Türkiye Çocuk Hastalıkları Dergisi / *Turkish Journal of Pediatric Disease*

ANKARA BİLKENT ŞEHİR HASTANESİ ÇOCUK HASTANESİ

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Official Journal of Ankara City Hospital, Child Hospital

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ÇOCUK HASTANESİ

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Kapak SayfasınınHazırlanması:

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

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

Önemli Uyarı: Kapak sayfası ayrı bir belge olarak yüklenmelidir.

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

Anahtar kelimeler:

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

YAZI TÜRLERİ

Orijinal Araştırma Makalesi

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

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

Başlık: En çok 20 kelime

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

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

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

Kaynaklar: En çok 40.

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

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

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

Derleme:

Kelime sayısı: En fazla 5000

Özet: En fazla 500 kelime

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

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

Kaynaklar: 80'e kadar

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

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

Olgu Sunumu:

Kelime Sayısı: En fazla 2000 kelime

Özet: En fazla 200 kelime

Anahtar Kelime: En az üç en fazla altı kelime

Tablo ve Şekil: Toplamda en fazla beş ile sınırlandırılmıştır.

Kaynaklar: En fazla 15

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

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

Editöre mektup:

Kelime sayısı: En fazla 1500 kelime

Şekil ve tablolar: En fazla 3

Kaynaklar: En fazla 15

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

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

Çalışma Metodları:

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

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

Tablolar

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

Şekiller ve şekil alt yazıları

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

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

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

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

KAYNAKLAR

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

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

Kaynak dergi ise;

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

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

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

Kaynak dergi eki ise;

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

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

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

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

Kaynak kitap ise;

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

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

Kaynak kitaptan bölüm ise;

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

Baskı yılı:Bölümün ilk ve son sayfa numarası.

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

Kaynak toplantıda sunulan bildiri ise;

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

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

Kaynak elektronik dergi ise;

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

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

Kaynak web sitesi ise:

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

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

Kaynak tez ise:

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

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

Düzeltme istenmesi aşaması:

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

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

Yazar Listesi/Sırası Değişimi

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

Yazının Geri Çekilmesi Talebi

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

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

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

INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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

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

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.

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İÇİNDEKİLER / CONTENTS

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Olgu Sunumları / *Case Reports*

Health Related Quality of Life of Children Aged 2-18 Years with Familial Mediterranean Fever

Ailevi Akdeniz Ateşi Olan 2-18 Yaş Arası Çocuklarda Sağlıkla İlişkili Yaşam Kalitesinin Değerlendirilmesi

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ABSTRACT

Objective: We aimed to evaluate both child-self reported and parents proxy reported health related quality of life of children with familial Mediterranean fever (FMF) aged between 2-18 years old and to compare the scores with their healthy peers.

Material and Methods: Fifty -one patients with FMF and fifty one gender and age matched controls were enrolled in the study. Children aged 8-18 years completed the PedsQL4.0 child form questionnaires. Parents of all cases completed the PedsQL4.0 parent form.

Results: Lower scores in the FMF group, with no statistical significance, was found between the FMF cases and healthy volunteers aged 8-18 years for the physical health, social health, school functioning, psychosocial total and scale total score of PEDsQL4.0 child self-report. The parent proxy report PedsQL4.0 scores of all patients with FMF were lower than the healthy group for physical, emotional, social, psycho-social, school functioning scores and scale total score but the difference was not statistically significant. A significant correlation was present between PedsQL4.0 child self-report and parent PedsQL4.0 report in all subscales except for social health total score. There was not a significant correlation between the demographic variables and clinical features of the patients and the child subscales of PedsQL4.0.

Conclusion: The scores of FMF cases from the scales were lower than those of the healthy volunteers from the questionnaires but this difference was not statistically significant. Considering the relatively small sample size of the study it is obvious that more comprehensive prospective studies are required on this subject.

Key Words: Children, Familial Mediterranean fever, Quality of life, Parent

ÖZ

Amaç: Bu çalışmada ailevi Akdeniz ateşi (AAA) olan 2-18 yaş arası çocuk hastaların ve ebeveynlerinin sağlıkla ilgili yaşam kalitesini değerlendirmek ve aynı yaş grubundaki sağlıklı çocuklar ile karşılaştırmak amaçlandı.

Gereç ve Yöntemler: Ailevi Akdeniz ateşi olan 51 çocuk ile yaş ve cins olarak eşleştirilmiş 51 sağlıklı gönüllü çalışmaya dahil edildi. Sekiz-18 yaş arası çocuklar PedsQL4.0 çocuk formunu doldururken, tüm yaş gruplarında ebeveynler PedsQL4.0 ebeveyn formunu doldurdu.

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study is conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Keçiören Training and Research Hospital (No: 10.12.2014/703).

Contribution of the Authors / Yazarların katkısı*: *YASAR DURMUS S: 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. ***OZLU SG:*** 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 the writing of the whole or important parts of the study. ***COP E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in 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. ***BULBUL M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Sekiz-18 yaş grubu çocuk formlarının değerlendirilmesinde, istatistiksel anlamlı olmamakla birlikte, fiziksel sağlık, sosyal sağlık, okul işlevselliği, psikososyal total skor ve ölçek toplam skoru açısından AAA olan çocukların puanlarının daha düşük olduğu saptandı.

Ebeveyn PedsQL4.0 değerlendirildiğinde ise tüm yaş gruplarında AAA olan çocukların ebeveynlerinde fiziksel, duygusal, sosyal, psikososyal, okul işlevselliği skorları ve ölçek toplam skorlarının sağlıklı çocukların aileleri ile karşılaştırıldığında daha düşük olduğu ancak istatistiksel anlamlı düzeye ulaşmadığı saptandı. Sosyal sağlık toplam skoru hariç tüm ölçeklerde AAA olan çocuklar ve ebeveynlerinin PedsQL4.0 değerlendirmeleri arasında anlamlı korelasyon olduğu saptandı. Demografik değişkenler ve klinik bulgular ile çocuk PedsQL4.0 arasında anlamlı ilişki saptanmadı.

Sonuç: Ailevi Akdeniz ateşi olan olgularda ölçek skorları istatistiksel anlamlı olmasa da sağlıklı kontrollere göre daha düşüktür. Çalışmamızda göreceli olarak az sayıda hasta olduğu göz önünde bulundurulduğunda bu alanda daha kapsamlı ve fazla sayıda hasta içeren çalışmalara ihtiyaç olduğu sonucuna varılmıştır.

Anahtar Sözcükler: Çocuklar, Ailevi Akdeniz Ateşi, Yaşam kalitesi, Ebeveyn

INTRODUCTION

Familial Mediterranean Fever (FMF) is a self-limiting autosomal recessive auto-inflammatory disease characterized by recurrent fever and episodes of inflammation in the serous membranes such as the peritoneum, pleura, pericardium, and synovia (1). The disease is especially common in certain populations such as the Turks, Armenians, Arabs, and Jews living in the Mediterranean and the Middle East (2).

The Tel Hashomer criteria, mostly based on clinical evaluation, are used in the diagnosis (3). The gene MEFV causing the disease has been described in 1997 at the 16p13.3 localization and to date 389 mutations and polymorphisms have been reported so far (4-6).

Colchicine has been the first choice of treatment for FMF patients since it had been discovered in 1972 (7, 8). It is effective in preventing attacks of FMF and preventing amyloidosis which is the most devastating complication of FMF (9).

The concept of quality of life (QoL) is often used in everyday life and also in the practice of medicine in recent years. It can briefly be defined as the individual's evaluation of its current situation using his/her own system of values and culture. Health-related QoL (HRQoL) is the perception of the effects created by a disease or its treatment on the patient (10). Health-related QoL studies are useful to understand disease and their effects on the individual, and to develop treatment plans and health policies (11).

The evaluation of QoL in rheumatic disorders is becoming increasingly important in recent years. Quality of life has been shown to be decreased in systemic rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis, fibromyalgia and FMF in adult studies (12,13). Studies on HRQoL in children were first conducted in the 1980s. Health-related QoL is an important factor in terms of evaluating a disease and planning its treatment in children with rheumatological disorders (10,11). In FMF, conditions such as; recurrent characteristic of disease, retention from school, regular medical visits, having to use medications for life, affect the QoL (11). Buskila et al. (14) were the first to conduct QoL studies in adult FMF patients and found it decreased compared to healthy controls. Press et al. (15) reported that the QoL was also decreased in the parents of children with FMF. The QoL of pediatric FMF patients and their parents was first investigated by Makay et al. (16). They evaluated the QoL of children and adolescents with FMF aged 8-18 years and their parents in their study and detected that QoL scores of children aged between 8- 12 years with FMF were significantly lower than healthy peers for physical and psychosocial functioning for both children and parents.

In this study, different from previous studies, in addition to the QoL of children aged 8-18 years we also evaluated the QoL of children between 2-7 years old together with their families and identified the influencing factors. The aim of this study to evaluate both child-self reported and parents proxy reported HRQoL of children with FMF aged between 2- 18 years old and to compare the scores with their healthy peers and to determine the factors which affect the QoL of children with FMF.

PATIENTS and METHODS

Fifty-one children with FMF aged 2-18 years, followed-up at least six months and age-sex matched 51 healthy volunteers were included in this study who had been followed at Department of Pediatric Nephrology and Rheumatology of our hospital; between January 2015 and April 2015. FMF diagnosis was made according to Tel Hashomer criteria. Patients were diagnosed by using Yalçınkaya-Özen criteria after the year 2009. The majority of patients who had diagnosed with FMF were screened for the most common 12 MEFV mutations based on reverse hybridization with the CE/IVD-labeled FMF Strip Assay (Vienna Lab Diagnostics, Vienna, Austria).

In pediatric nephrology and rheumatology department of our hospital, patients with FMF continue to follow up quarterly. Healthy volunteers were picked up from children who were admitted to out-patients clinics of department of general pediatrics. They did not have any history of acute or chronic diseases.

Inclusion criteria: Patients who had diagnosed with FMF due to Tel Hashomer criteria between 2 to 18 years old, who do not have comorbid diseases and accepted to answer all questions of questionnaire were included in the study

Exclusion criteria: Patients who had diagnosed FMF and older than 18 years old, who had comorbid diseases or FMF attack at the time of the evaluation, did not answer the all questions of questionnaire were excluded from study.

Sociodemographic form was developed and applied by the authors to record characteristics of participants such as age and gender. The diagnosis duration, annual mean number of attacks, annual mean number of hospitalizations due to an attack, the dose of colchicine used, disease severity scores of 51 FMF cases and MEFV gene mutation were also recorded.

The duration of FMF was classified as 0-5 years, 5-10 years, and 10 years and higher. The mean annual number of attacks and the mean annual number of hospitalizations due to an attack were grouped as 0-1 low, 2-4 moderate and 5 and above frequent. The disease severity scores were graded as mild, moderate and severe using the method identified by Pras (17). Children aged 8-18 years completed the Quality of Life Scale for Children (PEDsQL) Child Form questionnaires. Parents of all cases completed the PEDsQL parent form.

We used the PedsQL4.0 scales developed by Varni et al. (18,19). Turkish reliability and validity were done by Üneri (20) (for the age of 2-7 years) and Memik (21) (for the age of 8-18 years). Physical health, emotional and social functioning and school functioning, all characteristics of health as identified by the World Health Organization, are queried with PedsQL. The PedsQL4.0 scale includes 21 items for 2-4 years and 23 items for all other age groups. Each item is scored between 0 and 100. An answer of 'never' receives 100 points, 'rarely' 75 points, 'sometimes' 50 points, 'often' 25 points and 'almost always' 0 (17). The scale total score (STS), physical health total score (PHTS) and psycho-social health total score (PSHTS; this is the mean computed sum of the items divided by the number of items answered in the Emotional (EHTS), Social (SHTS) and School functioning (SFTS) scales) are then calculated. Higher PedsQL4.0 total scores indicate better HRQoL.

This study is conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Keçiören Training and Research Hospital (No: 10.12.2014/703).

Statistics

SPSS 15.0 program (Statistical Package for Social Sciences, Chicago, SPSS Inc.) was used for statistical analysis. The normality of the distribution of numerical variables was determined via the Kolmogorov-Smirnov test. Numerical variables with normal distribution are shown as mean ± SD and those not normally distributed are shown as median. Frequency and (%) are used for categorical variables. G*Power v.3.0.10 (G*Power Franz Faul, Universitat, Kiel, Germany) was used to determine the sample size required for the study (22). Taking a sample of ≥ 102 cases (51 cases per group) was calculated to achieve 80% power with d=0.50 effect width, α=0.05 type 1 error, β=0.20 type 2 error (23).

Student's t test or Mann-Whitney U test (which was appropriate according to distribution of variables) was used to compare variables like age, gender, STS, PHTS, EHTS, SHTS, SFTS, and PSHTS scores between two groups. To measure the difference between the means of STS, PHTS, EHTS, SHTS, SFTS, and PSHTS scores of PEDsQL child form and of PEDsQL parent form, dependent sample t-test was done. Correlation analysis was done to evaluate the relation between STS, PHTS, EHTS, SHTS, SFTS, PSHTS scores and age, gender, duration of disease, mean annual number of attacks, mean annual number of hospitalizations due to an attack, dose of colchicine used, MEFV gene mutation, disease severity score of the FMF group. A p value of <0.05 was accepted as significant.

RESULTS

Fifty-one children with FMF and 51 healthy children were included in our study. Socio-demographic characteristics of the FMF cases including age, gender, diagnosis duration, mean annual number of attacks, mean annual number of hospitalizations due to an attack, dose of colchicine used and disease severity scores are summarized in Table I.

A mathematical difference, with no statistical significance, was found between the FMF cases and healthy volunteers aged 8-18 years for the PHTS, SHTS, SFTS, PSHTS and STS of PEDsQL4.0 child self-report. All of the caregivers of FMF patients had lower PHTS, EHTS, SFTS, PSHTS, STS, SHTS

Table I: Socio-Demographic features of participants.

Socio-Demographic features	FMF patients	Healthy volunteers	Statistics
Girls n (%)	25 (49)	24 (47.1)	p=0.84 X^2=0.39
Age, mean±SD (years)	11.2±4.1	11.7±3.8	p=0.48
Age at diagnosis,mean±SD (years)	6.3±3.5	-	-
Duration of disease, mean±SD (years)	4.9±3.7	-	-
Number of attacks in a year*		-	-
Mild	34 (66.7)		
Moderate	11 (21.6)		
Severe	6 (11.8)		
Number of hospitalizations*		-	-
Rare	48 (94.1)		
Moderate	2 (3.9)		
Frequent	1 (2)		
Dose of colchicine*		-	-
0.5 mg	16 (31.4)		
1 mg	26 (51)		
1.5 mg	8 (15.7)		
2 mg	1 (2)		
Disease severity scores*		-	-
Mild	37 (72.5)		
Moderate	14 (27.5)		

***n(%), **FMF:** familial Mediterranean fever, **SD:** Standard Deviation*

Table II: Comparisons of Quality of Life Scale for Children scores of healthy volunteers and familial Mediterranean fever patients (ages between 8-18 years) reports and their parent reports.

Comparison	FMF Patients (n=51)			Healthy Volunteers (n=51)			p
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
PedsQL children report							
PHTS	596.7±154.2	637.5	(300-800)	618.9±123.5	625	(250-800)	0.493
EHTS	379.6±90.9	387.5	(100-500)	370.9±80.2	375	(225-500)	0.664
SHTS	453.2±80.9	500	(200-500)	455.4±64.8	475	(200-500)	0.505
SFTS	333.5±89.7	325	(150-500)	366.8±72.4	375	(225-500)	0.081
PSHTS	333.5±89.7	1175	(105-1425)	1187.1±186.5	1225	(700-1450)	0.384
STS	1759.2±290.7	1850	(1050-2225)	1812.1±278	1850	(1200-2250)	0.426
PedsQL parent report							
PHTS	582.8±170.6	600	(250-800)	597.0±130.4	625	(275-775)	0.638
EHTS	341.1±87.4	350	(150-500)	353.9±94.6	375	(175-500)	0.482
SHTS	485.7±476.9	450	(200-500)	426.9±77.9	450	(175-500)	0.387
SFTS	339.2±102.2	350	(100-500)	458.2±586.1	375	(225-475)	0.156
PSHTS	1075.0±245.9	1125	(100-1475)	1139.2±246.3	1200	(100-1475)	0.190
STS	1675±338.3	1675	(925-2250)	1753.9±293.5	1750	(1150-2250)	0.217

PedsQL: *Quality of Life Scale for Children,* ***PHTS:*** *Physical health total score,* ***EHTS:*** *Emotional health total score,* ***SHTS:*** *social health total score,* ***SFTS:*** *School functioning total score,* ***PSHTS:*** *psycho-social health total score,* ***STS:*** *scale total score,* ***FMF:*** *familial Mediterranean fever,* ***SD:*** *Standard Deviation*

Table III: Intercorrelations of Quality of Life Scale for Children scale scores between familial Mediterranean fever patients and their caregivers; healthy volunteers and their caregivers.

PedsQL	FMF patients and their caregivers		Healthy volunteers and their caregivers	
	r	p	r	p
PHTS	0.631	<0.001*	0.606	<0.001*
EHTS	0.635	<0.001*	0.555	<0.001*
SHTS	0.278	<0.091	0.553	<0.001*
SFTS	0.696	<0.001*	0.694	<0.001*
PSHTS	0.457	<0.001*	0.644	<0.001*
STS	0.722	<0.001*	0.638	<0.001*

PedsQL: *Quality of Life Scale for Children,* ***PHTS:*** *Physical health total score,* ***EHTS:*** *Emotional health total score,* ***SHTS:*** *Social health total score,* ***SFTS:*** *School functioning total score,* ***PSHTS:*** *Psycho-social health total score,* ***STS:*** *Scale total score,* ***FMF:*** *familial Mediterranean fever Bold values are significant, *p<0.05*

Table IV: Correlation of the Quality of Life Scale for Children scores according to demographic features.

	PHTS	EHTS	SHTS	SFTS	PSHTS	STS
	p	p	p	p	p	p
Age	0.206	0.744	0.887	0.608	0.711	0.360
Gender	0.075	0.710	0.552	0.057	0.836	0.477
Age at diagnosis	0.899	0.077	0.913	0.415	0.182	0.565
Duration of disease	0.135	0.262	0.986	0.196	0.140	0.100
Number of attacks per year	0.111	0.069	0.973	0.432	0.413	0.470
Number of hospitalization per year	0.647	1.0	0.201	0.264	0.190	0.491
Dose of colchicine	0.075	0.955	0.800	0.130	0.605	0.397
MEFV mutation	0.679	0.150	0.476	0.978	0.496	0.639
Disease severity score	0.747	0.056	0.202	0.374	0.091	0.245

PHTS: *Physical health total score,* ***EHTS:*** *Emotional health total score,* ***SHTS:*** *Social health total score,* ***SFTS:*** *School functioning total score,****PSHTS:*** *Psychosocial health total score,* ***STS:*** *Scale total score,* ***MEFV:*** *Mediterranean Fever*

Table V: Summary of the studies about health related quality of life for patients with familial Mediterrenean fever in the literature.

Authors[ref], year	Study Group	Number of Cases	Assessment Methods	Results
Buskila et al.[13]	Adult FMF patients	102 FMF patients vs. 124 healthy controls	QOL Scale	The QOL of FMF patients were impaired
Press et al.[14]	Mothers of children with FMF	Mothers of 35 FMF children vs. 23 healthy controls	QOL Scale	The QOL of FMF mothers were impaired
Makay et al.[15]	Children with FMF	51 children with FMF vs. 81 healthy controls	PedsQL™ 4.0	The PedsQL children with FMF were impaired
Deger SM et al.[23]	Adult FMF patients	90 FMF patients vs. 67 healthy controls	SF-36	The SF-36 physical components scores of FMF patients SF-36 were impaired
Sahin S. et al[12]	Adult FMF patients	100 FMF patients vs. 100 healthy controls	SF-36	The all SF-36 scores of FMF patients were impaired
Giese A et al.[24]	Adult FMF patients	40 FMF patients from Turkey vs. 40 FMF patients from Germany vs.40 healthy controls from Germany	WHOQOL-BREF	The physical health QOL scores of all FMF patients were impaired
Düzçeker Y et al.[25]	Children with FMF, SLE	26 children with FMF, 25 children with SLE	HRQL	FMF patients global QL were the best

QOL: *Quality of Life,* ***SF-36:*** *Short Form-36,* ***WHOQOL-BREF:*** *World Health Organization Quality of Life Questionnaire-Short Form,* ***HRQL:*** *Health related quality of Life.*

of PEDsQL4.0 parent report compared to all healthy children's care givers, but the difference was not statistically significant Table II.

A statistically significant correlation was present between PEDsQL4.0 child self-report PHTS, EHTS, SFTS, PSHTS, STS of FMF patients in the 8-18 years age group and those of PEDsQL4.0 parent report of their caregivers, no such correlation was found for SHTS. There was a statistically significant positive correlation for between PEDsQL4.0 child self-report subscores of healthy controls in the 8-18 years age group and subscores of PEDsQL parent report of their caregivers Table III.

The PHTS, EHTS, SHTS, SFTS, PSHTS, STS of PEDsQL4.0 child self-report of FMF patients did not have a statistically significant correlation with age, gender, duration of FMF, mean number of attacks per year mean annual number of hospitalizations due to an attack, dose of colchicine used, MEFV gene mutation, and disease severity score Table IV.

DISCUSSION

The most important result of this study is that HRQoL of FMF patients with mild and modarate disease severity scores are not affected in comparison to healthy volunteer peers between 2-18 years of age. Our study is the first, to the best of our knowledge, evaluating the QoL in FMF cases between 2-8 years of age with questionnaires filled by the parents.

Studies evaluating the QoL in the pediatric cases are quite limited in the literature. Quality of life of FMF patients was first investigated in adults by Buskila et al. (14). in 1997 and shown to be lower than the healthy control group. Following studies on the QoL of adult FMF patients, supported the findings of study of Buskila et al. (12-14). The first relevant study about children with FMF was conducted by Press et al. and the QoL was found to be lower in mothers of children with FMF than in that of healthy children (15). Makay et al. (16) first evaluated the HRQoL of children 8-18 years of age. Summary of the studies about health related QoL for patients with familial Mediterranean fever in the literature are shown in Table V.

According to study of Makay et al. (16) the physical and psycho-social health scores for the 8-12 years age group and the physical health, emotional health and school functioning scores for the 13-18 years age group were significantly lower in the FMF patients than the healthy control group while the social health scores of the FMF cases in the 13-18 years age group were the same as the control group. In our study, physical health, psycho-social health, and school functioning scores of the 8-18 years age group were lower than in the control group but the difference was not statistically significant. Although the emotional health total score was interestingly found to be higher in the same age group, this difference also was not statistically significant. Additionally, no difference was found between all score types calculated from the questionnaires completed by the caregivers of the cases diagnosed with FMF from 2-18 years age groups. In our study the reason of no significance between HRQoL scores of FMF patients and controls is due to the fact that 66% of our patients annual attack rates were as low as 0-1. As seen in the study of Makay et al. (16) there were a negative correlation between number of attacks and HRQoL scores of patients (r=-0.571, p=0.000). This result as well supports our point of view.

While a statistically significant correlation was present for the physical health, emotional health, school functioning and psychological health scores obtained from the questionnaires completed by the group of FMF patients aged 8-18 years and from the person providing care to the same age group, no such relationship was found between the social health scores; this may reflect the difference between the family's perception of and adaptation to the chronic disease of their child and the child's perception of and adaptation to his/her own disease. Additionally families of the children aged between 8-18 years may not observe social relationship of their children at school closely so it was thought that they might have concerns about this issue.

Makay et al. (16) reported an inverse relationship between the scores of their patients and the disease severity score, annual number of attacks, and hospitalization frequency with the scale total scores decreasing as the disease severity score, annual number of attacks, and hospitalization frequency increased. In contrast to study of Makay et al. (16) we found no statistically significant relationship between the scores obtained from the questionnaires of the FMF cases in the 8-18 years age group and their age, gender, diagnosis duration, annual mean number of attacks, annual mean number of hospitalizations due to an attack, the dose of colchicine used, MEFV gene mutation, and disease severity score. The reason may be the higher annual number of attacks and hospitalization frequency and higher disease severity scores of the cases in the Makay et al. (16) study than our study.

Giese et al. (24) has reported that no statistically significant relationship between the disease severity score and the QoL of the adult patients. They have been stated that the possible reasons were the used QoL scale and the inadequacy of disease severity scoring (24). Similarly, in our study, the lack of a statistically significant relationship between disease severity scores and the QoL could be associated with the fact that a modified form of the Pras severity scoring has been used for study patients however Pras severity scoring has mainly been developed for adult patients (17).

In this study, there were no relationship between disease severity scores and PedsQoL. Disease severity scores were mild in 72.5% of our patients and moderate in 27.5% of them. None of the patients had severe disease severity score, therefore, this study has revealed that in the absence of relationship may be due to the mild and moderate disease severity scores in all of our patients.

Makay et al. (16) evaluated relationship between the PedsQoL scores of FMF patients and MEFV mutaions. They found no statistically significant difference (16). Similarly, no relationship was found between the mutation analysis results and PedsQoL in our study. In the study of Yalçınkaya et al. (25) about genotype-phenotype correlation in Turkish patients with FMF, they reported that the genotype can't always predict disease severity. They emphasized that environmental factors and genetic changes that are yet unknown can also affect the phenotype of the disease (25). This findings could explain the lack of the relationship between the genetic mutation and QoL in our study.

Limitations of this study are; the small sample size of patients and control group, patients without severe disease severity scores, patients attended from a specific geographic region and same rheumatology clinic. More comprehensive, multicentral studies which have large sample size of patients and evaluate HQoL for each disease severity score levels, in different geographic and ethnical regions are required on this subject.

In conclusion, the QoL in cases diagnosed with FMF was not found to be affected by socio-demographic factors in this study. Children with FMF agree with their parents about HRQoL apart from social health. Clinicians who follow children with FMF, may consider that there are limited studies about HRQoL in this field. It should be kept in mind when the disease severity score increases, the possibility of deterioration of HRQoL may arise and clinicians should be careful in the clinical evaluation process. Importance should be given to patient education to improve the quality of life in children with FMF and their parents.

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Çocuk Acil Servisinde Anafilaksi Hastalarının Klinik ve Tedavi Özelliklerinin Değerlendirilmesi

Evaluation of Clinical and Therapeutic Characteristics of Patients with Anaphylaxis at the Pediatric Emergency Department

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ÖZ

Amaç: Anafilaksi ani başlayan, ağır ve hayatı tehdit edebilen, çoklu sistemi etkileyen bir alerjik reaksiyondur. Anafilaksinin başarılı yönetimi; anafilaksinin hızlı tanınması ve adrenalin ile tedavi edilmesini içerir. Acil servisler anafilaksi yönetiminde hayati rol oynar. Bu çalışmanın amacı çocuk acil polikliniğine anafilaksi nedeniyle başvuran hastaların demografik, klinik ve laboratuvar özelliklerini değerlendirmektir.

Gereç ve Yöntemler: Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji ve Onkoloji Eğitim Araştırma Hastanesi Çocuk Acil Polikliniği'nde beş yıllık sürede (2014-2019) 'anafilaksi' tanı kodu verilmiş hastaların klinik ve laboratuvar bilgilerine geriye dönük olarak dosya kayıtlarından ulaşıldı. Anafilaksi tetikleyicileri, adrenalin uygulamaları, adrenalin oto-enjektör reçete edilme oranı, klinik bulgular, hastaneye yatış oranı, hastanede ve acilde kalış süresi değerlendirildi.

Bulgular: Çalışmaya alınan 40 hastanın 25'i (%62.5) erkek, ortanca yaşları 7.8 yıldı. Hastaların 32'sinde muhtemel bir alerjen ile temas öyküsü vardı. En sık muhtemel alerjen (13 hasta) besin idi. Hastaların tümüne adrenalin uygulanmıştı. Başvuru anında 36 hastada cilt-mukoza, 25 hastada solunum sistemi, 21 hastada gastrointestinal sistem ve dört hastada kardiyovasküler sistem belirti ve bulguları vardı. Hastaların altısında önceden bilinen besin, beşinde ilaç, ikisinde arı venom ve birinde inhalan (polen ve küf) alerji öyküsü vardı. Önceden anafilaksi öyküsü olan yedi hastanın adrenalin oto-enjektörü vardı; beş hasta başvuru öncesinde oto-enjektör ile adrenalin uygulamıştı. Hastaların hastanede kalış süresi ortalama 25.5 ± 5.9 saat olup hiçbir hastada bifazik reaksiyon gelişmemişti. 29 hastaya taburculukta adrenalin oto-enjektörü reçete edilmişti.

Sonuç: Çocuklarda anafilaksinin en sık tetikleyicisi besinlerdir. Acil servislerde tedavinin ilk basamağında adrenalin uygulanması ve taburculukta adrenalin oto-enjektör reçete edilmesi çok önemlidir.

Anahtar Sözcükler: Acil, Anafilaksi, Çocuk

ABSTRACT

Objective: Anaphylaxis is a severe, life-threatening, and multisystemic allergic reaction. Successful management of anaphylaxis includes rapid recognition of anaphylaxis and immediate treatment with adrenalin. Emergency departments are vital in the management of anaphylaxis. The purpose of this study was to evaluate the demographic, clinical and laboratory characteristics of patients with anaphylaxis who presented to the pediatric emergency department.

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Yazarların katkısı / Contribution of the Authors*: *AKCAN YILDIZ L: 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 bütününün veya önemli bölümlerinin yazımında sorumluluk almak. ***ÇETİN M:*** Hasta takibinde sorumluluk almak, ilgili biyolojik malzemelerin toplanması, veri yönetimi ve raporlama, deneylerin yürütülmesi. ***DİBEK MISIRLIOĞLU E:*** Araştırma ve/veya makalenin hipotezini veya fikrini oluşturan, Sonuçlara ulaşmak için planlama/metodoloji belirleme, Araştırma/çalışmanın sorumluluğunu üstlenmek, ilerlemenin seyrini denetlemek, Sonuçların mantıksal olarak Yorumlanması ve sonuçlandırılması, Çalışma için gerekli literatür taramasında sorumluluk almak, Çalışmanın bütününün veya önemli bölümlerinin yazımında sorumluluk almak, Yazım ve dilbilgisi dışında bilimsel olarak gönderilmeden önce makaleyi gözden geçirme.

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Material and Methods: Clinical and laboratory data of patients who presented to the Pediatric Emergency Department of Ankara Pediatrics, Hematology and Oncology Training and Research Hospital within a five-year period (2014-2019) were retrieved retrospectively via hospital records. Triggers of anaphylaxis, administration of adrenalin, prescription rate of adrenalin autoinjectors, clinical findings, hospitalization rates and length of hospital or emergency department stay were evaluated.

Results: Among the 40 patients enrolled, 25 (62.5%) were male, and the median age was 7,8 years. 32 patients had probable exposure to an allergen. The most common (13 patients) probable allergen was foods. Adrenalin had been administered to all patients. At the time of presentation, 36 patients had cutaneous-mucosa, 25 had respiratory, 21 had gastrointestinal and four had cardiovascular involvement. History of allergy to foods, drugs, bee venom, and inhalants (pollen and mold) was present in six, five, two an one patient, respectively. Seven patients with previous history of anaphylaxis had epinephrine autoinjectors, five of whom had used their autoinjectors prior to presentation. Mean length of hospital stay was 25.5±5.9 hours, and no biphasic reactions were observed. 29 patients were prescribed an adrenaline autoinjector upon discharge.

Conclusion: Foods are the most common triggers of anaphylaxis in children. At emergency departments, it is very important to administer adrenalin as the first-line treatment and prescribe adrenalin autoinjector upon discharge.

Key Words: Emergency, Anaphylaxis, Pediatrics

GİRİŞ

Anafilaksi ani başlayan, ağır ve hayatı tehdit edebilen, çoklu sistemi etkileyen bir alerjik reaksiyondur. Çocukluk çağı anafilaksilerinin en sık tetikleyicileri besinlerdir. Dünya çapında anafilaksi sıklığının son on yılda arttığı bildirilmiştir (1). Anafilaksinin başarılı yönetimi anafilaksinin hızlı tanınmasını ve adrenalin tedavisi uygulanmasını içerir. Adrenalin tartışmasız, ilk basamak tedavi olarak uygulanacak ilaçtır (2). Adrenalin uygulanmasına gecikme anafilaksinin ölümcül seyretmesine neden olabilir.

Acil servisler anafilaksi yönetiminde hayati rol oynar. Acil serviste çalışan hekimlerin ve diğer sağlık çalışanlarının anafilaksi farkındalığının arttırılması, adrenalin tedavisinin geciktirilmeden uygulanması ve hastaların taburculuk sonrası alerji bölümüne yönlendirilmesi konularında yapılan iyileştirme girişimlerinin hasta bakım kalitesini arttırdığı gösterilmiştir (1). Bu çalışmanın birincil amacı, üçüncü basamak bir hastanenin çocuk acil polikliniğinde beş yıllık sürede 'anafilaksi' ön tanısıyla değerlendirilmiş vakaların demografik, klinik ve laboratuvar özelliklerini tanımlamaktı. İkincil amaç olarak da çocuk acilde anafilaksi hastalarına mevcut klinik yaklaşımın değerlendirilmesi ve iyileştirilebilecek noktaların belirlenmesi hedeflenmiştir.

GEREÇ ve YÖNTEMLER

Çalışma retrospektif tanımlayıcı olarak planlandı. Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji ve Onkoloji Eğitim Araştırma Hastanesi Çocuk Acil Polikliniği'ne 1 Ocak 2014 ile 31 Aralık 2019 tarihleri arasında başvurmuş olan ve "anafilaksi" ön tanısı (ICD tanı kodu T78.0 ve T78.2) verilmiş hastaların elektronik tıbbi kayıtları geriye dönük olarak değerlendirildi. Hastalara ait yaş, cinsiyet, alerjik veya kronik hastalıklar, başvuru yakınması, şüpheli tetikleyici, yakınmaların süresi, evde veya daha önce başvurduğu sağlık kuruluşunda uygulanan tedaviler, klinik belirtiler, vital bulgular, acil serviste uygulanan tedavi, klinik seyir, acilde ve hastanede kalış süresi, taburculuk sonrası tedavi ve yönlendirmeler kayıt edildi.

Anafilaksi tanı kriterleri olarak Sampson ve ark. (3) tarafından 2006 yılında tanımlanmış klinik kriterler kullanıldı. Aşağıdaki kriterlerden birini karşılayan hastaların anafilaksi kriterlerini karşıladığı belirtildi:

1) Bir alerjenin (ilaç, besin veya arı venomu gibi) alınmasından dakikalar veya saatler sonra aniden ortaya çıkan yaygın ürtiker, kaşıntı veya kızarıklık; dudaklarda dilde uvulada şişme. Ve ek olarak aşağıdakilerden en az birinin olması:

a. Solunum sistemi tutulumu (dispne, hırıltılı solunum, bronkospazm, stridor, hipoksemi)

b. Kardiyovasküler yetmezlik (hipotansiyon, kollaps)

2) Muhtemel bir alerjenle karşılaşmadan sonra aşağıdaki kriterlerden en az ikisinin görülmesi:

a. Deri ya da mukoza tutulumu (yaygın ürtiker, kaşıntı-kızarıklık, dudaklarda-dilde-uvulada şişme)

b. Solunum sistemi tutulumu (dispne, bronkospazm, stridor, hipoksi)

c. Kardiyovasküler yetmezlik (hipotansiyon, kollaps)

d. Sindirim sistemi tutulumu (kramplı karın ağrısı, kusma)

3) Bilinen bir alerjenle karşılaştıktan sonra hipotansiyon

Çocuklarda hipotansiyon tanımı (sistolik kan basıncı):

1 ay-1 yaş <70 mmHg

1 yaş – 10 yaş <70 mmHg + 2 x yaş

11 yaş – 17 yaş < 90 mmHg

Hastaların anafilaksi tanı kriterlerini karşılayıp karşılamadıklarına, hastaya ait bilgilerin bir pediatrist, bir çocuk acil uzmanı ve bir alerji uzmanı tarafından birlikte değerlendirilmesiyle karar verildi. Çalışma için Ankara Çocuk Sağlığı Hematoloji ve Onkoloji Eğitim ve Araştırma Hastanesi Klinik Etik Kurulu' ndan izin alındı (2019-076/25.03.2019).

BULGULAR

Çalışma süresinde çocuk acile başvurmuş olan anafilaksi (ICD tanı kodu T78.0 ve T78.2) ön tanılı 41 hastanın elektronik tıbbi

Tablo I: Hastaların demografik ve klinik özellikleri (n=40 hasta).

Yaş* ortanca (yıl) Ortalama+SS (min-maks)	**7.8 9.9 ± 6.2 (1-18)**
	Hasta Sayısı (%)
Cinsiyet (Erkek)	25 (62.5)
Başvuru Yılı	2014: 5 (12.5) 2015: 7 (17.5) 2016: 5 (12.5) 2017: 15 (37.5) 2018: 3 (7.5) 2019: 5 (12.5)
Muhtemel bir alerjen ile temas	32 (80.0)
Muhtemel alerjen	ilaç: 13 (32.5) besin: 13 (32.5) arı venomu: 6 (15.0)
Alerjen ile temas yolu	oral: 22 (55.0) subkutan: 6 (15.0) im: 2 (5.0) iv: 2 (5.0)
Tutulan sistem	
Cilt-mukoza	36 (90.0)
Solunum sistemi	25 (62.5)
Gastrointestinal sistem	21 (52.5)
Kardiyovasküler sistem	4 (10.0)

*****ortanca, **im:** intramuskuler, **iv:** intravenöz*

kayıtları incelendiğinde 40 hastanın anafilaksi tanı kriterlerini karşıladığı saptandı. Çalışmaya 40 hasta dahil edildi. Çalışmaya alınan 40 hastanın 25'i (%62.5) erkek, ortanca yaşları 7.8 yıldı.

Dokuz hasta (%22.5) acil yardım ambulansı, 31 hasta (%77.5) ise kendi olanakları ile acil servise başvurmuştu. Hastaların triyaj düzeyleri incelendiğinde; 14 hastanın triyaj düzeyinin kırmızı ve 26 hastanın sarı olduğu saptandı. Başvuru anında 36 hastada (%90) cilt-mukoza (ürtiker, anjioödem, uvula ödemi), 25 hastada (%62.5) solunum sistemi (öksürük, hışıltı, solunum sıkıntısı), 21 hastada (%52.5) gastrointestinal sistem (karın ağrısı, bulantı, kusma) ve dört hastada (%10.0) kardiyovasküler sistem (senkop, hipotansiyon) belirti ve bulguları olduğu görüldü. Hastaların genel özellikleri ile başvuru anındaki klinik belirti ve bulguları Tablo I'de verilmiştir.

Hastaların başvuruya ait öyküleri ve klinik izlemleri incelendiğinde; 32 hastada (%80.0) muhtemel bir alerjen ile temas öyküsü olduğu görüldü. Hastaların hepsine acil serviste adrenalin uygulandığı görüldü.

Bir hastada kronik hastalık öyküsü (global gelişme geriliği) vardı.

Hastaların önceden bilinen alerjileri incelendiğinde; altı hastada besin, dört hastada ilaç, bir hastada arı, bir hastada hem arı hem de penisilin ve bir hastada inhalan (polen ve küf) alerjisi olduğu saptandı. Yedi hastada önceden bilinen alerjik hastalık öyküsü (iki hastada astım, üç hastada atopik dermatit ve iki hastada kronik ürtiker) vardı. Hastaların yedisinde daha önce anafilaksi geçirme öyküsü olup adrenalin oto-enjektörleri bulunuyordu. Bilinen alerjisi olan hastalardaki alerjenler ve anafilaksi ile başvurusunda öyküde yer alan tetikleyiciler Tablo II'de sunulmuştur.

Tablo II: Hastalardaki bilinen alerjiler ve başvuru sırasındaki tetikleyiciler.

Hasta	Bilinen alerji öyküsü	Başvuru anındaki muhtemel alerjen
1	Mercimek	Mercimek
2	Mercimek	Mercimek
3	Süt	Salam
4	Süt	Sucuk
5	Süt	Muhallebi
6	Süt, yumurta	Tereyağı, pilav
7	Penisilin	İbuprofen
8	Penisilin + arı venomu	Arı sokması
9	Seftriakson	Seftriakson
10	Seftriakson	Seftriakson
11	Arı venomu	Arı sokması

Çalışmaya dahil edilen hastaların hepsine adrenalin tedavisi uygulanmıştı. Tüm hastalara adrenalin uygulamasından sonra steroid ve antihistaminik tedavi de verildiği görüldü. Hiçbir hastada bifazik reaksiyon gelişmediği saptandı. Eksitus olan hasta yoktu.

Dört hastaya hastanemizden önce başvurduğu başka merkezde adrenalin uygulanmıştı. Hastaların klinik özellikleri değerlendirildiğinde dört hastanın da anafilaksi kriterlerini karşıladığı görüldü. Bu hastaların ikisine hastanemize başvurduktan sonra ikinci doz adrenalin de uygulanmıştı. Bu hastalardan birinde bilinen mercimek alerjisi vardı ve hasta mercimek ile karşılaşmıştı. İkinci hastada ise bilinen alerji yoktu ve balık tüketimi sonrası anafilaksi gelişmişti.

Adrenalin oto-enjektörü bulunan yedi hastadan beşine başvurudan önce aileleri tarafından oto-enjektör ile adrenalin uygulamıştı. Bu beş hasta anafilaksi kriterlerini karşılıyordu ve hastanemize başvurusundan sonra ikinci doz adrenalin uygulanmıştı. Üç hastanın bilinen besin, iki hastanın bilinen ilaç alerjisi vardı.

Hastaların 33'ünde (%82.5) serum triptaz düzeyi çalışılmıştı. Triptaz düzeyi ortalaması 10.0±5.4 ng/ml olup bu hastaların 13'ünde triptaz düzeyi referans aralığının (11.4 ng/ml) üzerinde di. Triptaz düzeyi yüksek bulunan hastalardaki tetikleyiciler şöyle sıralanıyordu: Üç hastada arı sokması, dört hastada ilaç (iki hasta steroid dışı anti inflamatuvar ilaç (NSAİİ), bir hasta D-vitamini, bir hasta amoksisilin), beş hastada besin (bir hasta mercimek, bir hasta yer fıstığı, iki hastada süt, bir hastada sucuk), bir hastada tetikleyici net olmamakla birlikte hastanın astım tanısı ve inhalan alerjen duyarlılığı vardı.

Bütün hastaların Acil Gözlem Odası'nda izlendiği saptandı. Hastaların hastanede kalış süresi ortalama 25.6±5.9 saat

Tablo III: Alerji değerlendirmesi sonrasında hastalarda saptanan alerjiler (n=34).

Saptanan alerjiler	n (%)
Besin	18 (52.9)
Süt	7 (17.5)
Baklagiller	3 (7.5)
Yumurta	2 (5;0)
Kabuklu yemiş	2 (5.0)
Balık	1 (2.5)
Bezelye	1 (2.5)
Ceviz-fındık	1 (2.5)
Diğer besinler	1 (2.5)
İlaç	13 (32.5)
Antibiyotik	7 (17.5)
Seftriakson	3 (7.5)
Amoksisilin	2 (5.0)
Penisilin	2 (5.0)
NSAİİ	4 (10.0)
D-vit	1 (2.5)
Ranitidin	1 (2.5)
Venom	1 (2.5)
Hamamböceği-küf-polen	1 (2.5)
Bilinmiyor	1 (2.5)

NSAİİ: *steroid-dışı antiinflamatuvar ilaç*

(minimum 12.0 maksimum 36.0; ortanca=24.0 saat)'di. 29 hastaya (%72.5) acil servisten taburculukta adrenalin oto-enjektörü reçete edilmişti.

Hastaların hepsi taburculuk sonrası çocuk alerji polikliniğine yönlendirilmiş ve 39'u (%97.5) Çocuk Alerji Bölümü'ne başvurmuştu. Hastaların alerji değerlendirmeleri sonrası nihai tanıları Tablo III'de sunuldu.

