Esansiyel Tremor Tanılı Çocuk ve Ergenlerin Demografik, Klinik ve Tedavi Özellikleri: Geriye Dönük Kesitsel Bir Analiz

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

Arzu YILMAZ

Ankara Eğitim Araştırma Hastanesi, Çocuk Nörolojisi Bölümü, Ankara, Türkiye

ÖZ

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

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

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

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

Anahtar Sözcükler: Çocuk, Ergen, Esansiyel tremor, Propranolol

ABSTRACT

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

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

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

YILMAZ A : 0000-0003-2550-9324

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

Etik Kurul Onayı / *Ethics Committee Approval*: Bu çalışmada ulusal ve uluslararası etik kurallara uyulmuştur. Çalışma için Ankara Eğitim ve Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu'ndan 21.04.2020-245 karar numarası ile onay alınmıştır.

Yazarların katkısı / *Contribution of the Authors*: *YILMAZ A:* Araştırma ve/veya makalenin hipotezini veya fikrini oluşturan, Sonuçlara ulaşmak için planlama/metodoloji belirleme, Araştırma/çalışmanın sorumluluğunu üstlenmek, ilerlemenin seyrini denetlemek, 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, Yazım ve dilbilgisi dışında bilimsel olarak gönderilmeden önce makaleyi gözden geçirme.

Atıf yazım şekli / *How to cite* : Yılmaz A. Esansiyel Tremor Tanılı Çocuk ve Ergenlerin Demografik, Klinik ve Tedavi Özellikleri: Geriye Dönük Kesitsel Bir Analiz. Türkiye Çocuk Hast Derg 2022;16:1-4.

Yazışma Adresi / Correspondence Address:
Arzu YILMAZ
Ankara Eğitim Araştırma Hastanesi, Çocuk Nörolojisi Bölümü, Ankara, Türkiye
E-posta: arzuotken@yahoo.com

Geliş tarihi / Received : 10.11.2020
Kabul tarihi / Accepted : 15.12.2020
Elektronik yayın tarihi : 12.03.2021
Online published
DOI: 10.12956/tchd.824209

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

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

Key Words: Child, Adolescent, Essential tremor, Propranolol

GİRİŞ

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

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

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

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

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

ET'de motor belirtilere ek olarak bireyde bilişsel (kognitif) değişikliklerin ve psikiyatrik semptomların gözlenebilmektedir (9,10). Günlük yaşam aktivitelerini engelleyecek şiddette titremesi olan hastaların tedavi edilmesi önerilmektedir. Kesin bir tedavisi olmayan ET'de ağır bileklik ve su içerken ağır bardak kullanma gibi yöntemler tremorun azaltılmasına katkı sunabilir. İlaç tedavisi hastaların %50'sinde tremorda kısmen bir azalma sağlar ve maalesef %30-50 hastada etkisizdir. İlk tercih edilen ilaç beta-adrenerjik blokerler (en sık propranolol)'dir (7).

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

GEREÇ ve YÖNTEMLER

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

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

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

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

BULGULAR

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

Tablo I: Esansiyel tremorlu 93 olgunun demografik özellikleri.

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

a: *Medyan (minimum-maksimum),* ***†:*** *n(%)*

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

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

****:*** *Fisher's exact test,* ***†:*** *n(%)*

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

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

****:*** *Fisher's exact test,* ***†:*** *n(%)*

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

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

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

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

TARTIŞMA

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

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

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

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

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

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

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

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

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

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

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

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

KAYNAKLAR

1. Kızıltan G. Çocuk ve ergende nörolojik hastalıklara yaklaşım rehber kitabı 2015. 163. Chapter. Tremor ve İlişkili Durumlar. İstanbul Üniversitesi, Cerrahpaşa Tıp Fakültesi, Nöroloji AD. Türk Nöroloji Derneği Kitabı 163-9.
2. Keller S, Dure LS. Tremor in childhood. Semin Pediatr Neurol 2009; 16: 60-70.
3. Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. Nat Rev Neurol 2020;16:84-96.
4. Sullivan KL, Hauser RA, Zesiewicz TA. Essential Tremor Epidemiology, Diagnosis, and Treatment. The Neurologist 2004;10:250-8.
5. Charles PD, Esper GJ, Davis TL, Maciunas RJ, Robertson D. Classification of Tremor and Update on Treatment. Am Fam Physician 1999; 59:1565-72.
6. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 1998; 13 Suppl 3: 2-23.
7. Tüzün S, Çiftçili S, Apaydın-Kaya Ç. Tremor I: Tanı ve tedavi. Türk Aile Hek Derg 2009; 13:200-5.
8. Louis ED. Essential tremor. Lancet Neurol 2005;4:100-10.
9. Acar BA, Acar T. Esansiyel Tremor Sadece Hareket Hastalığı Değildir; Uyku ve Anksiyetenin Hastalıkla İlişkisi. Nöropsikiyatri Arşivi 2019;56:18-22.
10. Chandran V, Pal PK, Reddy JYC, Thennarasu K, Yadav R, Shivashankar N. Non-motor features in essential tremor. Acta Neurol Scand 2012;125: 332-7.
11. Hubble JP, Busenbark KL, Pahwa R, Lyons K, Koller WC. Clinical expression of essential tremor: Effects of gender and age. Movement Disorder 1997;12: 969-72.
12. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord 2010; 25: 534 41.
13. Hardesty DE, Maraganore DM, Matsumoto JY, Louis ED. Increased risk of headtremor in women with essential tremor: longitudinal data from the Rochester Epidemiology Project. Mov Disord 2004;19:529-33.
14. Louis ED. Essential tremor: a nuanced approach to the clinical features. Pract Neurol 2019;19:389-98.
15. 15.Louis ED. The Roles of Age and Aging in Essential Tremor: An Epidemiological Perspective. Neuroepidemiology. 2019;52(1-2):111-8.
16. Yaşar H, Balıbey H, Tekeli H, Alay S, Şenol MG, Türker T, Bayar N. Genç Erkek Esansiyel Tremor Hastalarında Anksiyete ve Depresyon Düzeyleri. Journal of Mood Disorders 2014; 4: 66-9.
17. Sengul Y, Sengul HS, Yucekaya SK, Yucel S, Bakim B, Pazarci NK, et al. Cognitive functions, fatigue, depression, anxiety and sleep disturbances: assesment of nonmotor features in young patients with essential tremor. Acta Neurol Belg 2015; 115: 281-7.
18. 18.Zesiewicz TA, Chari A, Jahan I, Miller AM, Sullivan KL. Overview of essential tremor. Neuropsychiatr Dis Treat 2010; 6:401-8.

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

Sistin Taşı Olan Çocuk Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

Fatma Semsa CAYCI[1], Banu CELIKEL ACAR[2], H.Tugrul TIRYAKI[3], Umut Selda BAYRAKCI[4]

[1] University of Health Sciences, Ankara City Hospital, Department of Pediatric Nephrology, Ankara, Turkey
[2] University of Health Sciences, Ankara Hospital, Pediatric Rheumatology Clinic, Ankara, Turkey
[3] University of Health Sciences, Ankara City Hospital, Department of Pediatric Urology, Ankara, Turkey
[4] University of Yıldırım Beyazit, Ankara City Hospital, Department of Pediatric Nephrology, Ankara, Turkey

ABSTRACT

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

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

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

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

Key Words: Child, Cystinuria, Urolithiasis, Kidney stones

ÖZ

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

CAYCI FS : 0000-0001-6779-275X
CELIKEL ACAR B : 0000-0002-0561- 6504
TIRYAKI HT : 0000-0002-9544-1137
BAYRAKCI US : 0000-0002-5301-2617

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*: The study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Medical Research Ethics Committee of Ankara Child Health Hematology-Oncology Training and Research Hospital (Protocol Number:2014-041).

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

How to cite / *Atıf yazım şekli* : Cayci FS, Celikel Acar B, Tiryaki HT, Bayrakci US. Evaluation of Children with Cystine Stones: A single-Center Experience. Turkish J Pediatr Dis 2022; 16: 5-10.

