya hafif semptomatik COVID-19 hastalığından sonra görülen olası bir post-enfeksiyöz sendromdur. MIS-C'li çocuklar akut hipotansiyon, kardiyojenik şok ve çoklu organ yetmezliği geliştirir. Bu hastalarda baş ağrısı, bilinç bozukluğu, aseptik menenjit, ensefalit, nöbet, ataksi gibi nörolojik belirtiler bildirilmiştir. MIS-C'li çocuklarda nörolojik tutulum insidansı % 25-50 arasındadır (25,32).

Nörolojik Bulguların Gelişiminde Öngörülen Mekanizmalar

COVID-19 hastalarında görülen nörolojik bulguların gelişiminde öngörülen farklı mekanizmalar bulunmaktadır (33,34). İlk mekanizma, virüsün sinir sistemine invazyonudur. Virüs SSS'ye farklı yollardan girebilir. Virüs, iki olası mekanizma yoluyla kan beyin bariyerini aşabilir. Endotel hücreleri ACE2 reseptörünü eksprese eder ve virüs tarafından yüksek oranda enfekte olma riski taşırlar. Virüs, enfekte olmuş vasküler endotelial hücreler aracılığıyla taşınabilir. Ayrıca virüs ile enfekte olan lenfositler de kan beyin bariyerini aşarak kandan SSS'ye geçebilir. Bu yollar dışında virüs SSS'ye ulaşmak için retrograd aksonal taşımayı da kullanabilir. Virüs, sinir uçlarına invaze olup, nöronal sinapslar boyunca yayılabilir ve SSS'ye ulaşabilir. Virüs, retrograd aksonal taşıma için olfaktör, respiratuar ve enterik sinir sistemi ağlarını kullanabilir (1). İkinci mekanizma, virüs tarafından tetiklenen artmış immün yanıtıdır. IL-6, IL-10 ve TNF dahil olmak üzere sitokin ve kemokin seviyeleri yükselir ve bu duruma "sitokin fırtınası" adı verilir. Bu hiperinflamatuvar durum çocuklarda ensefalopati, ensefalit, miyelit ve ayrıca multisistem inflamasyon sendromuna neden olabilir (1,4). Üçüncü mekanizma, sistemik hastalığın sonucudur. Akciğer hasarına bağlı hipoksi, beyin oksijenlenmesini bozabilir (34). Ayrıca çoklu organ yetmezliği beyin işlevini etkileyebilir. Virüs, vasküler endotel hücrelerine zarar verip ve trombotik yolları aktive edebilir. Artmış pıhtılaşma durumu ve vasküler endotel hasarı inme riskini artırabilir (14). Son mekanizma ise diğer viral enfeksiyonlardan sonra da görülebilen post-enfeksiyöz immün aracılı mekanizmadır (4).

SONUÇ

COVID-19 sinir sistemini etkileyebilir. Hekimler, hem erişkinlerde hem de çocuklarda görülen nörolojik tutulum konusunda dikkatli olmalıdır. Nörolojik bulguların erken tanınması, bu bulgularla başvuran hastalarda hızlı tanı konulmasını sağlayacaktır. Ayrıca hastalığın uzun vadeli etkileri de bilinmemektedir. Bu hastalığı geçiren hastaların uzun dönem nörolojik etkilenme açısından da takibi önemlidir. Ayrıca sinir sistemi tutulumu ile ilgili öngörülen patofizyolojik mekanizmaların detaylı araştırmalarla aydınlatılması gerekir.

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Use of Phenytoin in Vertigo/Dizziness

Vertigoda Fenitoin Kullanımı

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ABSTRACT

Phenytoin is an antiepileptic agent that has been in clinical use for approximately 80 years, particularly due to its antiepileptic and antineuralgic activity and antiarrhythmic effects. Phenytoin has also become increasingly widely used in recent years in various clinical applications, including wound healing, migraine, dizziness, myocardial infarction, bipolar disorder, various types of ulcer, and burns. Vertigo/dizziness is frequently seen in children. Numerous causes play a role in the etiology of vertigo/dizziness. Antiepileptic drugs (particularly carbamazepine and diphenylhydantoin) are also known to give rise to vertigo/dizziness. There are no specific studies concerning the treatment of vertigo/dizziness in childhood, and treatment is reported to involve treatment of the underlying etiology.