TARTIŞMA

Çalışmamızda hastanemizin Çocuk Acil Polikliniği'ne başvuran anafilaksi olguları değerlendirildi. Anafilaksi tanısı olan bütün hastalarımıza adrenalin tedavisi uygulanmış olduğu, hiçbir hastada bifazik reaksiyon gelişmediği saptandı. Hastaların en sık olarak cilt-mukoza ve takiben solunum sistemi bulguları ile başvurdukları ve anafilaksi tetikleyicisi olarak en sık besinlerin ve ikinci sıklıkta ilaçların geldiği belirlendi.

Anafilaksi tanısında öykü ve fizik muayene önemli yer tutar. Yakınma, klinik bulgular, muhtemel tetikleyici ve tetikleyici ile karşılaşma yoluna odaklı bir değerlendirme anafilaksi tanısına erişebilmek için gereklidir (4). Ani başlangıçlı ve ağır belirtiler ile ortaya çıkması, klinik belirti ve bulguların birçok başka hastalık ile karışabilmesi ve sağlık çalışanlarının anafilaksi farkındalığının düşük olması gibi nedenler ile acil servislerde anaflaksi tanısı ile ilgili sorunlar olabilmektedir. Bu nedenle anafilaksinin gerçek sıklığı tam olarak bilinmemektedir (5). Ayrıca hastalar, anafilaksi tanı kodu yerine diğer alerji ilişkili kodlar ve tek semptom kodları ile kayıt edilebilmektedir (6).

Çocuklarda anafilaksinin en sık tetikleyicileri besinlerdir; ardından venom ve ilaçlar gelmektedir (7,8). Hasta grubumuzda en sık anafilaksi tetikleyicisi besinler ikinci sıklıkta ilaçlardı; 18 hastada besin (en sık olarak süt) ve 13 hastada ilaç (en sık olarak antibiyotik) alerjisi saptandı. Anafilaksiden korunmada öncelikli olan alerjenden kaçınmaktır. Hastalarımızın 11'inde alerji olunan alerjenle karşılaşma sonrasında anafilaksi gelişmişti. Bilinen alerjenlerden kaçınmada aile eğitimi, besinler içinde yer alabilecek gizli antijenler, etiket okuma, hastalara alerji olunan alerji kartları düzenlenmesi çok önemlidir.

Anafilaksinin başarılı yönetimi; hızlı tanıma, ve adrenalin ile acil tedavi gerektirir (3,9). Adrenalin ilk basamak olarak uygulanacak ilaçtır; uygulamada gecikme anafilaksinin ölümcül seyretmesi ile ilişkilidir. Hastalarımızın tümüne acil serviste adrenalin tedavisi uygulanmıştı. Bu sonuç, adrenalin kullanım oranlarının düşük saptandığı önceki çocuk acil çalışmalarına göre yüksekti (8, 10). Acil serviste görev yapan bütün sağlık çalışanlarına anafilaksi tanı kriterleri hakkında eğitim verilmesi, adrenalinin ilk basamak ve en önemli tedavi olduğunun vurgulanması, hastalar acil servisten taburcu olurken adrenalin oto-enjektör reçetesi yazma ve taburculuk sonrası hastaların alerji bölümüne yönlendirilme uygulamaları önemlidir (11).

Anafilaksi tanısı klinik kriterler kullanılarak konur. Serum triptaz düzeyi gibi biyokimyasal aracıların ölçülmesi tanıda destekleyici olarak kullanılabilir. Triptaz düzeyi her zaman yüksek olmayabilir (12). Hipotansiyonun eşlik ettiği anafilaksilerde triptaz düzeyleri yüksek saptanabilmektedir (4). Besin ilişkili anafilaksilerde triptaz düzeyi ile anafilaksi şiddeti korelasyonunun daha zayıf olduğu belirtilmiştir (4). Platelet aktive edici faktör (PAF) ve diğer biyolojik aracıların ağır anafilaktik reaksiyonlar ile ilişkili olduğu ve hastalarda risk sınıflaması için kullanılabileceği belirtilmiştir. Ancak henüz bu bilgiler deneysel düzeydedir ve klinik uygulama yönergelerine geçmemiştir (9). Hastalarımızın %82.5'inin (33 hasta) triptaz düzeyinin ölçüldüğü, ortalama triptaz düzeyinin 10.0±5.4 ng/ml olduğu ve ölçülenlerin %39.3'ünün (13 hasta) triptaz düzeyinin yüksek olduğu saptandı.

Acil servisler anafilaksi yönetiminde hayati bir rol oynar. Kas içi adrenalin uygulanmasında gecikme ağır ve bifazik reaksiyon ile ilişkilidir (9). Anafilaksi hastalarında hastanın acil servise ulaştıktan sonra ilk adrenalin dozunun uygulanmasına kadar geçen sürenin kısaltılması amacıyla hastanın geçtiği bütün aşamalar gözden geçirilerek hangi aşamada gecikme olduğu tespit edilebilir. Hastanın triyaj ve muayene odasında değerlendirilmesi, ilaç isteminin verilmesi ve ilacın hazırlanması aşamalarının mümkün olduğunca hızlı yapılabilmesi hedeflenmelidir. Yakın zamanda yapılan bir çalışmada, çocuk acilde anafilaksi yönetimi için oluşturulmuş bir klinik rehberin uygulamaya geçirilmesi ile adrenalin uygulanmasına kadar geçen median süre 15 dakikadan 10 dakikaya kısaltılmıştır (1).

Bifazik anafilaksi riski nedeniyle anafilaksi hastalarının acil serviste ne kadar izleneceği konusunda klinik uygulama farklılıkları vardır.

Solunum yakınması olan hastaların 6-8 saat, dolaşım bozukluğu olan hastaların ise 12-24 saat izlenmesi önerilmektedir (13). Hastalarımızın ortalama izlem süresi 24 saatti. Anafilaksi sonrası izlem süresi kararı hastaya göre bireyselleştirilerek verilmelidir. Reaksiyonun ağırlığı, bifazik reaksiyon için risk faktörleri (kas içi adrenalin uygulanmasında gecikme, hışıltı gibi solunum sistemi bulguları, astım öyküsü ve hipotansiyon gibi) ve hastaneye ulaşma imkanları göz önünde bulundurulmalıdır. Üst hava yolu obstrüksiyonu, dirençli hışıltı veya solunum sıkıntısı ve şok bulguları olan hastalar hastaneye yatırılmalıdır (9). Önceden bilinen astım ve anafilaksi geçirme öyküsü bifazik reaksiyon için risk faktörü olarak kabul edilmekte, en önemli risk faktörünün adrenalinin geç uygulanması olduğu belirtilmektedir (9). Kortikosteroidlerin bifazik anafilaksi riskini azalttığına dair iyi kalitede yeterli kanıt bulunamamıştır (14). Çalışmamızda iki hastada astım, yedi hastada önceden anafilaksi geçirme öyküsü vardı. Bifazik reaksiyon gelişen hastamız yoktu.

Taburculuk öncesinde hastalar anafilaksinin tekrarlama riski açısından değerlendirilmelidir. Hastalara almaları gereken önlemler anlatılmalıdır. Hastalar acilden taburcu edilirken adrenalin oto-enjektörü reçete edilmeli ve hangi durumlarda nasıl kullanacakları hakkında bilgilendirilmelidir. Egzersiz ile tetiklenen anafilaksi, sakınılması olanaksız etkene bağlı anafilaksi (besin, venom), idiyopatik anafilaksi ve altta yatan mast hücre bozukluğu olan hastalar adrenalin oto-enjektörü reçete edilmesi için kesin endikasyonlar olarak belirlenmiştir (1, 4). Bizim çalışmamızda hastalarımızın %72.5'ine adrenalin oto-enjektörü reçete edilmişti

Anafilaksi geçiren çocuklarda anafilaksi tetikleyicilerini belirlemek için alerji bölümlerine yönlendirilmesi gerekmektedir (1,4,10). Hastalarımızdan 18'inde besin, 13'ünde ilaç, bir hastada arı venomu, bir hastada hamamböceği-küf-polen alerjisi saptandı. Bir hastada alerji etkeni saptanamadı ve idiyopatik anafilaksi olarak değerlendirildi. Çalışmalarda taburculuk sonrası alerji bölümüne yönlendirilme oranlarının oldukça değişken olduğu görülmüştür. Bu değişkenliğin nedenleri arasında bölgeler arasında sağlık hizmetlerine ulaşma olanaklarında farklılıklar veya acilden taburculuk sonrası hastaların izlemden çıkması gibi nedenler gösterilmiştir (10,15).

Bu çalışmanın en önemli kısıtlayıcı özelliği hastaların geriye dönük olarak tanı kodu ile tespit edilmiş ve değerlendirilmiş olmasıdır. Hastanemizdeki anafilaksi vaka sayısının saptadığımızdan daha yüksek olduğunu düşünüyoruz. Çalışmamız ürtiker ve döküntü tanı kodlarını içermediğinden vaka sayısı daha az saptanmış olabilir. Ancak hastalarımızın acil servisten taburcu edildikten sonraki izlem verilerine de ulaşılabilmiş olması çalışmamızı güçlendirmektedir.

Sonuç olarak, tek bir çocuk acil servisteki anafilaksi olgularını değerlendirdiğimiz bu çalışmada en sık anafilaksi tetikleyicilerinin besinler, ikinci sıklıkta ilaçlar olduğunu saptadık. Çalışmamızda anafilaksi tedavisi için adrenalin kullanım oranı ve taburculuk sonrası alerji bölümüne yönlendirilme oranı yüksekti. Acil servisten taburculukta adrenalin oto-enjektör reçete edilme oranı (%70) güncel rehberlere göre oto-enjektör reçete edilme kriterlerinin klinik uygulamamıza geçirilmesi yoluyla arttırılabilir.

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Does Perfusion Index in Term Neonate with Late-Onset Pneumonia Predict Disease Severity and Prognosis?

Geç Başlangıçlı Pnömonili Yenidoğanlarda Perfüzyon İndeksi Hastalığın Şiddeti ve Prognozu Öngörebilir mi?

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ABSTRACT

Objective: Pneumonia is an important disease that causes sepsis in newborns and constitutes the majority of deaths due to infections, especially in developing countries. Pulse oximeters that are widely used in clinics, can determine heart rate, arterial oxygen saturation, additionally perfusion index (PI). In this study, the role of PI in determining the severity and prognosis of the disease in newborns with late-onset pneumonia (LOP); the relationship between PI and respiratory support need and Silverman Anderson Retraction Score (SAS) were aimed to determine.

Material and Methods: In this prospective study, 30 term newborns diagnosed with late-onset pneumonia (LOP) were at the time of hospitalization,at the 24th hours of their treatment, and discharge; in the control group, PI measurements were made from the right upper extremity every 10 seconds for 3 minutes at the discharge of 30 term healthy newborns between December 2017 and June 2018. By comparing the data, it was aimed to determine the relationship of PI with the severity of the disease, prognosis, need for respiratory support and Silverman Anderson Retraction Score (SAS).

Results: Their mean birth weights was 2000 - 4600 g the mean was 3570 g in the study, 2800 - 4100 g the mean was 3610 g in the control group and there was no significant difference (p>0.05); Gestational ages were $36^{5/7}$ – $41^{3/7}$, mean $39^{2/7}$ in the study group, $37^{3/7}$ – $40^{5/7}$ in the control group, mean $39^{6/7}$ weeks, and the statistical difference between the groups was not significant (p>0.05). The ratio of female/male was similar in the groups. Their median age was 9.5 days (3-27) in the control, 21 days (5-28) in the study group, and higher in the study group (p<0.05). The median capillary refill time was 1.7 seconds in the control, 1.6 seconds in the study group, and similar between the groups. The mean PI was 2.3±0.9 in the control group. In the study group, it was 3.6±1.2 on hospitalization, 3.2±1.2 on the first day, 3.4±0.7 at discharge. In the study group, PI values on hospitalization and first day were higher (p<0.05).

There were reticular infiltration 50% bilateral, 30% right paracardiac, 10% left paracardiac, 3.3% right lower lobe. Alpha hemolytic streptococci in 1 (3.3%), *Acinetobacter iwoffii* in 1 (3.3%), Respiratory syncytial virus 6 (20%), Coronavirus 4 (13.3%), Rhinovirus 2 (6.7%) and Influenza A 1 (3.3%) patient were determined. We applied free flow oxygen 17 (56.7%), oxygen by hood 5 (16.7%), heated humidified high-flow nasal cannula 1 (3.3%), nasal continuous airway pressure 4 (13.3%), nasal intermittent positive pressure ventilation 4 (13.3%) cases. PI was higher in the patients needing positive pressure on admission (p<0.05). A positive correlation was found between SAS and PI on admission in the study group (p=0.008). The number of patients whose PI decreased during hospitalization increased over time.

Conclusion: In the neonates with LOP, the severity of the disease, the need for respiratory support and prognosis cannot be predicted by PI. There was no relation between SAS and PI.

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It was concluded that more accurate results can be achieved by measuring PI using more patients, more sensitive probes and technically more advanced monitors. New studies should be conducted to determine the role of PI in demonstrating well-being and early detection of life-threatening conditions in the healthy newborns.

Key Words: Late-onset pneumonia, Newborn, Perfusion index

ÖZ

Amaç: Pnömoni yenidoğanlarda sepsise neden olan önemli bir hastalık olup özellikle gelişmekte olan ülkelerde enfeksiyonlara bağlı ölümlerin çoğunluğunu oluşturmaktadır. Kliniklerde yaygın kullanılan nabız oksimetreler kalp atım hızı, arteriyal oksijen doygunluğu yanında perfüzyon indeksini (PI) de belirleyebilmektedir. Bu çalışmada geç başlangıçlı pnömoni (GBP) gelişen yenidoğanlarda PI'nin hastalığın şiddeti ve prognozunu belirlemedeki rolü;PI ile solunum destek ihtiyacı ve Silverman Anderson Retraksiyon Skorlaması(SAS) arasındaki ilişkinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu prospektif çalışmada Aralık 2017 - Haziran 2018 arasında geç başlangıçlı pnömoni (GBP) tanılı 30 term yenidoğanın yatışında, tedavininin 24.saati ve taburculuğunda; kontrol grubunda ise 30 term sağlıklı yenidoğanın taburculuğunda 3 dakika boyunca 10 saniyede bir sağ üst ekstremiteden PI ölçümleri yapılmıştır.Veriler karşılaştırılarak PI'nin hastalığın şiddeti, prognozu, solunum destek ihtiyacı ve Silverman Anderson Retraksiyon Skorlaması (SAS) ile ilişkisinin belirlenmesi amaçlanmıştır.

Bulgular: Olguların doğum ağırlığı ortalama çalışma grubunda 3570 g (2000-4600), kontrol grubunda 3610 g (2800–4100)olup aralarında fark yoktu (p>0.05). Gebelik yaşları ortalama çalışma grubunda $39^{2/7}$ ($36^{5/7}$–$41^{3/7}$), kontrol grubunda $39^{6/7}$ ($37^{3/7}$-405/7) hafta olup aralarındaki fark anlamlı değildi (p>0.05). Gruplarda kız/erkek oranı benzerdi. Yaş ortancası kontrol grubunda 9.5 (3-27), hasta grubunda 21 gün (5-28) olup hasta grubunda daha yüksekti (p<0.05). Ortanca kapiller dolum zamanı kontrol grubunda 1,7; hasta grubunda 1.6 saniye olup aralarında fark yoktu (p>0.05). Ortalama PI kontrol grubunda 2.3±0.9; çalışma grubunda yatışta 3.6±1.2, birinci gün 3.2±1.2, taburculukta 3.4±0.7'di. Çalışma grubunun yatış ve birinci gün PI değerleri, kontrol grubundan yüksekti (p<0.05).

Hastalarda %50 bilateral, %30 sağ parakardiyak, %10 sol parakardiyak, %3.3 sağ alt lobda retiküler infiltrasyon vardı. Kan kültürlerinde alfa-hemolitik streptokok 1 (%3.3), *Acinetobacter iwoffii* 1 (%3.3); solunum yolu sekresyonlarında Solunum Sinsityel Virus 6 (%20), Coronavirüs 4 (%13.3), Rhinovirüs 2 (%6.7) ve İnfluenza A 1 (%3.3) olguda gösterildi.

Serbest akış oksijen 17 (%56.7), hoodla oksijen 5 (%16.7), ısıtılmış nemlendirilmiş yüksek akışlı nasal kanül 1 (%3.3), nasal sürekli hava yolu basıncı 4 (%13.3), nasal aralıklı pozitif basınçlı ventilasyon 4 (%13.3) olguya uygulandı. Yatışta basınç ihtiyacı olanlarda PI daha yüksekti (p<0.05). Çalışma grubunda yatıştaki SAS ile PI arasında pozitif korelasyon saptandı (p=0.008). Yatış süresince PI düşen hasta sayısının arttığı saptandı.

Sonuç: Yenidoğanlarda GBP'lerde hastalığın şiddeti, solunum destek ihtiyacı ve prognozun PI ile öngörülemediği; SAS ile PI arasında ilişki olmadığı gösterildi. Güvenilir veriler için daha çok olgu, hassas prob ve monitörlerle çalışma yapılması gerektiği sonucuna varıldı. Ayrıca, sağlıklı yenidoğanlarda PI'nin iyilik halini gösterme ve hayati tehlikeyi erken saptamadaki rolünün belirlenebilmesi için yeni çalışmalar yapılmalıdır.

Anahtar Sözcükler: Geç başlangıçlı pnömoni, Yenidoğan, Perfüzyon indeksi

INTRODUCTION

Pneumonia is an important disease that causes sepsis in newborns and accounts for more than 96% of deaths due to neonatal infections in developing countries (1,2). According to the data of the Turkish Statistical Institute, pneumonia constitutes 11% of the reasons for admission to the hospital in children aged 0-6(3). Neonatal pneumonia is classified as early (first 72 hours) or late-onset (GBP, after 3 days).

Non-invasive techniques are widely used for diagnosis and treatment of diseases. These techniques accelerate the determination of invasive intervention requirements in patients and the decision of intervention. Pulse oximeters (PO) are devices that are widely used in the healthcare field and can determine the perfusion index (PI) in addition to heart rate (HR) and arterial oxygen saturation (SpO2). Pulse oximeters basically work on the principle of measuring the amount of absorption of infrared and infrared rays sent from the device to the tissues. PI, a non-invasive indicator, is calculated by the ratio of the non-pulsatile signal (static blood flow, skin and other tissues) to the pulsatile signal (arterial blood flow) and indicates peripheral perfusion (4). Since the non-pulsatile blood flow is constant in the tissues and in the venous bed, changing the amount of pulsatile blood flow in the peripheral tissues changes the PI. That is, PI is more related to the amount of arterial blood flow, not SpO2 in the blood (5). Normal values were found to be 0.02 - 20. Low PI values p<1.24) in newborns have been reported as a good indicator for determining the severity of the disease (5,6).

In this study, it was aimed to determine the severity of the disease and the need for respiratory support by using PI in term newborns diagnosed with GBP. In addition, it was aimed to evaluate the validity in determining the prognosis by comparing the PI with the Silverman Anderson Retraction Score (SAS).

MATERIALS and METHODS

This study was carried out by T.C. The study was conducted prospectively with 30 patients and 30 control groups after obtaining the approval of the local ethics committee of Health Sciences University Ankara Pediatrics Hematology Oncology

Training and Research Hospital dated 19/03/2018 and numbered 2017/131. Term newborns diagnosed with LOP and hospitalized in the neonatal intensive care unit (NICU) in our hospital between December/2017 and June/2018 were determined as the study group; The same number of term, healthy, non-respiratory problems newborns followed up with the mother were included as the control group. Age (days), gender, physical examination findings, capillary refill time, complete blood count parameters, C-reactive protein (CRP), blood gas parameters, SpO2, SAS at the time of hospitalization of the patients were recorded. In addition, the oxygen needs, respiratory support needs and total hospitalization times of these patients were determined. Non-invasive PI measurement is the ratio of pulsatile arterial flow in the peripheral area of infrared signals to non-pulsatile tissue components (venous blood, connective tissue, skin, bone, etc.) and provides important information in terms of hemodynamics, as it reflects instantaneous changes (7). In the study group, PI values were determined 3 times at admission, on the first day and at discharge.Values at discharge were recorded for the PI value of the control group. Nellcor Pulse Oximeter probe and Biolight Q5 (Made in Germany) patient monitor were used for peripheral PI measurement. To determine the PI value of the patients, a measurement was taken from the right hand every 10 seconds for 3 minutes. The value found by taking the average of the 18 measurements obtained was recorded as the PI value.The relationship between age, gender, complete blood count parameters, CRP, blood gas parameters, SpO2, SAS of the patients and during of hospitalization, oxygen demand, respiratory support needs and total hospitalization times and PI were evaluated.

Data analysis in our study was done with SPSS Computer Package Program version 22. Kolmogorov-Smirnov test in the evaluation of the distribution width of the data, mean and standard deviation in the representation of the data conforming to the parametric distribution; median, minimum and maximum values were used for those who did not comply. Categorical variables were shown as number of cases and percentile. Student t and Anova tests in the analysis of parametric data with categorical variables; Mann Whitney U Test from analysis of non-parametric data; Pearson Chi-square test in the analysis of categorical variables with each other; Pearson correlation test was used to compare quantitative data with each other. The variation of the data over time was analyzed by Paired samples test and Wilcoxon test. Significance level was accepted as $p<0.05$.

RESULTS

In our study, the mean birth weight was 3570 g (2000–4600) in the study group and 3611 g (2800–4100) in the control group, and there was no difference between them ($p>0.050$). The mean gestational age was $39^{2/7}$ weeks ($36^{5/7}$–$41^{3/7}$) in the study group, and $39^{6/7}$ weeks ($37^{3/7}$–$40^{5/7}$) in the control group, and there was no difference between the groups ($p>0.050$).

Table I: Pathological history and physical examination findings of the patients.

Pathological feature	n (%)
History	
Respiratory infection in family	8 (26.7)
Cough / Wheesing	25 (83.3)
Runny nose/ nasal congestion	6 (20)
Fever	2 (6.7)
Reduction in suction	2 (6.7)
Groaning	1 (3.3)
Hoarseness	1 (3.3)
Respiratory system examination findings	
Tachypnea	28 (93.3)
Ral / ronchus	25 (83.3)
Forced expiration	1 (3.3)
Use of accessory respiratory muscles,withdrawal	6 (20)
SpO2* (%)	82-94
Respiratory rate* (/per minute)	48-74

Minimum-maximum **Sp02: Arterial Oxygen Saturation*

Table II: Perfusion indices with Silverman Anderson Scores.

Parameter	PI at the time of hospitalization		PI on the first day		PI at discharge
	r	p	r	p	r
SAS	0.475*	0.008	0.243	0.196	0.144

The female/male ratio of the cases was 0.5 (10/20) in the control group and 0.7 (12/18) in the patient group, and there was no difference between the groups in terms of gender ($p>0.050$).

The median length of stay of the patient group was 9 days. The median age of the cases was 9.5 days (3-27) in the control group and 21 days (5-28) in the study group, which was higher in the study group ($p<0.050$). The pathological history and physical examination findings of the subjects in the study group are shown in Table I.

The median capillary refill time was 1.7 seconds in the control group and 1.6 seconds in the patient group, and there was no difference between the groups ($p>0.050$). The mean PI in the control group was 2.3±0.9; In the patient group, it was 3.6±1.2 during hospitalization, 3.2±1.2 on the first day, and 3.4±0.7 at discharge. Hospitalization and first day PI values of the study group were higher than the control group ($p<0.050$). PI changes of the cases during their hospitalization were not significant ($p>0.050$). However, it was found that the number of patients with PI increased over time.

The mean SAS values of the subjects in the study group at the time of hospitalization were 0.6 (0-2) A positive correlation was found between SAS and PI during hospitalization in this group ($p=0.008$) (Table II).

Complete blood count and CRP results of the study and control groups are given in Table III.

Table III. Complete blood count and CRP results of the study and control groups.

Laboratory findings	Patient group	Control group	p
Hemoglobin	14.0±2.8	16.0±2.9	0.008
Hematocrit	41.0±8.3	48.4±8.6	0.002
White blood cell count	9400 (5300-28500)	11050 (3700-26400)	0.185
Neutrophil count	3380 (700-8500)	3300 (1500-18400)	0.717
Lymphocyte sayısı	4400 (2200-11200)	3800 (2400-8700)	0.131
CRP	0.43 (0.05-15.5)	0.15 (0.02-1.12)	<0.001
I/T index	0.31 (0.12-0.9)	0.14 (0.04-0.60)	<0.001

I/T: *İmmmature/total neutrophil ratio,* ***CRP:*** *C-reactive protein.*

Table IV: Comparison of pressure and oxygen need with perfusion index.

Perfusion index	Pressure and oxygen need		p
	Yok (n: 22)	Var (n: 8)	
At the time of hospitalization	3.35±1.14	4.34±1.25	0.049
On the first day	3.10±1.20	3.29±1.36	0.729
At discharge	2.62±0.67	2.98±1.26	0.313

Data are expressed as mean±standard deviation, analysis by Student's t-test.

Hemoglobin and hematocrit levels of the study group were lower than the control group, and CRP and I/T ratios were higher (p<0.050); white blood cell, neutrophil and lymphocyte counts were similar (p>0.050).

Median pO2 level was 46 mmHg, mean pCO2 level was 39.6±6 mmHg, lactate level was 2.1 mmol/L, SpO2 was 78.3±11.5% in the study group. The median pO2 level was 58 mmHg, lactate level was 1.65 mmol/L, mean pCO2 level was 30.6±5.1 mmHg, SpO2 was 86.4±11% in the control group. The pO2 and SpO2 levels of the study group were low, pCO2 levels were high (p<0.050), and the lactate levels of both groups were similar (p>0.050).

In the chest radiographs of the patients in the study group, 50% bilateral reticular, 30% right paracardiac, 10% left paracardiac, and 3.3% right lower lobe reticular infiltration were detected; 6.7% were evaluated as normal. In blood cultures, alpha hemolytic streptococcus was isolated in 1 (3.3%) and *Acinetobacter iwoffii* in 1 (3.3%) patient. Respiratory Syncytial Virus (RSV) 6 (20%), Coronavirus 4 (13.3%), Rhinovirus 2 (6.7%) and Influenza A 1 (3.3%) cases by polymerase chain reaction (PCR) in respiratory tract secretions shown.

In the study group, free flow oxygen 17 (56.7%), in-hood oxygen 5 (16.7%), heated humidified high-flow nasal cannula (HHHFNC) 1 (3.3%), nasal continuous airway pressure (nCPAP) 4 (13.3%), nasal gap positive pressure ventilation (nIPPV) was applied to 4 (13.3%) cases.The maximum duration of oxygen administration to the patients in the study group was 11 days. In-hood oxygen was applied for 5 days, nIPPV for 6 days, and mechanical ventilation for a maximum of 0.25 days. Antibiotherapy was given to 18 (60%), antiviral treatment (oseltamivir) was given to 2 (6.7%) cases, and the mean duration of these treatments was 5-10 days. Eight (26.7%) of the subjects in the study group required positive pressure and oxygen support. The PI was higher in the patients who were given pressure and oxygen support (p<0.050).A positive correlation was found between the duration of support and the PI on the first day of treatment in patients who were given oxygen support with Hood (p<0.050) (Table IV).

There was no significant relationship between PI at hospitalization, first day and discharge of the study group and age, Hb, Hct, white blood cell,neutrophil,lymphocyte counts, CRP, pO2, pCO2, lactate levels, capillary refill time, hospitalization stay, free flow oxygen,nCPAP,nIPPV support times (p>0.050). There was a positive correlation between PI and pCO2 levels in the study group on hospitalization and on the first day (p<0.050).Again, a positive correlation was found between SAS and PI at the time of hospitalization (p<0.050). There was a positive correlation between the duration of support and PI on the first day in the patients applied in-hood oxygen(p<0.050).A positive correlation was found between SAS and PI at the hospitalizations of the subjects in the study group (p<0.050).

DISCUSSION

The studies related to PI in newborns are increasing in the literature. Granelli et al. reported that PI values did not change with age in their study on infants aged between 1 hour and 5 days (5). In this study, no significant relationship was found between PI and age and gender, in line with the literature.Unal et al. (8) reported that PI was similar to the control group in newborns with transient tachypnea and delayed labor. Lima et al. (4) stated that PI may be low in critically ill patients and highly variable in the normal population. In this study, PI

of term newborns with LOP was found to be higher on the first day of hospitalization and treatment. It was thought that this might be related to the follow-up of the cases in the emergency department or given supplemental oxygen before hospitalization. Thus, oxygen support might have increased oxygen transport to the tissues.

In this study, hemoglobin and hematocrit levels were low in newborns with LOP; CRP and I/T ratios were found to be higher, which was thought to be due to infection. Besides, no correlation was found between hemoglobin, hematocrit,CRP values, white blood cell-neutrophil and lymphocyte counts and PI in newborns diagnosed with LOP. A negative correlation was found between PI and I/T ratio at the time of hospitalization of the patients. Since perfusion is a measure of the blood flow to the region rather than the formed elements in the blood, it can be thought that there is no relationship between the parameters in the complete blood count and PI. Nutrition, intravenous therapy, jaundice, sleep-wake state, sleeping position, agitation, tremor, hypothermia, hypotension, arrhythmia, high carboxyhemoglobin and methemoglobin levels, nail paint (nail polish, henna, methylene blue, etc.), excessive light exposure (sun, heater and phototherapy lights), low perfusion, and improper placement of the probe have been reported to cause false peripheral PI readings (9-11). It is also reported that PI gives information about peripheral vasomotor tone. PI is different between the extremities and the highest value is obtained in the right upper extremity.Wide differences between extremity readings are thought to be most likely related to transitional circulation changes (12).

The arterial blood oxygen level in the primarily monitored area is affected by the amount of arterial blood flow rather than SpO2 (5). Since the non-pulsatile blood flow is the same in tissues, an increase or decrease in pulsatile arterial blood flow causes changes in peripheral perfusion. Serial measurements of serum lactate can be used to detect hypoperfusion and evaluate response to therapy, and above ≥4 mmol/L is considered critical for tissue oxygenation. Ramsey et al. (13) they reported that lactate level was significantly higher and PI was low in cases with severe sepsis. Kroesse et al. (14) did not find a relationship between lactate and PI in their study in newborns. In this study, lactate levels of the cases were not different in the control and study groups. This may be related to early admission of the cases, no patients with severe infection that impaired tissue oxygenation, or implementation of oxygen and circulatory supportive therapies during transport, in the emergency service and other centers before infant's hospitalization.

In this study, newborns with LOP had lower pH, pO2 and SpO2; but pCO2 level was found to be higher. However, there was no significant relationship between PI and pO2, pCO2, lactate levels. Pneumonia in newborns, increasing pCO2 by disrupting gas exchange and ventilation-perfusion in alveoli; it causes a decrease in pH, pO2 and SpO2. By developing tachypnea, the patient tries to compensate this situation by using accessory respiratory muscles and to keep the pH normal.If oxygenation is provided with these mechanisms and treatment, peripheral circulation may improve and PI may return to normal. In addition, it can be thought that supplemental oxygen applied to the patient may increase SpO2, PI and saturation.

Granelli et al.(5) evaluated PI with a single measurement and suggested that serial measurements may be more valuable for monitoring changes in peripheral perfusion. Cresi et al. (15) reported that while there was a significant difference between the first and the 3rd days in the median PI values, they did not detect a significant difference between the 3rd and 7th days. De Felice et al. (16) did not report any difference between the PI values measured immediately and in the first minutes and the first-fifth minutes after birth (16). This suggested that the waveforms in the preductal arteries remained stable despite the hemodynamic changes that occurred during transit the infants' PI remained stable. Unal et all reported that PI valueS decreased significantly during crying and increased activity in infants with transient tachypnea of the newborn (8). In our study, PI did not change significantly in term newborns with LOP, but the number of patients with decreased PI increased over time.While trying to reduce supportive treatments (oxygen, iv fluid, etc.) over time, PI may have decreased. The fact that the infants were sluggish at the time of admission due to respiratory distress, their activities increased after clinical improvement and their crying more may also have caused a decrease in PI.

Lima et al. (17) thought that PI could be used in the evaluation of hypoperfusion in critically ill patients, and reported that a PI value less than 1.4 showed a strong correlation with capillary filling time. However, these results are for adult patients and the authors found no association between changes in cardiac output and peripheral PI or poor peripheral perfusion. These findings were associated with possible heterogeneity in the regulation of skin blood flow during changes in blood flow, and were thought to be related to sympathetic nerve activity (18). In this study, there was no difference between the groups in terms of capillary refill time.In addition, no correlation was found between PI and capillary filling in the study group. The results were not considered reliable because of the low number of patients with severe pneumonia, in shock and in need of intubation.

Although the need for oxygen support was high (56.7%) in newborns who developed LOP in our study, no relationship was found between oxygen requirement, hospital stay and PI. Again, it was shown that administration of HHHFNC, nCPAP and nIPPV had no effect on PI. This may be related to no cases with severe pneumonia and the small number of patients undergoing invasive mechanical ventilation. A positive correlation was found between the PI and SAS scores of the patients during their hospitalization. It was thought that this might be related to the administration of additional oxygen and other supportive treatments to the patients in the emergency room, other centers or during transport.

The fist limitation of the study is the small number of cases. Another limitation is the low sensitivity of the monitors used in the study. It is thought that more reliable data can be obtained by using FDA approved monitors with a lower margin of error and filtering feature against artifacts.

In conclusion, although PI is known as a quotable, inexpensive, effective and non-invasive method that can be used to demonstrate the hemodynamic status and well-being of the newborn.Nevertheless, PI has not been found to be reliable in determining the severity and prognosis of the disease in term newborns with LOP. In order to use PI in the diagnosis and treatment of pneumonia in newborns, it was thought that studies involving patients with more and severe infections should be conducted.

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Behavioral, Emotional Problems and Fatigue in Adolescents After COVID-19 Infection: A Cross-Sectional Study

COVİD-19 Enfeksiyonu Sonrası Ergenlerde Davranışsal, Emosyonel Problemler ve Yorgunluk: Kesitsel Bir Çalışma

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ABSTRACT

Objective: This study aimed to investigate behavioral, emotional problems and fatigue in adolescents after COVID-19 infection. Also, we examined relationships between baseline inflammation levels, fatigue, and the current behavioral and emotional problems of adolescents.

Material and Methods: A total of 110 adolescents (56 boys, 50.9%, mean age 14.72 years) and their parents were included in the study. Psychiatric assessments of the adolescents were performed 7.31±2.35 months after discharge from hospital. Behavioral and emotional problems was assessed using the Child Behavior Checklist (CBCL) 6-18 parent-rated questionnaire.

Results: We collected baseline inflammatory markers including C-reactive protein (CRP), the neutrophil/lymphocyte ratio (NLR), the monocyte/lymphocyte ratio (MLR), and the systemic immune-inflammation index (SII). The proportions of adolescents that were in the clinical range in at least one behavioral and emotional domain were as follows: 44.5% in the entire sample, 35.7% in boys, and 53.7% in girls. Thought problems were the most common problems in the entire sample (25.5%). The rates of internalizing and externalizing symptoms were 33.6% and 16.4%, respectively. Somatic and attention symptoms were more frequent in females than in males. Inflammatory marker levels did not correlate with behavioral and emotional scores. Fatigue symptoms were determined in 36.4% of all adolescents. We found that somatic and attention problems are more common in fatigued adolescents.

Conclusion: Our findings demonstrated that screening for behavioral, emotional problems, and fatigue in adolescents with COVID-19 infection is necessary. Future studies with a follow-up design are needed to determine whether a relationship exists between behavioral, emotional problems and baseline inflammation levels after COVID-19 infection.

Key Words: Adolescent, COVID-19, Fatigue, Inflammation, Mental health

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Contribution of the Authors / Yazarların katkısı*: *AKCAY E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in 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. ***COP E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***SENSEN DINC G:*** 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 the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***GOKER Z:*** 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. ***OZKAYA PARLAKAY A:*** 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. ***MUTLU M:*** 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. ***DAMLA DEMIREL B:*** 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. ***KIRMIZI B:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results.

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ÖZ

Amaç: Bu çalışma, COVİD-19 enfeksiyonu sonrası ergenlerde davranışsal, emosyonel problemler ve yorgunluk belirtilerini araştırmayı amaçlamıştır. Ayrıca, ergenlerin başlangıç inflamasyon düzeyleri ile mevcut davranış, emosyonel problemler ve yorgunluk belirtileri arasındaki ilişkiler incelenmiştir.

Gereç ve Yöntemler: Çalışmaya toplam 110 ergen (56 erkek, %50.9, yaş ortalaması 14.72 yıl) ve ebeveynleri dahil edildi. Ergenlerin psikiyatrik değerlendirmeleri hastaneden taburcu olduktan 7.31±2.35 ay sonra yapılmıştır. Ergenlerdeki davranış, emosyonel problemler, Çocuk Davranışı Kontrol Listesi (CBCL) 6-18 ebeveyn formu kullanılarak değerlendirilmiştir.

Bulgular: COVİD-19 tanı anındaki C-reaktif protein (CRP), nötrofil/lenfosit oranı (NLR), monosit/lenfosit oranı (MLR) ve sistemik immün-enflamasyon indeksi (SII) dahil olmak üzere temel inflamatuar belirteçleri geriye dönük olarak saptanmıştır. En az bir davranışsal ve emosyonel problem alanında klinik aralıkta olan ergenlerin oranı tüm örneklemde %44.5, erkeklerde %35.7 ve kızlarda %53.7 olarak bulunmuştur. Düşünce sorunları tüm örneklemde (%25.5) en sık görülen sorunlar olarak bulunurken; içe yönelim ve dışa yönelim belirtilerinin oranları sırasıyla %33.6 ve %16.4 olarak saptanmıştır. Somatik ve dikkat belirtileri kadınlarda erkeklere göre daha sık olduğu bulunmuştur. İnflamatuar belirteç düzeyleri ile davranışsal ve emosyonel problem skorları arasında korelasyon saptanmamıştır. Tüm ergenlerin %36.4'ünde yorgunluk belirtileri saptanmıştır. Yorgunluk olan ergenlerde somatik ve dikkat problemlerin daha fazla olduğu bulunmuştur.

Sonuç: Bulgularımız, COVİD-19 enfeksiyonu olan ergenlerde davranışsal, emosyonel problemler ve yorgunluk belirtileri taramasının gerekli olduğunu göstermiştir. COVİD-19 enfeksiyonu sonrası davranışsal, emosyonel problemler ile başlangıç inflamasyon seviyeleri arasında bir ilişki olup olmadığını belirlemek için izlem çalışmalarına ihtiyaç vardır.

Anahtar Sözcükler: Ergen, COVİD-19, Yorgunluk, İnflamasyon, Ruh sağlığı

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2) infection, which the World Health Organization (WHO) declared as the source of a global pandemic on March 11th, 2020 (1). As the pandemic spreads worldwide, its effects on mental health become more evident (2-4). Preliminary results have shown that COVID-19 is associated with delirium, depression, anxiety, post-traumatic stress disorder (PTSD), obsessive-compulsive symptoms, fatigue, insomnia, and cognitive dysfunction at an early period after infection (4-8).

As the number of the recovered cases increases, there is rising concern regarding the long-term sequelae after COVID-19 infection. In a recent study, 35.8% of patients still had symptoms in the clinical range in at least one psychopathologic dimension 3 months after a COVID-19 infection. Moreover, persistent depressive symptoms and cognitive impairment, including attentional problems and dysfunction in information processing, have been reported in long-term follow-up after a COVID-19 infection (9). Recent evidence has shown that survivors of COVID-19 have an increased risk of mood and anxiety disorders in 3-month follow-up (2). In a retrospective cohort study, the risk of mood and anxiety disorders continued 6 months after COVID-19 infection, and the risk for psychotic disorder increased significantly (10). In a long-term follow-up study, an association was found between depression, cognitive impairment, and baseline inflammation markers of COVID-19 (9). Another recent study showed a significant burden of post-viral fatigue in survivors of COVID-19 and female preponderance in the development of fatigue in medium-term follow-up. However, no correlation has been found between fatigue and inflammation scores (8).

Despite evidence of the mental impact of COVID-19 on adults, there has been very limited research on the mental health of children and adolescents. In this context, we intended to determine the adolescent behavioral, emotional problems, feelings of fatigue, and relationships between these factors, and baseline inflammation levels after COVID-19 infection.

MATERIAL and METHODS

We retrospectively screened the health records of 504 patients who had COVID-19 infections between April 1st and December 25th, 2020, in our Pediatric Infectious Disease Unit. A total of 110 adolescents (56 boys, 50.9%) with a mean age of 14.72 (range, 11 - 18) years and their parents (74 mothers, 67.3%) who agreed to participate in the study were assessed for psychiatric symptoms.

An online survey was used that included a parent-rated questionnaire screening child behavioral and emotional problems along with socio-demographic variables. Other information (presence of fatigue for at least one month, sleep duration, relative's death due to COVID-19 infection) was collected from the adolescents through phone call interview. The presence of fatigue symptoms was determined with the question "Do you feel tired in a great part of the day?" Information was first given verbally on the phone, and then a survey link was sent to those who agreed to participate in the study. The survey data were collected between February 18th and February 28th, 2021.

For the evaluation of behavioral and emotional problems in adolescents, the Turkish version of the Child Behavior Checklist (CBCL) 6-18 parent-report questionnaire was used (11). Thomas M. Achenbach developed the CBCL, which consists of 113 items rated on a three-point scale (12). The CBCL consists of eight subscales; anxious/depressed, withdrawn/depressed, somatic problems, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior subscales. Raw scores are converted to sex- and

age-standardized scores (T scores). The clinical cut-offs of the eight subscales' T scores are 65-69 (borderline clinical) and >70 (clinical). Additionally, the CBCL consists of three summary scales: internalizing (anxious/depressed, withdrawn/depressed, somatic problems subscales), externalizing (rule-breaking behavior and aggressive behavior subscales), and total problems. The clinical cut-offs of the three summary scales' T scores are 60-63 (borderline clinical) and >63 (clinical). Higher scores indicate greater behavioral and emotional problems in adolescents. The reliability and validity of the CBCL for Turkish children and adolescents aged 6-18 years have been confirmed (11). The Depression Anxiety and Stress Scale (DASS-21) was used to determine the parents' current psychological status. DASS-21 is a self-report questionnaire that consists of three subscales (depression, anxiety, and stress) including seven items per subscale, which classify depression, anxiety, and stress according to cut-off scores (normal range: 0-9 points for depression; 0-7 points for anxiety; and 0-14 points for stress) (13). Higher scores indicate greater behavioral and emotional problems in parents. The reliability and validity of DASS-21 have been confirmed for the Turkish population (14).

The first hematologic analysis results of all patients at the time of COVID-19 positivity were obtained from our hospital records. These hematologic analyses associated with COVID-19 inflammation were highlighted in a recent meta-analysis [C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and the systemic immune-inflammation index (SII) (SII = platelets X neutrophils/lymphocytes)] as baseline inflammation markers (15). Regardless of the severity of the infection, all patients were hospitalized and isolated in our pediatric infectious diseases unit. Psychiatric assessments were performed 7.31±2.35 (range, 2 - 11) months after discharge.

Online informed consent was obtained from the parents, and assent was obtained from the children and adolescents. The study was approved by the Ankara City Hospital No. 2 Clinical Research Ethics Committee (Ethics ID-No: E2-21-21).

Data analyses

We used the Shapiro-Wilk test to analyze whether data were normally distributed. According to the normality of distribution, descriptive statistics are presented as mean ± standard deviation or median (min-max). Continuous clinical variables were analyzed using the Mann-Whitney U test according to their distribution characteristics in group comparisons. Differences in categorical variables in group comparisons were examined using Pearson's Chi-square and Fisher's exact analysis. The data were analyzed using the SPSS version 23 software package, and all statistical tests were two-tailed with the significance level set at $\alpha = .05$. Spearman's correlation coefficient was calculated to investigate the association among the clinical variables.