Correspondence Address / Yazışma Adresi:
Fatma Semsa CAYCI
University of Health Sciences, Ankara City Hospital,
Department of Pediatric Nephrology, Ankara, Turkey
E-posta: saltugan2001@yahoo.com

Received / Geliş tarihi : 24.11.2020
Accepted / Kabul tarihi : 16.12.2020
Online published : 21.12.2020
Elektronik yayın tarihi
DOI: 10.12956/tchd.830509

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

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

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

Anahtar Sözcükler: Çocuk, Sistinüri, Ürolitiazis, Böbrek Taşı

INTRODUCTION

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

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

MATERIAL and METHODS

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

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

The diagnosis of cystinuria was made based on elevated urine dibasic amino acids and cystine levels according to normal values for age in urine amino acid analyzes. Normal urine cystine excretion was reported as 30 mg/L per day (0– 100 µmol/g creatinine) (3). The diagnosis of the cystine urolithiasis (stones) was based on an analysis of stone samples that obtained by spontaneous passage or surgery using the X-ray absorption method at the Institute of Mineral Inspection and Research Laboratory.

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

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

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

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

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

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

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

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

Data analysis and statistics

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

RESULTS

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

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

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

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

The mean first-visit eGFR and last-visit eGFR were 141.8±55.2 ml/min/1.73 m^2 (range: 10-244 ml/min) and 149.3±48.4 ml/min/1.73 m^2 (range: 61-266 ml/min), respectively, and these were not significantly different (p>0.05).

Four patients with eGFRs <90 ml/min/1.73 m^2 at the beginning of the study, used thiol drugs regularly, and the eGFR values of these patients increased to >90 ml/min/1.73 m^2 after the follow-up period.

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

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

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

Table I: Characteristics of patients with cystine stones.

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

**Mean ± SD (min-max)*

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

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

**eGFR: estimated glomerular filtration rate.*

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

CONCLUSION

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

REFERENCES

1. Goodyer P, Saadi I, Ong P, Elkas G, Rozen R. Cystinuria subtype and the risk of nephrolithiasis. Kidney Int 1998;54:56-61.
2. Rezaee ME, Rule AD, Pais VM Jr. What are the main challenges to the pharmacological management of cystinuria? Expert Opin Pharmacother 2020; 21:131 3.
3. Claes DJ, Jackson E. Cystinuria: mechanisms and management. Pediatr Nephrol 2012;27:2031-8.
4. Knoll T, Zöllner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. Pediatr Nephrol 2005; 20:19-24.
5. Eggermann T, Venghaus A, Zerres K. Cystinuria: an inborn cause of urolithiasis. Orphanet J Rare Dis 2012; 5; 7:19.
6. Aydogdu SD, Kirel B, Coskun T, Kose S. Prevalence of cystinuria among elementary schoolchildren in Eskisehir, Turkey. Scand J Urol Nephrol 2009;43:138-41.
7. Tanzer F, Ozgur A, Bardakci F. Type I cystinuria and its genetic basis in a population of Turkish school children. Int J Urol 2007;14:914-7.
8. Girişgen İ, Yüksel S, Karcılı K, Becerir T. Evaluation of the composition of urinary tract stones in children from the Inner Western Anatolian Region in Turkey. Turk J Urol 2020;46:152-8.
9. Sumorok N, Goldfarb DS. Update on cystinuria. Curr Opin Nephrol Hypertens 2013;22:427-31.
10. Asplin DM, Asplin JR. The Interaction of thiol drugs and urine pH in the treatment of cystinuria. J Urol 2013; 189:2147-51.
11. Yüksel S, Elçi HT, Koçyiğit A, Deniz M, Becerir T, Evrengül H. Metabolic risk factors in children with urolithiasis: Single centre experience in southwest Turkey. Pam Med J 2015;97:11–7.
12. Fjellstedt E, Denneberg T, Jeppsson JO, Tiselius HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria. Urol Res 2001;29:295-302.
13. Kum F, Wong K, Game D, Bultitude M, Thomas K. Hypertension and renal impairment in patients with cystinuria: findings from a specialist cystinuria centre. Urolithiasis 2019; 47:357-63.
14. Nalcacioglu H, Ozden E, Genc G, Yakupoglu YK, Sarikaya S, Ozankaya O. An uncommon cause of acute kidney injury in young children: cystinuria. J Pediatr Urol 2013; 9:e58-63.
15. Lindell A, Denneberg T, Granerus G. Studies on renal function in patients with cystinuria. Nephron 1997; 77:76-85.
16. Edvardsson V. Urolithiasis in Children. In: Avner E, Harmon W, Niaudet P, Yoshikawa N, Emma F, Goldstein S (eds). Pediatric

Nephrology. 7th ed. Berlin Heidelberg: Springer-Verlag 2016:1821-61.

17. Muhari-Stark E, Burckart GJ. Glomerular Filtration Rate Estimation Formulas for Pediatric and Neonatal Use. J Pediatr Pharmacol Ther 2018;23:424-31.
18. Eisner BH, Goldfarb DS, Baum M, Langman CB, Curhan GC, Preminger GM, et al. Evaluation and medical management of patients with cystine nephrolithiasis: a consensus statement. J Endourol 2020;34:1103-10.
19. Shen L, Zhun H, Cong X, Ning B. Comparison of renal function and metabolic abnormalities of cystine stone patients and calcium oxalate stone patients in China. World J Urol 2013;31:1219-23.
20. Gürgöze MK, Sarı MY. Results of medical treatment and metabolic risk factors in children with urolithiasis. Pediatr Nephrol 2011; 26:933-7.
21. Tekin A, Tekgul S, Atsu N, Sahin A, Bakkaloglu M. Cystine calculi in children: the results of a metabolic evaluation and response to medical therapy. J Urol 2001; 165:2328-30.
22. Izol V, Aridoğan IA, Karsli O, Deger M, Satar N. The effect of prophylactic treatment with Shohl's solution in children with cystinuria. J Pediatric Urol 2013;9:1218-22.
23. Akakura K, Egoshi K, Ueda T, Nozumi K, Kotake T, Masai M, et al. The long-term outcome of cystinuria in Japan. Urol Int 1998;61:86-9.
24. Chow GK, Streem SB. Medical treatment of cystinuria: results of contemporary clinical practice. J Urol 1996;156:1576-8.
25. Ertan P, Tekin G, Oger N, Alkan S, Horasan GD. Metabolic and Demographic characteristics of children with urolithiasis in Western Turkey. Urol Res 2011;39: 105-10.
26. Assimos DG, Leslie SW, Ng C, Streem SB, Hart LJ. The impact of cystinuria on renal function. J Urol 2002; 168:27-30.

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

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

Ozge YILMAZ TOPAL[1], Ayse AKSOY[2], Ulkuhan OZTOPRAK[3], Cigdem GENC SEL[4], Erhan AKSOY[3], Hulya KAYILIOGLU[5], Ozge DEDEOGLU[6], Aysegul ZENCIROGLU[7], Neşe ONAT[8], Deniz YUKSEL[3]

[1]Ankara City Hospital,Pediatric Allergy and İmmunology Division, Ankara, Turkey
[2]Ondokuz Mayis University, Faculty of Medicine, Pediatric Neurology Division, Samsun, Turkey
[3]University of Health Sciences, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research Hospital, Pediatric Neurology Division, Ankara, Turkey.
[4]Ufuk University, Faculty of Medicine, Doctor Ridvan Ege Hospital, Pediatric Neurology Division, Ankara, Turkey
[5]Mugla Training and Research Hospital, Pediatric Neurology Division, Mugla, Turkey
[6]Mardin State Hospital, Pediatric Neurology Division, Mardin, Turkey
[7]University of Health Sciences, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research Hospital, Neonatology Division, Ankara, Turkey.
[8]University of Health Sciences, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research Hospital, Department of Pediatrics, Developmental-Behavioral Pediatrics Unit, Ankara, Turkey

ABSTRACT

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

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

YILMAZ TOPAL O : 0000-0001-5245-2488
AKSOY A : 0000-0001-7533-1638
OZTOPRAK U : 0000-0002-7309-3215
GENC SEL C : 0000-0002-3644-3124
AKSOY E : 0000-0002-7210-6715
KAYILIOGLU H : 0000-0001-7335-1985
DEDEOGLU O : 0000-0002-7492-5255
ZENCIROGLU A : 0000-0002-3488-4962
ONAT N : 0000-0003-2668-671X
YUKSEL D : 0000-0001-8990-023X

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*: The instutional review board approved the study design and protocols (University of Health Sciences, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research Hospital; No:73799008-799).

Contribution of the Authors / Yazarların katkısı*: *YILMAZ TOPAL O: 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. ***AKSOY A:*** 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, ***OZTOPRAK U:*** 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. ***GENC SEL C:*** 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. ***AKSOY E:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***KAYILIOGLU H:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, 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. ***DEDEOGLU O:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study. ***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 logical interpretation and conclusion of the results. ***ONAT N:*** 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, ***YUKSEL D:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in 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.