Key Words: Phenytoin, Treatment, Vertigo

ÖZ

Fenitoin, özellikle antiepileptik, antinöraljik aktivitesi ve antiaritmik etkileri nedeniyle yaklaşık 80 yıldır klinik kullanımda olan bir antiepileptik ajandır. Fenitoin ayrıca son yıllarda yara iyileşmesi, migren, baş dönmesi, miyokard enfarktüsü, bipolar bozukluk, ülser türleri ve yanıklar dahil olmak üzere çeşitli klinik uygulamalarda giderek daha yaygın bir şekilde kullanılmaktadır. Çocuklarda baş dönmesi sıklıkla görülür. Baş dönmesi etyolojisinde çok sayıda neden rol oynamaktadır. Antiepileptik ilaçların da (özellikle karbamazepin ve difenilhidantoin) baş dönmesine neden olduğu bilinmektedir. Çocukluk çağında baş dönmesi tedavisi ile ilgili spesifik bir çalışma yoktur ve tedavinin altta yatan etyolojinin tedavisini içerdiği bildirilmektedir.

Anahtar Kelimeler: Fenitoin, Tedavi, Vertigo

INTRODUCTION

We have read the article by Dilber et al. (1) titled, "Neurological Manifestations of Pediatric Acute COVID Infections: A Single Center Experience?" with interest. The second most common non-specific symptom reported in patients followed-up with Covid-19 was dizziness, observed in 14.3% of patients, 0.7% of whom were hospitalized. Diphenylhydantoin has been used in the treatment of patients hospitalized with dizziness, and a good clinical response has been reported. The use of diphenylhydantoin with this indication attracted our attention. However, it was stated that 25% of Covid-19 patients had

central nervous system findings and 2% of them had at least one seizure during the treatment process (2). Firat et al. (3), mentioned drug-drug interactions of clinical importance between anti-Covid-19 treatments (antiviral and immune therapies) and antiepileptic drugs. It has been emphasized that phenytoin reduces lopinavir/ritonavir serum levels by 30%. For this reason, it was emphasized that attention should be paid the dose of antiviral treatment in COVID-19 patients with epilepsy receiving phenytoin (3).

Phenytoin is an antiepileptic agent that has been in clinical use for approximately 80 years, particularly due to its antiepileptic and antineuralgic activity and antiarrhythmic effects (4,5). It is



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widely prescribed because of its low cost and easy availability (6). Phenytoin has also become increasingly widely used in recent years in various clinical applications, including wound healing, migraine, dizziness, myocardial infarction, bipolar disorder, various types of ulcer, and burns (7-9).

Vertigo is frequently seen in children. Numerous causes play a role in the etiology of vertigo/dizziness (including head trauma, central nervous system pathologies, vestibular pathologies, psychogenic factors, migraine, labyrinth/nerve pathologies, congenital, idiopathic, post-infectious, and toxic causes, malnutrition, and vascular, inflammatory, and oculomotor causes). Antiepileptic drugs (particularly carbamazepine and diphenylhydantoin) are also known to give rise to vertigo (10). The difficulty in treating pediatric vertigo may derive from its being a symptom identified late in childhood. There are no specific studies concerning the treatment of vertigo/dizziness in childhood, and treatment is reported to involve treatment of the underlying etiology (11). The treatment of vertigo/dizziness includes acute symptomatic therapy, behavioral therapy, specific therapy, and pharmacotherapy (propranolol, flunarizine, levetiracetam, lamotrigine, magnesium, dimenhydrinate, prednisolone, betahistine, carbamazepine, and acyclovir). We know that the antiepileptic agents levetiracetam, valproic acid, lamotrigine, and topiramate are used in patients with migraine involved in the etiology of vertigo, and that carbamazepine and oxcarbazepine are used in patients with vestibular paroxysm (11).

This article emphasizes the use of phenytoin in the treatment of patients with vertigo/dizziness, and that the symptoms duly resolved. The use of a drug whose side-effects include vertigo/dizziness in the treatment of vertigo/dizziness in patients diagnosed with Covid-19 is therefore a very recent application according to our review of the literature. In addition, the improvement of patients' symptoms is of great importance in terms of this therapeutic option entering into use.

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