RESULTS

One hundred ten adolescents (56 males, 50.9%) with a mean age of 14.72 (range, 11-18) years and their parents (74 mothers, 67.3%) were included in the study. The parents were all literate and had at least primary education. The rate of parents having COVID-19 at the same time as their adolescents was 67.2%. Before the COVID-19 infection, 15 (13.6%) adolescents had psychiatric histories. Of the adolescents, 17.3% had a relative who died of COVID-19 infection and 34.5% of the parents had lost their jobs during the COVID-19 pandemic. Fatigue symptoms were determined in 36.4% of all adolescents (n=40) and 46.3% of the female adolescents. There were no differences in age, duration after COVID-19 infection, sleep time per day, relatives death of COVID-19 infection, parents' job loss, and family income levels between the sexes ($p > .050$). However, there were differences in the presence of fatigue symptoms and psychiatric history before COVID-19 infection between the sexes ($p = .030$ and $p = .010$, respectively). The socio-demographic information of the sample is presented in Table I.

A significant proportion of the adolescents' parent-rated symptoms were in the clinical range in at least one problematic domain: 44.5% (n = 49) in the entire sample, 35.7% (n = 20) in the boys, and 53.7% (n = 29) in the girls. There was a marginally significant difference in the clinical range in at least one problematic domain between the boys and girls (χ^2 (1, N = 110) = 3.60, $p = .058$). The rates of internalizing and externalizing symptoms were 33.6% and 16.4%, respectively. There were no sex differences in internalizing and externalizing symptoms. Thought problems were the most common problems in the entire sample (25.5%) and the boys (25.0%); the majority of the behavioral and emotional problems in the girls was somatic problems (27.8%). There was a significant difference in somatic problems (χ^2 (1, N = 110) = 4.01, $p = .040$), attention problems (χ^2 (1, N = 110) = 5.57, $p = .010$) and fatigue (χ^2 (1, N = 110) = 4.52, $p = .033$) between the boys and girls; the other CBCL subscales were not different between the sexes. Adolescents with fatigue had more somatic symptoms (χ^2 (1, N = 110) = 6.13, $p = .010$), attention problems (χ^2 (1, N = 110) = 5.40, $p = .020$), and parental depression (χ^2 (1, N = 110) = 4.20, $p = .040$). Additionally, parent symptoms in the clinical range according to DASS-21 did not differ between the sexes. The percentage of adolescents and parents in the clinical range of psychiatric symptoms is shown in Table II.

Measures of inflammation at the first clinical assessment with the COVID-19 diagnosis and psychiatric symptoms scores after infection in the survivors of COVID-19 are presented in Table III. Inflammatory markers (CRP, NLR, MLR, and SII) were not significantly different between the boys and girls ($p > .050$). There was a marginally significant difference in somatic symptom scores between the boys and girls ($p = .059$); other parent-rated psychiatric symptoms scores were not different between sexes ($p > .050$). Inflammatory marker levels did

Table I: Sociodemographic and clinical information of the sample.

	Gender						Z or χ^2	p
	Whole sample (n=110)		Females (n=54)		Males (n=56)			
	Mean (SD) or n (%)	Median (Range)	Mean (SD) or n (%)	Median (Range)	Mean (SD) or n (%)	Median (Range)		
Age (year)	14.72	15 (11-18)	14.63 (1.83)	15.00 (11-18)	14.80 (1.96)	15.00 (11-18)	-.35	.720
Duration after COVID-19 infection to psychiatric assessment (month)	7.31 (2.35)	8.00 (2-11)	7.46 (2.49)	8.00 (3-11)	7.16 (2.24)	7.00 (2-11)	-.69	.480
Presence of psychiatric history prior to COVID-19 infection	15 (13.6)	-	3 (5.6)	-	12 (21.4)	-	5.88	.010*
Family income (TL/a month)	4014.75 (2745.66)	3000 (500-17000)	3489.06 (2147.61)	3000 (500-12500)	4521.66 (3156.38)	3000 (1000-17000)	-1.82	.060
Presence of fatigue symptoms	40 (36.4)	-	25 (46.3)	-	15 (26.8)		4.52	.030*
Duration of sleep (h/day)	8.35 (1.44)	8 (3-12)	8.61 (1.43)	8 (5-12)	8.09 (1.41)	8 (3-11)	-1.71	.080
Parent reports (mother)	74 (67.3)	-	39 (72.2%)	-	35(62.5)	-	1.18	.270
Relatives' death due to COVID-19 infection	19 (17.3)	-	9 (16.7)	-	10 (17.9)	-	.02	.860
Parents' losing job	38 (34.5)	-	21 (30.4)	-	17 (38.9%)	-	.88	.340

***** *p<.05;* ***χ^2value****: Chi Square test,* ***Z value:*** *Mann Whitney U test,* ***SD:*** *Standart Deviation.*

Table II: Percent of adolescents and parents at clinical behavioral and emotional symptoms levels divided according to sex.

	Gender			χ^2	p
	Whole sample (n=110)†	Females (n=54)†	Males (n=56)†		
Adolescents' CBCL scores at the clinical range					
Anxious/Depressed	26 (23.6)	12 (22.2)	14 (25)	.11	.730
Withdrawn/Depressed	26 (23.6)	12 (22.2)	14 (25)	.11	.730
Somatic Complaints	22 (20.0)	15 (27.8)	7 (12.5)	4.01	.040*
Social Problems	24 (21.8)	14 (25.9)	10 (17.9)	1.04	.300
Thought Problems	28 (25.5)	14 (25.9)	14 (25.0)	.01	.910
Attention Problems	14 (12.7)	11 (20.4)	3 (5.4)	5.57	.010*
Rule-Breaking Behavior	7 (6.4)	2 (3.2)	5 (8.9)	1.25	.260
Aggressive Behavior	15 (13.6)	7 (13.0)	8 (14.3)	.41	.840
Internalizing	37 (33.6)	20 (37.0)	17 (30.4)	.55	.450
Externalizing	18 (16.4)	10 (18.5)	8 (14.3)	.36	.540
Total problems	32 (29.1)	18 (33.3)	14 (25.0)	.92	.330
Parents' DASS-21 scores at the clinical range					
Depression	24 (21.8)	18 (33.3)	17 (30.4)	.11	.730
Anxiety	35 (31.8)	11 (20.4)	13 (23.2)	.13	.710
Stress	33 (30.9)	16 (29.6)	17 (30.4)	.00	.930

***** *p<.050;* ***†:*** *n(%),* ***χ^2value:*** *Chi-Square test,* ***DASS-21:*** *Depression and Anxiety Stress Scale,* ***CBCL:*** *Child Behavior Checklist.*

Table III: Measures of baseline inflammation at COVID-19 diagnosis and current behavioral and emotional symptoms in COVID-19 survivors, divided according to sex.

	Gender						Z	p
	Whole sample (n=110)		Females (n=54)		Males (n=56)			
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)		
C-reactive Protein (mg/L)	.017 (.03)	.004 (0-.16)	.014 (.03)	.003 (0-.16)	.020(.033)	.006 (0-.14)	-.91	.360
Neutrophil/lymphocyte ratio	3.25 (3.24)	2.67 (0.34-27.69)	2.73 (2.10)	1.88 (.55-10.86)	3.75 (4.00)	3.13 (.34-27.69)	-1.45	.140
Monocyte/lymphocyte ratio	.297 (.19)	.293 (.06-1.38)	.27 (.17)	.25 (.06-.85)	0.32 (.21)	0.29 (.06-1.38)	-1.51	.130
Systemic immune-inflammation İndex (SII)	787.13 (797.21)	647.18 (28.13-5206.39)	734.04 (793.50)	498.05 (120-4825.79)	838.32 (804.58)	746.67 (28.13-5206.39)	-1.14	.250
CBCL scores								
Anxious/Depressed	58.04 (10.12)	54 (50-90)	57.96 (9.91)	54 (50-83)	58.12 (10.40)	54 (50-90)	-.10	.910
Withdrawn/Depressed	59.89 (11.07)	57(50-100)	60.66 (11.08)	58.43(50-100)	59.16 (11.10)	55.5 (50-100)	-.84	.390
Somatic Complaints	58.49(10.20)	55 (50-90)	59.73 (9.98)	57 (50-90)	57.30 (10.36)	54 (50-89)	-1.88	.050*
Social Problems	57.20 (8.73)	54 (50-82)	58.01 (8.78)	54 (50-80)	56.42 (8.68)	52.5 (50-82)	-1.09	.270
Thought Problems	58.00 (9.35)	55 (50-87)	58.39 (8.89)	55.5 (50-81)	57.62 (9.84)	51 (50-87)	-.68	.490
Attention Problems	56.09 (7.81)	52 (50-93)	57.48 (9.49)	52 (50-93)	54.75 (5.52)	52.5 (50-69)	-.58	.550
Rule-Breaking Behavior	53.31 (6.94)	51 (50-84)	53.24 (6.41)	51 (50-83)	53.37 (7.47)	50 (50-84)	-.50	.610
Aggressive Behavior	54.96 (7.97)	51 (50-86)	55.25 (7.40)	51 (50-77)	54.67 (8.54)	50.5 (50-86)	-1.25	.200
Internalizing	56.22 (13.55)	56 (33-88)	57.17 (13.19)	56.65 (33-82)	55.30 (13.95)	54 (33-88)	-0.93	.340
Externalizing	48.91(11.61)	48 (34-83)	49.90 (10.85)	49 (34-79)	47.96 (12.33)	46 (34-83)	-1.25	.200
Total problems	52.12(14.32)	51 (24-89)	53.26 (14.14)	53.11 (24-82)	51.03 (14.53)	49.5 (24-89)	-1.15	.240
DASS-21 scores of parents								
Depression	5.40 (7.68)	2 (0-32)	5.07 (6.84)	2 (0-28)	5.71 (8.47)	1 (0-32)	-.30	.760
Anxiety	5.38 (7.51)	2 (0-34)	5.51(7.06)	2 (0-24)	5.25 (7.97)	2 (0-34)	-.41	.680
Stress	6.78 (8.15)	4 (0-34)	7.07 (8.16)	4 (0-34)	6.5 (8.20)	2 (0-32)	-.49	.620

***** *p<.05,* ***Z value:*** *Mann Whitney U test,* ***DASS:*** *Depression and Anxiety Stress Scale,* ***CBCL:*** *Child Behavior Checklist,* ***Systemic immune-inflammation index (SII)=*** *platelets X neutrophils/lymphocytes,* ***SD:*** *Standart Deviation*

not correlate with behavioral and emotional problems scores. Moreover, the adolescents' behavioral and emotional problems scores did not correlate with parent DASS-21 scores and post-COVID-19 time to psychiatric assessments (p > .050). Bivariate correlations between current behavioral, emotional symptoms and baseline inflammation markers are presented in Table IV.

DISCUSSION

Our study demonstrated that 44.5% of its sample was in the clinical range of at least one behavioral and emotional problematic domain, with particularly higher rates in girls. In the recent COVID-19 pandemic, various neuropsychiatric problems occurring after COVID-19 infection have been reported in adult samples (2,4,10,16). Preliminary data suggest that patients with COVID-19 may experience delirium, depression, anxiety, and insomnia in the early period (4). Another study reported high rates of PTSD, depression, anxiety, insomnia, and obsessive-compulsive symptoms in survivors of COVID-19 at 1-month of follow-up after hospital treatment (6). Our study found that internalizing symptom rates were higher than externalizing symptom rates in all adolescents. Thought problems involving symptoms such as obsessive thoughts, self-harm, hallucinations, compulsions, and strange behavior or ideas were the most common problems in the entire sample and boys; the majority of the behavioral and emotional problems in girls was somatic problems. Our findings are similar to the results from studies during previous coronaviruses outbreaks, which reported higher internalizing symptoms in patients with severe acute respiratory syndrome (SARS) in the long-term follow-up (17-19). One-quarter of the patients had PTSD and 15.6% had depressive disorders as late as 30 months after the SARS infection (20). Recent evidence indicated that survivors of COVID-19 were at increased risk of mood and anxiety disorders 3 months after infection (2). In a recent retrospective cohort study, COVID-19 was associated with an increased risk of neuropsychiatric disorders, including anxiety disorders and psychosis 6 months after a COVID-19 diagnosis (10). The high rates of psychiatric problems, particularly internalizing symptoms in the adolescents in our study, were in line with recent studies showing an increased risk for psychiatric disorders.

Regarding the difference in results between the sexes in our study, girls were more likely to present with somatic and attention problems. Studies in children and adolescents reported that female adolescents were more anxious and depressive than male adolescents in the COVID-19 pandemic ; however, a preadolescent sample showed no sex differences (21-23). Although most studies are about anxiety and depression in the COVID-19 pandemic, children and adolescents could present with various symptoms (3). A study with children and adolescents showed that 6-18–year-olds were more likely to show inattention problems, whereas younger children were more likely to present with clinginess and irritability (24). The girls had more attention problems than the boys in our study, which was discordant with the previous findings (25, 26). Screen exposure was not

Table IV: Correlation analysis between current adolescents' and parents' psychiatric symptoms and baseline inflammation markers of COVID-19 infection in the whole sample.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1.	C-reactive Protein (mg/L)	1	.349**	.223*	.288**	.114	.064	.005	.090	.009	.132	.074	.110	.094	.119	.092	.172	-.007	.090	-.289**	.060
2.	Neutrophil/lymphocyte ratio		1	.755**	.936**	.062	-.100	-.008	-.051	-.146	.071	-.016	.044	-.015	-.019	-.030	-.117	-.056	-.033	-.079	.132
3.	Monocyte/lymphocyte ratio			1	.704**	.063	-.176	.049	-.043	-.151	.018	-.007	-.039	-.032	-.052	-.055	-.084	-.072	-.037	-.051	.104
4.	Systemic immune-inflammation index (SII)				1	.024	-.090	.016	-.083	-.152	.036	.015	-.009	-.023	-.052	-.050	-.119	-.031	-.035	-.043	.064
5.	Anxious/Depressed					1	.713**	.647**	.755**	.688**	.647**	.615**	.748**	.892**	.779**	.853**	.009	-.066	.003	.058	.057
6.	Withdrawn/Depressed						1	.621**	.665**	.718**	.606**	.658**	.718**	.883**	.761**	.853**	.072	.051	.105	.004	-.135
7.	Somatic Complaints							1	.634**	.738**	.592**	.469**	.593**	.824**	.607**	.773**	.029	-.041	.029	-.029	.057
8.	Social Problems								1	.680**	.705**	.588**	.722**	.776**	.745**	.851**	.089	.009	.067	.051	-.083
9.	Thought Problems									1	.596**	.562**	.710**	.794**	.712**	.830**	.068	-.061	.089	-.006	.028
10.	Attention Problems										1	.547**	.697**	.702**	.714**	.809**	.013	-.025	.065	-.023	.100
11.	Rule-Breaking Behavior											1	.656**	.657**	.782**	.707**	.030	-.009	.078	-.042	-.068
12.	Aggressive Behavior												1	.777**	.937**	.866**	.051	-.015	.049	-.053	.053
13.	Internalizing													1	.822**	.947**	.040	-.048	.056	.018	.005
14.	Externalizing														1	.911**	.061	.003	.081	-.074	.068
15.	Total problems															1	.073	.002	.096	-.017	.030
16.	Parents' DASS-21 Depression																1	.747**	.773**	-.028	-.022
17.	Parents' DASS-21 Anxiety																	1	.775**	-.040	.013
18.	Parents' DASS-21 Stress																		1	.005	.078
19.	Duration after COVID-19 infection to psychiatric assessment																			1	-.224*
20.	Age																				1

*Spearman correlation analysis with rho coefficient, *p < .050, **p < .010*

evaluated in our adolescent sample, which could be associated with attention problems during the COVID-19 pandemic (27).

In adolescence, fatigue is a common problem that usually depends on hormonal pubertal changes and psychological problems (28). A pre-COVID-19 epidemiologic study showed that fatigue symptoms were present in 20% of female adolescents and 6% of male adolescents (29). In our study, fatigue symptoms after COVID-19 infection were reported in 36.4% of the entire sample; in particular, 46.3% of girls presented with fatigue symptoms. Prior studies showed that the chronic fatigue symptoms in survivors of SARS continued in long-term follow-up (18,30). Recent study results showed that 53.6% of survivors of COVID-19 presented with fatigue symptoms, 26.8% had anxiety and depression symptoms, and these symptoms had no association with pneumonia severity (31). We found fatigue more common in girls, and the rates of somatic symptoms, attention problems in fatigued adolescents were more than in non-fatigued individuals. Our results are consistent with studies showing that fatigue is often accompanied by other psychological problems, including anxiety, depression, somatic disorder, or physical symptoms such as headaches, stomachaches, and muscle aches, particularly in females (32-34). Considering that the girls had more attention problems and fatigue than the boys in our study, this could be related to the higher levels of cognitive fatigue in females, as indicated in previous studies (35,36). A recent study showed significant fatigue rates in survivors of COVID-19, and in particular in females at medium-term follow-up. However, no correlation was found between fatigue and inflammation levels (8).

Psychiatric symptoms after COVID-19 infection can result from an immune response related to the virus and or psychosocial factors (37). Neuroinflammation, blood-brain-barrier impairment, neurotransmission changes, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, cytokine dysregulation, and microglia activation are known to be associated with psychiatric problems (36,38-40). In a recent study, COVID-19 RNA in cerebrospinal fluid showed its neuroinvasive features (41). Patients with COVID-19 may present with neurologic manifestations such as headache, dizziness, hypogeusia, and hyposmia, supporting its neuroinvasive potential (37). A recent systematic review and meta-analysis reported that COVID-19 infection could activate immune responses and immune-inflammatory parameters such

as white blood cells (WBCs), lymphocytes, NLR, and CRP were correlated with disease severity (15). In a study of survivors of COVID-19 that investigated the role of inflammatory and clinical predictors, correlations were found between obsessive-compulsive symptoms and MLR at one-month follow-up (6). In our study, inflammatory markers at COVID-19 diagnosis (CRP, NLR, MLR, and SII) did not correlate with current behavioral and emotional problems. Furthermore, there were no significant differences between the girls and boys. In a recent retrospective cohort study of electronic health records, common psychiatric symptoms, including mood and anxiety disorders, continued beyond 6 months after COVID-19 infection. However, psychiatric symptoms showed a weaker association with the severity markers of COVID-19 than neurologic symptoms (10). These results may indicate the psychosocial impacts of COVID-19, rather than the direct effects of the infection and its severity.

Our study had the following limitations: it was conducted in a single center with a small sample, thus our findings cannot be generalized to other populations. Its cross-sectional design does not allow interpretation for causality. The general limitations of online surveys also apply to our study. Considering those who did not have internet access, our sample may not represent all survivors of COVID-19. Adolescents' behavioral and emotional states before COVID-19 infection were not known. In addition, only about 20% of children with COVID-19 infection were assessed, and the post-infection period was in a wide range (2-11 months). The behavioral and emotional problems of the adolescents and their parents could not be evaluated with face-to-face psychiatric interviews. Unfortunately, the pandemic continues, and there are many difficulties in making face-to-face evaluations of patients during this period. Although there were data on the presence of previous psychiatric diagnoses, no detail about which diagnoses were not reported in the online survey. The presence of fatigue was asked as 'yes' and 'no' to the adolescents, but no assessment was made regarding the fatigue's physical and mental characteristics. Another limitation of our study is that the CBCL scale's clinical cutoff scores were not validated for Turkish adolescents.

Despite the limitations mentioned above, our study contributes to the literature in several ways. To our knowledge, this is the first study to evaluate behavioral and emotional problems in adolescents after COVID-19 infections in the long term. This study may be important to demonstrate the long-term mental effects of COVID-19 infections on adolescents. Future studies are needed to confirm the high rates of behavioral and emotional problems in adolescents recovering from COVID-19 in comparison with non-infected adolescents. A follow-up design with larger samples may reveal the relationship between behavioral, emotional problems and inflammation in future studies.

CONCLUSION

Our results support that survivors of COVID-19 present with a high prevalence of behavioral and emotional problems; 44.5% of the sample was in the clinical range of at least one problematical domain. Additionally, the rate of fatigue reported by the adolescents was higher, especially among girls. Somatic symptoms and attention problems were more common in girls and fatigued adolescents. Considering the impact of COVID-19 infection on adolescent mental health, screening of behavioral, emotional problems and fatigue symptoms seems necessary in survivors of COVID-19.

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Evaluation of Neonatal Polycythemia in Terms of Gestational Age, Hematocrit, and Platelet Levels

Yenidoğan Polisitemisinin Gebelik Yaşı, Hematokrit ve Trombosit Düzeyleri Açısından Değerlendirilmesi

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ABSTRACT

Objective: The main concern in neonatal polycythemia is complication development due to hyperviscosity. We aimed to compare symptoms, clinical and laboratory features, and organ dysfunctions of polycythemic newborns with respect to gestational age, hematocrit (hct) levels and presence of thrombocytopenia.

Material and Methods: Between January 2013 and December 2016, all hospitalized newborns with a gestational age of ≥ 34 weeks were retrospectively evaluated and those with a venous hct value exceeding 65% were included. Exclusion criteria were infections, metabolic diseases and congenital anomalies. Newborns were grouped and compared according to hct values (65–69.9% vs. ≥70%), gestational age (late preterm vs. term) and thrombocytopenia (present/absent).

Results: Polycythemia incidence was 7.7% in the study group. The most common symptoms were hypoglycemia and hyperbilirubinemia, while 35.1% of newborns were asymptomatic. Hypoglycemia, hypocalcemia, and plethora were significantly more frequent in the severe polycythemia (hct ≥70%) group than in the moderate polycythemia (hct between 65–69.9%) group ($p = 0.027$, $p = 0.014$, $p < 0.001$, respectively). Hyperbilirubinemia was more common in late preterm babies than term babies ($p = 0.014$). Feeding difficulty, convulsion, hypoglycemia, hypocalcemia and liver function test abnormalities were significantly more common in newborns with thrombocytopenia than those without ($p = 0.002$, $p = 0.004$, $p < 0.001$, $p = 0.022$, $p = 0.043$, respectively).

Conclusion: It should be kept in mind that more than one-third of polycythemic newborns may be asymptomatic. While the most common symptoms were hypoglycemia and hyperbilirubinemia, liver function tests may also be adversely affected.

Key Words: Hematocrit, Hyperviscosity, Late preterm, Newborn, Thrombocytopenia

ÖZ

Amaç: Yenidoğan polisitemisinde esas sorun hiperviskoziteye bağlı komplikasyonlardır. Bu çalışmanın amacı polisitemik yenidoğanların semptomlarını, klinik ve laboratuvar özelliklerini ve organ işlev bozukluklarını; gestasyonel yaş, hematokrit (hct) düzeyleri ve trombositopeni varlığı açısından değerlendirmektir.

Gereç ve Yöntemler: Ocak 2013 ile Aralık 2016 tarihleri arasında, hastanede yatan gestasyonel yaşı≥34 hafta olan tüm yenidoğanlar geriye dönük olarak değerlendirildi. Venöz hct değerleri %65'in üzerinde olan yenidoğanlar çalışmaya dahil edildi. Enfeksiyon, metabolik hastalık ve konjenital anomalileri olan yenidoğanlar çalışma dışı bırakıldı. Yenidoğanlar hct değerlerine (Orta derece polisitemi [%65-69] ve Şiddetli derece polisitemi [≥%70]), gestasyonel yaşa göre (geç preterm/term) ve trombositopeni durumuna (var/yok) göre gruplandırıldı ve karşılaştırıldı.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Approval number E-73799008-799-188/05.04.2021 was obtained from the Medical Specialization Education Board of Sami Ulus Gynecology and Childhood Health and Diseases Training and Research Hospital.

Contribution of the Authors / Yazarların katkısı*: *YALCINKAYA R: 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. ***ZENCIROGLU 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 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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Bulgular: Çalışma grubunda polisitemi insidansı %7.7 olarak saptandı. En sık görülen semptomlar hipoglisemi ve hiperbilirubinemi iken, yenidoğanların %35.1'i asemptomatikti. Hipoglisemi, hipokalsemi ve pletore şiddetli polisitemi grubunda orta polisitemi grubuna göre anlamlı olarak daha sıktı (sırasıyla p= 0.027, p= 0.014, p< 0.001). Hiperbilirubinemi, geç preterm bebeklerde term olanlara göre daha sıktı (p= 0.014). Trombositopenisi olan yenidoğanlarda, beslenme güçlüğü, konvülziyon, hipoglisemi, karaciğer fonksiyon testleri anormallikleri, trombositopenik olmayanlara göre anlamlı olarak daha fazlaydı (sırasıyla p= 0.002, p = 0.004, p < 0.001, p = 0.022, p = 0.043).

Sonuç: Polisitemik yenidoğanların asemptomatik olabileceği akılda tutulmalıdır. En sık görülen semptomlar hipoglisemi ve hiperbilirubinemi iken, karaciğer onksiyon testleri de polisitemik yenidoğanlarda etkilenebilir.

Anahtar Sözcükler: Hematokrit, Hiperviskozite, Geç preterm, Yenidoğan, Trombositopeni

INTRODUCTION

Neonatal polycythemia, defined as a venous hematocrit (hct) value higher or equal to 65% at birth, is associated with blood hyperviscosity. As the viscosity increases, there is often progressive impairment of tissue oxygenation and perfusion, possibly causing significant damage. Although symptoms of hypoperfusion correlate better with blood viscosity as compared to hct value, viscosity is difficult to measure. Since instruments to measure viscosity are not available in most neonatal intensive care units, hyperviscosity is usually suspected in the presence of suggestive symptoms and/or an abnormally high hct values. The frequency of neonatal polycythemia is reportedly between 0.4–12%, but results are significantly affected by many confounding factors, including but not limited to gestational characteristics, maternal health, altitude, and the efficiency and swiftness of cord clamping after delivery (1,2).

Significant damage may occur in polycythemia due to impairment of tissue oxygenation and perfusion (3). To our knowledge, the number of studies which have evaluated neonatal polycythemia according to gestational age, hct levels, platelet levels (all together) are very limited. Therefore, this study was planned to determine the frequency and symptomatology of polycythemia in newborns, and also to compare the symptoms, clinical and laboratory findings of polycythemic newborns in terms of gestational age, hct groups, and presence/absence of thrombocytopenia.

MATERIALS and METHODS

This study was a retrospective evaluation of neonates who were hospitalized in a single tertiary neonatal intensive care unit between January 2013 and December 2016. Newborn babies with a gestational age of ≥34 weeks who had an hct value of 65% or higher in venous blood samples drawn at >4 hours of age were included. Exclusion criteria were infections, metabolic diseases and congenital anomalies.

Newborns were grouped and compared according to hct values (moderate polycythemia (65%- 69%) vs. severe polycythemia (≥70%)), gestational age (late preterm vs. term) and thrombocytopenia (present/absent). Gestational age groups of the babies were defined as late preterm ($34^{0/7}$–$36^{6/7}$weeks) and term ($37^{0/7}$–$41^{6/7}$ weeks). The gestational development of neonates was assessed according to Lubchenco's intrauterine growth curves (4). Small for gestational age (SGA) and large for gestational age (LGA) were defined as birth weight less than the 10^{th} percentile and higher than the 90^{th} percentile for gestational age, respectively. Neonates with a weight between the 10^{th} and 90^{th} percentiles were defined as appropriate for gestational age (AGA) (5). Hyperbilirubinemia was defined as bilirubin level which warranted phototherapy (6). Hypoglycemia was defined as a serum glucose level of <40 mg/dL, hypocalcemia was defined as a serum calcium level of <7.6 mg/dl, and thrombocytopenia was defined as a serum platelet level of <150.000/mm^3 (7). If the aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels were not within the reference range adjusted for age and sex, newborns were defined to have abnormal liver function test (LFT) (7). Creatinine elevation was defined as the detection of serum creatinine levels exceeding 1.3 mg/dl (8). Apnea was defined as cessation of breathing for more than 20 seconds, tachypnea was defined as respiratory rate greater than 60 breaths per minute. If the above findings (including apnea and convulsions) were caused by only polycythemia and other reasons were not present (such as hypoglycemia and hypocalcemia), the findings were recorded.

Newborns' sex, postnatal age (in hours) at polycythemia diagnosis, prenatal and natal history, recorded risk factors (in terms of SGA, fetal distress history, LGA, gestational diabetes, preeclampsia, maternal hypertension), type of birth, hct values at diagnosis, symptoms and findings associated with polycythemia (feeding difficulty, plethora, tachypnea, apnea, convulsion, cyanosis), treatment, and laboratory results consisting of complete blood count, creatinine, ALT, AST and C-reactive protein were recorded from the institutional electronic database. Laboratory tests were only performed in the presence of suspicion or risk factors for polycythemia. All newborn babies were evaluated by an attending neonatologist.

During the study period, the treatment approach of our neonatology clinic for polycythemic babies was as follows: Partial exchange transfusion (PET) was performed in those with a hct level in excess of 75% regardless of the presence or absence of symptoms. In those with hct levels between 65-74%, after evaluation for other possible causes, treatment was applied in two groups according to the symptoms. Asymptomatic newborns with hct values lower than 70% were monitored with oral feeding, whereas those with hct greater

than 70% received one of the following: close monitoring and intravenous (IV) hydration, or PET. The decision for treatment approach was based on the opinion of the attending physician. Local ethical approval was obtained from the committee of our institution (E-73799008-799).

Statistical Analysis

All statistical analyses were performed with SPSS (version 21) computer software (SPSS Inc., Chicago, IL, USA). Quantitative variables were given as mean ± SD and qualitative variables were given as frequency and percentage. The normality of distribution of quantitative variables was assessed via the Kolmogorov-Smirnov with Lilliefors correction. The comparison of groups based on hct levels (moderate/severe polycythemia), gestational age (late preterm/term) and thrombocytopenia (presence/absence) were performed with the Student's t-test (normal distribution) and the Mann Whitney-U test (non-normal distribution). The correlations between quantitative variables were checked by the calculation of Pearson and Spearman correlation coefficients depending on normality of distribution. Categorical comparisons were performed via Chi-squared tests. P-values lower or equal to 0.05 were considered to demonstrate statistical significance.

RESULTS

There were a total of 4497 hospitalized newborns with a gestational age ≥ 34 weeks during the study period. Among these, 421 newborns had a hct value of ≥ 65% in samples obtained at > 4 hours of age. Seventy-four newborns were excluded according to exclusion criteria. Thus, a final group of 347 neonates (189 (54.5%) males) were included in the analyses (Figure 1).

The frequency of neonatal polycythemia was 7.7% in our study group. Thirty-five percent of the babies (n= 122) were asymptomatic. The most common symptoms, in order of frequency, were as follows: hypoglycemia (32.5%), feeding difficulty (11.8%), tachypnea (6.9%), plethora (5.4%), cyanosis (5.1%), convulsion (2.8%), and apnea (1.1%) (Table I).

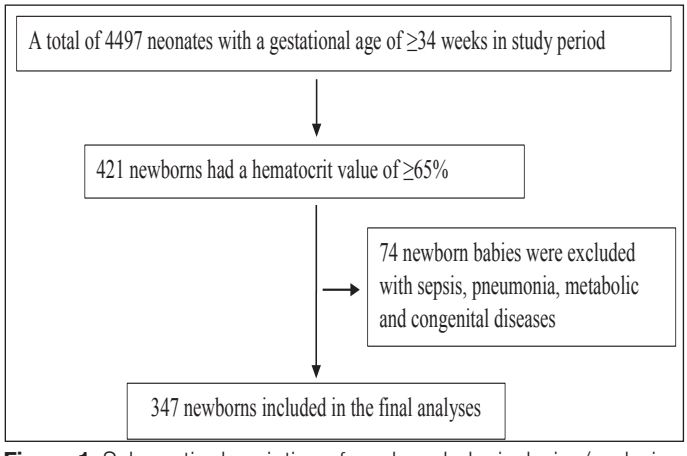

Figure 1: Schematic description of newborn baby inclusion/exclusion.

Table I: Demographic, clinical and laboratory data of all polycythemic newborn babies.

	Polycythemic newborns (n=347)
Gender, boys, n(%)	189 (54.4)
C/S, n(%)	232 (66.8)
Gestational age, weeks	38 ± 1.5
Birth weight, gram	2954 ± 681
Mother age, years	28.6 ± 6.3
SGA, n(%)	111 (31.9)
Late preterm, n(%)	60 (17.2)
Gestational diabetes, n(%)	22 (6.3)
Asymptomatic, n(%)	122 (35.1)
Symptoms, physical examination findings and laboratory results	
Feeding difficulties	41 (11.8)
Plethora	19 (5.4)
Tachypnea	24 (6.9)
Apnea	4 (1.1)
Convulsion	10 (2.8)
Cyanosis	18 (5.1)
Hypoglycemia	113 (32.5)
Hyperbilirubinemia	103 (29.6)
Thrombocytopenia	78 (22.4)
Hypocalcemia	15 (4.3)
Elevation of creatinine levels	10 (2.8)
LFT abnormality	9 (2.5)
Aspartate aminotransferase* (U/L)	309.4 ± 231.98
Alanine aminotransferase* (U/L)	127.5 ± 97.3
Treatment	
Observation	192 (55.3)
IV hydration	83 (23.9)
PET	72 (20.7)

mean ± SD, **C/S: Caesarian section, **IV:** Intravenous, **LFT:** Liver function tests, **PET:** partial exchange transfusion, **SGA:** Small for gestational age.*

With regard to risk factors, 111 (32%) of polycythemic newborns were SGA, 35 (10%) had fetal distress history, 32 (9.2%) were LGA, 26 (7.4%) had maternal gestational diabetes, and 11 (3.1%) mothers had preeclampsia or maternal hypertension.

When newborns were compared with regard to polycythemia severity (moderate vs. severe), the frequencies of any type of symptom, hypoglycemia, hypocalcemia and plethora were significantly higher in those with severe polycythemia (p= 0.028, p= 0.027, p= 0.014 and p< 0.001, respectively) (Table II).

Comparisons based on gestational age demonstrated that the frequency of hyperbilirubinemia was significantly higher in late-preterm newborns than term newborns (41.6% vs 27.1%, respectively; p= 0.014) (Table III).

When polycythemic newborns were compared with regard to presence of thrombocytopenia, thrombocytopenic ones

Table II: Comparison of polycythemic newborns in terms of hematocrit levels.

	Moderate polycythemia (n=273)	Severe polycythemia (n=74)	p
Asymptomatic, n,%	104 (38)	18 (24.3)	**0.028**
Symptoms, physical examination findings, laboratory results %			
Feeding difficulties	34 (12.4)	7 (9.4)	0.487
Plethora	8 (2.9)	11 (14.8)	**<0.001**
Tachypnea	20 (7.3)	4 (5.4)	0.564
Apnea	3 (1)	1 (1.3)	0.857
Convulsion	6 (2.1)	4 (5.4)	0.143
Cyanosis	12 (4.3)	6 (8.1)	0.194
Hypoglycemia	81 (29.6)	32 (43.2)	**0.027**
Hyperbilirubinemia	83 (30.4)	20 (27)	0.675
Thrombocytopenia	55 (20.1)	23 (31)	**0.046**
Hypocalcemia	8 (2.9)	7 (9.4)	**0.014**
Elevation of creatinine levels	6 (2.1)	4 (5.4)	0.153
LFT abnormality	7 (2.5)	2 (2.7)	0.957

LFT: *Liver function tests.*

Table III: Comparison of polycythemic newborns in terms of gestational age.

	Late preterm babies (n=60)	Term babies (n=287)	p
Asymptomatic, n,%	15 (25)	107 (37.2)	**0.070**
Symptoms, physical examination findings and laboratory results %			
Feeding difficulties	8 (13.3)	33 (11.4)	0.622
Plethora	5 (8.3)	14 (4.8)	0.285
Tachypnea	4 (6.6)	20 (6.9)	0.933
Apnea	1 (1.6)	3 (1)	0.682
Convulsion	0	10 (3.4)	0.142
Cyanosis	5 (8.3)	13 (4.5)	0.232
Hypoglycemia	25 (41.6)	88 (30.6)	0.098
Hyperbilirubinemia	25 (41.6)	78 (27.1)	**0.014**
Thrombocytopenia	13 (21.6)	65 (22.6)	0.868
Hypocalcemia	1 (1.6)	14 (4.8)	0.266
Elevation of creatinine levels	1 (1.6)	9 (3.1)	0.512
LFT abnormality	1 (1.6)	8 (2.7)	0.565

LFT: *Liver function tests*

Table IV: Comparison of polycythemic newborns in terms of thrombocytopenia.

	Thrombocytopenic newborns (n=78)	Non- thrombocytopenic newborns (n=269)	p
Asymptomatic, n,%	11 (14.1)	111 (41.2)	**<0.001**
Symptoms, physical examination findings and laboratory results %			
Feeding difficulties	16 (20.5)	25 (9.2)	**0.002**
Plethora	6 (7.6)	13 (4.8)	0.328
Tachypnea	9 (11.5)	15 (5.5)	0.068
Apnea	2 (2.5)	2 (0.7)	0.185
Convulsion	6 (7.6)	4 (1.4)	**0.004**
Cyanosis	7 (8.9)	11 (4)	0.076
Hypoglycemia	39 (50)	74 (27.5)	**<0.001**
Hyperbilirubinemia	26 (33.3)	77 (28.6)	0.219
Hypocalcemia	7 (8.9)	8 (2.6)	**0.022**
Elevation of creatinine levels	6 (7.6)	4 (1.4)	0.289
LFT abnormality	5 (6.4)	4 (1.4)	**0.043**

LFT: *Liver function tests.*

more frequently suffered from feeding difficulty, convulsion, hypoglycemia, hypocalcemia, and LFT abnormality compared to those without (p= 0.002, p= 0.004, p< 0.001, p= 0.022, p=0.043, respectively) (Table IV).

DISCUSSION

In the literature, the frequency of neonatal polycythemia is reported in a wide range between 0.4% and 12% (1). In the current study, we found a frequency of 7.7% in newborns with a gestational age of ≥ 34 weeks at our center. This value is in agreement with previous studies and also shows that newborn polycythemia is an important problem.

SGA is one of the known risk factors for neonatal polycythemia. In our study group, SGA was present in 32% of our patients. The literature on this topic reports ranging from 24.7% to 55.5% (9-11). Although data is limited on this topic, it is possible that these variations are caused by population-based characteristics. Polycythemia has also been associated with LGA, but the results of the few studies vary greatly, with reports ranging from a frequency of 4% to 20% (12,13). In our group, 9.2% of newborns were defined to be LGA. Because gestational characteristics are directly associated with maternal health and care during pregnancy, standardizing obstetric care and increasing physicians' awareness of this condition may benefit patients and clinicians alike.

Our evaluation revealed that 64.9% of our newborns were symptomatic. This frequency was compatible with literature in which percentages have been reported from 60% to 90% (14, 13). In this study, hypoglycemia and feeding difficulties were found to be the most frequent symptoms, representing almost 45% of the whole group. In two prospective studies, the most frequent symptoms of neonatal polycythemia were reported to be gastrointestinal symptoms (vomiting and feeding difficulties) in 17%, hypoglycemia in 12%, and cyanosis/apnea in 10% (15,16). We found that hyperbilirubinemia was present in 29.6% of our study group, which is in compatible with previous studies (29%, 46.5% and 33%) (17,11,13). Neurological symptoms, which are among the most feared consequences of polycythemia, were rare in this study. Only 10 newborns (2.8%) had convulsions, and no other problems were reported. A convulsion rate of 28% was reported in a study comprised of 18 newborns; whereas, no such events were reported in studies including 54 and 111 newborns, respectively (19, 16,18,19). Paucity of neurological findings in our study and also the latter studies may have been associated with the fact that newborn convulsions are often subtle and difficult to recognize which may lead to underestimation of frequency (20). Plethora was seen in only 14.9% of the babies with hct levels above 70% demonstrating that plethora is indeed an unreliable finding for polycythemia.

It is well-known that newborns with polycythemia have a significantly increased likelihood for developing symptoms such as hypoglycemia, hypocalcemia, hyperbilirubinemia and neurological problems (21). In this study, newborns with severe polycythemia were more likely to have any symptom related to polycythemia. Also, hypocalcemia, hypoglycemia, and plethora were more common in severe polycythemia group compared to moderate polycythemia. Level of 70% seems to be a threshold at which circulatory resistance shows dramatic increase (22). There is no consensus yet on which hct value requires treatment. Supportive treatment is generally recommended for asymptomatic patients above 65%, and partial blood exchange transfusion is recommended for symptomatic patients (23). Our findings emphasize that in newborns with hct above 65%, the signs and symptoms should be sought carefully, considering that the symptoms may be subtle in newborns.

Polycythemic newborns were also evaluated in terms of gestational age in this study. Although polycythemia is usually a problem in the post-term population, recent studies have revealed that early term and late preterm birth may also pose risks for polycythemia (24). The percentage of symptomatic newborns was not found to be significantly different in late preterm infants compared to term infants in our study but the frequency of hyperbilirubinemia was more frequent in the late preterm group. To our knowledge, there is currently no study that can provide comparative data of polycythemic term and preterm babies, however there is a study with 6402 babies -of which 681 were late preterm and 5721 were term- the authors aimed to compare morbidity and mortality between late preterm and term infants and provided an extensive dataset. Their findings demonstrated that hyperbilirubinemia was more common in late preterm babies than term ones (24). Although preterm babies are often thought to be predisposed to anemia because they do not go through the last trimester, our findings emphasize that physicians should be aware that polycythemia may also be seen in this group. However, it is difficult to differentiate whether the problems are associated with prematurity or polycythemia itself; thus, in order to be able to differentiate prematurity and polycythemia symptoms, all late preterm babies should be assessed carefully.

Thrombocytopenia is an expected finding in polycythemia. We found that thrombocytopenia was present in 22.4% of our patients. The literature on this topic shows a remarkably wide range; from 5% to 51% (25-27). It is known that patients with thrombocytopenia have increased risk for respiratory distress, apnea and convulsions and worse laboratory values including bilirubin and leukocyte levels (25,27). Similarly, we found that feeding difficulties, hypoglycemia, hypocalcemia, convulsions, and abnormalities in LFT were significantly more frequent in patients with thrombocytopenia. In a study which evaluated thrombocytopenia in 140 polycythemic newborns, hyperbilirubinemia was more common in babies with low plt levels (27). These results demonstrate the extreme importance

of monitoring platelet levels in patients with polycythemia in order to prevent morbidity and mortality.

The strengths of this study include the high number of newborns and the presence of detailed medical history. To our knowledge, this is the first study to include a newborn group of this size, and to perform evaluations based on hct levels, gestational age, and presence of thrombocytopenia. However, there are also limitations to be discussed. Firstly, this is a retrospective study and carries all limitations associated with this design even though we applied strict inclusion/exclusion criteria. Secondly, data records may not have been accurate in some instances (especially in antenatal history) and it is also possible that there were important differences among each physician with regard to their clinical notes. Lastly, the lack of long-term follow-up, especially for neurological problems, is an important limitation.

As conclusion, the analysis of our data indicates that polycythemia is a frequent problem in our newborn population. While two-thirds of newborns were symptomatic, one-third did not show any symptoms at all, indicating the importance of assessing risk factors and ordering blood tests accordingly. In this study, we demonstrated differences between groups formed on the basis of hct levels, gestational age and the presence of thrombocytopenia. Prospective studies are needed to determine the actual effects of polycythemia and its relationship with symptomatology.

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Early Approach to Primary Spontaneous Pneumothorax Treatment in Children

Çocuklarda Primer Spontan Pnömotoraks Tedavisinde Erken Yaklaşım

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ABSTRACT

Objective: Etiology, diagnosis, and treatment of primary spontaneous pneumothorax (PSP) are not well-established and subject to debate in the pediatric age group. Our study aims to clarify the subject and discuss it in the light of available literature.

Material and Methods: We performed a retrospective analysis of the age, sex, etiology, smoking habits, diagnostic methods, pneumothorax percentages, first treatment approach, and treatment results of the patients with PSP by examining the patients' records. A total of 71 patients, 65 (91.5%) male and six (8.5%) female, who were followed up and treated between 2010 and 2020 were included in the study. Descriptive statistical methods, Shapiro-Wilk test Mann-Whitney U test, Pearson chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test were used while evaluating the study data.

Results: The mean age of the patients was 16.23±0.81 (13–18 years). The etiology was not clear in most of the patients. However, among them, 14 (25.5%) patients had bullae and 23 (32.4%) patients had a smoking habit. The diagnosis was made by means of taking medical history, physical examination, and post-anterior (PA) chest X-ray. Treatment with nasal oxygen was initiated in 14 (19.7%) patients with a pneumothorax percentage <20%. For a total of 57 patients the first line of treatment was initiated with tube thoracostomy. Video-assisted thoracoscopic surgery (VATS) was performed in cases where tube thoracostomy failed.