How to cite / *Atıf yazım şekli*: Yilmaz Topal O, Aksoy A, Oztoprak U, Genc Sel C, Aksoy E, Kayilioglu H, et al. Postneonatal Epilepsy and Psychomotor Developmental Retardation Risk Factors in Term Neonatal Convulsions Without Hypoxic Ischemic Encephalopathy. Turkish J Pediatr Dis 2022;16: 11-17.

Correspondence Address / Yazışma Adresi:
Ozge YILMAZ TOPAL
Ankara City Hospital, Pediatric Allergy and İmmunology Division, Ankara, Turkey
E-posta: ozgeyilmaztopal@gmail.com

Received / Geliş tarihi : 14.10.2020
Accepted / Kabul tarihi : 29.12.2020
Online published : 06.01.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.810440

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

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

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

ÖZ

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

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

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

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

Anahtar Sözcükler: Yenidoğan konvulziyonları, Hipoglisemi, Postneonatal epilepsi

INTRODUCTION

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

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

Neonatal seizures are known to increase the risk of death, mental retardation and postnatal epilepsy in affected patients (8). These comorbidities become more prominent when patients develop epilepsy. The coexistence of mental retardation and cerebral palsy was found in 87% of the patients who had neonatal convulsions and developed epilepsy in the follow-up (9).

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

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

MATERIALS and METHODS

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

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

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

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

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

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

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

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

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

Statistical analyses were conducted using the IBM SPSS for Windows, Version 22.0 software package. Numerical variables were summarized as mean ± standard deviation and median [minimum – maximum] values. Categorical variables were expressed as number and percentage. Chi-square test or Fisher's exact test was used to compare categorical variables. McNemar's test was used to check whether there were differences between neonatal EEG and follow-up EEG values. Statistical significance was set at $p<0.05$.

RESULTS

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

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

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

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

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

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

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

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

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

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

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

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

Examination of the follow-up EEG findings of patients showed that 2 (4.1%) patients did not being performed EEG monitoring during follow-up. A total of 5 (10.6%) patients had EEG abnormalities including 3 (6.4%) patients with focal EEG findings and 2 (4.3%) patients with multifocal EEG findings. Forty two (89.4%) patients had normal EEG results. Epilepsy was present in all of these 5 patients with abnormal follow-up EEG results and epilepsy was absent in 38 (90.48%) out of 42 patients with normal follow-up EEG results (p=0.000).

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

REFERENCES

1. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. Neurology 2000;55:506-13.
2. Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. Pediatrics 1993;91:128-34.
3. Chapman KE, Raol YH, Brooks-Kayal A. Neonatal seizures: controversies and challenges in translating new therapies from the lab to the isolette. Eur J Neurosci 2012;35:1857-65.
4. Connell J, Oozeer R, de Vries L, Dubowitz LM, Dubowitz V. Continuous EEG monitoring of neonatal seizures: diagnostic and prognostic considerations. Arch Dis Child 1989;64:452-8.
5. Khan RL, Nunes ML, Garcias da Silva LF, da Costa JC. Predictive value of sequential electroencephalogram (EEG) in neonates with seizures and its relation to neurological outcome. J Child Neurol 2008;23:144-50.
6. Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe - a systematic review. Eur J Neurol 2005;12:245-53.
7. Malmqvist O, Ohlin A, Agren J, Jonsson M. Seizures in newborn infants without hypoxic ischemic encephalopathy - antenatal and

labor-related risk factors: a case-control study. J Matern Fetal Neonatal Med 2020;33:799-805.
8. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. Neurology 2007;69:1816-22.
9. Pisani F, Piccolo B, Cantalupo G, Copioli C, Fusco C, Pelosi A, et al. Neonatal seizures and postneonatal epilepsy: a 7-y follow-up study. Pediatr Res 2012;72:186-93.
10 Volpe JJ. Neurology of the Newborn. Philadelphia, PA: Saunders, 2008:178–214.
11. Epstein CM. Guidelines 2: minimum technical standards for pediatric electroencephalography. J Clin Neurophysiol 2006;23:92-6.
12. Garfinkle J, Shevell MI. Prognostic factors and development of a scoring system for outcome of neonatal seizures in term infants. Eur J Paediatr Neurol 2011;15:222-9.
13. Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, Stewart J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006;117:1270-80.
14. Pisani F, Facini C, Pelosi A, Mazzotta S, Spagnoli C, Pavlidis E. Neonatal seizures in preterm newborns: A predictive model for outcome. Eur J Paediatr Neurol 2016;20:243-51.
15. Holden KR, Mellits ED, Freeman JM. Neonatal seizures. I. Correlation of prenatal and perinatal events with outcomes. Pediatrics 1982;70:165-76.
16. Volpe JJ. Neonatal seizures. In: Volpe JJ, editor. Neurology of the newborn. 5th ed. Philadelphia: WB Saunders; 2008, p. 203-4.
17. Mellits ED, Holden KR, Freeman JM. Neonatal seizures. II. A multivariate analysis of factors associated with outcome. Pediatrics 1982;70:177-85.
18. Scher MS. Neonatal seizures and brain damage. Pediatr Neurol 2003;29:381-90.
19. Pisani F, Facini C, Pavlidis E, Spagnoli C, Boylan G. Epilepsy after neonatal seizures: literature review. Eur J Paediatr Neurol 2015;19:6-14.
20. Mizrahi EM WKSnsIRJ, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, et al. Epileptic syndromes in infancy, childhood and adolescence. Montrouge, France: John Libbey Eurotext 2005. p. 17-38.
21. Lai YH, Ho CS, Chiu NC, Tseng CF, Huang YL. Prognostic factors of developmental outcome in neonatal seizures in term infants. Pediatr Neonatol 2013;54:166-72.
22. Painter MJ, Sun Q, Scher MS, Janosky J, Alvin J. Neonates with seizures: what predict development? J Child Neurol 2012;27:1022-6.
23. Ortibus EL, Sum JM, Hahn JS. Predictive value of EEG for outcome and epilepsy following neonatal seizures. Electroencephalogr Clin Neurophysiol 1996;98:175-85.
24. Yildiz EP, Tatli B, Ekici B, Eraslan E, Aydinli N, Caliskan M, et al. Evaluation of etiologic and prognostic factors in neonatal convulsions. Pediatr Neurol 2012;47:186-92.

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

Okulların Çevresel Koşullarının Öğrenci Başarısı ve Devamsızlığı Üzerine Etkisi

Seher PALANBEK YAVAS[1], Cigdem CAGLAYAN[2]

[1] Istanbul University Faculty of Medicine Department of Public Health, Department of Environmental Health, Istanbul, Turkey
[2] Kocaeli University Faculty of Medicine, Department of Public Health, Kocaeli, Turkey

ABSTRACT

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

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

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

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

Key Words: Electromagnetic Fields, Noise, Lighting, School

ÖZ

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

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

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

PALANBEK YAVAS S : 0000-0002-8113-0477
CAGLAYAN C : 0000-0003-4811-7059

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*: The study was obtained from the Kocaeli University Clinical Research Ethics Committee with the decision number 4/18, dated 27.11.2015.

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

How to cite / *Atıf yazım şekli* : Palanbek Yavas S, Caglayan C. The Effect of Environmental Conditions of Schools on Student Success and Absenteeism. Turkish J Pediatr Dis 2022; 16: 18-24.

Correspondence Address / Yazışma Adresi:
Seher PALANBEK YAVAS
Istanbul University Faculty of Medicine Department of Public Health,
Department of Environmental Health, Istanbul, Turkey
E-posta: seher.palanbekyavas@istanbul.edu.tr

Received / Geliş tarihi : 07.10.2020
Accepted / Kabul tarihi : 06.01.2021
Online published : 08.04.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.807145

aydınlatma düzeyi ile not ortalamaları arasında negatif yönde anlamlı bir ilişki tespit edilmiştir (sırasıyla; r -0.498 p 0,011; r -0.548 p 0.021; r -0.563 p 0.004). Okulların bina standartları puanları ile öğrencilerin devamsızlık oranları arasında negatif yönde anlamlı bir ilişki tespit edilmiştir (r -0.371 p 0.011).

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

Anahtar Sözcükler: Elektromanyetik alanlar, Gürültü, Aydınlatma, Okul

INTRODUCTION

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

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

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

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

MATERIAL and METHOD

Population and sample

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

Variables of the research

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

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

1) School indoor environment physical characteristics: Electromagnetic field level in schoolyard (mG), noise level in schoolyard (dB), temperature in schoolyard (°C), and humidity levels (%), measurement parameters related to the electromagnetic field, lighting, noise, temperature, and humidity levels of the determined classrooms. In schools that had a library, the lighting level of the library was also measured.