Conclusion: Different forms of initial treatment modalities exist for spontaneous pneumothorax. However, we suggest that the first option in patients of the pediatric age group should be clinical follow-up and supportive treatment, if necessary, tube thoracostomy should be applied.

Key Words: Primary spontaneous pneumothorax, Nonoperative, Recurrence, Pediatric

ÖZ

Amaç: Çocuk yaş grubunda Primer Spontan Pnömotoraks (PSP) etyolojisi, tanı ve tedavisi henüz kesinleşmemiş ve tartışmalı bir konudur. Makalemizde konuya açıklık getirme ve literatür eşliğinde tartışılması amaçlanmıştır.

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Gereç ve Yöntemler: "Primer Spontan Pnömotoraks (PSP) nedeniyle takip ve tedavi ettiğimiz hastaların yaş, cinsiyet, etyoloji, sigara alışkanlıkları, tanı yöntemleri, pnömotoraks oranları, ilk tedavi yaklaşımımız ve sonuçları hastaların kayıtları incelenerek değerlendirildi. 2010-2020 yılları arasında takip ve tedavi edilen 65'i (%91.5) erkek, 6'sı (%8.5) kız, toplam 71 hasta çalışmaya alındı. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodlar, Shapiro-Wilk testi, Mann-Whitney U test, Pearson ki-kare test, Fisher's exact test, Fisher-Freeman-Halton exact test kullanıldı.

Bulgular: Hastaların yaş ortalaması 16.23±0.81 (13–18 years)'di. Hastaların çoğunda etyoloji belli değildi. Ancak 14 (%25.4) hastada bül saptanırken, 23 (%32.4) hastanın hikayesinde sigara içme alışkanlığı saptandı. Tanı, hikâye, fizik muayene ve PA Akciğer grafisi ile kondu. Pnömotoraks oranı %20'nin altında olan 14 (%19.7) hastaya nazal oksijen ile tedaviye başlandı. Toplam 57 hastaya ilk tedavi olarak tüp torakostomi uygulandı. Tüp torakostominin başarısız olduğu olgulara video yardımlı torakoskopik cerrahi (VATS) uygulandı.

Sonuç: Spontan pnömotoraks başlangıç tedavi yöntemleri arasında farklı uygulamalar mevcuttur. Ancak çocuklarda ilk seçenek klinik takip ve destek tedavisi gerekirse tüp torakostomi uygulaması şeklinde olmalıdır. Bu uygulamalar kolay, başarı oranı yüksek, güvenli ve etkili bir tedavi yöntemidir. İleri cerrahi uygulamalar seçilmiş olgularda yapılmalıdır.

Anahtar Sözcükler: Primer Spontan Pnömotoraks, Nonoperatif, Nüks, Çocuk

INTRODUCTION

Spontaneous pneumothorax is defined as the collection of air between parietal and visceral pleural layers resulting in the sudden onset of collapsed lung. The occurrence of a pneumothorax without any lung disease is called primary spontaneous pneumothorax (PSP), and its occurrence due to an underlying lung disease is called secondary spontaneous pneumothorax (SSP) (1).

The main cause of PSP in adults is air leakage following the rupture of subpleural bullae and blebs located at the apex of the lung. The generally accepted mechanism for the formation of blebs is the prolonged retention of high swelling pressure in the alveoli. PSP is more common in young, tall, and thin males due to high apical pleural negative pressure (1-4). SSP is caused by chronic obstructive pulmonary diseases such as asthma and cystic fibrosis (1, 5).

PSP is a rare disease in children. Its incidence in childhood is 3.4 in 100,000 cases. Except for the neonatal period, it is mostly observed in tall, thin adolescents at the ages of 13–17 (1, 4, 6). The male to female ratio is between 2:1 and 9:1 (5, 7). During physical examinations in patients who generally present with sudden onset of chest pain and shortness of breath, the hemithorax, where the pneumothorax is detected, is seen to be larger and less involved in breathing. Breathing sounds cannot be heard or detected at the corresponding side by listening alone. The diagnosis is made by visualizing the pleural line on the chest radiograph. Lateral chest radiography and computed tomography (CT) are used in the diagnosis of suspicious cases of PSP in children.

Despite the existence of appropriate guidelines for adults in the follow-up and treatment of PSP, a standard follow-up and treatment protocol has not been developed for pediatric patients (8-13). Observation, oxygen therapy, needle aspiration, tube thoracostomy, sclerosing agent administration, thoracotomy, or video-assisted thoracoscopic surgery (VATS) methods are used in the treatment of PSP in adults. The treatment modality is decided by the severity of symptoms, percentage of pneumothorax detected radiologically, recurrence, duration of drainage, and presence of bullae.

In the present study, we aimed to share our experience by evaluating the age, sex, etiology, diagnostic methods, smoking habits, rates of pneumothorax, early treatment modalities used, and treatment results of the patients that we followed up and treated for PSP.

MATERIALS and METHODS

Records of 71 patients who were followed up and treated with the diagnosis of PSP in Health Sciences University Umraniye Training and Research Hospital and Sakarya University Training and Research Hospital Pediatric Surgery Clinics from January 2010 through October 2020 were retrospectively examined upon the affirmative decision of the Clinical Research Ethics Committee of Umraniye Training and Research Hospital (B.10.1.TKH.4.34.H.GP.0.01/264, dated: 25.06.2020). Patients included in the study were evaluated in terms of age, sex, complaints at presentation, etiology, diagnostic methods, smoking habits, pneumothorax percentage, applied treatment methods, and treatment results.

Pneumothorax diagnosis was confirmed from the medical history, physical examination, and radiological examination

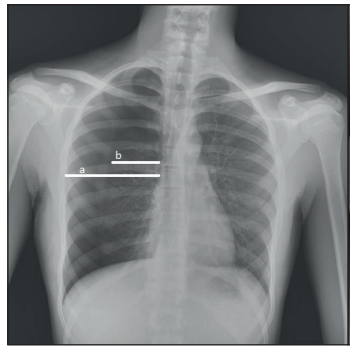

Figure 1: Post-anterior Image of Pneumothorax. **a:** Hemithorax diameter, **b:** Collapsed lung diameter.

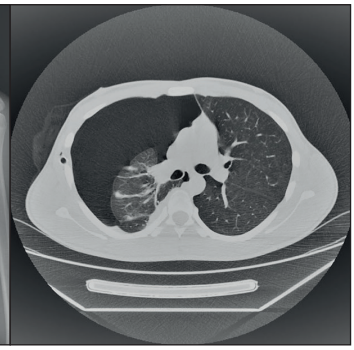

Figure 2: Appearance of Pneumothorax in CT.

findings. Posteroanterior (PA) chest radiography was performed in all patients (Figure 1). For etiology investigation, lung tomography was performed in cases of suspected PSP and those with recurrent PSP at the time of diagnosis or after the lung was fully expanded following tube thoracostomy drainage (Figure 2). Pneumothorax percentages of patients were calculated using the below formula as suggested by Light et al.(14):

Patients with a pneumothorax percentage < 20% at the time of diagnosis, nasal oxygen of 2–3 l/minute was given and were followed up.

All patients with a pneumothorax percentage > 20% and were symptomatic or with unstable vital signs were treated with tube thoracostomy and underwater seal drainage. Chest tube placement was performed in the operating room with sedation (midazolam at a dose of 0.15 mg/kg) as a standard in the 4th intercostal space from the anterior axillary line. A 16–20 F chest tube was used in such patients. Follow-up was performed clinically and based on PA chest radiography findings and the presence of air leakage through the drain. The drain was clamped for 6 hours in patients with expanded lungs as observed on PA chest radiography and with no air leak through the chest tube. Chest tube was removed upon patient's clinical complaint and if there was no air leak when the drain was opened. Failure to detect pneumothorax in control radiographic images taken 24 hours after chest tube removal was accepted as a successful treatment. Surgical treatment was performed in patients whose lungs were not expanded after chest tube was placed, in whom the air leak lasted longer than 7 days, or who had bullae on thorax CT images, and who developed recurrence.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. Pearson chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

Among the 71 patients included in the study, 65 (91.5%) were male and six (8.5%) were female. The average age was determined to be 16.23±0.81 years (13–18 years). Right pneumothorax was found in 33 cases (46.5%), left pneumothorax in 34 cases (47.9%), and bilateral pneumothorax in 4 cases (5.6%). The clinical characteristics of the patients are demonstrated in Table I.

Table I: Clinical Features of Primary Spontaneous Pneumothorax Cases.

	n (%)
Age range (years)*	16.23±0.81 16 (13-18)
Sex	
Female	6 (8.5)
Male	65 (91.5)
PSP location	
Left	34 (47.9)
Right	33 (46.5)
Bilateral	4 (5.6)
Bullae observed in CT (n=55)	
No	41 (74.5)
Yes	14 (25.5)
PSP percentage*	51.68±22.70 60 (10-90)
Smoking habit	
No	48 (67.6)
Yes	23 (32.4)
Treatment	
O_2	6 (8.5)
Tube thoracostomy	65 (91.5)
Drainage time (days)*	6.03±3.26 5 (318)
Length of hospital stay (days)*	7.70±3.77 7 (1-19)
Relapse	
No	63 (88.8)
Yes	8 (11.2)

***** *Mean±SD, Median (Min-Max)*

The most common symptoms observed were chest pain (n:71, 100%) and shortness of breath (n:30, 42.2%). Chest radiography was performed in all patients as a part of the first examination. In the first years, lung tomography was performed in 10 (14.1%) patients at the time of first presentation, and 45 (63.4%) patients after treatment with tube thoracostomy. However, bullae were found in the lungs of 14 (25.5%) out of 55 patients who underwent CT imaging. We noted unilateral bullae in 7 (50%) patients and bilateral bullae in 7 (50%) patients. Bilateral pneumothorax developed in 4 of the cases with bilateral bullae. Because of this low rate, CT imaging was not routinely performed during diagnosis in recently. Hence, CT imaging was not performed in 16 (22.5%) patients who presented recently.

Upon examination of the smoking habits of the patients, it was found that 23 (32.4%) patients were smokers. Whereas none of the female patients were found to be smokers, 23 (35.4%) out of the 65 male patients were smokers. The results of the comparison of the clinical features of pneumothorax between smoker and nonsmoker patients are given in Table II.

The pneumothorax percentage was <20% in 14 (19.7% of the studied cases) patients and >20% (30%–85%) in 57 (80.3%) patients. In 14 patients (19.7%) with a pneumothorax percentage

Table II: Clinical features according to smoking habit.

	Smoking habit		p
	No	Yes	
Treatment			[a]0.167
Tube thoracostomy	42 (87.5)	23 (100)	
O_2	6 (12.5)	0 (0)	
PSP percentage*	49.04±23.36 57.5 (10-90)	56.96±20.82 60 (10-85)	[b]0.198
Drainage time (days)*	5.86±3.22 5 (3-18)	6.35±3.37 5 (3-17)	[b]0.436
Length of hospital stay (days)*	7.23±3.48 6 (1-19)	8.7±4.22 7 (4-18)	[b]0.222
Bullae observed in CT (n=55)			[a]0.527
No	23 (71.8)	18 (78.3)	
Yes	9 (28.2)	5 (21.7)	
Relaps			[a]0.458
No	44 (89.8)	19 (86.4)	
Yes	5 (10.2)	3 (13.6)	

[a]Fisher's Exact Test, [b]Mann Whitney U Test, Mean±SD, Median (Min-Max)*

< 20%, administration of 2–3 l/min nasal oxygen therapy and observation were employed as the first line of treatment. While oxygen therapy and observation were sufficient in 6 of these patients (42.8%), tube thoracostomy was performed in addition to oxygen therapy in the remaining 8 (57.2%) patients due to increased respiratory distress observed during the follow-up. The average duration of stay of patients who received only oxygen therapy was 2 days. None of these patients were found to be smokers. Among the patients who needed tube thoracostomy, 3 were found to be smokers, whereas the other 5 were not.

Tube thoracostomy with sedation was performed in 8 patients with pneumothorax percentage <20% and increased respiratory distress and in 57 patients with pneumothorax percentage > 20%. Among the 65 (91.5%) patients, who underwent tube thoracostomy, no major complications were observed except subcutaneous emphysema in 2 and tube revision in 3 patients. Tube thoracostomy was discontinued in 51 patients whose air leak terminated and whose lungs were seen to expand. The mean drainage time of the patients treated with tube thoracostomy was 6.03±3.26 days (3–18 days), and the mean duration of hospital stay was 7.70±3.77 days (1–19 days). In 14 patients whose lungs were not fully expanded, the air leak continued for more than 7 days.

The success rate with nasal oxygen therapy was found to be 42.8% in patients with spontaneous pneumothorax and 78.5% in patients who underwent tube thoracostomy. The patients were followed up for an average of 22.83±17.55 months (1–74 months). Recurrence occurred in 8 (11.2%) patients during the follow-up period. The pneumothorax percentage of 3 patients who developed recurrence was < 20%. Observation was sufficient in these patients. Bullae were detected in the lung tomography images of 5 patients with recurrence and pneumothorax percentage > 20%. Among the patients who developed recurrence, 3 were smokers.

Surgical treatment was performed in 5 patients who developed recurrence after tube thoracostomy and whose lung tomography images revealed the presence of bullae, and in 14 patients with an air leak persisting for > 7 days in whom lung expansion could not be achieved during the treatment. VATS was preferred in choosing the surgical procedure.

DISCUSSION

PSP occurs as a result of the rupture of subpleural bullae and blebs located in the apex of the lung due to the high apical pleural negative pressure in young, tall, and thin male individuals without an underlying lung disease (1,2). Increased height and male sex are risk factors for spontaneous pneumothorax and smoking and atmospheric pressure changes are included in its etiology. In our study, consistent with the literature, pneumothorax was found to be more common in young men.

Although in most studies conducted in adults, subpleural blebs or rupture of the bullae at the apex of the lung was responsible for the formation of spontaneous pneumothorax, pneumothorax may also occur in children without any underlying lung disease. Subpleural blisters and blebs were found in 76%–100% of patients who underwent VATS in studies conducted in adults (2,4,15,16). In his study, Lopez et al. (4) detected bullae in 60% of the patients during CT scan and 98% of the patients during surgery. Therefore, the preferred approach for treatment in adults who have bullae is VATS.

However, there is not enough data on the occurrence of pneumothorax in the pediatric age group in the available literature. In most of the cases observed in our study, no obvious etiological factor was found. Only 14 (25.4%) of the patients had bullae. Thus, we suggest that follow-up and support should be the first treatment option in children, and if this is not sufficient, tube drainage is the appropriate method.

It has been suggested that smoking habit in adults has an important role in the development of pneumothorax. In the relevant studies, the risk of developing pneumothorax in men who smoke is 12%, whereas it is 0.1% in men who do not smoke. The risk increases 20 times in men who smoke (17). Although the smoking rate is higher in adults, Chiu et al. (5) found that 22% of adolescents smoked as well.

We found that 32.4% of our patients had a smoking habit. In our study, when smoking and non-smoking patients were compared, there was no statistically significant difference between smoker and non-smoker patient in terms of treatments, PSP percentages, tube durations, length of hospital stay, presence of bullae and recurrence rates of the cases (p>0.05). There is an increase in smoking among adolescents in our

country. We believe that the availability of data on adolescents who smoke is limited due to the fact that adolescents hide their smoking habits from their families and reply "I don't smoke" in spite of smoking. Thus, the actual smoking rate could be higher in our study.

The diagnosis of pneumothorax is made by the visualization of the pleural line in the chest radiography images taken after physical examination of the patients presenting with sudden chest pain and/or shortness of breath. In cases with insufficient PA chest radiographic findings, lateral chest radiography and thoracic CT findings can be used. All patients in this study reported chest pain, and 30 patients had shortness of breath accompanying chest pain. PA chest radiography imaging was performed in all our patients.

CT imaging is widely used in the diagnosis and etiology research of adult pneumothorax patients, and some authors advocate routine CT scanning in these patients. The reason for this is demonstrated to be the high probability of detecting an underlying pathology (bullae) (4,15).

Many authors argue that CT scanning in children should be used sparingly due to the inadequacy of the technique in the detection of bullae and blebs in pneumothorax and the high radiation dose used (3,4,5,9,11,18). Moreover, the rate detection of bullae or blebs was found to be quite low in our cases.

In our study, only 14 (25.4%) of the 55 patients who underwent thoracic CT scans had bullae. No pathology was found in the CT results of other patients. Due to the low rate of pathology detection and the high radiation dose used in CT, we recommend that CT scanning should not be performed at the first admission to hospital. However, it may be performed to investigate the underlying pathology in suspected cases at the time of diagnosis, cases with recurrence or cases where the lung is not expanded despite performing tube thoracostomy.

Despite the existence of standardized and important guidelines for adults in the follow-up and treatment of PSP, a similar standard follow-up and treatment protocol has not been developed for pediatric patients. The management of pneumothorax in children is based on various retrospective studies (11, 19). Observation, oxygen therapy, aspiration, tube thoracostomy, sclerosing agent administration, thoracoscopy, and thoracotomy are the modalities employed in the treatment of PSP in adults.

The American College of Chest Physicians (ACCP) recommends observation for small PSP in adults, chest tube application for large PSP, and surgical treatment for air leaks lasting longer than 4 days (12). The British Thoracic Society (BTS) recommends observation only for PSP without significant shortness of breath, regardless of its size. It also recommends that patients with significant dyspnea should be treated with needle aspiration or chest tube, and surgical treatment should be performed if there is an air leak that persists for 3–5 days (13).

There are different opinions about the treatment modalities and when to perform surgical treatment in children. Lee et al. (2) recommended conservative treatment in patients with a pneumothorax percentage of >15% and reported 80% success. Soccorso et al. (3) recommended tube thoracostomy as the initial treatment for children with PSP as 53% of patients with initial needle aspiration required tube thoracostomy. As a result of a survey conducted among North American Pediatric Surgeons, various treatment preferences emerged. Among the surgeons participating in the survey, 57% preferred chest tube drainage in the first instance, 29% followed with oxygen therapy alone, 3% preferred needle aspiration, and 4% preferred VATS. In this survey, there was a wide variability in the observation time when VATS decision is made. Among the participants, 40% of surgeons stated that they waited for 3 days, and 21% stated that they waited for 5 days (20).

Zganjer et al. (16) developed an algorithm for the treatment of spontaneous pneumothorax in children in their study of 16 patients in 2010. In children with chest pain, shortness of breath, and cough, they first performed chest radiography and subsequently a CT scan. Intercostal tube drainage was applied to all patients with pneumothorax, and observation was done. In the follow-up, patients with ongoing air leakage for 3–7 days underwent VATS and mechanical pleurodesis with apical bulla excision and wedge resection (16).

In our study, oxygen therapy and observation were performed in 14 patients with a pneumothorax percentage of 10–20%. While only oxygen therapy was sufficient for 6 of these patients, the other 8 patients continued to be treated with tube thoracostomy because the percentage of pneumothorax and respiratory distress increased. In total, tube thoracostomy was performed in 65 patients. The average treatment time with tube was 6.03 days (3–18 days), and average duration of hospital stay in patients treated with tube thoracostomy was found to be 7.70 days (1–19 days). We did not prefer to perform needle aspiration, which was included in adult treatment modalities, in the pediatric age group.

Although the number of patients we followed up and treated with oxygen therapy was limited, it was observed that oxygen therapy was effective in patients with a low percentage of pneumothorax and without clinical complaints. While administering oxygen therapy, tube thoracostomy was considered as an appropriate approach in cases with increased clinical complaints and pneumothorax percentage. When compared with the results of the available literature, in our study, it was found that the success rate of treatment with tube thoracostomy was higher and the duration of treatment with tube and the hospitalization period of the patients were longer.

In some studies, conducted in adults, although PSP was successfully treated with conservative treatment in the

beginning, it was reported that surgical treatment was required due to the recurrence rate of 40%–60% (2,4,5,11,19). However, recurrence after treatment (n:8) was found in 11.2% of our patients. Among the recurrent cases, the pneumothorax percentage of 3 patients was <20% while the rate of pneumothorax in 5 patients was >20%. It was observed that only 3 of the relapsed patients were smokers. There was no significant relationship among recurrence, pneumothorax percentage and smoking. While only observation was sufficient in 3 of our recurrent patients, bullae were detected in the axial CT images of the remaining 5 patients. VATS was applied to these patients.

In the treatment of pneumothorax, surgical treatment was performed in cases with air leak lasting longer than 5–7 days, non-expansion of lungs, and recurrence after tube thoracostomy treatment. Surgical treatment was applied to 5 patients who developed recurrence after tube thoracostomy and whose lung tomography images were found to have bullae and 14 patients with an air leak for more than 7 days and in whom lung expansion could not be achieved during the treatment. VATS was preferred as the surgical procedure.

CONCLUSIONS

As a result of our observations, we suggest that smoking may be an important risk factor for PSP in children as it is in adults. From our results, the underlying pathology and recurrence rate is low in children with pneumothorax, unlike in adults. Therefore, obtaining medical history and conducting physical examination and PA radiography should be sufficient for the diagnosis of PSP. CT imaging should be performed only in cases with recurrence and prolonged air leakage. As a treatment option, follow-up and supportive treatment, tube thoracostomy, and surgical treatment (VATS) can be applied in cases with prolonged air leak and recurrence. However, we believe that multi-center studies with more series and experience are needed to develop treatment algorithms in children.

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Nörofibromatozis Tip 1 Tanısı ile İzlenen Hastaların Klinik Özellikleri: Tek Merkez Deneyimi

Clinical Characteristics of Patients with Neurofibromatosis Type 1: A Single Center Experience

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ÖZ

Amaç: Nörokutanöz sendromlar sinir sistemini ve cildi tutan bir grup hastalıktır. Bunların arasında en sık görülen nörofibromatozis tip 1'dir (NF1). Bu çalışmanın amacı Gülhane Eğitim ve Araştırma Hastanesi Çocuk Nörolojisi Poliklini'ğinde izlenen NF1 tanılı hastaların klinik özelliklerini değerlendirmektir.

Gereç ve Yöntemler: Kasım 2016-Mart 2021 tarihleri arasında NF1 tanılı toplam 29 hastanın dosya kayıtları geriye dönük olarak gözden geçirildi. Hastaların aile öyküleri, demografik ve klinik özellikleri incelendi.

Bulgular: Hastaların 17'si (%59) erkek, 12'si (%41) kızdı. 10 hastada (%34.4) aile öyküsü mevcuttu. Hastaların 12'sinde (%41.3) NF1 geninde mutasyon saptanmıştı. Hastaların tamamında cafe au lait lekeleri mevcutken, aksiller ve/veya inguinal çillenmeye 18 hastada (%62) rastlandı. 10 hastada (%34.4) kognitif bozukluklar, 3 hastada (%10.3) epilepsi ve 2 hastada (6.9) makrosefali vardı. Lisch nodülü 10 hastada (%34.4) izlenirken, hiçbir hastada optik glioma rastlanmadı. Hastalar maligniteler açısından değerlendirildiğinde 3 hastada (%10.3) periferal nörofibrom, 1 hastada (%3.45) beyin sapı gliomu, 1 hastada (%3.45) akut miyeloid lösemi saptandı.

Sonuç: NF1 çoklu sistem tutulumu yapan geniş yelpazeli bir hastalıktır. Hastalar çok farklı klinik bulgular ile karşımıza çıkabilir. Makrosefali, öğrenme güçlüğü gibi nonspesifik nörolojik yakınmalarla çocuk nörolojisi polikliniğine başvuran hastalar dikkatli bir göz ve deri muayenesi ile NF1 tanısı alabilir. Hastalığın klinik özelliklerinin sıklığının bilinmesi tanı konulmasında yardımcı olacaktır.

Anahtar Sözcükler: Çocuk, Genetik, Klinik özellikler, Nörofibromatozis tip 1

ABSTRACT

Objective: Neurocutaneous syndromes are a group of diseases involving the nervous system and skin. Among them, the most common is neurofibromatosis type 1 (NF1). The clinical course of NF1 can be heterogeneous and complex. The aim of this study is to evaluate the clinical features of patients with neurofibromatosis type 1 followed in the Gulhane Training and Research Hospital Pediatric Neurology Outpatient Clinic.

Material and Methods: File records of 29 patients with neurofibromatosis type 1 between November 2016 and March 2021 were retrospectively reviewed. Family histories, demographic and clinical characteristics of the patients were examined.

Results: Seventeen (59%) patients were male and 12 (41%) were female. There was a family history in 10 patients (34.4%). Twelve patients (34.4%) had mutations in the NF1 gene. While all patients had cafe au lait spots, axillary and/or inguinal freckling was observed in 18 patients (62%). 10 patients (34.4%) had learning difficulties and cognitive

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disorders, 3 patients (10.3%) had epilepsy and 2 patients (6.9%) had macrocephaly. While Lisch nodule was observed in 10 patients (34.4%), optic glioma was not found in any patient. When the patients were evaluated in terms of malignancies, peripheral neurofibroma was found in 3 patients (10.3%), brain stem glioma in 1 patient (3.45%), and acute myeloid leukemia in 1 patient (3.45%).

Conclusion: NF1 is a wide spectrum disease with multisystem involvement. Patients may present with very different clinical findings. Patients who presented to the pediatric neurology outpatient clinic with nonspecific neurological complaints such as macrocephaly and learning difficulties can be diagnosed with NF1 with a careful eye and skin examination. Knowing the frequency of the clinical features of the disease will help in making the diagnosis.

Key Words: Child, Genetics, Clinical features, Neurofibromatosis type 1

GİRİŞ

Nörofibromatozlar sinir kılıfı tümörlerinin görüldüğü bir grup hastalıktır. Nörofibromatozlar Nörofibromatozis Tip 1 (NF1), Nörofibromatozis Tip 2 (NF2) ve schwannomatozis olmak üzere 3 grup hastalıktan oluşur. Periferal form NF1 olarak adlandırılırken, bilateral vestibuler schwannomların eşlik ettiği santral form NF2 ve vestibüler sinir harici diğer kranial sinirlerde, periferal sinirlerde ve medulla spinaliste nörofibromların görüldüğü üçüncü form schwannomatozis olarak adlandırılır (1).

Nörofibromatozların en sık görüleni NF1'dir ve vakaların yaklaşık %90'nını oluşturur (2). NF1 otozomal dominant olarak kalıtılır ancak hastaların %50'sinde aile öyküsü mevcuttur, kalan %50 ise de novo mutasyonlar nedeniyle gelişir (3).

NF1 ile ilişkili tümörlerin gelişiminde birkaç yolun rol oynadığı düşünülmektedir. NF1 geni, vücuttaki birçok hücresel süreci etkileyen çoklu sinyal yollarını etkileyen nörofibromin proteinini kodlar. Nörofibromin hücre büyümesi ve çoğalmasının negatif düzenleyicisi olarak hareket eder. Nörofibromin kaybı, sıçan sarkomu viral onkogen homolog (RAS) aktivitesini arttırır. Nörofibromin ayrıca siklik adenozin monofosfat (cAMP) seviyelerinin düzenlenmesi ile de ilişkilidir. cAMP hayvan modellerinde santral sinir sisteminde özellile optik yol gliomalarını gelişiminde sorumlu bulunmuştur (4). NF1'de tümör oluşumunun nedenlerinden biri de '2 vuruşlu hipotez' ile açıklanmaktadır. 'İlk vuruş' ile allellerden biri yapısal olarak etkisiz hale gelir. 'İkinci vuruş' ile ise diğer allelde somatik bir germ line mutasyon sonucu heterozigosite kaybı gelişir (5).

NF1, cafe au lait lekeleri, gözde Lisch nodülleri ve deri tümörleri ile karakterize bir hastalıktır. Bu hastalıkta çok sayıda tümörün yanı sıra bilişsel etkilenme, endokrin, kardiyak ve ortopedik problemler görülebilir (6). NF1'in doğru teşhisi, klinik izlem ve genetik danışmanlığın kişiselleştirilmesi için önemlidir.

Bu çalışmada geriye dönük olarak NF1 tanısı ile Çocuk Nörolojisi Polikliniği'nde takip edilmekte olan hastaların demografik ve klinik özelliklerinin incelenmesi amaçlandı.

GEREÇ ve YÖNTEMLER

Bu çalışmada; Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi Çocuk Nörolojisi Polikliniği'ne Kasım 2016-Mart 2021 tarihleri arasında başvuran NF1 tanılı hastaların dosya bilgileri geriye dönük olarak incelendi.

Her bir hastanın demografik bilgileri (yaş, cinsiyet), fizik muayene bulguları, beyin Manyetik Rezonans Görüntüleme (MRG), abdomen ultrason (USG), elektrokardiyografi (EKO) sonuçları ve laboratuvar verileri kaydedildi. NF1 tanısıyla takipli hastaların rutin kontrollerinde eşlik edebilecek endokrinolojik, kardiyolojik, ortopedik ve psikiyatrik patolojiler açısından yönlendirildikleri diğer polikliniklerin dosyaları da sistemden taranarak komorbidite varlığı araştırıldı. NF1'in tanısında Ulusal Sağlık Örgütleri (NIH) NF1 tanı kriterleri kullanıldı. Bu kriterlerden iki ve daha fazlasının varlığı ile hastaya NF1 tanısı konuldu (Tablo I) (7).

Çalışmaya dahil edilen NF1 hastaları kliniğimizde 6 ayda bir rutin muayene edilmişti. Hastalara yıllık göz muayenesi ve semptomu olması halinde endokrinolojik, kardiyak, ortopedik ve psikiyatrik kontroller eklenmişti.

BULGULAR

Çalışmaya alınan hastaların 17'si erkek (%59), 12'si (%41) kızdı. Hasta yaşları 2-15 yaş arasında değişiyordu. 10 hastada (%34,48) aile öyküsü bulunurken, 19 hastada (%65.52) aile öyküsüne rastlanmadı (Tablo II).

Hastaların klinik özellikleri ve bu klinik bulguların en büyük ve en küçük saptanma yaşları incelendi (Tablo III-IV). Hastaların tamamında cafe au lait lekeleri, 18 hastada (%62) aksiller ve/veya inguinal çillenme mevcuttu. 10 hastada (%34.4) Lisch nodülü saptanırken, hiçbir hastada optik glioma rastlanmadı.

Hastalar nörolojik açıdan değerlendirildiğinde; 10 hastada (%34.4) öğrenme güçlüğü ve kognitif bozukluklar, 3 hastada (%10.3) epilepsi, 2 hastada (%6.9) makrosefali mevcuttu. 12 hastaya (%41) nörolojik muayenelerinin normal olması nedeniyle herhangi bir görüntüleme yapılmamıştı. Görüntüleme planlanan 1 hastanın henüz sonucu çıkmamıştı. Görüntüleme yapılan 16 hastanın 9'unda (%31) T2 hiperintens lezyonlar saptanırken, 1 hastada (%3.45) ventriküllerde genişleme, 1 hastada (%3.45) optik sinir kılıfında BOS mesafesinde belirginleşme, 1 hastada (%3.45) kavernöz hemanjiom ve beyin sapı gliomu saptandı. Makrosefalisi olan iki hastanın birinde beyin MRG'de sağda optik sinir kılıfında BOS mesafesinde belirginleşme saptanırken, diğer hastada T2 hiperintens lezyonlar harici patoloji saptanmadı. Görüntüleme yapılan 5 hastada (%17.2) beyin Manyetik Rezonans Görüntülemede (MRG) herhangi bir patolojiye rastlanmadı.

Hastalar NF1'de sıklığı artan maligniteler açısından değerlendirildiğinde 3 hastada (%10.34) periferal nörofibrom,

Tablo I: Nörofibromatozis Tip 1 Tanı Kriterleri.

Altı veya daha fazla café au lait (sütlü kahve) makülleri (prepubertal hastalarda >5mm, postpubertal hastalarda >15 mm)
Aksiller ya da inguinal çillenme
İki veya daha fazla nörofibrom veya bir pleksiform nörofibrom varlığı
Optik glioma
İki veya daha fazla Lisch nodülü (iris hamartomu)
Ayırt edici kemik lezyonları (sfenoid displazi, uzun kemik kortekslerinde incelme)
Birinci derecede akrabada NF1 tanısının olması

NF1: *Nörofibromatozis Tip* 1

Tablo II: NF1 hastalarının sosyodemografik özellikleri.

Özellik	Sayı (%)
Cinsiyet Erkek Kız	17 (59) 12 (41)
Ortalama yaş	7.65 ± 4.25
Akrabalık	1 (3.44)
Pozitif aile öyküsü	10 (34.48)

Tablo III: NF1 hastalarının klinik özellikleri.

Klinik özellik	Hastalar (n=29)	≤8 yaş (n=17)	>8 yaş (n=12)
Café au lait lekeleri	29 (100)	17 (100)	12 (100)
Aksiller ya da inguinal çillenme	18 (62)	10 (58.8)	8 (66.6)
Nörofibrom	3 (10.3)	2 (11.7)	1 (8.3)
Optik glioma	0 (0)	0 (0)	0 (0)
Lisch nodülü	10 (34.4)	5 (29.4)	5 (41.6)
Kemik lezyonları	4 (13.79)	3 (17.6)	1 (8.3)
Bilişsel bozukluk	10 (34.4)	5 (29.4)	5 (41.6)
Epilepsi	3 (10.3)	2 (11.7)	1 (8.3)
Makrosefali	2 (6.9)	2 (11.7)	0 (0)
Boy kısalığı	4 (13.7)	2 (11.7)	22 (16.6)
Puberte prekoks	1 (3.45)	1 (5.8)	0 (0)

1 hastada (%3.45) beyin sapı gliomu, 1 hastada (%3.45) akut miyeloid lösemi saptandı. Olası gastrointestinal stromal tümör varlığı açısından hastaların 19'una (%65.5) abdomen USG yapıldığı ve hiçbir hastada patoloji saptanmadığı görüldü.

Endokrinolojik değerlendirmede 4 hastada (%13.7) boy kısalığı mevcutken, 1 hastada (%3.45) puberte prekoks saptandı. Kardiyak muayenesi yapılan toplam 9 hastanın 1'inde (%3.45) mitral valv prolapsusu (MVP) saptanırken, 8 hastada (%27.5) herhangi bir patolojiye rastlanmadı. Ortopedik komorbiditeler tarandığında 4 hastada (%13,79) ortopedik patoloji bulunurken (skolyoz, pes planus, kemik displazisi), 25 hastada (%86.2) herhangi bir patoloji saptanmadı.

Yirmidokuz hastanın 12'sinde (%41) genetik inceleme yapılmamıştı. Genetik inceleme yapılan 17 hastanın 12 tanesinde (%70.5) NF1 geninde mutasyon saptanırken, 5 hastanın (%29.5) NF1 dizi analiz sonuçları henüz çıkmamıştı (Tablo V). Hastaların mutasyonları 4 çerçeve kayması (frameshift), 3 anlamsız (nonsense), 2 kırpılma bölgesi (splice site), 1 yanlış anlamlı (missense), 1 çerçeve içi (inframe), 1 başlangıç kaybı (start loss) olarak sıralandı. Bu mutasyonların 2 tanesi ClinVar ve dbSNP veritabanlarında bildirilmemiş olup yeni (novel) mutasyonlardı.

Tablo IV: Klinik bulguların en küçük ve en büyük saptanma yaşları.

Klinik Bulgu	En Küçük Saptanma Yaşı	En Büyük Saptanma Yaşı
Café au lait lekeleri	Doğum	2 yaş
Aksiller ya da inguinal çillenme	4 yaş	12 yaş
Nörofibrom	7 yaş	15 yaş
Optik glioma	-	-
Lisch nodülü	3 yaş	15 yaş
Kemik lezyonları	4 yaş	9 yaş

TARTIŞMA

En sık görülen nörofibromatoz NF1'dir ve vakaların yaklaşık %90'nını oluşturur. Sıklığı 3000 canlı doğumda 1'dir (2). NF1 otozomal dominant olarak kalıtılır ancak hastaların %50'sin de aile öyküsü mevcuttur, kalan %50 ise de novo mutasyonlar nedeniyle gelişir (3). Bu çalışmada hastaların 10'unda (%34.48) aile öyküsü bulunurken, 19 hastada (65.52) aile öyküsüne rastlanmadı.

NF1 17q11.2'de lokalize NF1 genindeki mutasyonlara bağlı olarak oluşur (8). Her ne kadar kesin tanı için şart olmasa da klinik olarak şüphede kalınan vakaları doğrulamada genetik testler kullanılabilir. NF1'in klinik tanısını taşıyan hastaların yaklaşık yüzde 95'inde muhtemel patojenik varyantın bulunduğu bildirilmiştir (9). Bu nedenle, negatif bir test NF1 tanısını tamamen dışlamaz (10). Bu çalışmada 29 hastanın 12'sinde (%41) tanı klinik olarak konmuş ve genetik inceleme yapılmamıştı. Literatürde 78 NF1 hastasının incelendiği bir çalışmada toplam 52 mutasyon saptandığı bildirilmiştir. Bunların 30'u (%57.7) nokta mutasyon, 11'i (%21.2) splice site mutasyon, 8'i (%15.4) delesyon, 3'ü (5.8) insersiyon olarak bildirilmiş (11). Bu çalışmada genetik inceleme yapılan 17 hastanın 12 tanesinde (%70.5) NF1 geninde mutasyon saptanırken, 5 hastanın (%29.5) NF1 dizi analiz sonuçları henüz çıkmamıştı. Hastaların mutasyonları 4 çerçeve kayması (frameshift), 3 anlamsız (nonsense), 2 kırpılma bölgesi

Tablo V: Genetik incelemesinde mutasyon saptanan hastaların özellikleri.

	Mutasyon	Protein	Mutasyon tipi	Kalıtım şekli	CLINVAR	dbSNP
Hasta 1	c.2665delA	p.(Thr889HisfsTer13)	Çerçeve kayması	Heterozigot	Negatif	-
Hasta 2	c.6289delG	p.(Ala2097GlnfsTer14)	Çerçeve kayması	Heterozigot	Negatif	-
Hasta 3	c.499_502delTGTT	p.(Cys167GlnfsTer10)	Çerçeve kayması	Heterozigot	Pozitif	rs86201874
Hasta 4	c.1A>G	p.(Met1Val)	Başlangıç kaybı	Heterozigot	Pozitif	rs1060500252
Hasta 5	c.3113+1G>T	-	Kırpılma bölgesi	Heterozigot	Pozitif	rs267606599
Hasta 6	c.1246C>T	p.(Arg416*)	Anlamsız	Heterozigot	Pozitif	rs764079291
Hasta 7	c.1318C>T	p.(Arg440*)	Anlamsız	Heterozigot	Pozitif	rs778405030
Hasta 8	c.1738dupT	p.(Tyr580LeufsTer8)	Çerçeve kayması	Heterozigot	Pozitif	rs786204255
Hasta 9	c.2288T>G	p.(Leu763Arg)	Yanlış anlamlı	Heterozigot	Pozitif	rs19974762
Hasta 10	c.7159_7164delTAACTT	p.(Asn2387_ Phe2388del)	Çerçeve içi delesyon	Heterozigot	Pozitif	rs864622639
Hasta 11	c.2990+1G>A	-	Kırpılma bölgesi	Heterozigot	Pozitif	rs1135402836
Hasta 12	c.7909C>T	P(Arg2637*)	Anlamsız	Heterozigot	Pozitif	rs786201367

(splice site), 1 yanlış anlamlı (missense), 1 çerçeve içi (inframe), 1 başlangıç kaybı (start loss) olarak sıralandı. Bu mutasyonların 2 tanesi ClinVar ve dbSNP veritabanlarında bildirilmemiş olup yeni (novel) mutasyonlardı.

NF1'in en sık görülen bulgusu cafe au lait lekeleridir. Bu lekeler doğumdan sonraki ilk yıl içinde ortaya çıkan ve genellikle erken çocukluk döneminde artan düz, tekdüze hiperpigmente maküllerdir. Normal popülasyonun %15'inde 1-3 cafe au lait lekesi vardır; ancak ≥6 cafe au lait lekesi varlığı NF1 olma ihtimalini kuvvetle düşündürür (12). Bu çalışmada da literatürle uyumlu şekilde 29 hastanın tamamında cafe au lait lekeleri mevcuttu. Bu lekelerin en erken başlangıcı yenidoğan dönemiyken en geç başlangıcı 2 yaş olarak tespit edildi. Aksiller ve/veya inguinal çillenme sıklıkla doğumda bulunmaz ancak 3-5 yaş arasında görülebilir ve özellikle inguinal bölgede izlenir. Bu çalışmada da literatürle uyumlu şekilde 29 Çalışmada 18 hastada (%62) aksiller ve/veya inguinal çillenme mevcuttu. En erken çillenme tespit edilen hasta 4 yaşındayken, en geç tespit edilen hasta 12 yaşındaydı.

Lisch nodülleri irisin melanositik hamartomları olup NF1 için spesifiktir (6). Bu lezyonlar 2.5 yaşından itibaren iris yüzeyinde görülmeye başlar ve etkilenen erişkinlerin %90'ından fazlasında görülür (13). 162 NF1'li çocuk hastada yapılan bir çalışmada Lisch nodülü varlığı 3 yaşından küçük hastalarda %5, 3-4 yaş arasında %42, 4-5 yaş arasında %55 olarak saptanmıştır (14). Lisch nodülleri sıklıkla asemptomatik olup herhangi bir görme bozukluğuna yol açmaz ve tedavi gerektirmez (15). Bu çalışmada da literatürle uyumlu olarak 10 hastada (%34.4) Lisch nodülü saptandı. Lisch nodlünün en erken saptandığı yaş 3 yaşken, en geç Lisch nodülü tespit edilen hasta 15 yaşındaydı.

NF1'de Lish nodülüne ek olarak optik gliomlar da görülebilir. NF1 tanılı 5 yaşından küçük çocukların yaklaşık yüzde 15'inde optik gliomlar görülürken, daha büyük çocuklarda ve yetişkinlerde görülme ihtimali oldukça düşüktür (16). Bu çalışmada hiçbir hastada optik glioma rastlanmadı.

Bilişsel eksiklikler ve öğrenme güçlükleri, kaba ve ince motor alanlarda gelişimsel gecikmeler gibi pek çok nörolojik bozukluğun sıklığı NF1'de artar (6). Hastalar nörolojik açıdan değerlendirildiğinde; 10 hastada (%34.4) öğrenme güçlüğü ve bilişsel bozukluklar saptandı. NF1 hastalarında epilepsi sıklığı da normal popülasyona göre yaklaşık 2 kat artmıştır (17). Bu çalışmada 3 hastada (%10.3) epilepsi vardı. Hastaların tamamında jeneralize tonik klonik nöbetler mevcuttu. Birinci hasta valproik asit ve clobazam, ikinci hasta valproik asit ve levetirasetam, üçüncü hasta valproik asit, levetirasetam ve fenobarbital kullanıyordu. Epilepsisi olan hastaların beyin MRG'de ventriküllerde genişleme, diğer iki hastada T2 hiperintens lezyonlar mevcuttu.

NF1 hastalarında sıklıkla baş çevresi normalden büyük saptanır (18). Bunun nedeni beyin volümünde artıştır. Nadiren bazı hastalarda Chiari malformasyonu ve akuaduktal stenoza ikincil hidrosefali görülebilir (19, 20) Bu çalışmada 2 hastada (%6.9) makrosefali saptandı. Bu hastaların birinde beyin MRG'de sağda optik sinir kılıfında BOS mesafesinde belirginleşme saptanırken, diğer hastada T2/FLAİR hiperintensite harici patoloji saptanmadı.

Nörolojik muayenesi normal olan NF1 hastalarında rutin beyin ve boyun görüntülemenin takip ve tedavide yeri yoktur bu nedenle önerilmez (21). Görüntüleme yapılan NF1 hastalarında T2 ağırlıklı beyin MRG'de hiperintens lezyonlar (eski adıyla tanımlanmamış parlak nesneler / unidentified bright objects) kitle etkisi veya kontrast artışı olmaksızın hiperintens odak alanları olarak görünen iyi huylu ilerlemeyen lezyonlardır. En sık 8-16 yaş arası çocuklarda görülürler, yetişkinlikte kaybolma eğilimindedirler. Sayıları, büyüklükleri veya yerleşim yerleri öğrenme güçlüğü ve bilişsel bozukluğun varlığı ya da şiddeti ile korele değildir. En sık serebellumda, beyin sapında ve bazal ganglionlarda bulunurlar (22). Bu çalışmada 12 hastaya (%41) nörolojik muayenelerinin normal olması nedeniyle herhangi görüntüleme yapılmamıştı. Görüntüleme planlanan 1 hastanın henüz sonucu çıkmamıştı. Görüntüleme yapılan 16 hastanın

9 tanesinde (%31) T2 hiperintens lezyonlar saptanırken, 1 tanesinde (%3.45) ventriküllerde genişleme, 1 tanesinde (%3.45) kavernöz hemanjiom ve beyin sapı gliomu saptandı. 16 görüntüleme yapılan hastanın 5 tanesinde (toplam hastaların %17.2'si) beyin MRG'de herhangi bir patolojiye rastlanmadı.

NF1'de perieral nörofibrom, optik gliom, beyin sapı gliomları, malign sinir kılıfı tümörü, lösemi, gastrointestinal stromal tümörler gibi pek çok malignitenin sıklığı artmıştır (6). Bu çalışmada hastalar maligniteler açısından değerlendirildiğinde 3 hastada (%10.34) periferal nörofibrom, 1 hastada (%3.45) beyin sapı gliomu, 1 hastada (%3.45) akut miyeloid lösemi saptandı. Olası gastrointestinal stromal tümör varlığı açısından hastaların 19 tanesine (%65.5) abdomen USG yapıldığı ve hiçbir hastada patoloji saptanmadığı görüldü.

Endokrin, kardiyovasküler ve ortopedik pek çok komorbidite NF1'e eşlik edebilir (6). NF1'de boy kısalığı ve optik gliomlara bağlı puberte prekoks sıklığı artmıştır. NF'li hastaların %13'ünün boyu –2 standart sapmanın altında bulunmuştur (23, 24). Bu çalışmada 4 hastada (%13.7) boy kısalığı mevcutken 1 hastada (%3.45) puberte prekoks saptandı. Puberte prekoks olan hastanın optik gliomu ya da hipofizer adenomu bulunmuyordu. NF1 hastalarında konjenital kalp hastalıkları (özellikle pulmoner stenoz), hipertansiyon, renal arter steonzu gibi hastalıkların sıklığı artmıştır (21). Çalışmada 20 hastanın (%68.9) herhangi bir kardiyak muayenesinin olmadığı görüldü. Kardiyak muayenesi yapılan toplam 9 hastanın 1 tanesinde (%3.45) MVP saptanırken, 8 hastada (%27.5) patolojiye rastlanmadı. NF1'de bir diğer sıklığı artan komorbidite ortopedik komorbiditeler olup skloyoz, kifoz, kemik displazisi, nonossifiye fibrom gibi patolojiler NF1'de daha sık görülür. Hastalar ortopedik komorbiditeler tarandığında 4 hastada (%13.79) ortopedik patoloji bulunurken (skolyoz, pes planus, kemik displazisi), 25 hastada (%86.2) herhangi bir patoloji saptanmadı.

Sonuç olarak, NF1 klinik olarak karışık ve heterojen bir hastalıktır. Pek çok sistemi tutması, hastalarda malignite riskinin olması, eşlik edebilecek komorbiditeler ve bunların hayat kalitesine etkileri nedeniyle NF1 hastalarının yakından takip edilmesinin gerekli ve önemli olduğu kanısına varılmıştır.

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The Role of Hyperbaric Oxygen Therapy in Sudden Sensorineural Hearing Loss in Children

Çocuklarda Ani İşitme Kaybında Hiperbarik Oksijen Tedavisinin Yeri

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ABSTRACT

Objective: Sudden Sensorineural Hearing Loss (SSNHL) is an otological emergency. Permanent SSNHL can seriously affect the social life, psychology, and language development of pediatric patients. There is no consensus the treatment of SSNHL. We compared the etiology, prognostic factors, and treatment results in pediatric patients who received hyperbaric oxygen therapy (HBOT) in addition to systemic steroid therapy with a diagnosis of SSNHL.

Material and Methods: The files of 15 children were received HBOT with the diagnosis of SSNHL, between the ages of 8-18 years, and followed-up at least three months were retrospectively analyzed.

Results: The ages of patients with SSNHL ranged from 8 to 18 years of age (mean 14.47±3.31 years). Seven (46.7%) patients had complete recovery, and two (13.3%) patients had partial recovery, two (13.3%) patients had slight recovery, four (26.7%) patients had no improvement. While pre-treatment PTAs of the patients were ranged between 28 to 109 dB HL (mean±sd; 57.3±26.2 dB HL), post-treatment PTAs were 6 to 88 dB HL (38±27.3 dB HL), (p=0.002). No significant difference was found between age, gender, number of HBOT sessions and response to treatment (p = 0.581, p = 0.904, p = 0.357, p = 0.184, respectively).

Conclusion: Hyperbaric oxygen therapy is a safe and well-tolerated treatment modality for pediatric SSNHL patients. To avoid ethical and legal problems, we think that pediatric patients with a diagnosis of SSNHL should be initiated with the consent of the patient's parents.

Key Words: Adolescent, Child, Hyperbaric oxygen therapy, Prognosis, Sudden Hearing Loss

ÖZ

Amaç: Ani Sensörinöral İşitme Kaybı (ASNIK) otolojik bir acil durumdur. Kalıcı ASNIK, çocuk hastaların sosyal yaşamını, psikolojisini ve dil gelişimini ciddi şekilde etkileyebilir. ASNIK tedavisi konusunda fikir birliği yoktur. ASNIK tanısı ile sistemik steroid tedavisine ek olarak hiperbarik oksijen tedavisi (HBOT) alan çocuk hastalarda etiyoloji, prognostik faktörler ve tedavi sonuçları karşılaştırıldı.

Gereç ve Yöntemler: ASNIK tanısı ile HBOT uygulanan 8-18 yaşları arasında en az üç ay takip edilen 15 çocuğun dosyaları geriye dönük olarak incelendi.

Bulgular: ASNIK'li hastaların yaşları 8 ile 18 yaş arasındaydı (ortalama 14.47±3.31 yıl). Yedi (% 46.7) hastada tam iyileşme, iki (%13.3) hastada kısmi iyileşme, iki (% 13.3) hastada hafif iyileşme, dört (% 26.7) hastada düzelme olmadı.

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Contribution of the Authors / Yazarların katkısı*: *OZER EE: 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 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. ***AYSEL A:*** 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, Reviewing the article before submission scientifically besides spelling and grammar.

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Hastaların tedavi öncesi Saf Ses Ortalamaları (SSO) 28 ile 109 dB HL (ortalama±ss; 57.3±26.2 dB HL) arasında değişirken, tedavi sonrası PTA'ları 6 ile 88 dB HL (38±27.3 dB HL), (p=0.002). Yaş, cinsiyet, HBOT seans sayısı ve tedaviye yanıt arasında anlamlı bir fark bulunmadı (sırasıyla p = 0.581, p = 0.904, p = 0.357, p = 0.184).

Sonuç: Hiperbarik oksijen tedavisi, pediatrik SSNHL hastaları için güvenli ve iyi tolere edilen bir tedavi yöntemidir. Etik ve yasal sorunlara yol açmamak için ASNIK tanısı alan çocuk hastaların ailelerinin onayı ile tedaviye başlanması gerektiğini düşünüyoruz.

Anahtar Sözcükler: Ergen, Çocuk, Hiperbarik oksijen tedavisi, Prognoz, Ani İşitme Kaybı

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) develops within three days in a person with previously normal hearing and occurs with a hearing loss of more than 30 decibels at least three consecutive frequencies on the audiogram. SSNHL is an otological emergency (1). Permanent SSNHL can seriously affect the social life, psychology, and language development of pediatric patients (1,2).

SSNHL is found in all age groups that most commonly between the ages of 30-60, but fewer cases have been reported in children and the elderly (3). Alexander and Harris reported the incidence as 11/100000 in children under 18 years of age and 27/100000 in patients over 65 years of age (4). Most of the cases are unilateral; less than 2% of patients have bilateral hearing loss. However, the fact that the rate of spontaneous recovery of the disease is quite high and that most of these patients are not recorded because they do not consult a physician, it is thought that the real incidence is much higher than these reports (4).

Considering the gender distribution in SSNHL patients that observed no significant difference between the female and male rats (4).

The degree of hearing loss can range from mild to total hearing loss. Tinnitus, vertigo, and dizziness may accompany hearing loss (4).

Most of the cases of SSNHL are idiopathic. In the etiology of SSNHL that multiple factors such as infectious, vascular, autoimmune systemic diseases, neoplasia, trauma, ototoxic drugs (4).

There is no consensus the treatment of SSNHL, since there may be more than one factor in the etiology of SSNHL (4,5).

In clinical practice, many centers have developed combined treatment protocols containing multiple agents for the possible etiology of SSNHL. The main treatment methods are combined therapies including corticosteroids, hyperbaric oxygen therapy, vasodilators, antivirals, and vitamins. Hyperbaric oxygen therapy aims to increase oxygenation in the tissue and reduce inflammation and edema (6).

According to The Committee of the Undersea and Hyperbaric Medical Society, one of the indications for hyperbaric oxygen therapy (HBOT) is SSNHL (6). HBOT is used as a primary or recovery therapy as a combined method with intratympanic or systemic steroids (6,7). The use of HBOT in SSNHL treatment is based on an increase in perilymph oxygenation (8). HBOT reduces cochlear hypoxia, edema, and damage (6-8).

HBOT has been used frequently in the treatment of SSNHL in the last 20 years (6,7). HBOT must be explained to patients as a treatment option. Some authors recommend starting treatment within 48 hours or at the latest within 2 weeks (6-8). Some authors have suggested that HBOT can be combined with steroids, especially in patients with hearing loss greater than 70 dB (9). A clear consensus could not be reached on whether HBOT should be used alone or as an adjunct or recovery therapy for the SSNHL (9,10). However, considering its mechanism of action, HBOT should be used in combination with other treatments at an early stage (11).

HBOT is a medical treatment based on breathing 100% oxygen continuously or intermittently under pressure higher than 1 atmosphere absolute (1 ATA, 1 Bar, 760 mmHg) in the pressure chamber. Treatments usually take 90 to 120 minutes and depending on the indication, one or more sessions per day can be applied (11).

The most common complication of HBOT is barotrauma in the ear, sinus, and teeth due to pressure changes. Middle ear barotraumas are the most common among barotraumas and can also be prevented by patient education and slow compression-decompression (11,12). Ear equalization training is given to patients before treatment, especially with the Valsalva maneuver (11,12). You will appreciate that it is difficult in terms of treatment compliance to provide these training in children and for children to apply these maneuvers (11,12). Myringotomy may also be an option if there is an unsuccessful ear equalization (11,12). Due to the nature of the treatment, claustrophobia is another possibility. Parents can also accompany the treatment for support purposes, especially in young children (11,12). Of course, detailed anamnesis for parents should be taken especially in terms of pneumothorax risk. Lung barotrauma is another rare but serious complication (11,12). During decompression, alveolar rupture may occur in lesions that cause air trapping in the lung (cyst, cavern, etc.), bronchial obstruction (11,12). It can cause pneumothorax, pneumomediastinum, subcutaneous emphysema, and gas embolism (11,12). Therefore, a detailed history and consent should be taken before treatment from the patient's parents (11,12). The side effects mentioned are extremely rare. This makes the treatment selectable (11,12).

The literature on the use of hyperbaric oxygen therapy in hearing loss in the pediatric population is limited. In this study, we compared the etiology, prognostic factors, and treatment results in pediatric patients who received HBOT in addition to systemic steroid therapy with a diagnosis of SSNHL. We aimed to contribute to the literature with our cases.

MATERIALS and METHODS

A retrospective chart review was performed to identify patients who were admitted to our center with the diagnosis of SSNHL and received HBOT between January 2016 and October 2020. The files of 15 children, between the ages of 8-18 years and followed-up at least three months were retrospectively analyzed. The study, Health Sciences University Izmir Bozyaka Education and Research Hospital Clinical Research Ethics Committee approved (21.102020/08). Written informed consent was obtained from the patients participating in the study .

While patients with pure tone audiometry before and 5. Day, 14. day and at least 3 months after treatment were included, patients with acute-chronic otitis media, middle ear, and retrocochlear pathology, autoimmune inner ear disease, Meniere's disease, syndromic and genetic hearing loss, patients who underwent surgery were excluded in the study.

In pure tone audiometry, the average pure tone thresholds of 500 Hz, 1000 Hz, 2000 Hz , and 4000 Hz were accepted as pure tone averages (PTA). Following the American Speech and Hearing Association guidelines, the severity of hearing loss was based on the PTA as follows;

- 25-40 dB HL mild,
- 41-55 dB HL moderate,
- 56-70 dB HL moderate-severe,
- 71-90 dB HL severe
- >90 dB HL profound.

Patients' recovery status was determined according to Siegel's criteria (13) (Table I).

In pure tone audiometry, the average of 500, 1000, 2000, and 4000 Hz frequencies was calculated as the pure tone average (PTA).

Audiogram configurations were evaluated in three groups, ascending (hearing losses keeping 250-500 Hz), descending (hearing loss keeping 4000-8000 Hz), flat type (less than 20 dB difference between the best and worst hearing thresholds hearing losses) (14).

All patients were treated with systemic steroids. Oral methylprednisolone was administered at a dose of 1 mg/kg and tapered in 14 days. Patients who did not improve or had a PTA greater than 60 dB HL at the fifth-day control audiogram, were injected three doses (1 dose=0.5 ml=2mg) of intratympanic dexamethasone solution (Dekort, DEVA Corporation, Istanbul, Turkey) every other day if they tolerated the injection. Patients with a history of upper respiratory tract infection were tested for CMV, EBV, Mumps, Herpes viruses (HSV, VZV), and Influenza, and antiviral treatment was initiated in patients with positive viral serology.

All patients were administered 1 session 2.4 ATA a day for 120 minutes, for 4 weeks. (20 sessions in total) One HBOT session lasts 120 minutes. Patients breathe oxygen at 2.4 ATA for 90 minutes. There is a 5-minute air break between each oxygen period (30 minutes). Oxygen is inhaled through a mask in the pressure chamber.

Statistical Analysis

Descriptive statistics was calculated for all variables, an association between the groups were evaluated using the Chi-square test. The Independent Samples t-test was used to compare the means of two independent groups and the nonparametric Mann-Whitney U test was applied to investigate continuous variable prognostic factors. All statistical analyses were performed using SPSS version 22.0 (IBM SPSS Statistics, Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

RESULTS

Fifteen children were treated with the diagnosis of SSNHL during the study period. All patients had idiopathic etiology. The ages of patients with SSNHL ranged from 8 to 18 years of age (mean 14.47 ± 3.31 years).

Nine (60%) of the patients were boys and 6 (40%) were girls. While the hearing loss was on the right side in 46.7% (n = 7) of the children, it was on the left side in 53.3% (n = 8) (Table II). Hearing loss was bilateral in none of the patients.

Nine patients had tinnitus accompanying hearing loss (Table II). The degrees of sensorineural hearing loss were; 26.7% (n=4) mild, 40% (n=6) moderate, 20% (n=3) severe, 13.3% (n=2) profound.

Table I: Siegel Criteria.

Complete recovery	Final hearing level was better than 25 dB HL
Partial recovery	More than 15 dB HL of gain, final hearing 25-45 dB HL
Slight improvement	More than 15 dB HL of gain, final hearing poorer than 45 dB HL
No improvement	Less than 15 dB HL of gain or final hearing poorer than 75 HL dB

dB : *Decibel,* ***HL :*** *Hearing Level*

Table II: The clinic, demographics and history of patients

Case No	Age	Gender	Side	Degree of Hearing Loss	Audiometric Type	Outcomes (Siegel)	Concurrent Symptom	Comorbidity	HBOT Sessions	Treatment
1	10	G	L	moderate	Descen.	no impr.	none	none	15	SS+ITS
2	11	B	R	mild	flatting	no impr.	none	none	18	SS
3	11	B	R	severe	flatting	no impr.	none	none	20	SS
4	12	B	L	moderate	Ascen.	complete	tinnitus	none	15	SS
5	14	G	L	moderate	Descen.	complete	tinnitus	none	15	SS
6	15	B	L	moderate	flatting	complete	none	ADHD	10	SS+ITS
7	15	G	R	mild	Descen.	partial	tinnitus	none	20	SS
8	16	B	L	severe	Descen.	complete	none	none	13	SS
9	16	B	R	profound	flatting	slight	none	none	25	SS
10	17	G	R	mild	Descen.	complete	tinnitus	Type 1 DM	10	SS
11	18	B	R	moderate	flatting	partial	none	none	7	SS+ITS
12	18	G	L	mild	Descen.	complete	none	none	40	SS
13	18	B	R	moderate	Descen.	complete	tinnitus	none	10	SS
14	18	G	L	severe	Descend.	slight	none	none	20	SS
15	8	B	L	profound	flatting	no impr.	tinnitus	none	15	SS+ITS

***B:** Boy, **G:** Girl, **R:** Right, **L:** Left, **HBOT:** Hiperbaric Oxygen Therapy, **ADHD:** attention deficit and hyperactivity disorder, **SS:** Systemic Steroid, **ITS:** Intratympanic Steroid.*

Eleven patients received systemic steroids+HBOT, four patients received systemic steroids + intratympanic steroids+HBOT. There was no significant difference in improvement between the two groups (p = .40).

Of the nine patients with tinnitus, 2 of the patients had mild hearing loss, 2 had moderate hearing loss, one had mild-moderate, 3 had severe hearing loss, and 1 had profound hearing loss. After HBOT, in two patients with mild hearing loss, 1 patient was observed complete recovery, while 1 patient was observed no improvement. In two patients with moderate hearing loss, 1 patient was observed complete recovery, while 1 patient was observed no improvement. Partial recovery was seen in one patient with moderate hearing loss. In three patients with severe hearing loss, 1 patient was observed complete recovery, 1 patient had slight improvement, and 1 patient had no improvement. A slight improvement was observed in one patient with profound hearing loss (Table II).

6 patients did not have any symptoms. After HBOT, of these patients, 2 patients with mild hearing loss had a full recovery and 1 patient had partial recovery. In 3 patients with moderate hearing loss, three patients were observed complete recovery. In 1 patient with profound hearing loss, no improvement was

Tablo III: Clinical results of Cases.

	Mean±SD (Minimum-Maximum)
Age (years)	14.47±3.31 (8-18)
Initial treatment time (day)	5.73±6.62 (1-27)
Follow-up (month)	26.7±9.7 (7-39)
PTApre (dB HL)	57.3±26.2 (28-109)
PTApost (dB HL)	38 27.3 (6-88)

SD: *Standart Deviation,* ***dB:*** *decibel,* ***HL:*** *Hearing Level,* ***PTA:*** *Pure Tone Averages.*

observed (Table II). It was found that the presence of tinnitus and no additional symptoms did not significantly different treatment outcomes (p = .449).

Seven (46.7%) patients had complete recovery, two (13.3%) patients had partial recovery, two (13.3%) patients had a slight recovery, four (26.7%) patients had no improvement (Table II).

While pre-treatment PTAs of the patients were ranged between 28 to 109 dB HL (mean±sd; 57.3±26.2 dB HL), post-treatment PTAs were 6 to 88 dB HL (38±27.3 dB HL), (p=.002). According to the audiogram configurations, one patient had ascending type, 8 patients had a descending type, 6 patients had flatting type (Table II).

Five of the 8 patients with descending type audiogram, 5 patients had complete recovery, one patient had partial recovery, one patient had slight improvement, and one patient had no improvement. Of the six patients with a flatting type audiogram, one patient had complete, one patient had partial, one patient had slight improvement, while three patients had no improvement. One patient with ascending type audiogram had complete recovery (Table II). There was no significant difference between audiogram type and treatment outcomes (p = .509).

Ten of the 15 patients applied to us within the first five days after the onset of hearing loss. After HBOT, 4 patients had complete recovery, 2 patients had partial recovery, 1 patient had slight improvement, and 3 patients had no improvement (Table II).

The mean follow-up period ranged from 7 to 39 months (mean 26.7±9.7).

The time passed from hearing loss and initiation of the treatment was 1-27 days (mean 5.73±6.62) (Table III). The number of HBOT sessions the patients received was 16.87 ± 8.02 (7-40), (Table III).

It was observed that five patients who started treatment between the 6th and 27th days, 3 patients had complete recovery, one patient had slight improvement, and one patient had no improvement (Table II).

No significant difference was found between age, gender, number of HBOT sessions and response to treatment (p = .581, p = .904, p = .357, p = .184, respectively).

Complications such as rupture of the eardrum, serous otitis media, claustrophobia, and oxygen toxicity did not occur in any of the patients. Patients' demographics and history are summarized in Table II.

DISCUSSION

Since multiple mechanisms are blamed in the etiology of SSNHL, multiple treatment protocols are often preferred. Steroids, hyperbaric oxygen therapy, antiviral drugs, vitamins, anticoagulants, vasodilators are the most preferred treatment options used in different combinations (15). Hyperbaric oxygen therapy (HBOT) was first used for SSNHL in the late 1970s (16).

The cochlea is an organ that requires high oxygen but has a relatively limited vascular supply. With HBOT, 100% oxygen is given at high pressure to increase the diffusion of oxygen to the inner ear. Many studies have shown that early treatment with HBOT is more beneficial than late treatment (17-19). There is no clear information in the literature regarding the HBOT regimen.

According to the guidelines of the American Otorhinolaryngology Academy- Head and Neck Surgery Foundation published in 2019, HBOT and steroid combination is accepted as the initial treatment in the first 2 weeks, and HBOT + steroid combination, which is started within 1 month, is recommended as a rescue therapy (18,19).

In the literature, absolute atmospheric pressure (from 1.5-2.8 ATA) varied between the duration of the treatment session (30-120 minutes), and the amount amount amount amount number of sessions given (10-25 sessions) 18-20).

HBOT has been used either alone or in addition to other medical treatments in the treatment of SSNHL (19,20).

In some studies, they found that starting HBOT at the earliest time (up to 2 weeks at the latest) was beneficial, especially in severe hearing loss (over 70 dB) (20). In this study, HBOT+oral steroid was started in all our patients, and oral + intratympanic steroid+HBOT was started in 4 patients. HBOT was started in the first 2 weeks in 14 of 15 patients.

Early initiation of treatment, absence of vestibular symptoms, presence of tinnitus, ascending type hearing loss in the audiogram, and unilateral hearing loss are considered as good prognostic factors (18-20). Late initiation of treatment, descending type of hearing loss on the audiogram, presence of vestibular symptoms, bilateral hearing loss, total or total near-total hearing loss are considered as poor prognostic factors (18-20). In our study, improvement was found in 7 of 9 cases with tinnitus. These results supported the positive effect of tinnitus on prognosis.

One of the most important factors affecting the prognosis of the disease is the degree of initial hearing loss. Initially, the

severity of the hearing loss is a negative prognostic factor, and the deeper it is, the less expected recovery of hearing (20). In our study, one of the five patients with severe and profound hearing loss had complete recovery, two patients had slight improvement, and two patients had no improvement. Six of the 10 patients with mild, mild-moderate, and moderate hearing loss had complete recovery, two had partial recovery, and two had no improvement.

Another important prognostic factor determining the response in treatment is the time elapsed between the onset of hearing loss and the initiation of treatment, the earlier the treatment is initiated, the better the response will be obtained. It is thought that after 30 days, the active process resolves and the damage becomes permanent (20). Although there is no common consensus about the time to start treatment, the opinions are that it should be started as soon as possible. 14 of our patients were started treatment within the first 2 weeks.

According to audiogram types, some articles have shown that ascending type audiograms have a better prognosis compared to descending type audiograms (19-21). In our study, one patient had ascending type audiogram that was observed complete recovery. We found improvement in 7 of 8 patients with a descending type audiogram.

Overall (complete + partial+ slight) recovery rates in pediatric SSNHL were reported between 55.20% and 70.67% in the literatüre (20-22). In our study, overall recovery rates were reported 73.33% (n=11/15). The limitations of this study include its retrospective nature and the limited number of patients in the pediatric population. Another limiting factor is that we applied HBOT to all patients. The presence of a hyperbaric center in our hospital may cause this.

Although the early application of HBOT is recommended, it may not be possible in practice. Especially in Turkey, begun to spread HBOT centers as well as public and private centers in recent years it is not available in all provinces. Current HBOT centers can be found at www.sualti.org. It is cost-effective that is another question that comes to mind. There is a significant percentage of patients known to recover spontaneously (23).

However, it is not known which patient will be left to recover spontaneously. Failure to apply an available treatment can also be an ethical crime. HBOT costs are very low in Turkey compared to other countries in the World (24). Its addition to routine steroid treatment can be said to be cost-effective.

CONCLUSIONS

Hyperbaric oxygen therapy is a safe and well-tolerated treatment modality for pediatric SSNHL patients. To avoid ethical and legal problems, we think that pediatric patients with a diagnosis of SSNHL should be initiated with the consent of the patient's parents.

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Esansiyel Hipertansiyonlu Çocuklarda Renalaz Seviyeleri

Serum Renalase Levels in Children with Essential Hypertension

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ÖZ

Amaç: Sol ventrikül hipertrofisi, ekokardiyografinin yaygın kullanımı nedeniyle hipertansiyona bağlı hedef organ hasarı için en sık çalışılan indekstir. Renalaz, esas olarak böbrekler tarafından üretilen, katekolaminleri azaltarak kan basıncını düzenleyen ve kardiyovasküler fonksiyonlara etki eden bir monoamin oksidazdır. Bu çalışmada esansiyel hipertansiyonlu çocuklarda serum renalaz düzeyi ile hipertansif kardiyak değişiklikler arasındaki ilişki sağlıklı kontrol grubu ile karşılaştırıldı.

Gereç ve Yöntemler: Çalışmaya 4-18 yaş (ortalama 15.1±1.9 yıl) arasında 60 hipertansif çocuk (kız/erkek 20/40) dahil edildi. Vücut kitle indeksi normal (4-18, ortalama 14.2±1.3 yıl) ve benzer cinsiyete sahip (kadın/erkek 10/10) 20 sağlıklı çocuk kontrol grubunu oluşturdu. Hipertansif çocukların 30'unda (kadın/erkek: 9/21) ekokardiyografide sol ventrikül hipertrofisi görüldü. Geriye kalan 30 hipertansif hastanın (kadın/erkek: 11/19) ekokardiyografik bulguları normaldi. Hipertansif gruplardan biyokimyasal incelemeler ve renalaz düzeyi için venöz kan örneği alındı. İdrar örnekleri ve 24 saatlik idrar örnekleri toplandı. Hipertansif grupların kan basıncını ölçmek için 24 saatlik ambulatuar kan basıncı izleme (ABPM) kullanıldı. Hipertansif grupların kardiyak değerlendirmesi M-mod ekokardiyografi kullanılarak yapıldı.

Bulgular: Hipertansif gruplarda vücut kitle indeksi normal kan basıncı olan gruba göre anlamlı olarak daha yüksekti ($p<0.05$). Hipertansif gruplar karşılaştırıldığında beden kitle indeksi açısından anlamlı fark bulunmadı. Tüm gün sistolik, diyastolik; gece sistolik, diyastolik ve gündüz sistolik kan basıncı yükleri, hipertansif sol ventrikül hipertrofik grupta hipertansif hipertrofik olmayan gruba göre anlamlı olarak daha yüksekti ($p <0.05$). M-mod ekokardiyografide sol ventrikül kitle indeksi, sol ventrikül hipertrofik grupta 39.7 g/m^2 ve hipertansif hipertrofik olmayan grupta 27.9 g/m^2 olarak bulundu ($p <0.05$). Kan basıncı yükleri ile sol ventrikül kitle indeksi arasındaki ilişki gruplar arasında karşılaştırıldığında, gündüz sistolik kan basıncı yükü ile artmış sol ventrikül kitle indeksi arasında anlamlı bir ilişki bulundu ($p<0.05$). Renalaz düzeyi, hipertansif gruplarda normotansif gruba göre anlamlı derecede düşüktü ($p <0.05$). Renalaz eksikliği ile artmış sol ventrikül kitle indeksi arasında bir ilişki vardır.

Sonuç: Renalaz eksikliği ile artmış sol ventrikül kitle indeksi arasında bir ilişki vardır. Düşük renalaz düzeylerinin erken belirteç olarak kullanılmasının, sol ventrikül hipertrofisi ve uzun dönem hipertansiyon komplikasyonları açısından risk altındaki hastaları belirlemede yararlı ve değerli bir parametre olabileceğine inanıyoruz.

Anahtar Sözcükler: Çocuklar, Hipertansiyon, Renalaz, Sol ventrikül kitle indeksi

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ABSTRACT

Objective: Left ventricular hypertrophy is the most commonly studied index for hypertension related target organ damage due to the wide usage of echocardiography. Renalase is a monoamine oxidase, mainly produced by the kidneys, regulating blood pressure by reducing catecholamines and acting on cardiovascular functions. In this study, the relationship between serum renalase level and hypertensive cardiac changes in children with essential hypertension was compared with the healthy control group.

Material and Methods: A total of 60 hypertensive children (female/male 20/40) aged between 4-18 years (mean 15.1±1.9 years) were included in the study. Twenty healthy children with normal body mass index (4-18, mean14.2±1.3 years) and similar gender (female/male 10/10) formed the control group. In 30 of hypertensive children (female/male: 9/21), echocardiography showed left ventricular hypertrophy. Echocardiographic findings of 30 remaining hypertensive patients (female/male: 11/19) were normal. A venous blood sample was collected from the hypertensive groups for biochemical examinations and renalase level. Urine samples and 24-hour urine samples were collected. 24-hour ambulatory blood pressure monitoring (ABPM) was used to measure blood pressure of hypertensive groups. The cardiac evaluation of hypertensive groups was performed using M-mode echocardiography.

Results: The body mass index was significantly higher in hypertensive groups than the group with normal blood pressure ($p < 0.05$). In comparison of hypertensive groups, no significant difference was found in terms of body mass index. All day systolic, diastolic; night systolic, diastolic, and daytime systolic blood pressure loads were significantly higher in hypertensive left-ventricular hypertrophic group than hypertensive non-hypertrophic group ($p < 0.05$). Left ventricular mass index in M-mode echocardiography, revealed 39.7 g/m^2 in the left ventricular hypertrophic group and 27.9 g/m^2 in the hypertensive non-hypertrophic group ($p < 0.05$). When the relationship between blood pressure loads and left ventricular mass index was compared between the groups, a significant correlation was found between daytime systolic blood pressure load and increased left ventricular mass index ($p < 0.05$). Renalase level was significantly lower in hypertensive groups compared to normotensive group ($p < 0.05$). There is a relationship between renalase deficiency and increased left ventricular mass index.

Conclusion: There is a correlation between renalase deficiency and increased left ventricular mass index. We believe that utilization of low renalase levels as an early marker may be a useful and valuable parameter for determining the patients at risk for left ventricular hypertrophy and long-term complications of hypertension

Key Words: Children, Hypertension, Renalase, Left ventricular mass index

GİRİŞ

Hipertansiyon (HT) ileri yaşlarda ortaya çıkan kalp, beyin ve damar hastalıkları için temel risk faktörüdür ve kökleri çocukluk çağına uzanır. Çocukluk çağında hipertansiyon prevalansı erişkine göre daha düşüktür (1). Süt çocuğu ve küçük çocuklarda hipertansiyon varlığı daha çok altta yatan bir hastalığa işaret ederken (sekonder hipertansiyon), primer hipertansiyon prevalansı okul çağı çocukları ve ergenlerde obezite epidemisine bağlı olarak artmaktadır Esansiyel veya primer hipertansiyon kan basıncının belirli bilinen bir neden olmaksızın yükselmesidir (2).

Çocukluk çağında esansiyel/primer hipertansiyona bağlı son organ hasarı bulgularına rastlanmakta, sıklıkla da asemptomatik hipertansif çocuklar hedef organ bulguları nedeniyle başvurmaktadırlar. Hipertansif çocukların %40'ında sol ventrikül hipertrofisi ve erken ateroskleroz bulgusu olan intima-media kalınlaşması mevcuttur (3).

Hipertansiyona bağlı son organ hasarının patogenezinde yer alan biyolojik faktörlerin saptanması, yeni tedaviler geliştirilmesine olanak sağlaması açısından önemlidir. Renalaz esas olarak böbrekler tarafından üretilen ve dolaşımdaki katekolaminleri, özellikle de adrenalini azaltarak etki gösteren yeni keşfedilmiş bir monoamin oksidazdır (4). Renalaz eksikliği dirençli hipertansiyon ve dolaşımdaki yüksek katekolamin düzeylerine bağlı olarak artmış sempatik aktivite ile ilişkilidir. Renalaz katekolaminleri metabolize etmek için nikotin adenin dinükleotid kullanır. Renalaz uygulanması plazma epinefrin, L-Dopa ve dopamin düzeylerini çeşitli oranlarda azaltmaktadır. Renalaz kan seviyesi üç ana faktör tarafından belirlenmektedir. Bunlar böbrek fonksiyonu, renal perfüzyon ve kan katekolamin düzeyleridir. Son dönem böbrek yetmezliği olanlarda belirgin renalaz eksikliği bulunmaktadır (5).

Renalaz eksikliği, sol ventrikül hipertrofisi ve artmış sol ventrikül kitle indeksi ile ilişkilidir (6). Sol ventrikül hipertrofisi varlığı, hem tedavi hem de izlemi gerektiren bir hasar göstergesidir. Ekokardiyografi ile sol ventrikül kitle indeksi hesaplanarak, sol ventrikül hipertrofisinin niceliksel değerlendirilmesi yapılabilmektedir. Sol ventrikül kitle indeksi çeşitli ölçümler yapıldıktan sonra bu ölçümlerden Devereux formülü kullanılarak hesaplanır (7).

Bu çalışmadaki amacımız, renalazın esansiyel hipertansiyon ve hipertansif kardiyak değişiklikler ile ilişkisinin değerlendirilerek, renalazın hipertansiyon etiyolojisindeki rolünün belirlenmesidir.

GEREÇ ve YÖNTEMLER

Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji EAH pediatrik nefroloji polikliniğinden takipli 4-18 yaş arasında 60 hipertansif çocuk çalışmaya dahil edildi. Benzer yaş ve cinsiyet gibi özelliklere sahip, hipertansif olmayan 20 sağlıklı çocuk, kontrol grubunu oluşturdu. Olguların anamnez, özgeçmiş, soygeçmiş ile ilgili bilgileri, antropometrik ölçümleri, kan basıncı ölçümleri ile laboratuar bulguları daha önce basılmış ve üzerinde hastanın demografik bilgilerinin de bulunduğu

formlara kaydedildi. Çalışma için S.B. Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan onay alınmıştır (Etik kurul no:2017/074).

Ekokardiografi için Philips IE33 cihazında X5-1 probu kullanılarak yapıldı. Uzun eksen görüntülemede M- mode ekokardiyografi ile elde edilen veriler ekokardiyografi formlarına kaydedildi. Daha sonraki basamakta ekokardiyografik olarak sol ventrikülde hipertansif kardiyak değişikliği olan 30 primer hipertansiyonlu çocuk, ekokardiyografik olarak hipertansif kardiyak değişiklik saptanmayan 30 primer hipertansiyonlu çocuk ve kontrol grubunda yer alan, kan basıncı normal olan 20 sağlıklı çocuk ayrıntılı olarak değerlendirildi. Tüm hastalar HT'un olası sebepleri açısından değerlendirildi. Sekonder HT saptanan olgular ve çalışma sırasında fizik muayenede herhangi bir enfeksiyon bulgusu olanlar çalışmaya alınmadı. Çalışmaya alınan tüm çocuklar ve aileleri çalışma hakkında bilgilendirildikten sonra ebeveynlerinden izin alınarak onam formu imzalatıldı. Tüm olguların anamnez, özgeçmiş, soygeçmiş ile ilgili bilgileri, antropometrik ölçümleri, arteriyel KB ölçümleri ile laboratuar bulguları daha önce basılmış ve üzerinde hastanın demografik bilgilerinin bulunduğu formlara kaydedildi. One Way Anova, independent-t test ve ki-kare testleri kullanılarak verilerin analizleri yapıldı; $p \leq 0.05$ anlamlı kabul edildi.

Seçilen 80 çocuğun boyu,vücut ağırlığı ölçüldü, boy ve vücut ağırlıklarının persentilleri, vücut yüzey alanları, vücut kitle indeksleri hesaplandı. Kan basınç ölçümleri yapıldı. Boy ve vücut ağırlığı persentilleri için Neyzi ve ark. (8) yapmış olduğu çalışma temel alındı. Vücut yüzey alanı [4 x VA(kg) + 7] /[90+VA(kg)], VKİ ise [VA (kg)]/[Boy(m)^2] formülleri ile hesaplandı. Vücut kitle indeksi verilerine göre normotansif grubun %35'i obez, Hipertansif olup Ekoda bulgu olmayan [HTEKO (-)] grubun %46.7'si obez ve Hipertansif olup Ekoda bulgulu [HTEKO (+)] grubun %60'ı obezdi. Hastalarımızın hiçbirinde kronik böbrek yetersizliği yoktu. Kan basınçları, çocuğun nondominant koluna uygun boyutta manşon kullanılarak civalı manometre (ERKA D-83646Bad Tölz-Germany) ile en az 5 dakika oturarak dinlenme periyodu sonunda üç kez ölçüm yapılarak ve bu ölçümlerin ortalamaları alınarak hesaplandı. Sistolik kan basıncı korotkoff seslerinin başlangıcı olarak, diastolik kan basıncı ise 5.korotkoff sesi olarak tanımlandı.

Hipertansif gruplardan biyokimyasal incelemeler için venöz kan örneği toplandı. İdrar incelemeleri için sabah ilk idrar örnekleri ve 24 saatlik idrar örnekleri kullanıldı. Venöz kan örnekleri açken alınmış olup serum üre, kreatinin, total kolesterol, HDL-kolesterol, LDL-kolesterol, VLDL-kolesterol, trigliserid, adrenalin, T4,TSH düzeyleri çalışıldı.Plazma renin ve aldosteron ölçümleri için kan örnekleri alınmadan önce hastalar yaklaşık 30 dakika boyunca oturur pozisyonda bekletilmiş ve EDTA'lı tüpe alınan örnekler IRMA (Immünoradiometric assay) yöntemiyle çalışılmıştır.

Hipertansiyon nedenine yönelik istenen bu kan tetkiklerinin alınması sırasında hastalardan renalaz düzeyi bakılması için 2 cc kan örneği alınıp santrifüj edilerek renalaz düzeyi bakılmak üzere ayrıldı. Renalaz "LifeSpan Biosciences Human Renalase, ABD" kitiyle ELISA (Sandwich ELISA) yöntemi kullanılarak çalışıldı. Normal değerler kitinormal olarak algıladığı 0.78-50 ng/ml olarak belirlendi ve 0.78 ng/ml'nin altındaki değerler normalden düşük olarak kabul edildi. İdrar örneğinden tam idrar analizi yapıldı, idrar mikroskobisi incelendi ve idrarda adrenalin, mikroalbumin düzeyleri çalışıldı. Vanilmandelik asit (VMA) ve 5-Hidroksiindolasetik asit (5- HIAA), üç günlük vanilinden fakir diyet sonrası 24 saatlik idrarda çalışıldı.

Kan basıncı ölçümleri 24 saat boyunca yaşam içi kan basıncı monitörü ile hastalara uygun boyutta manşon takılarak uyanıklık döneminde 20 dakikada bir, uyku döneminde 30 dakikada bir yapıldı. AKBM için, Erkameter 24 ABPM (Bad Tölz, Germany) cihazı kullanıldı. Hasta ve kontrol grubunun uyku-uyanıklık dönemleri kaydedildi. Doğru veya tam olmayan ölçümler çalışmadan çıkarıldı. Çalışma gruplarının ölçümlerinde tüm gün, gece ve gündüz sistolik ve diastolik kan basıncı yükleri değerlendirildi.

Hastalar için 95 persentilin üzerinde ölçülen Kan basıncı(KB) değerlerinin normal KB değerlerine oranı KB yükü olarak tanımlandı. Kan basıncı yükü % 25'in altındaki değerler normal, %25'in üzerindeki değerler yüksek, %50'nin üzerindeki değerler ciddi yüksek olarak tanımlandı (8,9).

Ekokardiyografik değerlendirmede, sol ventrikül diastol sonu çap (SVDSç), interventriküler septum diastolik kalınlığı (IVSd), sol ventrikül arka duvar diastolik kalınlığı (SVADd) değerlerine bakılmış ve bu değerler kullanılarak sol ventrikül kitlesi (SVK) Devereux formülü kullanılarak hesaplanmıştır (10).

SV kitlesi = 1.04 ([SVDSç + SVADd +IVSd]3- [SVDSç]3) -13.6 g

Sol ventrikül kitlesinin hastanın metre cinsinden boyunun 2 kuvvetine oranlanmasıyla Sol ventrikül kitle indeks (SVKI) değeri hesaplandı. SVKI, < 38.6 g/m^2 olan değerler (95 p. den küçük olan değerler) normal olarak kabul edildi. Bu değerin üstü ise artmış SVKI olarak kabul edildi (7). Verilerin istatistiksel değerlendirmesi Statistical Package for the Social Sciences (SPSS) for Windows sürüm 15.0 kullanılarak yapıldı. Kantitatif veriler tablolarda ortalama, standart deviasyon (SD), median, minimum ve maksimum değerler şeklinde ifade edildi. Kategorik veriler ise "n" (sayı) ve yüzdelerle (%) ifade edildi. Bağımsız grupların ikili karşılaştırılmasında bağımsız örneklem t-testi ve çoklu grupların karşılaştırmasında Tek yönlü varyans analizi testi kullanıldı. Kategorik verilerin karşılaştırılmasında ise ki-kare testi kullanıldı. Tüm karşılaştırmalarda $p<0.050$ değerleri istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya 60 hipertansif (40 erkek, %66,6; 20 kız, %33.3), 20 sağlıklı çocuk (10 kız, %50; 10 erkek, %50) alındı (Tablo

Tablo I: Grupların demografik, klinik ve ekokardiyografik parametrelerinin karşılaştırılması.

Değişkenler	HTEKO (-) grup (n=30)	HTEKO (+) grup (n=30)	Normotansif grup (n=20)	p
Yaş (yıl)	14.8 ± 2.29	15.2 ± 1.57	14.1 ± 1.26	0.370
Boy (cm)	163.8 ± 12.5	167.1 ± 10.1	160 ± 6.5	0.070
Erkek Cinsiyet*	19 (63.3)	21 (70)	10 (50)	
Kız cinsiyet*	11 (36.7)	9 (30)	10 (50)	
VKİ (kg/m^2)	26.9 ± 4.9	28.3 ± 5.5	22.4 ± 7.1	
İzlem süresi (ay)	10.8 ± 5.7	19.9 ± 18.2		
Akrabalık*	3 (10)	5 (16.6)		
Kullanılan ilaçlar*				
ADEİ	2 (6.6)	5 (16.6)		
ARB	0 (0)	2 (6.6)		
KKB	11 (36.6)	13 (43.3)		
Çoklu ilaç	1 (3.3)	7 (23.3)		
Klinik SKB (mmHg)	129.1 ± 8.4	131.6 ± 8.7	103 (90-110)	0.420
Klinik DKB (mmHg)	80.3 ± 7.3	83 ± 8.2	68 (60-80)	0.610
SVKI (g/m^2)	27.9 ± 5.	39.7 ± 7.9	0.01	0.010

VKİ: *Vücut kitle indeksi;* ***ADEİ:*** *Anjiotensin dönüştürücü enzim inhibitörü;* ***ARB:*** *Anjiotensin reseptör blokeri;* ***KKB:*** *Kalsiyum kanal blokeri;* ***SVKI:*** *Sol ventrikül kitle indeksi;* ***SKB:*** *Sistolik kan basıncı;* ***DKB:*** *Diastolik kan basıncı,* ****:*** *n(%)*

Tablo II: Grupların kan basıncı yüklerinin karşılaştırılması.