1) Class properties: It consists of variables such as the hygiene of the classroom, type of the board, distance of the board from the desks, position of the windows, width of the door, space

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

Measurements

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

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

Lighting measurement; has been performed with a TES 1335A Digital Light –Meter luxmeter as 80 cm above the ground, 9 measurements from the front, middle, and back seats and 1 from the middle spot attached to the board, 10 measurement in total by pulling 1 m away from the device. The limit values in classrooms for lighting was based on at least 200 lux light intensity, which is in TS 9518/ General Physical Settlement Rules for Elementary Schools, maximum 500 lux (in the literature), and as for the libraries, it is based on 500 lux (17,18,21-23).

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

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

Statistical Analysis

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

RESULTS

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

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

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

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

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

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

The average of the electromagnetic field measurement while the electronic devices were on in the classrooms measured in our research, has been determined as 0.53±0.27 mG (minimum 0.20 mG-maximum1.20 mG). The average of the electromagnetic field measurement while the electronic devices were off has been determined as 0.47±0.26 mG (minimum 0.17 mG - maximum 1.12 mG). The electromagnetic field level measured in the administrative units of schools has been determined as 0.74 mG±0.40 mG in average. The electromagnetic field level of schoolyard has been determined as 0.63±0.26 mG (minimum 0.34 mG - maximum 1.50 mG) in average. The electromagnetic field level in all of the schools in our research is conforming with the recommended limit values.

The noise level in the classroom has been determined as 37.60±7.09 dB (minimum 24.60 dB - maximum 48.78 dB) in average when measured when the windows were open and as 35.23±6.76 dB (minimum 22.25 dB - maximum 46.42 dB) when measured when the windows were closed. The average noise level of the schoolyards has been determined as 57.43±7.77 dB (minimum 45.00 dB- maximum 69.50 dB). It has been determined in our research that, the schoolyard noise level of 47.6% of the schools, the noise level of 71.4% in the classroom when the windows are open, and the noise level of 59.5% when the windows are closed, comply with the values determined in the standards.

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

The temperature of the classrooms has been calculated as 26.83±2.12 ºC (minimum 23.25 ºC- maximum 33.66 ºC) in average and the humidity level as 50.61±5.73% (minimum %35.00 - maximum %60.33). According to the measurements made in the schoolyard, the temperature of the school environment has been determined as 28.08±3.06 ºC (minimum

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

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

*****7th Grades, † 6th Grades*

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

Inconvenient temperature and humidity values may disturb the students physically and thus affect their academic success negatively. It has been determined in our research that, the classroom temperature levels of the 42.9% schools, and the classroom humidity levels of the 97.6% conform with the standards. In the study, Teli et al. (36) has carried out in England, it has been determined that the temperature in classrooms rages between 19.2-28.9 °C and that the humidity levels are between 40-60%. In the study carried out by Haverinen-Shaughnessy et al. (37) it has been determined that, students who do not receive education under the conditions of a hot classroom have given 4% more correct answers in the test questions, in comparison to other students, and thus the high level of temperature has been associated with headache, having difficulty concentrating, and the increase of absence.

CONCLUSION

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

REFERENCES

1. Güler Ç. Environmental Health (with connections to Environment and Ecology). 1st Edition, Ankara, Yazıt Publishing, 2012.
2. Gündüz S, Albayrak HM. Okul Sağlığında Neredeyiz ?. Ankara Medical Journal 2014; 14: 29-33.
3. WHO (2004). Physical School Enviroment An Essential Component of Health Promoting School,The World Health Organization's İnformantion Series on School Health Document Series 2. [Online] Website: https://www.who.int/ceh/publications/cehphysical/en/ [accessed 18 September 2020]
4. American Academy of Pediatrics. Committee on School Health, School Health Policy and Practice, Fifth Edition 1993.
5. Earthman GI, Lemasters L. The Impact of School Buildings on Student Achievement and Behavior. PEB Exch 2012;30:11–15.
6. Turunen M, Toyinbo O, Putus T, Nevalainen A, Shaughnessy R, Haverinen-Shaughnessy U. Indoor environmental quality in school buildings, and the health and wellbeing of students. Int J Hyg Environ Health 2014;217:733–9.

7. Gilavand A, Hosseinpour M. Investigating the Impact of Lighting Educational Spaces Painted on Learning and Educational Achievement of Elementary Students in Ahvaz, Southwest of Iran. Int J Pediatr 2016;4:1387–96.
8. Clark C, Paunovic K. WHO environmental noise guidelines for the european region: A systematic review on environmental noise and cognition. Int J Environ Res Public Health 2018;15:285.
9. Hansen EK, Nielsen SML, Georgieva D, Schledermann KM. The Impact of Dynamic Lighting in Classrooms. A Review on Methods. In: Brooks A,Brooks E, Vidakis N. (eds) Springer 2018.
10. Porras-Salazar JA, Wyon DP, Piderit-Moreno B, Contreras-Espinoza S, Wargocki P. Reducing classroom temperature in a tropical climate improved the thermal comfort and the performance of elementary school pupils. Indoor Air 2018;28:892–904.
11. Kokate P, Mishra A, Lokhande S, Bodhe G. Extremely Low Frequency Electromagnetic Field (ELF-EMF) and childhood leukemia near transmission lines: a review. Advanced Electromagnetics 2016;5:30-40.
12. Tuncer M, Bal S, Özsüt A, Köse N. Gaziantep University Journal of Social Sciences. Ortaöğretim Kurumları Öğrenme Ortamlarının Çeşitli Değişkenler Açısından Değerlendirilmesi. Sos Bil D 2012;11: 85-101.
13. Bakır B, Babayiğit MA, Tekbaş ÖF, Oğur R, Kılıç A, Ulus S. Evaluation of Some Physical Hazards Which May Affect Health in Primary Schools. Turk Arc Pediatr 2014; 49: 217-23.
14. Şahin K, Şahin A, Bağcı HR. Sinop Şehri ve Yakın Çevresindeki Bazı Okullarda Gürültü Kirliliği . Studies of the Ottoman Domanin 2014; 4:20-31.
15. Kılıçarslan DD. Optimizing the Fenestration of Typical Turkish School Building with Respect to Daylight and Thermal Performance. Middle East Technical University, Building science in architecture, The Degree of Master of Science in 2013.
16. Turkish Standard 9518. Primary Schools-Physical Settlement-General Rules, Ankara 2000. Türk Standartı.9518.İlköğretim Okulları-Fizik Yerleşim-Genel Kurallar, Ankara 2000.
17. Turkish Standard 12014. Environmental Health Schools, Ankara,1996. Türk Standardı 12014.Çevre Sağlığı Okullar, Ankara 1996.
18. Microwave News (July/August 1995).A Report on Non-Ionizing Radiation. [Online] Website: http://www.microwavenews.com/ncrp1.html. [accessed 20 September 2020]
19. Regulation amending some articles of the regulation on the assessment and management of environmental noise (Official Gazette 27.04.2011 / 27917). Çevresel Gürültünün Değerlendirilmesi ve Yönetimi Yönetmeliğinin Bazı Maddelerinde Değişiklik Yapılmasına Dair Yönetmelik (RG 27.04.2011/27917)
20. World Health Organization (1999). Guidelines for community noise. [Online] Website: https://apps.who.int/iris/handle/10665/66217. [accessed 20 September 2020]
21. Licht. Wissen (02/2014). Good Lighting for a Better Learning Environment. [Online] Website: https://www.licht.de/fileadmin/Publications/licht-wissen/1201_lw02_E_Better_Learning_Environment_web.pdf .[accessed 20 September 2020]
22. Pulay AS. Awareness Of Daylighting On Student Learning In An Educational Facility, Presented to the Faculty of The Graduate College at the University of Nebraska. For the Degree of Master of Science,2010.
23. ASHRAE-52, STANDART 52- Enviromental conditions for human occupancy The American Society of Heating, Refrigerating, and Air-Conditioning Engineers Inc 1999.
24. Baker L, Bernstein H. The Impact of School Buildings on Student Health and Performance. The center for Green School (2012). [Online] Website: https://www.centerforgreenschools.org/sites/default/files/resource-files/McGrawHill_ImpactOnHealth.pdf. [accessed 25 September 2020]
25. Toksoy M. Indoor air quality and management in schools: today's practice, 12. National Plant engineering Congress 8-11 April, 2015. Toksoy M. Okullarda iç hava kalitesi ve yönetimi: günümüz pratiği, 12. Ulusal Tesisat Mühendisliği Kongresi 8-11 Nisan, 2015.
26. UNICEF (2009). The Child-Friendly Schools Manual. [Online] Website: https://www.unicef.org/publications/files/Child_Friendly_Schools_Manual_EN_040809.pdf. [accessed 25 September 2020]
27. Heath GA, Mendell MJ. Do Indoor Environments In Schools Influence Student Performance? A Review Of The Literature. Orlando, Lawrence Berkeley National Laboratory. Berkeley, CA, USA. January 2002. [Online] Website: https://eetd.lbl.gov/sites/all/files/publications/lbnl-49567.pdf [accessed 25 September 2020]
28. Bakó-Biró ZS, Kochhar N, Clements-Croome DJ, Awbi HB, Williams M.Ventilation Rates in Schools and Learning Performance. Proceedings of Clima 2007 WellBeing Indoors. [Online] Website: https://www.irbnet.de/daten/iconda/CIB7218.pdf. [accessed 7 October 2020]
29. Shaughnessy RJ. A Preliminary Study on the Association Between Ventilation Rates in Classrooms and Student Performance. Indoor Air.2006; 16:465-8.
30. Pujol S, Levain JP, Houot H, Petit R, Berthillier M, Defrance J, et al. Association between ambient noise exposure and school performance of children living in an urban area: A cross-sectional population-based study. J. Urban Heal. 2014;91:256–71.
31. Papanikolaou M, Skenteris N PS. Effect of external classroom noise on schoolchildren's reading and mathematics performance: correlation of noise levels and gender. Int J Adolesc Med Heal 2015;27:25-9.
32. Kazansamaz ZT. Lighting as Component of Indoor Environment Comfort in Schools, 12. National Plant Engineering Congress 8-11 April 2015 / İzmir. Kazanasmaz ZT. Okullarda İç Çevre Konfor Bileşeni Olarak Aydınlatma,12. Ulusal Tesisat Mühendisliği kongresi 8-11 Nisan 2015/İzmir.
33. Heschong Mahone Group (2002).Windows and Classrooms: A Study of Student Performance and the Indoor Environment. [Online] Website: https://www.aceee.org/files/proceedings/2004/data/papers/SS04_Panel7_Paper01.pdf. [accessed 7 October 2020]
34. Samani SA. The Impact of Indoor Lighting on Students Learning Performance in Learning Environments: A knowledge internalization perspective. Int J Bus Soc Sci 2012;3:127–36.
35. Eli D, Jentsch MF, James PAB, AbuBakr SB. Field study on thermal comfort in a UK primary school. Proceedings of 7th Windsor Conference: The changing context of comfort in an unpredictable world Cumberland Lodge, Windsor, UK, 12-15 April 2012.
36. Haverinen-Shaughnessy U, Turunen M, Metsämuuronen J, Palonen J, Putus T, Kurnitski J, et al. Health and Academic Performance of Sixth Grade Students and Indoor Environmental Quality in Finnish Elementary Schools. British Journal of Educational Research 2012; 2:42–58.