	HTEKO (-) grup	HTEKO (+) grup	p
24 saatlik AKBM			
Sistolik KBY*	44.5 ± 19.6	60.8 ± 21.3	0.020*
Diastolik KBY*	19.2 ± 16.2	33.3 ± 25.9	0.030*
Gündüz AKBM			
Sistolik KBY*	42.8 ± 21.1	60.2 ± 24.8	0.030*
Diastolik KBY*	18.8 ± 16.7	31.7 ± 26.8	0.440
Gece AKBM			
Sistolik KBY*	33.6 ± 27.7	59.0 ± 30.0	0.030*
Diastolik KBY*	17.5 ± 15.9	38.3 ± 30.7	0.020*

SD: *Standart Deviasyon;* ***SVKI:*** *Sol Ventrikül Kitle İndeksi;* ***HTEKO(-):*** *Hipertansif olup EKO da SVH olmayan;* ***HTEKO(+):*** *Hipertansif olup EKO da SVH olan,* ***AKBM:*** *Ambulatuvar kan basıncı monitorizasyonu Independent,* ***KBY:*** *Kan basıncı yükü Sample T-Tes,* ****:*** (%) mmHg

Tablo III: HTEKO(-) grup ve HTEKO (+) grup ile normotansif grubun renalaz düzeylerinin karşılaştırılması.

	Renalaz (ng/ml)	p
HTEKO(-) grup *	1.77 ± 0.98	0.015†
HTEKO(+) grup*	1.63 ± 1.14	
Normotansif grup*	27 ± 1.57	0.040†
Normotansif grup*	27 ± 1.57	

TSD: *Standart Deviasyon;* ***HTEKO(-):*** *Hipertansif olup EKO da SVH olmayan;* ***HTEKO(+):*** *Hipertansif olup, EKO da SVH olan One Way ANOVA,* ****:*** *Ortalama±SD,* ***†:*** *Anlamlı fark*

l). Hipertansif hastaların 30'unda (21 erkek, %70; 9 kız, %30) ekokardiyografide Sol ventrikül hipertrofisi (SVH) varken; kalan 30 hipertansif hastanın (19 erkek, %63.3; 11 kız, %36.7) ekokardiyografi bulguları normaldi. Sağlıklı çocukların yaş ortalaması 14.1±1.26 yıldı (Ortanca değer:14; minimum: 11 yıl; maksimum: 17 yıl). Hipertansif olup EKO da SVH olmayan [HTEKO (-)] grubun yaş ortalaması 14.81±2.29 yıl (Ortanca değer:15 yıl; minimum:9.5 yıl; maksimum:17 yıl) ve hipertansif olup EKO da SVH olan [HTEKO (+)] grubun yaş ortalaması 15.26±1.57 yıl (Ortanca değer:15 yıl; minimum:11.5 yıl; maksimum:17.5 yıl)'dı. Gruplar arasında cinsiyet ve yaş açısından anlamlı fark saptanmadı (Tablo I).

Hipertansif olan 60 hastanın 42 (%70)'i en az bir antihipertansif ilaç kullanırken, 18 (%30)'unun herhangi bir antihipertansif ilaç kullanımı yoktu. Antihipertansif ilaç kullanan 42 hastanın 8 (%19)'u anjiotensin dönüştürücü enzim inhibitörü (ADEİ), 2 (%4.8)'i anjiotensin reseptör blokeri (ARB), 24 (%57.1)'i kalsiyum kanal blokeri (KKB) kullanırken, 8 hasta (%19.1) birden fazla antihipertansif ilaç kullanmaktaydı. Hastaların izlem süresi ise ortalama 15 ay olarak bulundu (Tablo I).

Normotansif grubun klinik SKB ortalama 103 (90-110) mmHg, DKB ortalama 68 (60-80) mmHg iken; HTEKO (-) grubun klinik SKB ve DKB sırasıyla 129 (100-140) mmHg, 80 (70-100) mmHg ve HTEKO (+) olan grubun ise SKB ve DKB sırasıyla 131 (110-150) mmHg 83 (70-100) mmHg olarak bulundu. HTEKO (+) ve HTEKO (-) gruplar arasında ise klinik SKB ve DKB açısından anlamlı fark saptanmadı (Tablo I).

Normotansif grupta 3 (%15), HTEKO (-) grupta 12 (%40), HTEKO (+) grupta 15 (%50) olguda hipertansiyon tanılı birinci derece akraba öyküsü vardı (Tablo I).

Normotansif grupta VKİ ortalaması 22.47 (19.14-25.80) kg/m^2, HTEKO (-) grupta 26.94 (25.08-28.80) kg/m^2, HTEKO (+) grupta 28.34 (26.27-30.41) kg/m^2'di. HTEKO (-) ve HTEKO (+) olan gruplarda VKİ normotansif gruba göre anlamlı olarak yüksek saptandı. HTEKO (-) ve HTEKO (+) olan gruplar arasında ise VKİ açısından anlamlı fark saptanmadı (Tablo I). Vücut kitle indeksi verilerine göre normotansif grubun %35'i obez, HTEKO (-) grubun %46.7'si obez ve HTEKO (+) grubun %60'ı obezdi.

Gruplar arasında trigliserid, LDL, HDL, TSH, T4, üre, kreatinin, idrar adrenalin, kan adrenalin, kan noradrenalin, mikroalbuminüri,

Tablo IV: Grupların laboratuar sonuçlarının karşılaştırılması.

	HTEKO(-) grup (Ortalama±SD)	HTEKO(+) grup (Ortalama±SD)	Normal aralık	p
Üre (mg/dl)	23.5 ± 5.5	23.2 ± 5.7	11-39	0.870
Kreatinin (mg/dl)	0.79 ± 0.13	0.79 ± 0.1	0.5-1.2	0.860
fT4 (ng/dl)	0.87 ± 0.11	0.83 ± 0.09	0.6-1.03	0.120
TSH (uIU/ml)	2.1 ± 0.88	2.4 ± 1.1	0.5-4.3	0.290
Trigliserid (mg/dl)	102 ± 43.5	115.9 ± 46.6	0-150	0.260
LDL (mg/dl)	85.8 ± 23.1	86.5 ± 29.09	< 159	0.920
HDL (mg/dl)	47.3 ± 9.9	51.6 ± 12.03	40-60	0.130
Adrenalin (İdrar) (ug/24 saat)	6.85 ± 4.4	6.68 ± 5.3	0.2-10	0.890
Adrenalin (Plazma) (ng/ml)	56.4 ± 12.1	51.5 ± 7.9	< 90	0.070
Noradrenalin (Plazma) (ng/ml)	157.1 ± 37.2	176.2 ± 54.7	< 500	0.120
Mikroalbumin (24 S. İdrar)(mg/L)	14.7 ± 12.1	13.1 ± 11.8	0-30	0.640
5 HIAA (mg/24 saat)	3.45 ± 1.91	4.83 ± 3.71	1.0-6.3	0.070
VMA (mg/24 saat)	2.96 ± 1.52	3.13 ± 1.56	0-6	0.130

SD: *Standart Deviasyon;* ***fT4:*** *free tetraiodothyroinine;* ***TSH:*** *thyroid-stimulating hormone;* ***VMA:*** *Vanilmandelik Asit;* ***5 HIAA****: 5 Hidroksiindolasetik Asit;* ***LDL:*** *Low-density lipoprotein;* ***HDL:*** *High-density One-Way ANOVA*

Tablo V: Renalaz düzeyi ile cinsiyet, obezite, retinopati, SVKI ve laboratuvar bulguları (5-HIAA, adrenalin, noradrenalin, VMA düzeyleri) arasındaki ilişki.

	Renalaz düzeyi (ng/ml)		p
	<0.78 (Ortalama±SD)(n=9)	0.78-50 (Ortalama±SD) (n=51)	
Erkek cinsiyet	6 (66.7)	44 (62)	0.250
Kız cinsiyet	3 (33.3)	27 (38)	0.250
Obezite var	6 (66.7)	33 (46.5)	0.250
Obezite yok	3 (33.3)	38 (53.5)	0.250
Retinopati (+)	1 (11.1)	10 (19.6)	0.470
5 HIAA (mg/24 saat)	5.62 ± 5.25	3.88 ± 2.41	0.110
SVKI (g/m^2)	41.14 ± 9.67	32.59 ± 8.33	0.008*
VMA (mg/24 saat)	4.10 ± 1.63	3.27 ± 1.66	0.170
Adrenalin (Plazma) (ng/ml)	52.66 ± 6.91	54.19 ± 11.02	0.690
Noradrenalin (Plazma) (ng/ml)	171.99 ± 27.67	165.76 ± 50.23	0.710

VMA: *Vanil mandelik asit,****SD:*** *Standart Deviasyon,* ***VMA:*** *Vanilmandelik Asit;* ***5 HIAA:*** *5 Hidroksiindolasetik Asit (Independent T-test)*

5-HIAA, vanil mandelik asit düzeyleri açısından istatistiksel olarak farklılık saptanmadı.

Hasta ve Kontrol Gruplarında Ambulatuar Kan Basıncı Monitorizasyonu Sonuçlarının Karşılaştırılması

HTEKO (-) ve HTEKO (+) gruplara 24 saatlik ambulatuar kan basıncı monitorizasyonu (AKBM) uygulandı; gruplar arasında değerler karşılaştırıldı (Tablo II). AKBM parametrelerinden tüm gün, gündüz ile gece sistolik kan basıncı yükü (SKBY) ve diastolik kan basıncı yükü (DKBY) değerleri karşılaştırıldı. Tüm gün SKBY ve DKBY değerleri HTEKO (-) grupta % 44.5 (%23-95) ile %19.2 (%0-65) ve HTEKO (+) grupta %60.8 (%28-100) ile %33.3 (%5-98) olarak saptandı. HTEKO (+) grupta tüm gün SKBY ve DKBY HTEKO (-) gruba göre anlamlı olarak yüksek saptandı (p<0.050). Gündüz SKBY ve DKBY değerleri HTEKO (-) grupta %42.8 (%7-95) ile %18.8 (%0-63) ve HTEKO (+) grupta %60.2 (%18-100) ile %31.7 (%0-98) olarak saptandı. HTEKO (+) grupta gündüz SKBY, HTEKO (-) gruba göre anlamlı olarak yüksek saptandı (p<0.050).

Gece SKBY ve DKBY değerleri HTEKO (-) grupta %33.6 (%0-95) ile %17.5 (%0-69) ve HTEKO (+) grupta %59 (%11-100) ile %38.3 (%0-100) olarak saptandı. HTEKO (+) grupta gece SKBY ve DKBY HTEKO (-) gruba göre anlamlı olarak yüksek saptandı (p<0.050) (Tablo II).

HTEKO (-) grup ile HTEKO (+) karşılaştırıldığında; HTEKO (+) grupta, HTEKO (-) gruba göre tüm gün SKBY, gündüz SKBY, gece SKBY, tüm gün DKBY, gece DKBY anlamlı olarak yüksekti (p>0.050).

Çalışma Gruplarının M-Mode Ekokardiyografi Parametrelerinin Karşılaştırılması

M-mode ekokardiyografi (MME) ile yapılan değerlendirmede SVKİ, HTEKO (+) grupta 39.7±7.9 g/m^2 ve HTEKO (-) grupta 27.9±5.4 g/m^2 olarak saptandı. SVKİ, HTEKO (+) grupta HTEKO (-) gruba göre anlamlı olarak yüksek saptandı (EK-1).

Tüm gün, gündüz ve gece SKBY ve DKBY yüzdeleri ile SVKİ arasındaki ilişki karşılaştırıldığında gündüz SKBY %50 üzerinde olan olgularda gündüz SKBY % 25 altında olan ve SKBY %25-50 arasında olan olgulara göre SVKİ anlamlı yüksek saptandı (EK-1 ve 2).

Çalışma Gruplarının Kan Renalaz Düzeyi Sonuçlarının Karşılaştırılması

Renalaz düzeyi hipertansif grupta normotansif gruba oranla anlamlı olarak düşük saptandı. HTEKO (-) grup ile HTEKO (+) kendi arasında karşılaştırıldığında; gruplar arasında renalaz düzeyleri açısından istatistiksel olarak anlamlı fark saptanmadı (p>0.05) (Tablo III). Renalaz düzey 0.78 ng/ml'nin altında olan grubun SVKI 41.14 g/m^2 iken; Renalaz düzeyi 0.78-50 ng/ml olan grubun SVKI 32.59 g/m^2 olarak bulundu. Düşük renalaz düzeyi ile artmış SVKI arasında istatiksel olarak anlamlı ilişki saptandı (Tablo III).

Tablo IV'da HTEKO (-) grup ile HTEKO (+) grupların laboratuar sonuçlarının karşılaştırılmıştır.

Renalaz düzeyi; cinsiyet, obezite durumu, retinopati varlığı, üriner usg anormalliği ve dopplerde artmış rezistif indeks, 5-HIAA (5-Hidroksi İndol Asetik Asit), adrenalin (plazma), noradrenalin (plazma), VMA parametreleri ile karşılaştırıldığında istatistiksel olarak anlamlı fark saptanmadı (p>0.050) (Tablo V).

TARTIŞMA

Hipertansiyon, uygun olarak yapılan üç ayrı ölçümde Kan basıncının yaşa, cinsiyete ve boya göre 95 persantil (p) üzerinde olması olarak tanımlanır (11). Çocukluk çağında HT sıklığı erişkine göre düşüktür; ancak erişkin dönemdeki hipertansiyonun köklerinin çocukluk çağına uzandığını kanıtlayan çalışmaların sayısı gün geçtikçe artmaktadır. Bu da çocukluk çağı KB ölçümlerini ve dolayısıyla çocukluk çağı hipertansiyonunu daha önemli hale getirmektedir (12). Geçmişte hipertansiyonun çocuklarda özellikle küçük yaş grubunda nadir olduğu ve sekonder kökenli olduğu düşünülüyordu. Buna karşın artık yeni yayınlar çocukluk çağı hipertansiyonunda özellikle primer hipertansiyon olarak da bilinen esansiyel hipertansiyonda artan bir prevalans olduğunu desteklemektedir (13). HT prevalansındaki artış; obezitede artma, beslenme alışkanlıklarındaki olumsuz değişiklikler sonucu yüksek kalori alımı, aşırı yağ ve tuz içeren besinlerin fazla tüketilmesi, fiziksel aktivitede azalma ve artan stres faktörlerine bağlanmaktadır. Son 40 yılda obezite prevalansının yaklaşık olarak %40 arttığı gösterilmiştir (12). Akış ve ark. (14) Bursa ilinde, 12-14 yaş arası 2478 okul çocuğunda yaptıkları çalışmada HT sıklığı ile kilo artışı arasında pozitif korelasyon tespit etmişlerdir. Çocukluk çağı hipertansiyonu artan prevalansı ilişkili sekelleri nedeniyle önemli bir sağlık sorunu haline gelmiştir (14). Hipertansiyon nedeniyle refere edilen çocuklarda yaptığımız çalışmada hipertansif grupta vücut kitle indeksi ve obezite prevalansı normotansif gruba göre anlamlı olarak yüksek saptandı (p<0.050).

Yapılan çalışmalar AKBM'nun tanı için daha hassas bir metot olduğunu ve hedef organ hasarı ile daha yakın ilişkili olduğunu göstermiştir (15,16). Ambulatuar kan basıncı monitörizasyonu ile hastanın kan basıncı doğal ortamında ölçülmektedir. Buna ek olarak AKBM; obezite, diabetes mellitus ve kronik böbrek hastalığı gibi durumlarla ilişkili artmış kardiyovasküler riskleri saptamada klinik kan basıncı ölçümlerine üstündür ve bu yüzden gelişebilecek kardiyovasküler hastalıkları önlemek için girişimlere karar verilmesine olanak tanır. Bu nedenle biz çalışmamızda hipertansiyon tanısı için "altın standart" olarak tanımlanmış olan AKBM metodunu kullandık. He ve ark. (17) obez çocuklarda özellikle SKB düzeylerinin yüksek olduğunu göstermişlerdir. Biz de çalışmamızda hipertansif grubun vücut kitle indeksinin normotansif gruba oranla daha yüksek olduğunu gösterdik (p<0.050). Yaptığımız çalışmada gruplar arasında serum lipid düzeyleri yönünden fark bulamadık.

Birçok çalışma relatif ağırlığın, serum lipid düzeyleri ve KB ile yakın ilişkili olduğunu göstermiştir (18). Hiperlipideminin özellikle obezitesi olan primer HT'lilerde daha sık görüldüğü bildirilmektedir (19). Bizim vakalarımızın belli bir yaş grubunda yoğunlaşması ve obezitesi olan vakaların sayısının gruplar arasında değişkenlik göstermesi lipid parametrelerinde farklılık bulmamızı engellemiş olabilir.

Erişkinlerde hipertansiyonun tanımlanması için KB yükü sınırı %25 olarak kabul edilir; ancak çocuklarda böyle bir KB yükü sınırı yoktur. Çocuklarda yapılan çalışmalarda bu sınır net olarak belirlenmemiş olup %25-40 arasında değişmektedir (15). Biz çalışmamızda KB yükünün sınırını hem SKB hem de DKB için %25 olarak belirledik. HTEKO (+) grubun tüm gün sistolik ve diastolik KB yükü, gece sistolik ve diastolik KB yükü ile gündüz sistolik KB yükünü; HTEKO (-) gruba göre anlamlı olarak yüksek bulduk (p<0.05). Yaptığımız çalışmada SVKI sınırını 38.6 g/m^2'nin altı normal, 38.6-51 g/m^2 hafif artmış, 51 g/m^2'nin üstü ciddi artmış olarak tanımladık. Bu rakamlara göre değerlendirildiğinde SVKI artışı ile gündüz SKBY artışı arasında anlamlı ilişki bulduk (p<0.050).

Renalaz (RNZ), böbrekte sentezlenen ve dolaşımdaki katekolaminleri metabolize ederek hipertansiyonun önlenmesinde önemli role sahip bir monoamin oksidazdır. Xu ve ark. (20) hayvan modelleri üzerinde yaptığı çalışmada renalaz eksikliğinin hipertansiyon gelişiminde etkisinin olduğu ve artmış kardiyak iskemik hasara yol açtığı gösterilmiştir. Biz çalışmamızda hipertansif grubun renalaz düzeyinin normotansif gruba oranla daha düşük olduğunu gösterdik. Çalışmamızda ayrıca renalaz

düzeyi normalden düşük olan grupta SVKI' nin, renalazı normal aralıkta olan gruba göre artmış olduğunu gösterdik. Bu durum renalaz eksikliğinin hipertansiyon oluşumunda ve ileri dönemlerde gelişebilecek kardiyak değişiklikler üzerinde rolü olabileceğini göstermektedir.

Sonuç olarak söylenebilir ki, renalaz düzey düşüklüğü ile artmış sol ventrikül kitle indeksi arasında bir ilişki vardır. Bu nedenle hipertansiyon gelişimi ve hipertansiyonun uzun dönem komplikasyonları açısından risk altında olan çocuklarda renalaz düzey düşüklüğünün erken bir belirteç olarak kabul edilmesinin erişkin dönemde gelişebilecek komplikasyonları önlemede kullanışlı ve değerli bir parametre olduğu kanısındayız.

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EK -1: Genel sistolik / Genel diyastolik kan basıncı yüklerinin artışı ile SVKİ'nin karşılaştırılması.

	KB yükü Genel Sistolik				KB yükü Genel Diastolik			
	<%25 n (%)	%25-50 n (%)	>%50 n (%)	p	<%25 n (%)	%25-50 n (%)	>%50 n (%)	p
SVKI (38.6-51g/m^2)	0 (0)	22 (81.5)	21 (63.6)	0.39	26 (70.3)	11 (78.6)	6 (66.7)	0.78
SVKI (>51g/m^2)	0 (0)	5 (18.5)	12 (36.4)		11 (29.7)	3 (21.4)	3 (33.3)	

SVKI: *Sol Ventrikül Kitle İndeksi,* ***HTEKO(-):*** *Hipertansif olup EKO da SVH olmayan,* ***HTEKO(+):*** *Hipertansif olup EKO da SVH olan,* ***KB:*** *Kan basıncı.*

EK-2: Gündüz / Gece sistolik/diyastolik kan basınçları yüklerinin artışı ile SVKİ'nin karşılaştırılması.

	Gnd SKB yükü	Gc SKB yükü	Gnd SKB yükü	Gc SKB yükü	Gnd SKB yükü	Gc SKB yükü	p	Gnd DKB yükü	Gc DKB yükü	Gnd DKB yükü	Gc DKB yükü	Gnd DKB yükü	Gc DKB yükü	p
	<%25 n (%)	<%25 n (%)	%25-50 n(%)	%25-50 n(%)	>%50 n (%)	>%50 n (%)		<%25 n (%)	<%25 n (%)	%25-50 n(%)	%25-50 n(%)	>%50 n (%)	>%50 n (%)	
SVKI (38.6-51 g/m^2)	5 (62.5)	15 (88.2)	20 (90.9)	12 (66.7)	18 (60)	16 (64)	0.040* (Gndn SKB yükü/ SVKI için)	27 (73)	25 (69.4)	10 (83.3)	9 (81.8)	6 (54.5)	9 (69.2)	0.290* (Gc DKB yükü/SVKI için)
SVKI (>51g/m^2)	3 (37.5)	2 (11.8)	2 (9.1)	6 (33.3)	12 (40)	9 (36)	0.190 (Gc KB yükü SVKI için)	10 (27)	11 (30.6)	2 (16.7)	2 (18.2)	5 (45.5)	4 (30.8)	0.710 (Gc DKB yükü SVKI için)

Gnd SKB yükü: *Gündüz sistolik KB yükü,* ***Gc SKB yükü:*** *Gece Sistolik Kan basıncı yükü,* ***Gnd DKB yükü:*** *Gündüz Diyastolik kan basıncı yükü,* ***Gc DKB yükü:*** *Gece Diyastolik Kan basıncı yükü,* ***SVK:*** *Sol Ventrikül Kitle İndeksi.*

Methamphetamine Intoxication in Children: A Single-Center Experience

Çocuklarda Metamfetamin İntoksikasyonu: Tek Merkez Deneyimi

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ABSTRACT

Objective: Illicit substances, especially methamphetamine, are becoming increasingly popular with adolescents in Turkey as well as around the world. Most of the studies conducted for this purpose in Turkey are survey studies. Our study therefore aimed to evaluate the clinical features and laboratory parameters of patients who applied to our hospital and were found to have methamphetamine intoxication.

Material and Methods: Patients under 18 who applied to the Ankara City Hospital Pediatric Emergency Department (PED) between August 2019 and December 2021 and were found to be positive for methamphetamine in the urine drug screening were included in the study,and their data were evaluated retrospectively.

Results: We reviewed 10 cases presenting to our PED with methamphetamine intoxication. The mean age was 16.3 ± 0.94 (14-17) and 80% of patients were male. Eight patients concealed substance use at admission. The most frequent complaints upon presentation were cardiovascular, neurological, and gastrointestinal system symptoms. Concomitant alcohol use was detected in four patients, multidrug use in one patient. No significant pathology was observed in the laboratory tests. Gastric perforation was detected in one patient with abdominal pain, and pneumomediastinum was detected in one patient with chest pain.

Conclusion: There are no specific clinical and laboratory indicators of methamphetamine intoxication, and substance abuse should be considered in all cases where a possible reason cannot explain the patient's clinical findings. Children who use alcohol should be questioned about substance abuse, care should be taken in terms of multiple substance use, and follow-up and rehabilitation plans for patients should be made accordingly.

Key Words: Alcohol, Children, Methamphetamine, Substances, Urine Drug Screening

ÖZ

Amaç: Yasa dışı uyuşturucu maddeler, özellikle de metamfetamin, dünyada olduğu gibi Türkiye'de de ergenler arasında giderek daha popüler hale gelmektedir. Türkiye'de bu amaçla yapılan çalışmaların çoğu anket çalışmalarıdır. Çalışmamız ise hastanemize başvuran ve metamfetamin intoksikasyonu saptanan hastaların klinik özelliklerini ve laboratuvar parametrelerini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Ağustos 2019-Aralık 2021 tarihleri arasında Ankara Şehir Hastanesi Çocuk Acil Servisi'ne başvuran ve idrar toksik madde taramasında metamfetamin pozitif saptanan 18 yaş altı hastalar çalışmaya dahil edildi ve verileri retrospektif olarak değerlendirildi.

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Contribution of the Authors / Yazarların katkısı*: *YIGIT M: 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 necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***GOKDOL MY***: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KALAYCI F***: Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AKCA CAGLAR A***: Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***AKCAN YILDIZ L***: Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study. ***KURT F***: Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AKCA H***: Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Çalışmamızda metamfetamin intoksikasyonu saptanan 10 hastayı inceledik. Ortalama yaş 16.3 ± 0.94 (14-17)'di ve hastaların %80'i erkekti. Sekiz hasta başvuru sırasında madde kullanımını gizledi. Başvuru anında en sık kardiyovasküler, nörolojik ve gastrointestinal sistem semptomları görüldü. Dört hastada eşzamanlı alkol kullanımı, bir hastada çoklu uyuşturucu kullanımı saptandı. Laboratuvar testlerinde önemli bir patoloji gözlenmedi. Karın ağrısı olan bir hastada mide perforasyonu, göğüs ağrısı olan bir hastada pnömomediastinum tespit edildi.

Sonuç: Metamfetamin intoksikasyonunun spesifik klinik ve laboratuvar göstergeleri yoktur ve olası bir nedenin hastanın klinik bulgularını açıklayamadığı tüm durumlarda madde kötüye kullanımı düşünülmelidir. Alkol kullanan çocuklarda madde kullanımı sorgulanmalı, çoklu madde kullanımı açısından dikkatli olunmalı, buna göre hasta takip ve rehabilitasyon planları yapılmalıdır.

Anahtar Sözcükler: Alkol, Çocuk, Metamfetamin, Uyuşturucu Maddeler, İdrar Uyuşturucu Taraması

INTRODUCTION

Despite all measures that have been taken, Substance Use Disorder has steadily become more widespread in Turkey as it has around the world. Commonly given slang names such as "crystal," "fire-ice," "meth," methamphetamine is one of the most widely used narcotic after cannabis derivatives (1). Methamphetamine is a methylated analog of amphetamine that functions as a central nervous system stimulator. While carrying pharmacological properties similar to amphetamine, because of its higher lipophilicity, methamphetamine has a more powerful effect and a longer half-life. Its potential to do harm is consequently greater (2,3). It is estimated that there are about 24 million methamphetamine users worldwide (4). Its popularity has grown steadily in the last twenty years, especially in Southeast Asia, and it has surpassed heroin as the most popular illegal narcotic (4). Its easy production, low cost and comparatively better accessibility has steadily increased the use of methamphetamine in recent years (2). The exact statistics for methamphetamine use in Turkey is unknown (5). In a study by Karakukcu et al. (6), it is reported that according to laboratory findings of a reference drug screening centre in Kayseri, Turkey, amphetamine/methamphetamine has been the most commonly used substance group between 2014 and 2016. Factors such as young age, a low level of education, use of other psychoactive substances have been found to be associated with methamphetamine abuse (7).

The signs and symptoms of methamphetamine toxicity in adults are typically mydriasis, sweating, tachycardia, hypertension, chest pain, cardiac arrythmia, and myocardial infarction. Paranoia, agitation, hallucinations, and aggressive behavioral disorders are also widely noted. Adrenergic symptoms in children are similar to those observed in adults. At the same time, pediatric patients can present with symptoms such as vomiting, stomachache, agitation, irritability, and recurring stereotypic behavior. These atypical and nonspecific findings challenge the clinician in making a diagnosis and lead to further medical examinations (8,9).

The aim of this study was to assess the symptoms and findings, laboratory parameters and clinical characteristics of patients presenting at the Pediatric Emergency Department with methamphetamine intoxication.

MATERIALS and METHODS

Data belonging to patients below the age of 18 who had presented at the Ankara City Hospital Pediatric Emergency Department over the period August 2019-December 2021 and displayed a methamphetamine positive result on a panel drug urine test were evaluated retrospectively.

Urine samples for methamphetamine analysis were studied using the enzymatic immunoassay test within the first three hours of admission and positive presence in urine was confirmed using the hyphenated mass spectrometry chromatographic method. Methamphetamine use was considered positive if the level was above 1000 ng/mL.

The vital signs (temperature, pulse, blood pressure) of patients at the time of testing positive for methamphetamine in urine were extracted from the nurse's observation forms, the medical history and physical examination findings (neurological, gastrointestinal, chest pain and other systemic findings) from doctor's notes, and the laboratory results (blood glucose, blood ketones, blood gases, urea, creatinine, transaminases, coagulation parameters, ethanol levels) and imaging findings were obtained from the hospital data system. Treatments applied to patients and their clinical course were reviewed from their discharge records.

The Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, New York, USA) was used to analyze the data. Descriptive statistics (including frequencies and means) for all variables were calculated. Results were expressed as mean ± standard deviation, frequency and percentage (%). The Kolmogorov-Smirnov test was used to examine whether the numerical variables showed normal distribution.

This study was conducted in conformity with the principles of the Declaration of Helsinki and approved by the Republic of Turkey Ministry of Health, the Ethics Committee of Ankara City Hospital Ethics Committee, and the Institutional Review Board of the Children's Hospital of Ankara City Hospital (E2-21-1141).

RESULTS

A total of 414 urine drug panel results of pediatric patients sent to laboratories over the period August 2019-December

2021 were examined. Drugs were found in the urine of a total of 25 pediatric patients. It was found that 14 of these findings indicated methamphetamine. Two patients were excluded from the study because their clinical data could not be accessed. Another two patients were excluded because it was considered that their treatment with methylphenidate due to Attention Deficit Hyperactivity Disorder may lead to false positive testing. The clinical and laboratory findings of 10 patients were ultimately reviewed.

Eight boys and two girls were taken into the study. The patients' mean age was 16.3 ± 0.94 years. While two of the patients revealed their use of drugs at their first application, evidence of drug use was found in the testing results of the remaining eight. None of the patients had a history of any previously diagnosed psychiatric disorder or of the use of any psychiatric medication. The patients more commonly presented at the emergency department for cardiovascular system (tachycardia, chest pain, hypertension), neurological system (dizziness, hallucinations), and gastrointestinal system (nausea and stomachache) symptoms. When severe poisoning findings related to methamphetamine use were examined, 80% of the patients had tachycardia, 30% had chest pain, 20% had hypertension, 20% had hallucinations, and 10% had syncope. Interestingly, hyperthermia, convulsion, delirium, hyperkalemia and metabolic acidosis were not observed in any patients. While four patients exhibited higher than normal blood ethanol levels, accompanying alcohol use was not detected in the other six. Out of the four patients who were found to be using alcohol in addition to methamphetamine, three tested positive for blood ketones while seven patients tested negative for blood ketones. The patients' blood glucose, blood gases, biochemical tests and coagulation tests did not reveal any significant pathology. Stomach perforation was found in one patient who complained of stomachache, while pneumomediastinum was detected in another case. Still another patient tested positive on the urine drug panel for marihuana and benzodiazepine. Two patients who displayed neurological symptoms at presentation but did not disclose any drug use underwent cranial computerized tomography; both results were normal. While six patients were discharged from the emergency department, two patients were followed up in the intensive care unit and two were admitted into the pediatric department for observation. The patients' complaints, symptoms, and findings at presentation, as well as their laboratory results at presentation can be seen in Table I and Table II.

Table I: Clinical symptoms of the patients

Symptoms	n (%)
Hyperthermia	0 (0)
Sweating	2 (20)
Tachycardia	8 (80)
Hypertension	2 (20)
GIS symptoms	5 (50)
Chest pain	3 (30)
Neurological findings	7 (70)
Dizziness	4 (40)
Hallucinations	2 (20)
Agitation	1 (10)
Syncope	1 (10)
Concomitant substance use	1 (10)
Concomitant alcohol intake	4 (40)

Tablo II: Laboratory test results of the patients

Parameter	Mean ± SD
Blood glucose (*mg/dL*)	92 ± 11.2
Urea (*mg/dL*)	25.7 ± 9.3
Creatinine (*mg/dL*)	0.80 ± 0.12
Uric acid (*mg/dL*)	5.3 ± 1.37
Sodium (*mEq/L*)	138.2 ± 3.6
Potassium (*mEq/L*)	3.95 ± 0.42
pH	7.39 ± 0.08
pCO2 (*mmHg*)	37.6 ± 8.6
HCO3 (*mmol/L*)	22.6 ± 2.5
Anion gap	11.3 ± 4.2
Lac (*mmol/L*)	2.5 ± 1.8
AST (U/L)	33.7 ± 18.4
ALT (U/L)	24.6 ± 15.8
INR	1.17 ± 0.14
aPTT	25.1 ± 4.1

DISCUSSION

Substance use disorder is among the most critical health problems that should be addressed because it causes severe clinical and social problems. Since methamphetamine use has recently become widespread in adolescents because it is both easily affordable and accessible, it is essential that studies are conducted with adolescent patients. Most studies on substance use in children in Turkey are survey studies; there are not enough clinical studies on substance use in children, especially in the case of methamphetamine. At the same time, there is a lack of adequate and comprehensive clinical studies on methamphetamine intoxication in children in Turkey and in the world. In this regard, we believe that our study may contribute to the pediatric literature in this area.

In the study of Gordon et al. (10), urine tests came back positive in 10 (11.8%) out of the 85 adolescent patients who presented with blunt or penetrating trauma and who had had urine drug screening. In the study of Yurtseven et al. (11), from Turkey, 131 (24%) out of the 548 adolescent patients who had urine drug screening tested positive. In a similar study by Kozer et al. (12), the frequency of positivity in urine drug screening was found to be 8% in the adolescent age group. In our study, the rate of positivity in urine screening was approximately 6%. Among the reasons behind the variability in positivity frequency

in the patients who were tested can be cited late admission to the hospital after substance abuse, the failure to take urine samples while the patient is under surveillance, and the fact that clinicians carried out more urine toxicology scans than necessary because the clinical picture caused by substance use is similar to that of many diseases.

Mild and non-specific clinical findings can be seen in methamphetamine use, as well as cardiac arrhythmia, strokes, cerebral hemorrhage, ischemic infarction, renal failure, rhabdomyolysis, coma, or even death in severe cases (18,19). Clinical findings and symptoms of methamphetamine intoxication can vary widely, depending on dose, route, duration (acute and/or chronic), and pattern of use (2). In the study by Chen et al. (20), in which the authors examined applications to the United States poison control centers between 2000 and 2019, the most common complaints were reported as tachycardia (35.5%), agitation (29.4%), hypertension (15.3%), and hallucinations/delusions (6.8%). In the study of Malasock et al.(9) in children and adolescents, the most common symptoms related to methamphetamine intoxication in the adolescent group were reported as hypertension, tachycardia, mydriasis, and GIS symptoms. In our study, the most common clinical findings were tachycardia, GIS symptoms and neurological findings. Furthermore, no significant disorder was detected in the patients' laboratory findings. No patient died in our study. The patients were discharged after a short-term follow-up, except for two patients with gastric perforation in one and pneumomediastinum in the other, both of whose blood alcohol levels were normal. Martínez-Aguirre et al. (21) found in their study that there was a trend in the methamphetamine user group to develop peptic ulcer perforation at earlier ages compared with the nonuser group, and concluded that methamphetamine use is related to ulcer perforation in age groups of younger patients. Vaghefi et al. (22) also reported a 23-year-old patient with perforated duodenal ulcer after taking methamphetamine. Although there are not sufficient clinical observational studies, several methamphetamine-associated pneumomediastinum cases, mostly following inhalation of methamphetamine have also been reported in the literature (23–25). Although spontaneous pneumomediastinum and peptic ulcer perforation are rare findings, it is essential to elicit a thorough history including illicit drug use, particularly regarding amphetamines and other stimulants. To the best of the authors' knowledge, methamphetamine intoxication accompanied by gastric perforation and pneumomediastinum has not been previously described in the Turkish literature.

In both adults and adolescents, psychoactive substance use has been found to be associated with having a psychiatric disorder and people with substance use disorders are seen to have much higher rates of comorbid mental disorders. A strong direct association between the severity of comorbidity and the severity of substance use disorders has been also found (13,14). In addition, it has been suggested that substance use may lead to psychiatric disorders (15). Gau et al. (16) found in their longitudinal study that the most significant predictive factors for substance use in adolescents included male gender, attention-deficit hyperactivity disorder, and conduct disorder. However, none of the patients with methamphetamine detected in urine tests in our study had a previously diagnosed psychiatric disease. Therefore, just as it is essential to follow up on patients with psychiatric diseases in terms of substance use risk, the close and careful follow-up of substance users is crucial in terms of the detection of additional psychiatric disease.

Substance abuse, especially methamphetamine, is becoming increasingly more common in adolescents. In addition, alcohol-substance co-use and multiple substance use are also increasing. Chen et al. (20) showed in their study that the rate of multiple-substance exposures in which methamphetamine was the first-ranked substance was 24.4 % (n=13210). Karakükcü et al. (6) found that the rate of multiple substance abuse increased significantly over the years and the most common and the second most common multiple substance usage were metamphetamine with cannabis and metamphetamine with opiate, respectively. In our study, a second substance was detected in the urine analysis of only one patient, and high blood alcohol levels were found in almost half of the patients. Thus, concomitant substance use and alcohol use should be questioned in adolescent patients admitted to the hospital; similarly, patients admitted for substance abuse should be questioned for concomitant alcohol use and multiple substance use. Rehabilitation programs should be planned based on abuse patterns.

The present study had some limitations. First, due to the retrospective nature of the study, some important unregistered information could not be obtained; including the way the patients used substance and their ECG records. Second, no blood methamphetamine concentrations were obtained. Additionally a sample size of 10 is merely enough to obtain meaningful data. Still, this study contributes meaningfully to the literature due to the dearth of pediatric studies.

CONCLUSIONS

Since there are no specific clinical and laboratory indicators of methamphetamine intoxication, substance abuse should be considered in all cases where a possible reason cannot explain the clinical findings of the patients. Children with psychiatric illness should be followed up for substance abuse; similarly, children who use illicit substances should be investigated for psychiatric illness. Children who use alcohol should be questioned about substance abuse, care should be taken in the case of multiple substance use, and follow-up and rehabilitation plans should accordingly be made for patients. In addition, multicenter clinical observational studies should be conducted

throughout the country on the use of methamphetamine in pediatric patients in Turkey, as in Europe and the USA.

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Transthoracic Echocardiography and Fluoroscopy Guided Transcatheter Atrial Septal Defect Closure with Device in Children, Adolescents, and Young Adults

Çocuklarda, Ergenlerde ve Genç Yetişkinlerde Transtorasik Ekokardiyografi ve Floroskopi Kılavuzluğunda Cihazla Transkateter Atriyal Septal Defekt Kapatılması

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ABSTRACT

Objective: The aim of this study was to evaluate the safety and efficacy of transcatheter atrial septal defect (ASD) closure guided by fluoroscopy and transthoracic echocardiography (TTE) and to present our experiences.

Material and Methods: In this study, we evaluated 108 patients' files taken to the catheter laboratory for transcatheter ASD closure retrospectively. The procedure was abandoned in ten patients because of septum device disproportion (6) and deficient rims (4), mainly inferior vena cava rim.

Results: Transcatheter ASD closure guided by TTE was performed in 98 patients (59 female). The mean age of patients was 9.5±6 years (2.6-46), and the mean weight was 30.3±15.3kg (12-80). TTE-guided ASD closure was successfully performed in 92 of 98 (94%) patients. The median largest ASD diameter measured by TTE was 10.75 mm (interquartile range (IQR) 9.12-14. The median stretched balloon diameter measured by fluoroscopy was 14 mm (IQR 12.4-18). The median device waist diameter was 14 mm (IQR 13-18), the median device left atrial (LA) disk diameter was 28 mm (IQR 26-31), and the median ratio of LA disc diameter to total septal diameter was 75% (IQR 68-81). The median fluoroscopy and procedural times were 8 minutes (IQR 5.6-13.75) and 36.5 minutes (IQR 30-49) respectively.

Conclusion: Transcatheter ASD closure guided by TTE and fluoroscopy is safe and effective in children, adolescents, and young adults.

Key Words: Atrial septal defect, Transthoracic echocardiography, Transcatheter ASD closure

ÖZ

Amaç: Bu çalışmanın amacı, floroskopi ve transtorasik ekokardiyografi (TTE) eşliğinde transkateter atriyal septal defekt (ASD) kapatılmasının güvenlik ve etkinliğini değerlendirmek ve deneyimlerimizi sunmaktır.

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ankara City Hospital Ethics Committee (E2-22-1688/27.04.2022).

Contribution of the Authors / Yazarların katkısı: KAVURT AV: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in 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. ***TORUN G:*** 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. ***KILIC A:*** 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. ***BAGRUL D:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***GURSU HA:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***ECE I:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***CETIN II:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

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Gereç ve Yöntemler: Bu çalışmada transkateter ASD kapatılması için kateter laboratuvarına alınan 108 hastanın dosyası geriye dönük olarak incelendi. On hastada septum/cihaz orantısızlığı (6) ve başta vena cava inferior rimi olmak üzere eksik rimler (4) nedeniyle işlemden vazgeçildi.

Bulgular: Toplam 98 hastaya (59 kadın) TTE rehberliğinde transkateter ASD kapatma uygulandı. Hastaların ortalama yaşı 9.5 ± 6 yıl (2.6-46) ve ortalama ağırlığı 30.3 ± 15.3 kg (12-80)'di. TTE kılavuzluğunda ASD kapatma 98 hastanın 92'sinde (%94) başarıyla uygulandı. TTE ile ölçülen en büyük ASD çapı ortanca değeri 10.75 mm (çeyrekler arası aralık (ÇAA) 9.12-14)'dü. Floroskopi ile ölçülen gerilmiş balon çapı ortanca değeri 14 mm (ÇAA 12.4-18)'di. Ortanca cihaz bel çapı 14 mm (ÇAA 13-18), ortanca cihaz sol atriyal (SlA) disk çapı 28 mm (ÇAA 26-31) ve SlA disk çapının toplam septal çapa oranı ortanca değeri %75 (ÇAA 68-81)'di. Ortanca floroskopi ve işlem süreleri sırasıyla 8 dakika (ÇAA 5.6-13.75) ve 36.5 dakika (ÇAA 30-49)'du.

Sonuç: TTE ve floroskopi kılavuzluğunda transkateter ASD kapatılması çocuklarda, ergenlerde ve genç erişkinlerde güvenli ve etkilidir.

Anahtar Sözcükler: Atriyal septal defekt, Transtorasik ekokardiyografi, Transkateter ASD kapatma

INTRODUCTION

Successful nonsurgical closure of atrial septal defect (ASD) was first reported in 1974 by King and Mills (1). Today, transcatheter device closure of secundum ASDs has become the preferred method of treatment over surgery in suitable anatomies (2,3).

Echocardiography guidance is critical in the transcatheter closure of ASDs (4). Correct device selection requires careful evaluation of defect size, morphology, and rims with echocardiography and balloon sizing. Also, echocardiography for allows proper positioning of the device in the defect and determining any residual shunts, obstruction to venous inflow, and atrioventricular valve regurgitation.

Transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) were widely used to guide the procedure (5,6). However, since patients cannot tolerate TEE, it is usually performed under general anesthesia and endotracheal intubation. Also, TEE use may lead to oropharyngeal and oesophageal traumas (7-9). ICE is expensive and still large, creating a risk of vascular injury, especially in small children (10)

However, comparative studies are showing that transthoracic echocardiography (TTE) can be considered an effective alternative to TEE for the evaluation and guidance of pediatric ASD closure (11, 12).

Herein, we present a single center's experience on TTE guidance in transcatheter ASD closure.

MATERIALS and METHODS

Study population

This was a retrospective study including all patients who had cardiac catheterization for ASD closure in the pediatric cardiology department of Ankara City Hospital, University of Health Sciences between December 2019 and March 2022. The study was approved by the Ankara City Hospital Ethics Committee (E2-22-1688/27.04.2022).

Patient records were reviewed for demographic data also including previous echocardiograms and catheterization reports and angiograms. Patients' age, weight, height, ASD diameter, total septal diameter, balloon-stretched ASD diameter, left atrium (LA) disk diameter of the device, type of device, procedure, and fluoroscopy time were all recorded.

Length of follow-up and complications including device migration/ embolization, residual shunt, device-related cardiac perforation, valve regurgitation, endocarditis, thromboembolism, conduction disorders, hemolysis, stroke, and migraine-like headaches associated with nickel allergy were also recorded.

For transcatheter ASD closure under the guidance of TTE, 108 consecutive patients with a definite diagnosis of secundum type ASD were admitted to the catheterization laboratory at our institute. The procedure was abandoned in ten patients because of septum device disproportion (6) and deficient rims (4), mainly inferior vena cava rim. Therefore, TTE-guided transcatheter ASD closure was performed on 98 patients.

Pre-interventional TTE evaluation

Cardiac anatomy was evaluated by 2D-TTE using a Vivid-S60N machine (General Electric, Norway) before the procedure in all patients.

A detailed 2D-TTE was performed using standard protocol for the atrial septal and defect anatomy including measurement of defect size, its rims, and total septal length in different views; subxiphoid long-axis (frontal) or left anterior oblique, subxiphoid short-axis (sagittal), apical four-chamber and parasternal short-axis. The defect was measured in each of these views and a maximum defect diameter was determined. The atrial septal rims were also measured in these views (13).

The exclusion criterion for TTE-guided transcatheter ASD closure was poor transthoracic acoustic windows.

The interventional procedure, TTE assessment during the procedure

The Vivid-7 machine (General Electric, Norway) was used for TTE assessment during the procedure in all patients. If the images from the initial diagnostic TTE were not considered adequate, additional TTE imaging was performed in the catheterization laboratory before the procedure. This was carried out following induction with general anesthesia and before the patient was prepared.

In all patients, a sizing balloon catheter was inflated at the defect level until a waist was detected in the middle of the balloon. The waist was measured and calibrated on the sine-angiographic frame. These measurements were used to determine the diameter of the ASD occluding device. An identical device with the stretched ASD diameter was used in patients with sufficient rims, whereas 1 to 2 mm larger devices were selected in patients with borderline ASD rims.

The implant procedure was guided by fluoroscopy. In addition, gently pulling and pushing the delivery system were done to ensure a stable position. Some different deployment maneuvers, such as rapid deployment technique, left atrial roof technique or right upper pulmonary vein technique were used in cases where the standard deployment maneuvers have failed. Once the device was in place and felt to be in a good position, the drape was pulled back, allowing the echocardiographers to access the chest to perform a brief assessment of the device. If TTE imaging was reassuring and confirmed an adequate positioning, the patient was re-draped, and the device was released under fluoroscopic observation.

Oximetric, hemodynamic and angiographic studies were performed only if there was an additional cardiac anomaly detected or suspected in echocardiography (eg a partially pulmonary venous connection or pulmonary hypertension).

Procedural success was defined as the presence of all three following criteria: successful device delivery without peri-procedural complications; well-positioned device as assessed by TTE after 6 and 24 hours with no device migration; and hospital discharge on the first day after the procedure.

Devices

We used Amplatzer Septal OccluderTM (Abbott St. Paul, MN, USA) in 86 patients, Amplatzer Multi-fenestrated Septal Occluder (AGA Medical Corporation, Golden Valley, MN, USA) in 1 patient, Cera Septal Occluder™ (CSO, Lifetech Scientific Corporation, Shenzhen, China) in 2 patients, MemoPart™ Atrial Septal Occluder (MASO, Shanghai Shape Memory Alloy Co., Ltd. Shanghai, China) in 9 patients.

Follow-up

Aspirin was given in a dose of 3–5 mg/kg until 6 months after closure. TTE was performed immediately after the procedure, at the 24th hour, and 1, 3 and 6 months after the procedure in all patients to systemically evaluate the therapeutic effects and complications of transcatheter ASD closure. A residual shunt was considered if Doppler color flow mapping showed a left-to-right shunt across the interatrial septum.

Complications

Cardiac erosion, pericardial effusion, air embolus, device-related valvular regurgitation, thromboembolism, pulmonary edema, stroke, atrioventricular block, major atrial arrhythmias (minor transient short-term atrial arrhythmias not included) or ventricular arrhythmias, hemolysis, and infective endocarditis were considered major complications at peri-procedural or follow-up.

Statistical analysis

Statistical Package for the Social Science (SPSS_17.0.1 for Windows; SPSS Inc) was used for statistical analysis. The normal distribution test of continuous variables was performed by using the Shapiro-Wilk test. Spearman correlation analysis was performed to detect correlational relations between variables where the assumption of the normal distribution is not provided. Normally distributed continuous data were presented as mean ± standard deviation (SD) (minimum-maximum) and the nonnormally distributed continuous data were reported as median {interquartile range (IQR)}. Categorical data are presented as numbers (n) and percentages (%). Statistical significance was defined as a two-tailed p value of<0.050.

RESULTS

Transcatheter ASD closure guided by TTE was performed in 98 patients (59 female). The mean age of patients was 9.5±6 years (2.6-46), the mean weight was 30.3±15.3 kg (12-80), the mean

Table I: General characteristics of the patients.

	Patients (n=98)
Age (years)	9.5±6 (2.6-46)
Gender (female) number (%)	59 (59.5%)
Body weight (kg)	30.3±15.3 (12-80)
Height (cm)	129±21 (82-173)
BSA (m^2)	1±0.34 (0.5-1.9)

Mean ± SD (min-max), or n (%) ***BSA:*** *body surface area*

Table II: Procedural characteristics and outcomes

	Patients (n=98)
Procedural success n %	92 (94%)
ASD diameter by TTE (mm)	10.75 (9.12-14)
Total septal diameter (mm)	39 (34-42.75)
ASD diameter/ Total septal ratio (%)	28 (24-36)
Multipl ASD n (%)	6 (6.1%)
Balloon-stretched diameter (mm)	14 (12.4-18)
Balloon-stretched diameter index (mm/m^2)	15 (11.5-20)
Device waist diameter (mm)	14 (13-18)
Device LA disk diameter (mm)	28 (26-31)
Device LA disk / Total septal ratio (%)	75 (68-81)
Fluoro time (min)	8 (5.6-13.75)
Procedure time (min)	36.5 (30-49)
Length of follow-up (months)	9.6±7.6 (2-28)

Values are mean±SD (minimum-maximum) or median (interquartile range), n (%). ***ASD:*** *atrial septal defect,* ***LA:*** *left atrial,* ***TTE:*** *transthoracic echocardiography*

Table III: Procedural and Follow-up complications

	Patients (n=98)
Device migration	0
Residual shunt	7 (7.6%)
Device-related cardiac perforation	0
Device -related valve regurgitation	0
Device -related endocarditis	1 (1.1%)
Device -related thromboembolism	0
Device -related major conduction disorders	0
Device -related hemolysis	0
Stroke	0
Migraine-like headaches associated with nickel allergy	1 (1.1%)

height was 129±21 cm (82-173) and the mean body surface area (BSA) was 1±0.34 m^2 (0.5-1.9) (Table I).

Procedural characteristics and outcomes are shown in Table II. TTE-guided ASD closure was successfully performed in 92 of 98 (94%) patients. The median largest ASD diameter measured by TTE was 10.75 mm (IQR 9.12-14), the median total septal diameter measured by TTE was 39 mm (IQR 34-42.75), and the median ratio of ASD diameter to total septum diameter was 28% (IQR 24-36). The median device waist diameter was 14 mm (IQR 13-18), the median device left atrial (LA) disk diameter was 28 mm (IQR 26-31), and the median the ratio of LA disc diameter to total septal diameter was 75% (IQR 68-81). The median stretched balloon diameter measured by fluoroscopy was 14 mm (IQR 12.4-18). The median fluoroscopy and procedural times were 8 minutes (IQR 5.6-13.75) and 36.5 minutes (IQR 30-49) respectively. The mean duration of follow-up for our patients was 9.6±7.6 months (2-28 months).

In two patients, pulmonary balloon valvuloplasty was performed in addition to transcatheter ASD closure.

TTE-guided transcatheter ASD closure was performed in 6 (6.1%) patients with multiple ASDs (Table II). Four of these ASDs were closed successfully, only one had a residual shunt. In patients with multiple ASD, ballon sizing was performed through the largest defect, and this defect was closed in such a way that the discs would cover the other defects as much as possible.

Complications during the procedure and follow-up are shown in Table III. A mild residual shunt was detected immediately after the procedure in 7 of the patients who underwent successful transcatheter ASD closure. During the follow-up, it was determined that the residual shunt improved in two of these patients.

A patient who underwent successful ASD closure presented with fever four days after the implantation. Acute phase reactants were increased, and also three consecutive blood cultures were positive (*Staphylococcus aureus*). There was

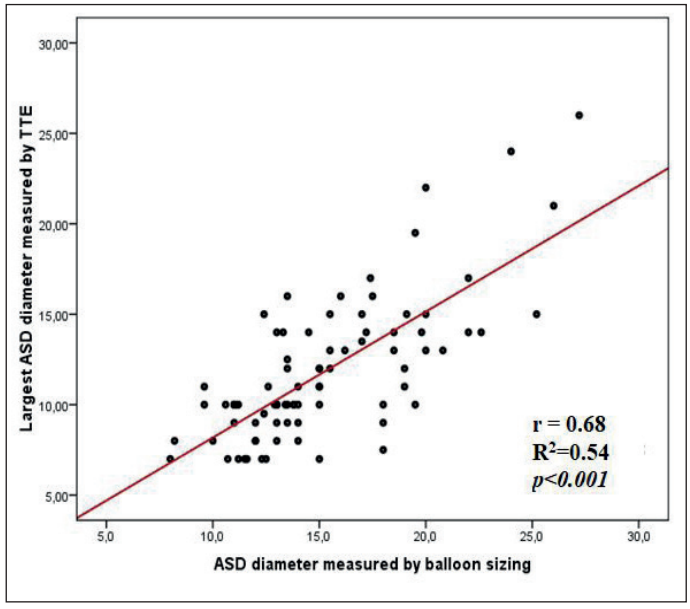

Figure 1: Correlation graph between the largest atrial septal defect (ASD) diameter measured by transthoracic echocardiography (TTE) and ASD diameter measured by balloon sizing (stretched balloon diameter measured angiographically) (Spearman Correlation Analysis, r = 0.68 R^2=0.54 p<0.001).

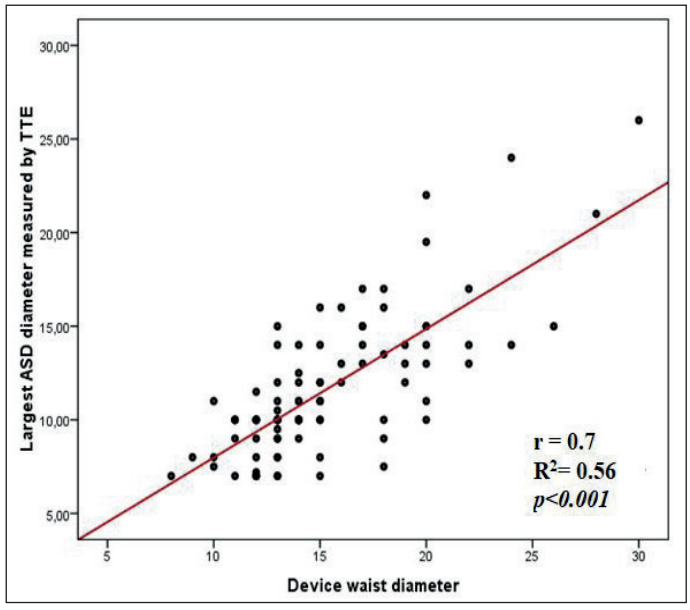

Figure 2: Correlation between the largest ASD diameter measured by TTE and device waist diameter (Spearman Correlation Analysis, r = 0.7 R^2= 0.56 p<0.001)

no echocardiographic evidence of vegetation or thrombus. However, echocardiography revealed moderate mitral valve regurgitation that was not detected after the procedure, newly emerged. After 6 weeks of appropriate antibiotic treatment, blood cultures became negative, AFR returned to normal, and no mitral valve insufficiency was detected in echocardiography. No recurrent infective endocarditis or any other complication was observed during the 1-year follow-up. Endocarditis prophylaxis was consistently recommended.

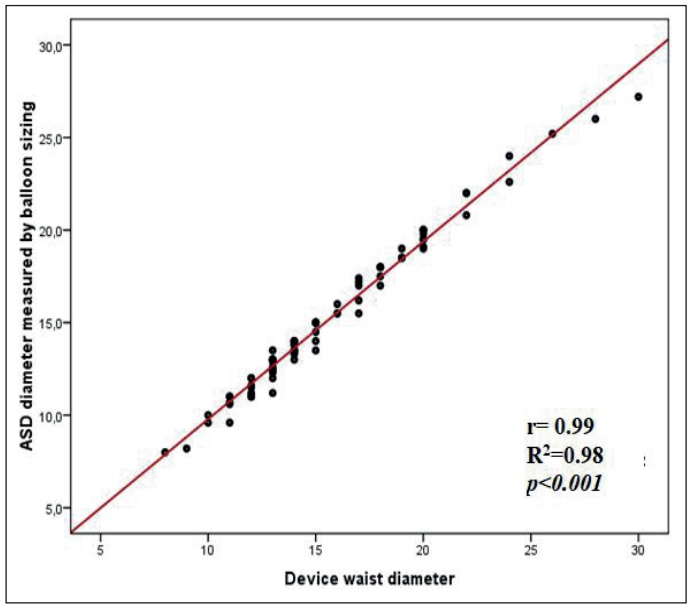

Figure 3: Correlation between ASD diameter measured by balloon sizing and device waist diameter (Spearman Correlation Analysis, r= 0.99 R^2=0.98 p<0.001).

Migraine-like headache associated with nickel allergy was considered in only one patient. In this patient, 16 mm Amplatzer Septal Occluder was implanted and the ratio of left atrial disc diameter of the septal occluder to total septal diameter was 0.76. He had no complaints before implantation. Nausea, vomiting, and migraine-like headaches started within 1 day of device implantation. Nickel allergy was confirmed by the patch test. Symptoms were controlled with aspirin, clopidogrel, and acetaminophen. At 3 months of follow-up, the symptoms disappeared completely.

The largest ASD diameter measured by TTE showed a moderate correlation with the ASD diameter measured by balloon sizing (stretched balloon diameter measured angiographically) and device waist diameter (r = 0.68 R^2=0.54 p<0.001 and r = 0.7 R^2= 0.56 p<0.001, respectively) (Figure 1,2). On the other hand, the correlation between ASD diameter measured by balloon sizing and device waist diameter was fairly strong (r= 0.99 R^2=0.98 p<0.001) (Figure 3).

DISCUSSION

TEE has been widely used for ASD assessment, device selection, and guidance during implantation (14-16).

In the last 10 years, TTE has begun to replace TEE to guide transcatheter closure in most patients with secundum ASD due to its various advantages. In previous studies, the advantages of TTE were stated as; allowing to shorten both procedure time and fluoroscopy time in spontaneously breathing children and avoiding general anesthesia, orotracheal intubation, and TEE-related complications (11,12,17).

In our clinic, we prefer TTE guiding for all transcatheter ASD closures, except for patients with poor transthoracic acoustic windows.

With TTE guidance, our successful ASD device implant rate was 94 %. This was similar to procedural success rates of 95.7% in the Amplatzer Septal Occluder FDA study, 96.7% in the study of Baruteau AE et al. (11), 96% in the MAGIC report, 95% in the C3PO report, and 95.7% in the IMPACT Registry (3,16,18,19).

In our study, major complication rate was 1%. This rate compares with 1.6% in the FDA study, 1.3% in the report of Baruteau et al., (11) 7.6% in the study of Erdem A et al., (12) 1.1% in MAGIC patients, 4.7% in C3PO patients, and 1.2% in IMPACT patients (3,16,18,19).

In studies comparing TEE and TTE guidance in transcatheter ASD closure, no significant difference was reported between procedural success rates (11,12,17, 20). Also, in another study, it was reported that there was no difference in TTE-guided transcatheter ASD closure success rate compared to TEE in anterior superior rim insufficiency (21).

In the study of Baruteau AE et al. (11), no significant difference was found between the TEE and TTE groups in the ratio of ASD diameter to total septum diameter and the ratio of LA disc diameter to total septal diameter. In our study, the ratio of ASD diameter to total septum diameter (28% versus 38.4%), and the ratio of LA disc diameter to total septal diameter (75% versus 86.3%) were similar to the results in Baruteau AE et al's study (11). We think that the selection of the device by balloon sizing under fluoroscopy and TTE guidance is successful in choosing a proper device.

In addition, fluoroscopy time and procedure time of transcatheter ASD closure by TTE guidance were reported significantly lower than TEE guidance (12,17). In our study, the procedure and fluoro times (median 36.5 and 8 min respectively) were comparable to the procedure time and fluoro time of transcatheter ASD closure in the TTE group in the study of Erdem A et al. (12) (median 60 and 13 min respectively) and in the study of Bartakien S et al. (17) (mean 95.7 and 8.9 min respectively).

However, complication rates were found to be significantly higher in the TEE group in the study of Erdem A et al. (12), and no difference was found between the two groups in the study of Bartkian et al. (17). In the study of Baruteau et al. (11), device migration was reported significantly higher in the TTE group, whereas no significant difference was found between the two groups regarding other complications. In another study, device embolization was reported in one patient in a group of 22 children <13 years who underwent TTE-guided ASD closure (22). While there was no device migration in our study, the only major complication was infective endocarditis in one patient. Procedure-related early infective endocarditis was developed

in this patient. However, vegetation thrombus was not detected on the device or other cardiac structures by imaging methods. He was treated with appropriate antibiotic therapy for 6 weeks.

Device-related aortic erosion has been reported as 0.3% in the literature (23). We did not see this frightening late complication in the follow-up. Also, we did not detect rare late adverse events such as conduction abnormality, late infective endocarditis, thrombo-embolism or aortic valve regurgitation (18,23,24).

The activation of local inflammatory reaction by the device that causes the formation of platelet adhesions or release of inflammatory mediators into the left atrium is thought to be the possible mechanism of migraine-like headache (25,26).

In one study, new-onset or increased postprocedural migraine headaches were reported in 7 of 150 patients who underwent transcatheter patent foramen ovale or ASD closure (27). Migraine-like headache related to nickel allergy generally lasts for several months and is controllable with aspirin, acetaminophen, or clopidogrel (25,28). In our study, there was one patient with a migraine-like headache due to nickel allergy, his symptoms completely resolved in 3 months with medical treatment.

In a recent study evaluating 208 patients who underwent transcatheter ASD closure, it was found that there was no correlation between the defect diameters measured by TTE, TEE, and balloon sizing (29). On the other hand, in our study, there was a strong positive correlation between the angiographically measured stretched balloon diameter and the device waist diameter, while there was a moderate positive correlation between the ASD diameter measured by TTE and the device waist diameter. We think that the reason for the correlation difference is that we used balloon sizing measurements in device selection. Therefore, our study supports that nowadays transcatheter ASD closure with TTE and fluoroscopy guidance and balloon sizing is safe and effective. However, in some recent studies, TTE or TEE-guided transcatheter ASD closure without fluoroscopy guidance has been shown to be feasible, safe, and effective in children and adults (30-33). Also, It has been reported that successful transcatheter ASD closure can be performed with expert operators without balloon sizing under the guidance of fluoroscopy and TTE in suitable adult cases (34).

The main limitation of our study is that we did not have a control group that underwent TEE-guided transcatheter ASD closure.

CONCLUSION

This study supports the view that TTE with angiographically stretched balloon diameter measurement is sufficient to evaluate isolated secundum ASD and guide device selection and implantation in most patients with adequate windows.

In the future, comparative studies with large patient groups are needed for TTE-guided transcatheter ASD closure in children without balloon sizing and/or fluoroscopy, in order to reduce radiation exposure.

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Evaluation of the Relationship Between Cyberbullying Perpetration and Cyber Victimization With Social Media and Game Addiction Among Youth

Gençlerde Siber Zorbalık ve Siber İstismar ile Sosyal Medya ve Oyun Bağımlılığı Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: Both cyberbullying perpetration and cyber victimization are becoming a increasingly important problem among adolescents with the development of technology. It is suggested that there are many factors in the emergence of cyberbullying. This study, it is aimed to evaluate the relationship between cyberbullying and victimization, social media addiction, and game addiction.

Material and Methods: A total of 537 adolescents aged 10-18 were included in our cross-sectional study. Participants filled out the sociodemographic data form, social media addiction scale, game addiction scale, and cyberbullying scale.

Results: In our study, both cyber perpetrators (0.021) and cyber victims (p<0.001) were more frequent in girls. While social media addiction scores were higher in cyber victims (p=0.020), gender (OR [Odds Ratio]= 0.09 CI [Confidence interval]:[0.04- 0.23]) and game addiction score were found to be predictors. (OR=1.09 CI: [1.03-1.16]).

Conclusion: Social media and game addiction seem to be especially related to cyber victimization. Although a causal relationship could not be revealed in our study, it is thought that it may be useful to increase the awareness of adolescents about cyberbullying during gaming and using social media, which have an important place in their lives, and to evaluate the groups with addiction in terms of cyber victimization.

Key Words: Adolescence, Cyberbullying perpetration, Cyber victimization

ÖZ

Amaç: Teknolojinin gelişmesiyle birlikte, hem siber zorbalığı uygulama hem de siber istismara uğrama, ergenler arasında giderek artan önemli bir problem haline gelmiştir. Siber zorbalığın ortaya çıkmasında birçok faktör olduğu ileri sürülmektedir. Bu çalışmada siber zorbalık ve istismar ile sosyal medya bağımlılığı ve oyun bağımlılığı arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışma kesitsel nitelikli olup, çalışmaya 10-18 yaş aralığında toplam 537 ergen dahil edilmiştir. Katılımcılar sosyodemografik veri formu, sosyal medya bağımlılığı ölçeği, oyun bağımlılığı ölçeği ve siber zorbalık ölçeğini doldurmuştur.

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Ethics committee approval of the study was obtained from the Gülhane Faculty of Medicine, Scientific Research Ethics Committee in 2021 (2021-409).

Contribution of the Authors / Yazarların katkısı: DURMAZ N: 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. ***ATES BO:*** 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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Bulgular: Çalışmamızda kızlarda hem siber zorbalık (p=0.021) hem de siber mağduriyet (p<0.001) daha sıktı. Siber zorbalığa uğrayanlarda sosyal medya bağımlılığı skoru daha yüksek olup (p=0.020), siber istismar için cinsiyet (OR [Odds Ratio]= 0.09 GA [güven aralığı]: [0.04-0.23]) ve oyun bağımlılığı puanı yordayıcı olarak bulunmuştur. (OR=1.09 GA: [1.03-1.16]).

Sonuç: Sosyal medya ve oyun bağımlılığı özellikle siber istismar ile ilişkili görünmektedir. Çalışmamızda nedensel bir ilişki ortaya konulamamakla birlikte, ergenlerin yaşamlarında önemli bir yere sahip olan sosyal medya kullanımı ve oyun oynama sırasında siber zorbalığa karşı farkındalıklarının artırılmasının ve bağımlılık saptanan grupların siber istismar açısından değerlendirilmesinin yararlı olacağı düşünülmektedir.

Anahtar Sözcükler: Ergenlik, Siber zorbalık, Siber istismar

INTRODUCTION

Cyberbullying is thought to be a special form of traditional bullying (1). It includes all the behaviors such as the abuse of power systematically by a person or people using information and communication technologies or causing harm technically or relationally (2-3). A standard definition becomes difficult due to the uncertainty of the repetitive nature and power imbalance in the traditional definition of bullying (2). Nevertheless, the concept of cyberbullying, which negatively affects both the physical and mental health of youths, is gaining importance recently (4).

Exposure to cyberbullying a person or group with digital technologies is defined as cyber victimization and the person being bullied is called the cyber victim. Additionally, the person doing the bullying is the perpetrator, cyberbullying perpetration is the aggressive and hostile individual or group behaviors through technology to harm or inconvenience others (5-6).

Many methods such as short messages, e-mails, websites, and online game sites mediate cyberbullying (7). With the advancement of technology, accessing these methods becomes easier for youths both who bully and who have been bullied, and the methods can change over time. Studies reveal that the frequency of online communication, the time spent online, and the use of social networks are associated with cyberbullying (8,9). This condition suggests the relationship between cyberbullying and its technology addictions.

Technology addictions are defined as behavioral addictions that involve human-machine interactions (10). Although there are concepts such as social media addiction, game addiction, and internet addiction in the literature, in DSM 5, only internet gaming disorder is included (11-14). It has been defined as a disorder characterized by the presence of at least five of signs of mental preoccupation with internet games, signs of withdrawal and tolerance, inability to control entering internet games, loss of interest in hobbies other than internet games, continuing excessive use despite the presence of psychosocial problems, deceiving others about the amount of playing, using games to alleviate or eliminate a negative mood, endangering job, education, or career opportunities (14). Although addiction to social networks is not included in the diagnosis manuals, it is stated in the literature that it was characterized by withdrawal symptoms and tolerance observed in behavioral addictions, excessive involvement with social networks, loss of control, deterioration in interpersonal relationships, and relapse symptoms (11).

Youths with technological addiction such as gaming or social media addiction stay longer in online environments (15). Based on the literature data, it has come to mind that when addicted youth encounter cyber victims and cyber perpetrators on social media and in games, they may not be able to avoid it due to their addictive characteristics. Additionally, it has been shown that screen time increases during the pandemic both during and after the closure of schools (16). In the available literature, no study was found in which both game addiction and social media addiction were evaluated together during the post-pandemic normalization period. Therefore, this study, it was aimed to evaluate the relationship between both social media and game addiction with the cyberbullying perpetration and cyber victimization among youth during the postpandemic normalization period.

METHOD

Sampling and Procedure

This research was carried out as the “Evaluation of Cyberbullying and Cyber Victimization among Adolescents “ part of the “Safe Internet Use among Adolescents and Internet Addiction After the Pandemic” project. Ethics committee approval of the study was obtained from the Gulhane Faculty of Medicine, Scientific Research Ethics Committee in 2021 (2021-409). Following the approval of the ethics committee, adolescents, aged 10-18 years, in 10 youth centers affiliated to the Provincial Directorate of Youth and Sports, which were determined within the scope of the project, and of whom informed consent was obtained themselves and their families were included. Adolescents whose consent could not be obtained from themselves or their parents and who were not able to read and write at a sufficient level were excluded from the study. Finally, 537 adolescents were included in the study. The participants were asked to fill out the sociodemographic data form, the cyberbullying scale, the social media addiction scale, and the game addiction scale.

Data Collection Tools

Sociodemographic data form: In the form designed by the researchers, the age, gender, age of the parents, education level, number of people in the family, monthly mean income level, time spent on the phone/tablet/computer, the purpose

of using the phone, tablet/computer, the information of used social media accounts were asked.

Cyberbullying scale: In the scale with a total of 16 items, which was developed by Stewart et al. (17), the total internal consistency coefficient, was calculated as 0.87. In the first two multiple-choice questions, it was asked whether the person had been bullied in various ways, whether he had bullied someone or not, and in the next 14 questions, it is evaluated whether he had been bullied with a 5-point Likert type scale and the validity and reliability of the scale in Turkish were conducted by Kuçuk, Inanıcı, and Ziyalar (18).

Social media addiction scale for adolescents: This is a 5-point Likert type scale and there are no reverse-scored items. A minimum of 9 points and a maximum of 45 points can be obtained in the scale, which consists of a total of 9 items. The high total score calculated indicates that the social media addiction of the individual is high, and the low score indicates that the addiction is low. Its development, validity, and reliability study was carried out by Ozgenel et al. in 2019 (19). The scale has a single-factor structure and has no cut-off value.

Game addiction scale for adolescents (short form): The scale was developed by Lemmens, Valkenburg, and Peter in 2009 (20), and the validity and reliability of the scale in adolescents aged 12-19 were conducted by Anlı and Taş. The scale consists of 9 items in total. It is a 5-point Likert type and has no cut-off value. It has a single-factor structure (21).

Statistical analysis

SPSS 21.0 package program was used in our study. The Chi-square test was used for the analysis of qualitative data, and Fisher's exact test was used in cases where the necessary assumptions were not met. The Kolmogorov Smirnov test was used to evaluate the normal distribution, and the variables showing normal distribution were compared with the Student's t-test and those not with the Mann-Whitney u test. Spearman test was used in correlation analysis. The significance value was accepted as 0.05.

RESULTS

Sociodemographic Data

The median age and interquartile range of the participants were 15 (13-16) years. The age range is between 10 and 18. 199 (37.1%) were female and 335 (62.4%) were male.

Cyber Victimization

According to our results, 36 (18.1%) of the girls and 10 (3%) of the boys experienced cyber victimization at least once and cyber victimization was statistically more frequent in girls (p<0.001). The mean age of the cyber victims was 15.347 (SD=1.934) years while it was 14.418 (SD=1.935) years for those who had never experienced cyber victimization and the age of cyber victims were statistically significantly older (p=0.001).

Table I: Sociodemographic characteristics of cyber victims

	Cyber Victimization		
	No	Yes	p
Age*	14.418 (1.935)	15.347 (1.934)	0.001
Gender†			
Girl	163 (81.9)	36 (18.1)	<0.001
Boy	324 (97.0)	10 (3.0)	
Mother's education level†			
Lower than high-school	129 (90.8)	13 (9.2)	0.903
High-school or higher	314 (90.5)	33 (9.5)	
Mother's job†			
Not working	322 (91.2)	31 (8.8)	0.908
Working	150 (90.9)	15 (9.1)	
Father's education level†			
Lower than high-school	86 (89.6)	10 (10.4)	0.705
High-school or higher	357(90.8)	36 (9.2)	
Father's job†			
Not working	20 (95.2)	1 (4.3)	0.494
Working	449 (90.9)	45 (9.1)	
Mean monthly income†			
<3000TL	49 (92.5)	4 (7.5)	
3000-10.000TL	252 (89.7)	29 (10.3)	0.552
>10.000TL	149 (92.5)	12 (7.5)	

***:** *Mean(SD),* **†:** *n(%)*

Table II: Social media addiction and game addiction data of cyber victims.

	Cyber Victimization Mean (SD)		p
	No	Yes	
Social media addiction score	16.904 (7.34)	19.087 (7.18)	0.020
Game addiction score	15.692 (6.63)	18.174 (8.28)	0.054

In our study, no statistically significant difference was found in terms of the education status of their parents, employment status, and monthly mean income of the parents of adolescents who experienced cyberbullying at least once. Details are presented in Table I.

The Role of Social Media Use and Gaming in Cyber Victimization

It was evaluated whether adolescents used social media and for what purposes they used technological devices the most. Although there was no statistically significant difference in terms of cyber victimization between adolescents having and not having social media accounts (p=0.054). Cyber victims were statistically significantly less likely to use technological devices for gaming than those who had never experienced cyber victimization (p=0.015). No significant differences were found for internet surfing (0.440) and for using social media accounts (p=0.283) between cyber victims and others. No significant difference was found between cyber victims and others in terms of time spent in front of the screen (p=0.260).

Table III: Sociodemographic features of cyberbulling perpetrators

	Cyberbullying Perpetration		p
	No n(%)	Yes n(%)	
Mother's education level			
Lower than high-school	139 (97.9)	3 (2.1)	0.765
High-school or higher	337 (97.1)	10 (2.9)	
Mother's job			
Not working	347 (98.3)	6 (1.7)	0.127
Working	158 (98.5)	7 (4.2)	
Father's education level			
Lower than high-school	93 (96.9)	3 (3.1)	0.726
High-school or higher	383 (97.5)	10 (2.5)	
Father's job			
Not working	21 (100.0)	0 (0.0)	1.000
Working	481 (97.4)	13 (2.6)	
Mean monthly income			
<3000TL	51 (96.2)	2 (3.8)	0.719
3000-10.000TL	275 (97.9)	6 (2.1)	
>10.000TL	156 (96.9)	5 (3.1)	

Table IV: Social media addiction, gaming addiction and cyberbullying data of cyberbullying perpetrators

	Cyberbullying Perpetration		p
	No	Yes	
Social media addiction score*	17.024 (7.36)	20.000 (6.35)	0.055
Game addiction score*	15.837 (6.77)	19.000 (8.40)	0.173
Cyberbullying score*	20.416 (8.16)	28.769 (8.92)	<0.001

**Mean(SD)*

It was observed that the social media addiction score of cyber victims was found to be statistically significantly higher (p=0.020) and no significant difference was found in terms of game addiction score (p=0.054) between cyber victims and those who have never experienced cyber victimization. Details are presented in Table II.

Cyberbullying Perpetration

Cyberbullying perpetration rate was found to be 4.5% (n=9) in girls and 1.2% (n=4) in boys and was significantly higher in girls (p=0.021). While the mean age of cyberbullying perpetrators was 15.538 (SD=2.106) years, the mean age of those who never did cyberbully was 14.472 (SD=1.942) years and there was not a significant difference between the two groups in terms of age (p=0.054). Also, no differences were found in terms of mother and father's education level, mean monthly income, and working status, and the details are presented in Table III.

Role of Social Media Use and Gaming in Cyberbullying Perpetration

There were no differences between cyberbullying perpetrators and those who did not cyberbully, in terms of using technological devices for gaming (p=0.465), internet surfing (p=0.440), using social media accounts (p=0.283), and the time spent in front of the screen (p=0.293). Also, cyberbullying perpetrators and those who have never been cyberbullied were compared; no difference was observed in terms of social media addiction scores (p=0.055) and game addiction scores (p=0.173), details are presented in table IV. Nevertheless, the cyberbullying scale scores of cyberbullying perpetrators were statistically significantly higher (p=0.001) (Table IV). The rate of cyberbullying perpetrators who had previous experience of cyber victimization was 84.6%, (n=11) while those who had no experience of cyber victimization were 15.4% (n=2), which was statistically significant (p<0.001).

When the relationship between social media addiction, game addiction, and cyberbullying scores were examined by Spearman correlation analysis, a positive correlation was found between cyberbullying scale score and game addiction (r=0.320 p<0.001) and social media addiction (r=0.375 p<0.001) scale score. Similarly, social media addiction and game addiction scale scores showed a positive correlation (r=0.433, p<0.001).

Logistic Regression Analysis

The enter binary logistic regression model was used to reveal the predictive factors in cyber victimization. Age, gender, mean monthly income, mother's education level, father's education level, screen time, game addiction, and social media addiction scores were included in the model that was created to determine the predictors of cyber victimization (Nagelkerke R2=0.214). In the created model, gender (OR=0.09 CI: 0.04-0.23 p<0.001) and, game addiction scores were found to be predictive (OR=1.09 CI:1.03-1.16 p=0.001).

DISCUSSION

In the study that aimed to evaluate the relationship between cyberbullying and social media and game addiction, both cyberbullying perpetration and cyber victimization were observed more frequently in female adolescents. Also, in the cyber victims, while the use of phones, tablets, and computers for gaming was significantly lower, their social media addiction scores were found to be high. For cyber victimization, the increase in game addiction scores and gender were found to be predictors. In addition, a weak positive relationship was observed in social media addiction, game addiction, and cyberbullying scores.

The frequency of cyberbullying perpetration and cyber victimization varies within countries and years (22). In a meta-analysis published in 2019, the frequency of lifetime cyber victimization was reported as 7.02% and the frequency of cyberbullying perpetration as 3.45% (23). In our study, closely, while the lifetime prevalence of cyberbullying perpetration was 2.4%, the frequency of experiencing cyber victimization at least once in a lifetime was 8.6%. On the other hand, in a study evaluating the frequency of cyberbullying in primary school age in Turkey, it was reported that 27% were cyber victims

and 18% were cyberbullies, a frequency quite above our study data. In the literature, it is stated that the generalizability of the obtained data was low, for different reasons such as the terminological differences used in the studies evaluating the frequency of cyberbullying perpetration and cyber victimization, the evaluation method used, and the quality of the studies (24,25). In addition, it should be noted that the data obtained in our sample cannot be generalized to the whole society, since our study was conducted in youth centers where activities such as sports, arts, and language education are offered to youths.

When the relationship between gender and cyberbullying was evaluated, it has been shown in the studies that while being cyberbullied was more common in girls, cyberbullying was more common in boys (22,26,27). Following the literature, cyber victimization was higher among girls in our study. However, unlike the literature, the frequency of cyberbullying perpetration was found to be higher in female adolescents. Considering that being a cyber victim is one of the leading risk factors for cyberbullying perpetrators, it comes to mind that the frequency would be higher because girls more frequently use bullying behavior to other people for reasons such as identification with the aggressor, modeling, and behavioral mimicry (28-30).

In our study, it was determined that social media addiction scores were higher in those who experienced cyber victimization. Consistent with the result of our study, in a study involving adolescents aged 11-15 from 42 countries, it was revealed that experiencing cyber victimization showed a strong and consistent relationship with problematic social media use (31). From a clinical point of view, an individual with an addiction may be exposed to this behavior repeatedly on social media platforms, which is one of the most widely used areas for cyberbullying (32). The reasons can be explained as a loss of control over the use of social networks and continuing to use despite negative consequences when faced with cyberbullying (11). Considering that experiencing cyberbullying plays a mediating role between the use of social networks, suicide attempts, and mental problems, the relationship between social media addiction and cyberbullying becomes even more important (33).

When the game addiction scores and using purposes of technological devices were evaluated, it was seen that cyber victims used their technological devices less for playing games. However, at the same time, game addiction scores were found to be an important risk factor for cyber victimization.

Although this condition seems inconsistent, it has been revealed that the most common methods used by adolescents to cope with cyberbullying are avoidance and seeking social support (34). While these strategies can be used in individuals who do not have game addiction or internet gaming disorder, it has not been determined which strategies are used in individuals who lose control while gaming and cannot stop playing games despite the problems they experience. This may result in adolescents with a game addiction not being able to get away even if they experience cyberbullying. The data from the literature have shown that online game addiction increases the risk of cyberbullying perpetration and cyber victimization at the same time (35).

Our study is one of the studies evaluating the relationship between both game addiction, social media addiction, and cyberbullying in secondary and high school students in Turkey. The strength of our study is that the data was collected from a wide age range, including both secondary and high school students in the post-pandemic normalization period. It is aimed that our study will contribute to the literature on game addiction data and it has been evaluated together with game addiction and social media addiction scores. Although it is known that it measures two different concepts, it is thought that evaluating the social media and game addiction variables together will contribute to the literature, since multi-player games have become huge social interaction environment, and applications defined as social networks are platforms where games and game-related interactions are shared (36,37). In our study, which included social media addiction and game addiction different from the other studies, it was found that game addiction, which was not significant in the basic statistics, was a predictor in the last logistic regression model. In addition, during the pandemic, considering that the time of playing games and the rate of technological addictions may increase due to reasons such as the duration of staying at home and in quarantine, it may be useful to evaluate the relationship between cyberbullying and technological addiction in the post-pandemic period (38,39).

However, our study has some limitations. Since our study data was collected from Ankara, it limits its generalizability to Turkey. In terms of gender, the participants were not equally distributed, and the frequency of boys was high. In addition, the absence of a determined cut-off value in the scales used does not allow the data to be compared in groups with and without addiction.

CONCLUSION

Cyberbullying perpetration and cyber victimization is an important problem among adolescents which is especially seen more commonly in adolescents with technological addictions such as social media addiction and game addiction. Therefore, it may be useful to evaluate cyberbullying behaviors and being cyberbullied in detail during the evaluation of technological addictions.

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Evaluation of Lung Magnetic Resonance Imaging of Patients Followed Up With Bronchopulmonary Dysplasia

Bronkopulmoner Displazi Tanısı ile İzlenen Hastaların Akciğer Manyetik Rezonans Görüntülemelerinin Değerlendirilmesi

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ABSTRACT

Objective: Bronchopulmonary dysplasia is a common long-term complication of preterm birth. The evaluation of patients with advanced radiologic methods at early ages is essential in terms of determining the severity of the disease and follow-up. As a non-ionizing modality, magnetic resonance imaging is particularly appropriate for the repeated radiological assessment of pulmonary pathologies associated with bronchopulmonary dysplasia.

Material and Methods: Patients who were followed up with the diagnosis of bronchopulmonary dysplasia and underwent lung magnetic resonance imaging between August 2017 and August 2019 were evaluated retrospectively. Coronal and axial T2-weighted magnetic resonance imaging was performed (TR/TE: 4500-5300/90-106 msec). A pediatric radiologist evaluated magnetic resonance imaging findings. Pulmonary structural findings and their distribution were determined (fibrotic bands, distortion). The findings were compared with bronchopulmonary dysplasia patients' severity, clinical and demographic characteristics. The imaging was performed during the patient's sleep time without sedation or by giving chlorhydrate.

Results: A total of 7 patients were included in the study. Three patients were female, and 4 were male. According to bronchopulmonary dysplasia classification, 1 patient was mild, 3 patients were moderate, and 3 were severe bronchopulmonary dysplasia. The median gestational week was 26.2. In mild bronchopulmonary dysplasia patients, fibrotic bands were seen in <3 segment, and there was no parenchymal distortion. Bronchovascular distortion was observed in moderate and severe bronchopulmonary dysplasia patients.

Conclusion: Pulmonary magnetic resonance imaging can reveal structural abnormalities in patients with bronchopulmonary dysplasia, and can be used as an imaging method in the follow-up of patients.

Key Words: Bronchopulmonary dysplasia, Magnetic Resonance imaging, Prematurity

ÖZ

Amaç: Bronkopulmoner displazi erken doğumun sık görülen uzun vadeli bir komplikasyonudur. Hastaların erken dönemde en yeni radyolojik teknikler kullanılarak değerlendirilmesi, hastalığın şiddetinin değerlendirilmesi ve takip

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Contribution of the Authors / Yazarların katkısı*: *ERYILMAZ POLAT S: Planning methodology to reach the Conclusions, Taking responsibility for patient follow-up, collection of relevant biological materials, data management, and reporting, execution of the experiments, Taking responsibility for the logical interpretation and conclusion of the results, Taking responsibility in critical literature review for the study, Taking responsibility in the writing of the whole or essential parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***HIZAL M:*** Taking responsibility for patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, and taking responsibility in critical literature review for the study. ***TUGCU GD:*** Taking responsibility for logical interpretation and conclusion of the results. ***GUNES A:*** Taking responsibility for logical interpretation and conclusion of the results. ***CINEL G:*** Constructing the hypothesis or idea of research, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking responsibility for the research/study, Taking responsibility for critical literature review for the study, Taking responsibility in the writing of the whole or essential parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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planının yapılması açısından çok önemlidir. İyonize olmayan bir modalite olan manyetik rezonans görüntüleme, bronkopulmoner displazi ile ilgili akciğer patolojilerin radyolojik değerlendirmesi ve izleminde yol gösterici olabilir.

Gereç ve Yöntemler: Ağustos 2017-Ağustos 2019 tarihleri arasında bronkopulmoner displazi tanısı ile takip edilen ve akciğer manyetik rezonans görüntülemesi yapılan hastalar retrospektif olarak değerlendirildi. Koronal ve aksiyel T2 ağırlıklı magnetik rezonans görüntüleri incelendi (TR/TE: 4500-5300/90-106 msn). Manyetik rezonans görüntüleme bulguları bir pediatrik radyolog tarafından değerlendirildi. Akciğerlerin yapısal durumu ve patolojik bulguları değerlendirildi (fibrotik bantlar, distrosiyon). Bulgular, BPD hastalarının şiddeti, klinik ve demografik özellikleri ile karşılaştırıldı. Görüntüleme sedasyon yapılmadan veya kloralhidrat verilmeksizin hastanın uyku süresinde yapıldı.

Bulgular: Toplamda yedi hasta araştırmaya dahil edildi. Hastaların dördü erkek, üçü kızdı. Bonkopulmoner displazi sınıflamasına göre 1 hastanın hafif, 3 hastanın orta düzeyde ve 4 hastanın şiddetli bronkopulmoner displazisi vardı. Ortalama gebelik haftası 26.2 haftaydı. Hafif bronkopulmoner displazi hastalarında <3 segmentte fibrotik bantlar görüldü ve parankimal distorsiyon saptanmadı. Orta ve şiddetli bronkopulmoner displazi hastalarında bronkovasküler distorsiyon gözlendi.

Sonuç: Akciğerlerin manyetik rezonans görüntüleme ile değerlendirilmesi bronkopulmoner displazili hastalarda yapısal anormallikleri gösterebilir ve hastaların takibinde görüntüleme yöntemi olarak kullanılabilir.