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

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

Ayşe AKBAS, Fadime KILINC

Ankara City Hospital, Department of Dermatology, Ankara, Turkey

ABSTRACT

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

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

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

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

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

ÖZ

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

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

AKBAS A : 0000-0002-1626-1796
KILINC F : 0000-0001-9137-2675

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was approved by the, YBU Yenimahalle Education and Research Hospital Clinical Research Ethics Committee (IRB NO:17/10/2017-2017/08/09-2017/47).

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

How to cite / *Atıf yazım şekli* : Akbas A, Kılınç F. Clinical and Demographic Characteristics of Pediatric Patients Diagnosed with Localized Scleroderma: A Retrospective Analysis. Turkish J Pediatr Dis 2022; 16: 25 - 31.

Correspondence Address / Yazışma Adresi:

Fadime KILINC
Ankara City Hospital, Department of Dermatology, Ankara, Turkey
E-posta: fykilinc@yahoo.com

Received / Geliş tarihi : 24.11.2020
Accepted / Kabul tarihi : 08.01.2021
Online published : 22.03.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.830628

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

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

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

INTRODUCTION

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

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

MATERIAL and METHODS

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

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

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

RESULTS

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

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

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

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

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

Patient Groups P.No	Concomitant Diseases, Travma story Family story	ANA, AntiDsDNA Positivity The other lab findings P.No	Treatments P.No
0-2 years (1)	Restriction of left leg motion -	-	Topical Steroid
3-5years (3)	-	1-ANA +	1-Topical steroid 2-Methotrexate 1-Hydroxychloroquine 2-Systemic Steroid 1-Calsipotriol
6-11y (12)	2-Vitamin D defiency 1-Anemia (iron defiency,) 1-Genital Lichen sclerosus 1-Deformites of leg 1-Diyabetes Mellitus 1-Travma story +	5-ANA+ 1-Anti dsDNA + 1-CRP +	2-Topical steroid+2-Calsipotriol 6- Calcineurin inhibitors 2-Methotrexate 3-Colchichine 1-Systemic Steroid 2-UVA -1
12-18y (23)	6-Anemia (Iron defiency) 5-VitaminB_{12} defiency 1-Hashimoto tiroiditis 3-Travma story +1-Artiritis story of his brother	6-ANA+ 1-Anti dsDNA + 1-CRP + 3-Borrelia antibodies 2-RF +	8-Topical steroid+Calsipotriol 6-Calcineurin inhibitors 7-Colchichine 2-Methotrexate 1-Systemic Steroid 1-Hydroxychloroquine 2-Narrow bandUVB, 1-Laser 2-Depigmentation therapy 1-İsotretinoin
Total % (39)	7-Anemia (iron defiency), 17.9% 5-VitaminB12 defiency, 12.8% 2-Vitamin D defiency 5.1% 1-Genital LS, 2.5 % 1-Hashimoto tiroiditis, 2.5% 1-Diyabetes mellitus, 2.5% 4-Travma story +,10.2% 2-Deformites of leg, 5.1% 1-Artiritis story of his brother, 2.5%	12- ANA +, 30.7% 2 Anti ds DNA, 5.1% 3- Borrelia antibodies, 7.7% 2-RF +, 5.1% 2-CRP +, 5.1%	1-Topical steroid, 2.5 % 10-Topical steroid+Calsipotriol, 25.6 % 12-Calcineurin inhibitors, 30.7% 10-Colchichine, 25.6% 6-Methotrexate, 15.4% 2-Hydroxychloroquine, 5.1% 4-Systemic Steroid, 10.2 % 1-İsotretinoin, 2.5 % 2-Narrow band UVB, 5.1% 2-UVA-1, 5.1% 2-Depigmentation therapy, 5.1% 1-Laser, 2.5%

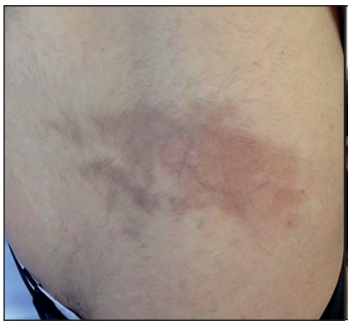


Figure 1: Plaque morphea.

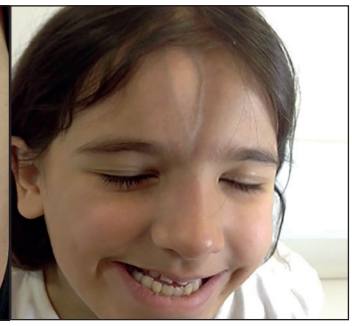


Figure 2: En coup de sambre lesion on forehead.

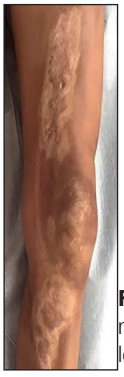


Figure 3: Linear morphea on the leg.

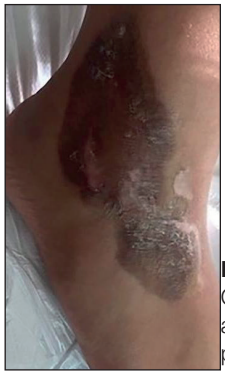


Figure 4: Generalized atrophic plaque lesions.