Anahtar Sözcükler: Bronkopulmoner displazi, Manyetik rezonans görüntüleme, Prematürite

INTRODUCTION

In premature infants, bronchopulmonary dysplasia (BPD), a chronic lung condition, frequently develops as a result of oxygen and mechanical ventilation during the early neonatal period (1). Fifty years ago, it was first described as chronic lung disease in newborns who had been intubated after being given a diagnosis of respiratory distress syndrome (2). The prevalence of BPD remains high despite improvements in clinical care, such as the use of prenatal steroids and postnatal surfactants, because severely premature newborns are now more likely to survive (3). The survival rates of preterm neonates, especially those born at an exceptionally low gestational age, have increased significantly in recent decades due to significant advancements in neonatal intensive care and the creation of novel treatments. Even though the course of this illness has probably improved, the burden of BPD has remained constant (4). Although the actual cause of BPD is unknown, it is believed to be complex (5). Prematurity, low birth weight, duration of mechanical breathing, oxygen toxicity, infection, patent ductus arteriosus, and genetic factors are the main variables influencing the etiology of BPD (6-8). The definition of the BPD diagnosis is a contentious matter that has evolved throughout time (9, 10). The severity of the disease is defined and categorized using a variety of clinical data. The current consensus definition of BPD, a severity-based scale for infants born younger than 32 weeks who require supplemental oxygen at 36 weeks postmenstrual or at least 28 days prior to the assessment of continued oxygen demand at discharge, was first proposed by the National Institutes of Health in 2000 (9). The scope of this definition's impartiality is restricted to variations in oxygen delivery between institutions (11). As a result, definitions of BPD lack prognostic information and do not consider problems. Effective biomarkers are required for BPD follow-up to identify the disorder's severity and nature, anticipate how it will progress, and assess each patient's response to treatment. BPD is also a long-lasting disease with effects that last into adulthood, and preterm birth should be recognized as a chronic condition that requires long-term follow-up for the prevention and treatment of potential health sequelae into mid-adulthood. Lung function typically increases progressively throughout development and adolescence, plateauing at about age 23-25. It is now known that those who enter adulthood with a lung function that is below average have a higher risk of subsequently getting the chronic obstructive pulmonary disease (12). It is crucial to prevent early infant lung injury because of this. BPD and preterm birth are two glaring instances of how damage might be connected to health problems that last throughout adulthood.

The radiographic evaluation of BPD has begun to play a new role in diagnosing and treating the disease as the diagnostic criteria for BPD have evolved. In cases of severe BPD, findings on standard chest X-rays that suggest fibrosis and hyperinflation are visible and correlate with the severity of BPD. With its excellent resolution and ability to identify structural abnormalities, computed tomography (CT) is a highly effective tool for monitoring BPD patients (13, 14). Given the total amount of ionizing radiation that patients are exposed to, it is not suitable for monitoring disease progression. Modern developments in radiological imaging, particularly magnetic resonance imaging (MRI), can help assess lung structures and may direct therapeutic care techniques for disorders like BPD that develop early in infancy and require regular follow-up. By noninvasively detecting the pulmonary structural alterations early on, initiating treatment sooner, and avoiding problems by assessing the present course of therapy, the morbidity and mortality of these individuals can be decreased. The chosen imaging modalities should be simple, radiation-free, and sensitive to show pulmonary abnormalities. Radiological examination of BPD has taken on a new significance in diagnosing and managing the condition as the diagnostic criteria for BPD continue to change. Due to image opacities, lucensiles, and ventilation heterogenity, radiographic phenotypes on chest X-rays including fibrosis and hyperinflation have been postulated. Patients with severe BPD can see this phenotype on routine chest radiographs, and the severity of BPD is correlated with this phenotype (1). The traditional gold standard of chest imaging, CT, has been given a qualitative scoring system that considers hyperinflation, emphysema, fibrosis, and radiologists' personal opinions.

However, CT is not well suited for longitudinal disease progression monitoring, particularly in pediatric patients, due to the risk of ionizing radiation. BPD is a chronic lung condition that requires breathing assistance at 36 postmenstrual weeks, but structural complications like lung hyperinflation are frequently immeasurable. Without sedation, MRI allows for tomographic determination of lung volumes and densities during quiet breathing (silent breathing).

In this study, the long-term follow-up of BPD patients in our pediatric pulmonology clinic was examined with the pulmonary MRI characteristics. In addition, by identifying these patients' demographic, clinical, laboratory, and radiological traits, it was hoped to assess the value of pulmonary MRI in the long-term follow-up of patients.

MATERIALS and METHODS

Retrospective analysis of the lung MRI findings of the patients who received a BPD diagnosis and were followed up at the Health Sciences University of Ankara Pediatrics Hematology Oncology Training and Research Hospital Pediatric Chest Diseases Clinic was done between August 2017 and August 2019. The patients' MRI results were compared to their demographic information and most recent chest X-ray results. Medical records were used to acquire patients' demographic, clinical, laboratory, and radiological information. Without using intravenous contrast material, MRI imaging was carried out in two sequences (axial and coronal T2-weighted, average 7 minutes), with pictures corresponding with breathing. MRI was performed with or without superficial anesthesia while the patient was asleep (chlorohydrate). Coronal and axial T2-weighted MRI imaging was performed (TR/TE: 4500-5300/90-106 msec) without giving sedation or by giving chlorhydrate, and the average imaging time was 6-7 minutes. The descriptive statistics of the study were shown as a number, percentage, median and interquartile range (IQR). Statistical analysis was evaluated in SPSS 23 package program.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (24.05.2019 – 2019-186).

RESULTS

The study comprised seven patients with the diagnosis of bronchopulmonary dysplasia who were being monitored. Four of the patients (57.1%) were male. The patients' median age was 19.4 months (11-34). The patients' median corrected age was 16 months. The patients had all previously undergone hospitalization in the neonatal intensive care unit. The average stay was 92.5 (28-214) days. Four of the patients (57.1%) required positive pressure ventilation (PPV). All except one of the patients received surfactant treatment. During the neonatal era, all patients required oxygen for longer than 28 days, and one patient was still receiving it. All patients had continuous positive airway pressure (CPAP) during the postnatal period, with a mean time of 9.1 (1-20) days. In the newborn phase, mechanical breathing was required in five individuals (71.4%). None of the patients had Respiratory Syncytial Virus (RSV) infection, and all patients received RSV prophylaxis. Pulmonary hypertension was not seen in any of the patients throughout the newborn phase echocardiographic assessments. Five patients (71.4%) in the newborn critical care unit had a history of sepsis. Three patients received oxygen after they were transferred out of the Neonatal intensive care unit (NICU). Table I provides an overview of patients' demographic and clinical characteristics.

Table I: Demographic and clinical results of the study group.

Age (month)	19.4 (IQR:7)*
Corrected age (month)	16 (IQR:7.25)*
Sex (Male/Female)	57.1 / 42.9†
Gestational age (week)	26.2 (IQR:2)*
Neonatal intensive care unit length of stay (day)	92.5 (IQR:85)*
Surfactant	85.7†
Medical history of pneumonia	57.1†
Medical history of bronchiolitis	28.5†
Gestational age (week)	26.2 (IQR:2)*

*****The median and interquartile range were shown by IQR (interquartile range), **†**(%)

Three patients exhibited retardation compared to their contemporaries, even though the developmental evaluation of 4 patients was commensurate with that of their peers. According to their medical histories, four patients had pneumonia, six had bronchiolitis, and four had recurrent bronchiolitis. When the severity of BPD was assessed, 3 patients had severe BPD, 3 patients had moderate BPD, and 1 patient had mild BPD. The mean age at the time of lung MRI of the patients was 17.8 (11-34) months.

Lung MRI of the patient with mild BPD had fibrotic band changes in 2 segments. All patients with moderate BPD (n=3) had fibrotic band changes and areas of distortion. While 1 of the patients (n=3) with severe BPD had fibrotic band changes, the other two had both fibrotic band changes and areas of distortion. The patient with mild BPD had a reticular appearance and bilateral hyperaeration areas in the right lung on the chest X-ray. Patients with moderate BPD (n=3) had bilateral hyperaeration areas in one patient, bilateral peribronchial thickenings in one patient, and bilateral hyperaeration areas and bilateral peribronchial thickening in one patient. While all patients with severe BPD (n=3) had bilateral areas of hyperaeration, one patient had additional bilateral peribronchial thickenings. Table II compares

Table II: Patient characteristics and results of imaging modalities.

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Gestational age (week)	27	25	27	24	26	27	28
Birth weight (gram)	1080	845	975	705	780	1230	950
APGAR 1 minute	7	5	6	5	6	6	6
APGAR 5 minute	8	6	7	6	7	7	8
BPD severity*	mild	severe	moderate	severe	severe	moderate	moderate
Respiratory support as discharge	oxigene	oxigene	none	none	none	oxigene	none
Age at lung MRI (month)	16	15	22	13	22	18	30
Lung MRI findings	band=2 segments reticular appearance on the right lung, bilaterally hyperaeration	band=3 segments bilaterally hyperaeration	band=5 segments, distortion: 3 lobes bilateral peribronchial thickening, bilaterally hyperaeration	band=6 segments, distortion: 3 lobes bilateral peribronchial thickening, bilaterally hyperaeration	band=2 segments, distortion:2 lobes bilaterally hyperaeration	band=6 segments, distortion: 4 lobes bilateral peribronchial thickening	band=2 segments, distortion: 1 lobes bilaterally hyperaeration
Chest X-Ray findings							

**assessed 36 weeks postmenstruel age or discharge*

the results of the patients' chest X-rays and MRIs taken during the same time period.

DISCUSSION

In this retrospective study, a total of 7 patients underwent lung MRI. None of the patients had newly developed respiratory complaints during lung MRI. Again, none of the patients had any newly developed pathological findings in the chest X-ray. Chest radiography is a simple, quick, and common technique used for imaging patients or control purposes. However, it is not sufficient to follow the lung structure in terms of sequelae and development in the follow-up of the disease (15). Chest radiography, the most used imaging technique in premature infants, enables the assessment of the pulmonary parenchyma status. Interstitial thickness, localized or generalized hyperexpansion, and atelectasis are chest X-ray characteristics of BPD (16). In our study, patients' simultaneous chest radiographs tended to show bilateral hyperaeration and hyperexpansion. In addition, reticular appearance and chronic changes were noted, albeit these assessments are unrelated to the patients' BPD severity (Table II). None of the patients had thorax CT. Routine thorax CT is not performed in the follow-up of BPD patients in our clinic, but it is requested when necessary. The abnormalities seen on chest CT in patients with BPD, such as reduced attenuation, emphysematous changes, linear and subpleural opacities, and thickening of the bronchial wall, are more easily detected on CT. Additionally, it has been demonstrated that the clinical severity of BPD correlates with the amount of structural abnormality on CT (17).

BPD still carries a heavy burden of morbidity and mortality in survivors of extreme prematurity, and it causes significant health expenditures. The radiographic assessment of the lungs is crucial for determining the severity and consequences of the disease in both historical and modern medicine (18). Therefore, it is crucial to assess imaging methods for identifying lung anomalies in BPD patients. Although the roles of chest radiography and CT in BPD are well understood, technological advancement and ongoing imaging modality development have opened the door to pulmonary structural assessment using lung MRI and functional assessment using breathing. Knowing more about recent technology advancements and the possibilities of new techniques is becoming increasingly crucial. Chest imaging plays an essential role in the diagnosis and evaluation of potential complications of BPD (19). Imaging abnormalities may persist into adolescence and adulthood. In our study, patients with chest radiographs that remained unchanged from earlier chest radiographs and who were in a stable clinical state were assessed using MRI. While clinically stable lung MRI had the distortion in one or more lobes in all moderate and severe BPD patients, no distortion was found in the patient with mild BPD. There were bilateral hyperaeration

areas in the simultaneous chest X-ray of 6 patients. Three patients had bilateral peribronchial thickening, but chest X-ray findings were not associated with BPD severity. Due to the small sample size, no correlation was found between chest X-ray findings and MRI findings. MRI appears to be the ideal modality for cross-sectional imaging in the pediatric population because it is an imaging technique that does not require exposure to ionizing radiation. However, conventional MRI's significant inherent limitations severely restrict its application in pediatric thoracic imaging. The lung parenchyma has a low proton density and numerous natural air-tissue contacts. As a result, it produces a rapidly degrading signal at very low intensities, leading to images of the lung parenchyma with very low resolution (14). Lung architectural distortion detected in the patients in our study may be a distinctive feature of any pulmonary fibrosis process. Parenchymal bands also often extend from the visceral pleural surface and pass through the lung parenchyma. They can develop in various ways and are often accompanied by lung architecture deformation (20). In the follow-up of BPD patients, pulmonary MRI findings can be followed sequentially from these aspects in the follow-up of stable patients. With the advancement of technology, there are new developments in imaging techniques. These improvements in MRI technology make it possible to detect fibrosis and hyperinflation in young children using sensitive tomographic imaging without the need of ionizing radiation. As a new technique, ultrashort echo time (UTE) MRI, which better visualizes proton density in parenchymal tissue, where the MR signal typically displays rapid T*2 relaxation, provides higher image quality. Additionally, UTE MRI is less susceptible to motion inaccuracies than conventional MR sequences (14, 21, 22). Although it has limitations due to the low proton density of the lung, short T2*, high magnetic susceptibility at various air-tissue interfaces, and motion artifacts from the heart and lungs, magnetic resonance imaging (MRI) may be a better option (23).

The relatively small sample size of our study is one of its critical limitations. Additionally, the BPD patients included in the study could be regarded as "survivors" of the condition due to their numerous potential comorbidities and the possibility of recurring respiratory issues in early infancy. As a result, our patient group may contain individuals with more severe diseases. Further research into the pathophysiology of the illness, especially studies of younger children and infants who develop BPD, may be beneficial. Given the small sample size of this study, it is difficult to determine the benefit of pulmonary MRI imaging in the further follow-up of BPD. MRI has the potential as a tool for the longitudinal assessment of BPD. However, widespread clinical use will require more effective validation in a larger patient population and greater automation of the techniques used. Several cross-sectional studies have looked at school-aged and older BPD survivors and revealed airway blockages, although we lack the proper technology to evaluate lung function in newborns (24, 25). Both "old" and "new" BPD survivors have been described as having reduced lung function, which has been linked to an increase in respiratory symptoms and aberrant chest imaging results (26).

Additionally, longitudinal investigations of preterm and BPD survivors have found a decline in lung function during childhood and adolescence. According to the Padova BPD study (27), adult lung function does not reach its peak in the presence of severe airway obstruction in infancy and remains until age 24. In addition, since patients with BPD are a group that should be followed up until adulthood in terms of the respiratory system, it is very important to determine the appropriate method for longitudinal follow-up in these patients.

CONCLUSION

In terms of imaging the lungs in the long-term follow-up of BPD patients, MRI is a non-ionizing technique, unlike other imaging modalities; this is particularly important for imaging children who are more vulnerable to the harms of radiation exposure and is important for chronic disease cases where longitudinal monitoring is desired. With larger studies, MRI may become the gold standard.

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Çoklu Konjenital Anomali Vakası: Parsiyel Trizomi 14 ve Parsiyel Trizomi 22

A Case With Multiple Congenital Anomaly: Partial Trisomy 14 and Partial Trisomy 22

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ÖZ

Bu yazıda intrauterin gelişme geriliği, dismorfik yüz bulguları ve konjenital kalp anomalisine sahip bir yenidoğanda tespit edilen kısmi trizomi 14 ve kısmi trizomi 22 vakası tartışılmıştır. Canlı doğumlarda konjenital anomali görülme sıklığı %2-6 olup, bunların %60-80'inden genetik nedenlerin sorumlu olduğu düşünülmektedir. Kromozomal değişiklikler, konjenital anomalilerin %25-35'inde görülür. Resiprokal translokasyonlar, bu kromozomal yeniden düzenlemelerin en yaygın nedenidir. Yapılan incelemelerde hastanın tekrarlayan düşük öyküsüne sahip ebeveynlerinde 46, XY t(14;22) (q24;q11.2) dengeli resiprokal translokasyon taşıyıcılığı tespit edilmiştir. Bu gibi durumlarda ebeveynlere genetik danışmanlık sağlamak ve sonraki gebelikler için doğum öncesi tanı seçeneklerini tartışmak oldukça önemlidir.

Anahtar Sözcükler: Dengeli translokasyon, Konjenital anomali, Kromozomal anomali

ABSTRACT

In this article, the diagnosis of partial trisomy 14 and partial trisomy 22 detected in a newborn with intrauterine growth retardation, dysmorphic facial features and congenital cardiac anomaly is discussed. The incidence of congenital anomalies in live births is 2-6%, and it is thought that genetic reasons are responsible for 60-80% of them. Chromosomal anomalies are seen in 25-35% of congenital anomalies. Reciprocal translocations are the most common cause of these chromosomal rearrangements. In the examinations performed, 46, XY t(14;22) (q24;q11.2) balanced reciprocal translocation carriage was detected in the newborn's parents with a history of recurrent miscarriage. In such cases, it is essential to provide parents with genetic counseling and discuss prenatal diagnosis options for subsequent pregnancies.

Key Words: Chromosomal anomalies, Congenital anomalies, Reciprocal translocations

GİRİŞ

Doğumdan itibaren bulunan normalden farklı olan yapısal bozukluklar konjenital-doğumsal anomali adını alır. Major konjenital anomaliler, tıbbi ve cerrahi bakım gerektiren konjenital kalp hastalıkları, anensefali, gastroşizis, yarık dudak/damak, meningomyelosel gibi anomalilerdir. Minör konjenital anomaliler ise düzeltilmesi için hayatı tehdit edici müdahale gerektirmeyen simian çizgisi, epikantal katlantılar, beşinci parmak klinodaktilisi gibi anomalilerdir (1). Yenidoğanda majör konjenital anomaliler yaklaşık %75 oranında izoledir, %25 oranında birden fazla majör anomali birlikteliği görülebilir. Tüm konjenital anomalilerin yaklaşık %60-80'inden genetik nedenler sorumludur (1). Kromozom anomalilerinin yenidoğanlarda görülme sıklığı 1/160 olarak bildirilmiştir (2). Konjenital anomalilerin yaklaşık %25-35'inde bir kromozomal değişiklik mevcuttur (1). Kromozomal anomaliler, konjenital malformasyonlar ve deformasyonlar 1 yaş altı çocuk ölümlerinin %21'inden sorumludur (3). Kromozomal

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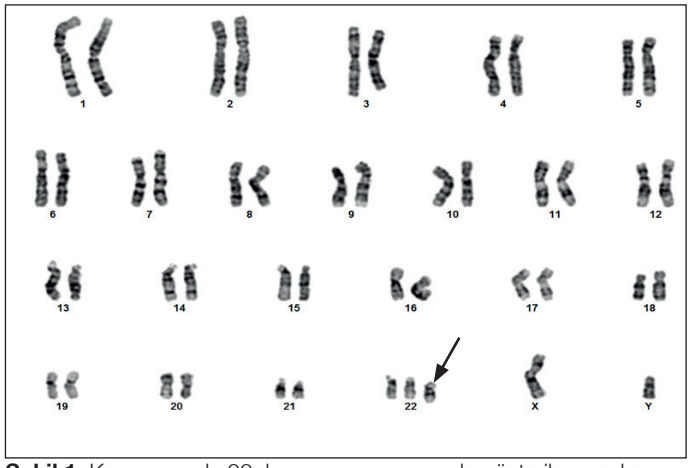
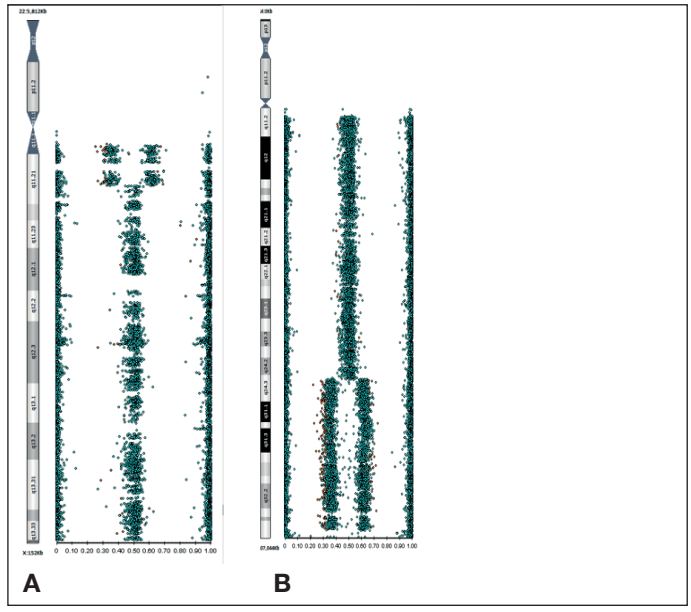
anomaliler oldukça geniş bir klinik spektruma sahiptir. Sayısal ya da yapısal çok sayıda kromozom anomalisi, büyüme ve gelişme geriliği, zihinsel yetersizlik, dismorfik yüz, majör, minör doğumsal anomaliler, infertilite, düşük doğum ağırlığı ya da ölü doğumlar ile ilişkilendirilmiştir (2). Bu yazıda çoklu doğumsal anomalisi düşük doğum ağırlığı, dismorfik bulguları ve konjenital kalp hastalığı olan bir kısmi trizomi 14 ve kısmi trizomi 22 vakası tartışılmıştır.

OLGU SUNUMU

Yirmidört yaşındaki annenin dördüncü gebeliğinden birinci yaşayan olarak 37. gebelik haftasında 2100 gr (<10p) ağırlığında, 42 cm (<10 p) boyunda doğan olgu postnatal 3. günde aktivitesi ve emmesi zayıf olduğu için yenidoğan yoğun bakım ünitesine yatırıldı. Periferik siyanozu olan hastanın solunum sıkıntısı olması ve yapılan kan tetkiklerinde septik bulguları bulunması sebebiyle erken neonatal sepsis tanısıyla iv ampisilin ve amikasin tedavileri başlandı ve nazal CPAP (sürekli pozitif hava yolu basıncı) ile izleme alındı. İlk fizik bakısında geniş ön fontaneli, dar palpebral aralıkları, uzun-silik filtrumu, ince üst dudağı, düşük arkaya dönük kulakları ve bilateral inmemiş testis mevcuttu. Kardiyovasküler sistem muayenesinde 2/6 derece sistolik üfürüm duyulması nedeniyle çekilen ekokardiyografide atriyal septal defekt (ASD) ve ventriküler septal defekt (VSD) saptandı. Yapılan transfontanel ultrasonografi ve beyin manyetik rezonans görüntülemede (MRG) tetkiklerinde kanama odakları dışında majör bir bulgu saptanmadı. Abdominal ultrasonografide ek majör anomali görülmedi. Hastanın başlangıç biyokimyasal analizleri ve metabolik paneli normaldi. Konjenital kalp hastalığı ve dismorfik bulguları olan hastadan öncelikle kromozom analizi istendi. Kromozom analizinde 47,XY +der(22), t(14;22)(q24;q11) saptandı (Şekil 1). Illumina 850k® cipleri ile yapılan mikrodizin analizi sonucunda arr[GRHCh38] 14q24.3-q32.33(74244027_106879456)x3 bölgesinde 32.8 Mb boyutunda duplikasyon ve arr[GRCh38]



Şekil 1: Karyogramda 22. kromozomun yanında gösterilen marker kromozom



Şekil 2: A) mikroarray analizinde 22p11, **B)** 14q24 bölgelerinde duplikasyon.

22p11.2-q11.21(10753385_20140031)x3 bölgesinde 9.4 Mb büyüklüğünde duplikasyon saptandı (Şekil 2). Soygeçmişinde tekrarlayan düşük öyküsü olması nedeniyle yapılan parental kromozom analizinde ebeveynlerinden birinde, daha önce 46,XY t(14;22) q(24;q11.2) dengeli resiprokal translokasyon taşıyıcılığı tespit edildiği öğrenildi. Ailenin gebelik boyunca perinatoloji bölümünde takip edildiği ancak prenatal tanı testlerini kabul etmediği öğrenildi. Dengesiz kromozomal yapıda gamet oluşumu sonucu oluşan parsiyel trizomi 14 ve parsiyel trizomi 22 hastanın fenotipinden sorumlu olarak değerlendirildi. Aileye genetik danışma verildi, pre-implantasyon ve prenatal tanı imkanları konusunda bilgilendirildi.

TARTIŞMA

Ağır doğumsal anomaliler yenidoğan ölümlerinin %20'sinden sorumludur. Spontan düşüklerin yarısında ve canlı doğumların %1'inde kromozomal hastalıklar görülür (4). Kromozom hastalıkları abortus, erken doğum, düşük doğum ağırlığı, doğumsal anomali, nöromotor gerilik ve zihinsel yetersizliğe sebep olabilir. Bahsedilen bu vakada mevcut olan intrauterin büyüme geriliği, dismorfik yüz görünümü, eşlik eden majör doğumsal anomalilerin varlığı ve ailede tekrarlayan düşük öyküsü kromozomal hastalık olasılığını akla getirmiştir. Doğumsal anomali etiyolojisini aydınlatmak için öncelikli olarak kromozom analizi ve ardından mikrodizin analizi yapılmış olup sorumlu olan kromozomal patoloji aydınlatılmıştır. 22q11.2 kromozomal bölgesinin yeniden düzenlenmesinin, özellikle delesyon ve duplikasyonlarının çoklu doğumsal anomalilere sebep olduğu bilinmektedir. Hastanın sitogenetik analiz sonucundaki 22. kromozom duplikasyonunu 22q11.2

(DiGeorge/ Velokardiyofasiyal sendrom (DGS/ VCFS) bölgesini de kapsamaktadır. 22q11.2 delesyon sendromu, 1/4000 canlı doğumda bir olarak tahmin edilen prevalansı ile en sık görülen mikrodelesyon sendromudur (5). Bu kritik kromozomal bölgenin delesyonu, büyüme gelişme geriliği, konotrunkal kalp hastalığı, yarık damak, hipotroidi, timik hipoplazi, oküler ve renal anomaliler gibi majör ve minör doğumsal anomalilerde ilişkili olduğu bilinmektedir. 22q11.2 mikroduplikasyon sendromu, 22q11.2 delesyon sendromundan farklı bir klinik antitedir. Mikroduplikasyonlar literatürde DGS/ VCFS ile örtüşen ancak yüksek fenotipik değişkenliğe sahip ayrı bir sendromu temsil eden özelliklerle tanımlanmıştır (6). Bu bölgenin duplikasyonlarında klinik ve fenotipik bulguların 22q11.2 delesyon sendromuna benzemekle beraber, daha hafif ve değişkendir (5). Trizomi 14 ise, yukarda bahsedilenin aksine hayatla bağdaşmamakla birlikte, ebeveynlerinde dengeli bir translokasyon bulunan olgularda kısmi trizomi 14 görülebilmektedir (7). Oldukça nadir görülen 14. kromozomun uzun kolunun kısmi trizomisinde ise kardiyak defektler, göz anomalileri, dismorfik yüz görünümü, epilepsi ve zihinsel yetersizlik görülebilir (8). Hafiften şiddetli malformasyonlara kadar değişen fenotipik özellikler gösterebilir. Parsiyel trizomi 14 hastalarının prognozu, yapısal anormallik içeren kromozom segmentinin büyüklüğüne bağlı olarak değişkenlik gösterir (9).

Dengeli resiprokal translokasyonlar en sık görülen kromozomal yeniden düzenlenmelerdendir. Dengeli resiprokal translokasyonlar yaklaşık 600 yenidoğanda bir görülür (10,11). Bu tür yeniden düzenlenmeler, homolog olmayan kromozomları içeren kırılma sonucunda veya rekombinasyon sırasında kopan ve rekombinan bölümlerin karşılıklı değişimleri sonucunda oluşur. Resiprokal translokasyon taşıyıcısı bireyler, genetik materyalde herhangi bir kazanç veya kayıp olmadığı için fenotipik olarak normaldir ancak kromozomal olarak dengesiz gamet üretme riskine sahiptirler (12). Bu durumda ileride kromozomal düzensizliği olan gamet oluşturma riskinin %10-15 olması nedeniyle, dengeli kromozomal translokasyon taşıyıcılığı olan bireylerin tüm gebeliklerinde prenatal sitogenetik tanı endikasyonu vardır (13). Bu yazıda sunulan vakadaki tekrar eden gebelik kaybı öyküsü kromozomal analiz sonucunda saptanan resiprokal translokasyon taşıyıcılığı ile uyumludur.

Sonuç olarak, yapısal veya sayısal krozomal anomaliler, çoklu doğumsal anomalilerin bilinen en sık genetik nedenlerindendir. Kromozom analizi ile saptanamayan subkromozal mikrodelesyon ve duplikasyonların tanısında mikrodizin analizinin önemi oldukça büyüktür ve bu sayede her geçen gün hastalıklarla ilgili yeni genler tanımlanmaktadır (2). Çoklu doğumsal anomalilere sahip, dismorfik özellikler barındıran, ailede tekrarlayan düşük veya ölü doğum öyküsü olan hastalarda sitogenetik ve moleküler genetik analiz endikasyonu vardır (14). Ülkemizden bildirilen, çeşitli endikasyonlarla amniyosentez uygulanan 315 vakayı içeren bir seride, ileri anne yaşı nedeniyle amniyosentez yapılan olgularda %2.7 oranında, üçlü tarama testinde risk yüksekliği nedeniyle amniyosentez yapılan hastalarda ise %1.6 kromozomal anomali saptandığı görülmüştür (15). Literatüre bakıldığında, preimplantasyon genetik tanı yöntem endikasyonlarının sıklıkla ileri anne yaşı, tekrarlayan düşükler ve implantasyon başarısızlıkları olduğu görülmektedir. Ülkemizden yapılan preimplantasyon genetik tanı yöntemlerinin incelendiği bir vaka serisinde, en sık rastlanan kromozomal bozukluk monozomiler olup, preimplantasyon genetik tanı yöntemi uygulanan hastalarda %18.8'lik bir canlı doğum oranı bulunmuştur (16). Prenatal veya postnatal kromozomal anomaliye sahip bebek öyküsü olan, ebeveynlerden birinde konjenital anomali veya tekrarlayan düşük öyküsü olan bireylerin kromozom analizi yaptırması, olası kromozom dengesizliklerinin tespiti ve aileye prenatal ve preimplantasyon tanı yöntemlerini içeren genetik danışma verilmesi açısından önem taşır.

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Anesthesia Management of the Premature Newborn with Giant Sacrococcygeal Teratoma

Dev Sakrokoksigeal Teratomlu Prematür Yenidoğanda Anestezi Yönetimi

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ABSTRACT

Sacrococcygeal teratomas originate from the embryonic germ cell layers and are the most common neonatal tumor. The tumor is usually benign and has solid and cystic structures, but may be prone to bleeding due to increased vascularization. The anesthesia management of these patients is challenging due to the risk of bleeding, hemodynamic instability, electrolyte imbalance, hypothermia, and acidosis. Complications may cause serious perioperative morbidity and mortality.In this case report, important steps in the anesthesia management of a female patient, who was born at 29 weeks and 6 days of gestation, weighed 2190 g, and was operated for a mass compatible with sacrococcygeal teratoma on the 3rd day of her life were emphasized.The importance of the close monitoring of the preoperative preparation, invasive artery monitoring, blood, fluid and electrolyte replacement is presented with literature.

Key Words: Anesthesia Management, Giant Sacrococcygeal Teratoma, Premature Newborn

ÖZ

Sakrokoksigeal teratomlar embriyojenik germ hücre katmanlarından köken alan, yenidoğanın en sık görülen tümörüdür. Genellikle iyi huylu olan tümör solid ve kistik yapıya ek olarak vaskülarizasyondaki artış nedeniyle kanamaya eğilimli olabilir. Bu olguların kanama riski, hemodinamik instabilite, elektrolit imbalansı, hipotermi, asidoz riski nedeniyle anestezi yönetimi özelliklidir. Gelişen komplikasyonlar perioperatif ciddi morbidite ve mortaliteye sebep olabilir. Bu olgu sunumunda postnatal 3. gününde opere edilen, 29 hafta 6 günlük, 2190 gr ağırlığında sakrokoksigeal teratomla uyumlu kitlesi olan kız hastanın anestezi yönetimindeki önemli adımlar vurgulanmıştır. Preoperatif hazırlık, invaziv arter monitorizasyonu, kan, sıvı ve elektrolit replasmanının yakın takibinin önemi literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: Anestezi Yönetimi, Dev Sakrokoksigeal Teratom, Prematüre Yenidoğan

INTRODUCTION

Teratomas can be found in sacrococcygeal, gonadal, mediastinal, retroperitoneal, cervical and intracranial regions. Sacrococcygeal teratoma (SCT) is a rare tumor and occurs in 1:35.000 to 40,000 live births.The female-male ratio has been reported as 3:1 to 4:1. Teratomas can be malignant depending on maturity and the cell types.Elevated Alpha fetoprotein (AFP) and beta human chorionic gonadotropin (β-hCG) levels may be predictive for malignancy.The most common presentation in newborns is benign, sacral masses recognized prenatally or at birth (1). The primary treatment for SCT is early surgical resection with complete excision of the coccyx (2). The tumor has both solid and cystic structures. The presence of dense vascularity in solid tumors may cause problems (3).

Teratomas can be divided into 4 groups based on the Altman classification (4).

- **Type I :** Tumors predominantly external (sacrococcygeal) with only a minimal presacral component,
- **Type II :** Tumors presenting externally but with a significant intrapelvic extension,

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- **Type III :** tumors are apparent externally but the predominant mass is pelvic and extended into the abdomen,
- **Type IV :** Presacral with no external presentation.

CASE REPORT

The patient was born at twenty nine weeks and six days of gestation with a birth weight of 2190 g. Her 1st and 5th minute APGAR scores were 5 and 7, respectively. She was consulted at our preoperative anesthesia outpatient clinic for sacrococcygeal teratoma. On physical examination, a pseudoencapsulated solid-cystic mass of 130×110×70 mm was observed in the sacrococcygeal region (Figure 1). Also a nodulation was also present on the surface of mass. Echocardiography revealed secundum atrial septal defect (ASD) (5 mm) with left-to-right shunt, tricuspid regurgitation (TR) grade 1-2 and a 3.5 mm ductus opening with a left-to-right shunt. Her hemoglobin was 15.4 g/dl, hematocrit was 46%, leukocyte count was 7000 (x109/L), platelet count was 209.000 (x 09/L), results of kidney function tests and coagulation tests were normal. Alpha fetoprotein and β-hCG of patient were above 20.000 micro/L and 72 mIU/ml, respectively. Blood products were prepared in the preoperative period. Patient was taken to the operation room on postnatal 3rd day, she came as intubated and with an umbilical vein and artery catheterization. In addition to routine monitoring (oxygen saturation, electrocardiogram, noninvasive blood pressure), blood pressure was monitored continuously from the umblical artery. A urinary catheter was inserted and a nasopharyngeal temperature probe was placed. Arterial blood pressure (ABP) was 65/35 mmHg, heart rate(HR) was 128/min and oxygen saturation was 99 with 50% FiO2. The operating room was heated to 24 degrees and a pediatric heating blanket was placed under the patient (warm touch, Covidien IIc, 15 Hampshire Street, Mansfield, MA 02048 USA). Extremities outside of the surgical field and head were wrapped with cotton. The induction was done by adminitering 2% sevoflurane, 50-50 % oxygen-air mixtures,1 mg/kg ketamine, 0.5 mcg /kg fentanyl and 0.5 mg/kg of rocuronium and operation was started in prone position.The dosages of drugs were adjusted according to birth weight. Potassium replacement (4 meq in 250 cc saline, 7 cc/h infusion) was started due to low potassium in the first arterial blood gas. In addition 6 cc/h of 10% dextrose-1/5 saline and 15 cc/h of 0.9% saline was given to patient. As the arterial blood pressure decreased to 24/16 mmHg due to bleeding from leakage, sevoflurane, which has a cardiac depressant effect, has been switched off and has a sempathomimetic effect of 0.5 mg of ketamine administered in every 30 minutes. The infusion rate of 0.9% saline was increased from 15 cc/h to 20 cc/h, and 10 mcg of adrenaline was applied twice.

Figure 1: Preintervention view of the mass.

Afterwards, blood (warming) transfusion was started at a rate of 10 ml/kg/45 minutes. Mean arterial pressure (MAP) was maintained about 25 mmHg. The operation, simultaneously with the end of the blood transfusion, was completed at 2.5 hours. 15 mg/kg paracetamol was administered for postoperative analgesia. The mass that was compatible with Altman type 1 sacrococcygeal teratoma was excised together with coccyx and its capsule while its integrity was preserved. There was a total of 25-30 ml bleeding throughout the entire operation, with the lowest Hb was 10.3 g/dL and hematocrit was 31%. Since the intraoperative potassium value was determined as 3.17 mmol/l in the blood gas, the potassium infusion was stopped. Urine output was approximately 4-5 ml throughout the case. At the end of the surgery, the patient's blood pressure values were at the lower limit (42/20 mmHg) according to corrected gestational week specific reference values so dopamine infusion (5 mcg/kg/min) was started (Table I) (5). The intubated patient was transferred to neonatal intensive care unit with no acidosis, hypothermia, or hypoglycemia. The patient, whose weight was 1120 g on the postoperative 1st day, was extubated on the 2nd day and discharged on the 49th day.

DISCUSSION

Sacrococcygeal teratomas are the most common congenital tumors in newborns and can be treated with surgical intervention (6). In cases where surgical intervention is not possible, the tumor may transform into malignant within months, or it may continue to grow and reach gigantic dimensions, as is often the case with postsacral teratomas (4). In addition, they can cause hemorrhagic complications and coagulopathies (7).

Surgical interventions in newborns, especially in preterm infants, have very important effects including creating a catabolic response, transfer of fluid to the interstitial space sodium and free water retention due to increased capillary permeability. Perioperative fluid management, which may seriously affect the infant's prognosis, should be aimed at preserving intravascular volume, renal and cardiovascular functions (8). Our patient is in the risk group because of her low birth weight prematurity and low infant / mass weight ratio.

The aim of intraoperative fluid management is to replace the preoperative fasting deficit and losses from surgical field, prevent

Table I: Normal blood pressure values in newborns according to corrected gestational week (5).

Gestational week	Highest systolic	Mean	Lowest systolic	Highest diastolic	Mean	Lowest diastolic	Calculated average highest	Mean	Calculated average lowest
24	68	49	33	46	29	14	53	36	20
25	69	51	36	47	30	15	54	37	22
26	70	52	38	48	31	17	55	38	24
27	71	54	40	49	32	18	56	39	25
28	72	55	41	50	33	19	57	40	26
29	73	56	42	51	34	20	58	41	27
30	78	59	43	52	35	21	60	43	28
31	78	61	46	53	36	22	61	44	30
32	80	62	48	54	37	23	63	45	31
33	81	63	50	55	38	24	64	46	33
34	83	66	51	56	39	25	65	48	34
35	84	69	52	57	40	26	66	50	35
36	87	71	55	58	41	27	68	51	36
37	89	72	57	59	42	28	69	52	38
38	90	75	59	60	43	29	70	54	39
39	91	78	60	60	44	30	70	55	40

electrolyte disturbances, prevent hypo- and hyperglycemia, while maintaining the maintenance fluid requirement. The maintenance fluid requirement is replaced at a constant rate, but the rate of replacement fluids, which may vary according to the amount of losses, must be adjusted separately. Since our case did not have night fasting, replacement was performed considering the maintenance and losses throughout the operation. The maintenance of losses to the third spaces is 15-20 mL/kg/hour for major surgical interventions. These losses should be covered with crystalloid solution, but blood losses should be covered with blood or colloid solution (5% albumin) at a ratio of 1:1. Heart rate, blood pressure, and capillary refill time should be closely monitored (8).

Newborns have insufficient vasoconstriction and adrenergic response, so they are at high risk for hypotension and shock. As bleeding increases during surgery, mortality and morbidity rates increase.The mortality rate of hemorrhage was 3.8 % in a previous study (9). It is important to make a detailed evaluation with the surgical team in the preoperative period for the type of the mass and the expectation of bleeding. Gümüş et al. (10) reported management of bradycardia, hypotension and circulatory collapse in a 3420 g preterm infant who underwent excision of a giant sacrococcygeal teratoma at 32 weeks of gestation .In our case due to closed follow up of the intraoperative monitorization we did not encounter the bradycardia and hypotension.

Since the mass in our case was compatible with Altman type 1 sacrococcygeal teratoma, we thought that the expected blood loss could be replaced in a more controlled manner. Hypotension arose due to approximately 25-30 cc of bleeding and loss of 1000 g mass in the intraoperative period, and normotension was regained with erythrocyte replacement and positive inotropic support. The amount of blood volume lost, the rate of loss, the patient's total blood volume, preoperative hematocrit value, presence of cardiac or lung disease, the nature of the surgery, and the benefit-harm ratio of transfusion are taken into consideration for determining the need for transfusion in preoperative period.

Acute massive transfusion may lead to complications such as increased intracranial pressure and cardiac overload (11). In our case, we maintained the hemodynamic stability by replacing the losses over time and adding inotropic support. In our case, we started erythrocyte suspension replacement and dopamine intraoperatively and these supports were terminated in accordance with the hemogram, blood gas and vital follow-ups in the postoperative ICU.

Two points are very important in preventing intraoperative shock, arrest and transfusion complications in hemorrhagic surgery of premature newborns: instant hemodynamic monitoring with arterial moniterization and well-known of guidelines that approaching hypotension according to the week and weight of preterms (5). In our case, blood pressure values of the patient were evaluated according to the gestational week through artery monitoring during surgery; treatment and supports were applied accordingly (Table I). We did not experience shock or arrest in our case.

The glucose content of intraoperative fluids has also been re-evaluated in recent years. It has been understood that not only long-term hypoglycemia but also transient hypoglycemia

can cause neurological damage during surgery. However, the risk factors of perioperative hyperglycemia are well known. Stress-induced insulin resistance is a factor contributing to the development of hyperglycemia during surgery. Osmotic diuresis caused by hyperglycemia can lead to dehydration, electrolyte disturbance and increased lactate. However, it is suggested that slightly elevated blood glucose levels in newborns protect the brain against ischemic damage and that they are protected from lactic acidosis because of their high lactate clearance. In cases where SCT equisation has been conducted so far, glucose infusion has been done by checking intermittent blood glucose in the blood gas. However, we have taken into account the glucose dose recommended by the nutritional guides as our case is more sensitive to hypoglycemia due to prematurity and low birth weight. According to the Nutrition Guidelines for Premature and Sick Term Infants that were updated in 2018, it is appropriate to start with a glucose infusion rate of 4-6 mg/kg/min in term and >1000 g of premature babies (12). We also applied glucose infusion at 5 mg/kg/min in our case and we did not observe hypoglycemia in our follow-ups.

It is known that pediatric patients are at higher risk of hypothermia during surgical procedures than adults. Although studies showing the frequency of hypothermia in pediatric patients are limited, it has been reported between 4.2% and 60% (13). Pediatric patients tend to develop hypothermia higher in the perioperative period (core temperature ≤36°C) than adults due to decreased weight-body surface area ratio, increased heat loss from the head region, and insufficient subcutaneous adipose tissue. Anesthesia induction during surgical procedures is also an important risk factor for hypothermia. Anesthetic agents used in the perioperative period inhibit thermogenesis, create vasodilation and muscle relaxation and prepare the ground for the formation of hypothermia (13,14). In our premature newborn patient, we preferred a blanket with blown heating in addition to preoperative room temperature adjustment and heating of replacement fluids in order to maintain intraoperative body temperature. Although the body is not in full contact with the blanket due to the chest supports in prone position; we created a heated area (like a bathtub) between the blanket and the upper surgical cover by blowing hot air from the bottom. In this way, we kept the body temperature at 36-37°C.

CONCLUSION

Preoperative surgical prediction and preoperative close hemodynamic follow-up are very important in large and hemorrhagic surgeries of low birth weight premature newborns. Replacement treatments should be planned in appropriate amounts and in a way that does not harm the patient, accompanied by invasive monitoring and in accordance with the guidelines. More than one effective precaution must be taken for heat loss.

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