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

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

DISCUSSION

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

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

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

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

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

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

In juvenile morphea frequently autoimmune diseases can accompany the disease. This ratio can vary from 1% to 3% (20). In some studies, the association of autoimmune diseases with morphea has been reported as high as 17% (20). In a study conducted by Leitenberger et al. (19), 4.9 % of morphea cases showed an accompanying autoimmune or rheumatologic disease such as vitiligo, psoriasis, celiac disease, alopecia areata, autoimmune thyroiditis, etc, similar to what Ceylan et al. (26) reported from our country. In our study, there were only one case of autoimmune thyroiditis, diabetes mellitus and lichen sclerosis. However, among our patients, there were 7 cases with (17.9 %) iron deficiency anemia and 5 (12.8%) cases with vitamin B_{12} deficiency, which are frequently found in this age group. This may be related to inadequate intake of iron and vit B_{12} in the diet of children.

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

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

Among the studies conducted, changes in various laboratory parameters were indicated in patients with morphea (5,28,29). Patients with extracutaneous involvement were found to have increased levels of inflammatory parameters such as ESR and CRP (9). In those who have joint damage, the RF rate increases up to 25 %-40% (9). In terms of the inflammation parameters, only 2 cases (5.12%) had elevated CRP and RF in our patient group.

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

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

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

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

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

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

CONCLUSION

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

REFERENCES

1. Zancanaro PC, Isaac AR, Garcia LT, Costa IM. Localized scleroderma in children: clinical, diagnostic and therapeutic aspects. An Bras Dermatol 2009;84:161-72.
2. Fett N, Werth VP. Update on morphea: Part I. epidemiology, clinical presentation, andpathogenesis. J Am Acad Dermatol 2011;64:217-28.
3. Khamaganova I. Localized scleroderma predisposing and trigerring factors. The Open Dermatology Journal 2017;11:1-11.
4. Rőcken M and Ghoreschi K. Morphea and lichen sclerosus. In: Bolognia JL, et al.Dermatology. (second edition). Mosby Elsevier, Spain 2008:1469-76.
5. Bielsa Marsol I. Update on the classification and treatment of localized scleroderma. Actas Dermosifiliogr 2013;104:654-66.
6. Koç S, Uzun S. Skleroderma. Turkiye Klinikleri J Dermatol Special Topics 2014;7:33-43.
7. Peterson LS, Nelson AM, Su WP, Mason T, O’Fallon WM, Gabriel SE. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-1993. J Rheumatol 1997;24:73-80.
8. Laxer RM, Zulian F. Localized scleroderma. Curr Opin Rheumatol 2006;18:606-13.
9. Vallongo C, Woo P, Russo R, Ruperto N, Harper J, et al. Localized scleroderma in childhood is not just a skin disease. Arthritis Rheum 2005;52:2873-81.
10. Murray KJ, Laxer RM. Scleroderma in children and adolescents. Rheum Dis Clin North Am 2002; 28: 603–24.
11. İzol B, Sarıcaoğlu H, Başkan EB, Toka SO, Adım SB, Aydoğan K, et al. Pediatrik morfea (lokalize skleroderma) 14 olguya ait epidemiyolojik klinik ve laboratuar bulguları. Türkderm 2011;45:132-6.
12. Bulur I, Erdoğan HK, Karapınar T, Saracoglu ZN. Morphea in Middle Anatolia, Turkey: a 5-year single-center experience. Postepy Allegol 2017;34:334-8.
13. Parlak N, Akay BN, Şanlı HE, Akyol A. Hastalarda klinik özellikler, laboratuvar bulguları, seçilen tedavi yöntemi ve takip sonuçları. Turkderm 2013;47:209-13.
14. Zulian F, Athreya BH, Laxer R, Nelson AM. Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. Rheumatology 2006;45:614-20.
15. Christen-Zaech S, Hakim MD, Afsar FS, Paller AS. Pediatric morphea (localized scleroderma): review of 136 patients. J Am Acad Dermatol 2008;59:385–96.
16. Mertens JS, Seyger MM, Kievit W, Hoppenreijs EP, Jansen TL, van de Kerkhof PC, et al. Disease recurrence in localized scleroderma: aretrospective analysis of 344 patients with paediatric- or adult-onset disease. Br J Dermatol 2015;172:722-8.
17. Marzano AV, Menni S, Parodi A, Borghi A, Fuligni A, Fabbri P, et al. Localized scleroderma in adults and children. Clinical and laboratory investigations on 239 cases. Eur J Dermatol 2003;13:171-6.
18. Wu EY, Li SC, Torok KS, Viekud Y, Fuhlbrigge R, Rabinovich E et al. A28: Description of the Juvenile Localized Scleroderma Subgroup of the CARRA Registry. Arthritis Rheumatol 2014;66: 43–4.
19. Leitenberger JJ, Cayce RL, Haley RW, Adams-Huet B, Bergstresser PR, Jacobe HT. Distinct autoimmune syndromes in morphea: a review of 245 adult and pediatriccases. Arch Dermatol 2009;145:545-50.
20. Lis-Święty A, Skrzypek-Salamon A, Ranosz-Janicka I, Brzezińska-Wcisło L. Localized scleroderma: clinical and epidemiological features with emphasis on adulthood-versus childhood-onset disease differences. J Eur Acad Dermatol Venereol 2017;31:1595-603.
21. Török E, Ablonczy E. Morphea in children. Clin Exp Dermatol 1986; 11: 607–12.
22. Herrick AL, Ennis H, Bhushan M, Silman AJ, Baildam EM. Clinical features of childhood localized scleroderma in an incidence cohort. Rheumatology 2011;50:1865-8.

23. Liou JS, Morrell DS. Firm and dyspigmented linear plaques: childhood linear morphea. Pediatri Ann 2007;36:792-4.
24. Zulian F. New developments in localized scleroderma. Curr Opin Rheumatol 2008;20:601-7.
25. Weber K. Is juvenile localized scleroderma related to Lyme borreliozis? J Am Acad Dermatol. 2009; 61:901.
26. Ceylan N, Gürel MS, Kiremitçi Ü, Demirkesen C. Lichen scleroatrophicus in combination with generalized morphea.Türk Patoloji Derg 2008;24:179-83.
27. Piram M, McCuaig CC, Saint-Cyr C, Marcoux D, Hatami A, Haddad E, et al. Short- and long-term outcome of linear morphoea in children. Br J Dermatol 2013;169:1265-71.
28. Guevara-Gutiérrez E, Yinh-LaoJ, García-GutiérrezP, Tlacuilo-ParraA: Frequency of antinuclear antibodies in mestizo Mexican children with morphea. Clin Rheumatol 2010;29:1055-9.
29. Sato S, Fujimoto M, Ihn H, Kikuchi K, Takehara K. Clinical characteristics associated with antihistone antibodies in patients with localized scleroderma. J Am Acad Dermatol 1994;31:567-71.
30. WooTY, Rasmussen JE. Juvenile linear scleroderma associated with serologic abnormalities Arch Dermatol 1985;121:1403-5.
31. Alimova E, Farhi D, Plantier F, Carlotti A, Gorin I, Mouthon L, et al. Morphea (localized scleroderma):baseline body surface involvement and antinuclear antibody may have a prognostic value. Clin Exp Dermatol 2009;34: 491-2.
32. Fett N, Werth VP. Update on morphea: Part II. Outcome measuresand treatment. J Am Acad Dermatol 2011;64: 231-42.
33. Careta MF, Romiti R. Localized scleroderma: clinical spectrum and therapeutic update. An Bras Dermatol 2015; 90:62-73.
34. El-Sakka AI, Bakircioglu ME, Bhatnagar RS, Yen TS, Dahiya R, Lue TF, et al. The effects of colchicine on a Peyronie's-like condition in an animal model. J Urol 1999;161:1980-3.
35. Noh JW, Kim J, Kim JW. Localized scleroderma: a clinical study at a single center in Korea. Int J Rheum Dis 2013;16:437-41.
36. Zulian F, Vallongo C, Patrizi A, Belloni-Fortina A, Cutrone M, Alessio M, et al. A long-term follow-up study of methotrexate in juvenile localized scleroderma (morphea). J Am Acad Dermatol 2012;67:1151-6.

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

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

Tulin GUNGOR, Fehime KARA EROGLU, Evrim KARGIN CAKICI, Fatma YAZILITAS, Gokce CAN, Eda Didem KURT SUKUR, Semanur OZDEL, Evra CELIKKAYA, Deniz KARAKAYA, Mehmet BULBUL

Department of Pediatric Nephrology, Dr Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Ankara, Turkey

ABSTRACT

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

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

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

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

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

ÖZ

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

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

GUNGOR T : 0000-0002-5881-1565
KARA EROGLU F : 0000-0003-2364-4282
KARGIN CAKICI E : 0000-0002-1697-6206
YAZILITAS F : 0000-0001-6483-8978
CAN G : 0000-0002-5881-1565
KURT SUKUR ED : 0000-0003-1451-4443
OZDEL S : 0000-0001-5602-4595
CELIKKAYA E : 0000-0003-2695-2045
KARAKAYA D : 0000-0001-7720-4923
BULBUL M : 0000-0001-9007-9653

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was approved by the Clinical Research Ethics Committee of Ankara Keçiören Training and Research Hospital (1963 / 11.09.2019).

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

How to cite / *Atıf yazım şekli* : Gungor T, Kara Eroglu F, Kargin Cakici E, Yazilitas F, Can G, Kurt Sukur ED. Mycophenolate Mofetil Treatment in Childhood Steroid-sensitive Nephrotic Syndrome: Single Center Experience. Turkish J Pediatr Dis 2022;16: 32-36.

Correspondence Address / Yazışma Adresi:

Tulin GUNGOR
Department of Pediatric Nephrology, Dr Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Ankara, Turkey
E-posta: tulingungor84@gmail.com

Received / Geliş tarihi : 28.10.2020
Accepted / Kabul tarihi : 22.01.2021
Online published : 12.03.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.817363

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

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

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

INTRODUCTION

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

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

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

MATERIALS and METHODS

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

Patient medical records, including clinical and demographic characteristic like age, gender, weight, height, and BMI, physical examination findings, including BP at presentation and each follow-up visit, and laboratory findings, such as serum creatinine, albumin, urinalysis, urinary protein creatinine ratio and 24-h protein excretion, were retrospectively reviewed.

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

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

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

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

Statistical Analysis

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

RESULT

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

The mean age of the patients was 164.8±24.1 months, and the mean age of diagnosis was 70.8±34.1 months. The female to male ratio was 0.8. The mean duration of the disease was 93.3±25.0 months, and the mean duration of the MMF onset was 33.9±16.7 months after diagnosis. The mean dosage of MMF used was 1046.8±78.4 mg/m^2/day. Ten of the patients had SDNS; six patients had FRNS. The renal biopsies were consistent with minimal change disease in nine patients, focal segmental glomerulosclerosis in six patients, and mesangial proliferation in one patient.

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

Compared to the previous year, before the start of the MMF treatment, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. Relapse numbers of the SSNS patients before and after MMF treatment are given in Figure 1. The mean cumulative steroid dose was 232.5±27.3 mg/kg/year for 0-12 months before MMF and the mean cumulative steroid dose 0-12 months post MMF decreased to147.1±94.3 mg/kg/year (p = 0.004).

The median BMI z-score decreased from 0.8 (IQR;-1.3 - 2.4) at the time MMF was initiated to 0.5 (IQR;-1.4 - 2.9) at the last follow-up visit (p = 0.25). However, no significant difference was detected. The median height z-score at the time of MMF initiation was –0.8 (IQR; -3.2-0.9) and the median height z-score at the last follow-up visit was –0.7 (IQR; -2.4-1.3). The height z score in patients improved significantly after the MMF treatment (p = 0.003).

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

DISCUSSION

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

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

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

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

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

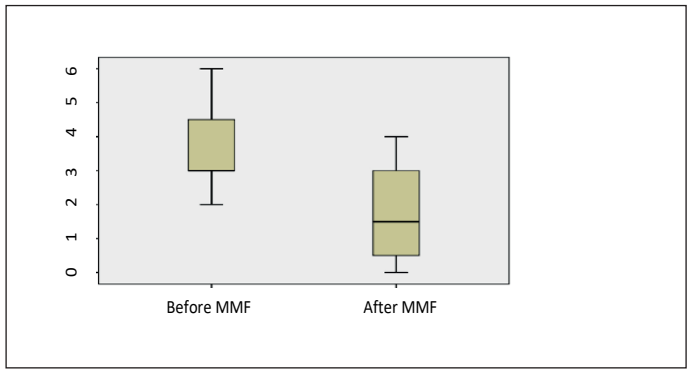


Figure 1: Relapse numbers of the SSNS patients before and after MMF treatment.

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

It should be noted that there is considerable non-uniformity in both the MMF dosage and duration and in the other drugs used both before the MMF and with the MMF. The MMF dosage was calculated based on the body weight and the body surface area, and it varied from 600 mg/m^2/day to 1200 mg/m^2/day and from 25 mg/kg to 40 mg/kg, respectively. The mean dosage of MMF used was 1046.8±78.4 mg/m^2/day in our study. In addition, there seems to be a wide variation in the therapy duration, from three months to seven years. The previous studies have not shown any significant variations in the outcomes regarding the efficacy and side effects based on the MMF dosage administered per day (5,9,16,17). However, the studies involving MMF for longer durations provide an indication that the MMF is more efficacious for maintaining remission if the therapy duration is increased from several months to several years. Some studies have concluded that administering MMF for more than 12 months is more efficacious than administering it for six months. Moreover, the treatment continuation beyond 12 months resulted in sustained steroid-sparing and reduced the need for alternative treatments while maintaining low relapse rates (14,17,18). The mean duration of the MMF onset was 33.9±16.7 months after diagnosis. This study included the use of MMF for more than 12 months for the benefit of maintaining remission.

The principal toxicities of MMF are gastrointestinal and hematological and they include leukopenia, diarrhea, and vomiting. MMF has an efficacy similar to that of cyclosporine, but with fewer side effects, especially no risk of nephrotoxicity and no adverse cosmetic events. Digestive trouble, infectious events, anemia, lymphopenia and thrombocytopenia have been reported in several studies, but they were always mild and transient (4,18-20). None of the patients in our study required an MMF withdrawal due to unacceptable side effects.

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

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

REFERENCES

1. MacHardy N, Miles PV, Massengill SF, Smoyer WE, Mahan JD, Greenbaum L, et al. Management patterns of childhood-onset nephrotic syndrome. Pediatr Nephrol 2009; 24: 2193-201.
2. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev 2005;25:CD001533.
3. Lombel RM, Gipson DS, Hodson EM; Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol 2013; 28: 415-26.
4. van Husen M, Kemper MJ. New therapies in steroid sensitive and steroid-resistant idiopathic nephrotic syndrome. Pediatr Nephrol 2011; 26: 881–92.
5. Hogg RJ, Fitzgibbons L, Bruick J, Bunke M, Ault B, Baqi N, et al. Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. Clin J Am Soc Nephrol 2006; 1: 1173-8.

6. Dorresteijn EM, Kist-van Holthe JE, Levtchenko EN, Nauta J, Hop WC, van der Heijden AJ. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatr Nephrol 2008; 23: 2013–20.
7. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016; 34: 1887-920.
8. Baudouin V, Alberti C, Lapeyraque A-L, Bensman A, Andre JL, Broux F, et al. Mycophenolate mofetil for steroid-dependent nephrotic syndrome: a phase II Bayesian trial. Pediatr Nephrol 2012; 27: 389–96.
9. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome.Pediatr Nephrol 2003; 18: 833–7.
10. Bansal SB, Saxena V, Pokhariyal S, P Gupta, V Kher, R Ahlawat, et al. Comparison of azathioprine with mycophenolate mofetil in a living donor kidney transplant programme. Indian J Nephrol 2011; 21: 258–63.
11. Abeyagunawardena AS, Dillon MJ, Rees L, van't Hoff W, Trompeter RS. The use of steroid-sparing agents in steroid sensitive nephrotic syndrome. Pediatr Nephrol 2003; 18: 919–24.
12. Fujinaga S, Ohtomo Y, Umino D, Takemoto M, Shimizu T, Yamashiro Y, et al. A prospective study on the use of MMF in children with cyclosporine dependent nephrotic syndrome. Pediatr Nephrol 2007; 22: 71–6.
13. Gellermann J, Weber L, Pape L, Tönshoff B, Hoyer P, Querfeld U. Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. J Am Soc Nephrol 2003; 24: 1689–97.
14. Afzal K, Bagga A, Menon S, Hari P, Jordan SC. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. Pediatr Nephrol 2007; 22: 2059–65.
15. Al-Akash S, Al-Makdama A. Mycophenolate mofetil in children with steroid-dependent and/or frequently relapsing nephrotic syndrome. Ann Saudi Med 2005; 25: 380–4.
16. Novak I, Frank R, Vento S, Vergara M, Gauthier B, Trachtman H. Efficacy of mycophenolate mofetil in pediatric patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2005; 20: 1265–8.
17. Hassan AV, Sinha MD, Waller S. A single-centre retrospective study of the safety and efficacy of mycophenolate mofetil in children and adolescents with nephrotic syndrome. Clin Kidney J 2013; 6: 385–9.
18. Banerjee S, Pahari A, Sengupta J, Patnaik SK. Outcome of severe steroid-dependent nephrotic syndrome treated with mycophenolate mofetil. Pediatr Nephrol 2013;28: 93–7.
19. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid dependent nephrotic syndrome. Am J Kidney Dis 2003; 42: 1114–20.
20. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil. Pediatr Nephrol 2004; 19: 101–4.

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

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

Günay KAPLAN[1], Halil İbrahim YAKUT[2], Güzin CİNEL[3]

[1]İstanbul Sancaktepe Şehit Prof.Dr. İlhan Varank Eğitim ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, İstanbul, Türkiye
[2]Ankara Şehir Hastanesi, Çocuk Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, Ankara, Türkiye
[3]Ankara Şehir Hastanesi, Çocuk Hastanesi, Çocuk Göğüs Hastalıkları Kliniği, Ankara, Türkiye

ÖZ

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

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

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

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

Anahtar Sözcükler: Ampiyem, Parapnömonik, Pediatrik, Plevral efüzyon

ABSTRACT

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

KAPLAN G : 0000-0001-7752-445X
YAKUT Hİ : 0000-0001-6946-4995
CİNEL G : 0000-0002-6209-196X

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

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

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

Atıf yazım şekli / *How to cite* : Kaplan G, Yakut İH, Cinel G. Çocukluk Çağı Plevral Efüzyon Nedenleri, Klinik Bulguları ve Yönetimi; Retrospektif Bir Analiz. Türkiye Çocuk Hast Derg 2022; 16: 37-41.

Yazışma Adresi / Correspondence Address:

Günay KAPLAN
İstanbul Sancaktepe Şehit Prof.Dr. İlhan Varank Eğitim ve Araştırma Hastanesi,
Çocuk Sağlığı ve Hastalıkları Kliniği, İstanbul, Türkiye
E-posta: gunayyildiz90@gmail.com

Geliş tarihi / Received : 10.12.2020
Kabul tarihi / Accepted : 25.01.2021
Elektronik yayın tarihi : 24.02.2021
Online published
DOI: 10.12956/tchd.839021

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

Results: 74 (54.8%) of 135 patients diagnosed with pleural effusion were male and the mean age was 8.4±5.3. 78 of the patients (57.8%) were diagnosed with parapneumonic effusion, 14 (10.4%) sepsis, 10 (7.4%) rheumatological disease. The most common presenting symptoms were fever (62.2%), cough (45.9%) and shortness of breath (32.6%). The most common finding on physical examination was tachypnea (39.3%). More than half of the patients (59.2%) had chronic disease. Among these diseases, the most common neurological diseases were found. Thoracentesis was performed in 94 (74%) of 127 patients whose data could be accessed; chest tube was inserted in 70 of them (55.5%). Of the patients diagnosed with parapneumonic effusion, 42 (53.8%) were diagnosed with simple parapneumonic effusion and 36 (46.2%) were diagnosed with complicated parapneumonic effusion (empyema). The most commonly isolated agent was *Streptococcus pneumoniae*. Fibrinolytic therapy was the most preferred treatment for empyema. Detection of 'pH ≤ 7,1' and 'LDH ≥ 1000' in pleural fluid was found to be significant in patients with empyema compared to patients with simple parapneumonic effusion, respectively (p:0.003) (p:0.001). Considering the distribution of parapneumonic effusions over the years, there has been an increase in the frequency of empyema in recent years. It was observed that vaccination with pneumococcal vaccine did not make any difference in the development of simple parapneumonic effusion and empyema (p: 0.351).

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

Key Words: Empyema, Parapneumonic, Pediatric, Pleural effusion

GİRİŞ

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

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

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

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

GEREÇ ve YÖNTEMLER

Tek merkezli retrospektif tanımlayıcı nitelikte olan bu çalışmada Ocak 2012- Aralık 2017 tarihleri arasında Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Sağlık Uygulama ve Araştırma Hastanesi, Pediatri Servisleri ve Yoğun Bakım Ünitesi'nde plevral efüzyon tanısı ile yatırılarak izlenen 0-18 yaş arasındaki 135 hastanın özellikleri incelendi.

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

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

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

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

BULGULAR

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

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

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

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

Eksuda vasıflı sıvıların %89'una, transuda vasıflı sıvıların %80'ine göğüs tüpü takılmıştı ve aralarında anlamlı fark saptanmadı (p:0.600). Plevral efüzyonu olan 135 hastanın 78'inde pnömoniye sekonder plevral efüzyon geliştiği görüldü. Bu 78 hastanın 42'si (%53.8) basit parapnömonik efüzyon, 36'sı (%46.2) ampiyem tanılı hastalardan oluşmaktaydı. Başvuru semptomları incelendiğinde nefes darlığının ampiyemde basit parapnömonik efüzyona göre anlamlı olarak daha fazla görüldüğü saptandı (p:0.047).

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

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

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

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

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

Tablo I: Plevral efüzyon etyolojisi.

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

Tablo II: Ampiyemde plevra kültür sonuçları.

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

TARTIŞMA

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

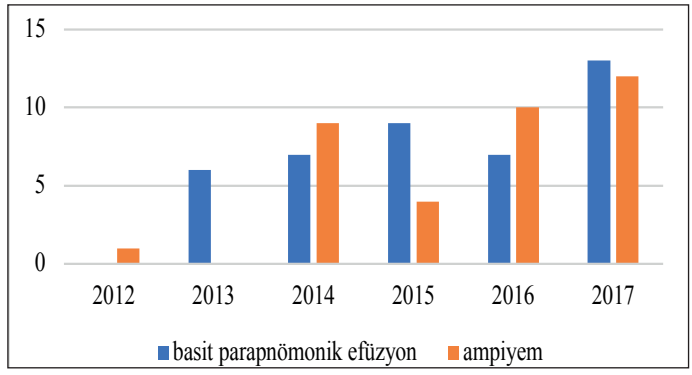
Altta yatan diğer hastalıklar ise sıklık sırasına göre sepsis, romatolojik hastalık, kardiyak hastalık tanılarını aldı. Çalışmamıza yoğun bakım hastalarının da dahil edilmesi sepsis tanılı hasta sayısını arttırmıştır olabilir.

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

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

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

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



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

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

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

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

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

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

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

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

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

KAYNAKLAR

1. Hardie W, Bokulic R, Garcia VF, Reising SF, Christie CDC. Pneumococcal pleural empyemas in children. Clin Infect Dis 1996;22:1057–63.
2. Efrati O, Barak A. Pleural Effusions in the Pediatric Population. Pediatr Rev 2002;23:417–26.
3. Mocelin HT, Fischer GB. Epidemiology, presentation and treatment of pleural effusion. Paediatr Respir Rev 2002;3:292–7.
4. Ütine GE, Özçelik U, Kiper N, Doğru D, Yalçin E, Çobanoğlu N, et al. Pediatric pleural effusions: Etiological evaluation in 492 patients over 29 years. Turk J Pediatr 2009;51:214–9.
5. Liese JG, Schoen C, van der Linden M, Lehmann L, Goettler D, Keller S, et al. Changes in the incidence and bacterial aetiology of paediatric parapneumonic pleural effusions/empyema in Germany, 2010–2017: a nationwide surveillance study. Clin Microbiol Infect 2018;18:1–8.
6. Diaz-Guzman E, Budev MM. Accuracy of the physical examination in evaluating pleural effusion. Cleve Clin J Med 2008;75:297–303.
7. Mitrouska I, Klimathianaki M, Siafakas NM. Effects of pleural effusion on respiratory function. Can Respir J 2004;11:499–503.
8. Wernecke K. Ultrasound study of the pleura. Eur Radiol 2000;10:1515–23.
9. Lichtenstein DA. Ultrasound in the management of thoracic disease. Crit Care Med 2007;35:250–61.
10. Piette E, Daoust R, Denault A. Basic concepts in the use of thoracic and lung ultrasound. Curr Opin Anaesthesiol 2013;26:20–30.
11. McGrath EE, Anderson PB. Diagnosis of pleural effusion: A systematic approach. Am J Crit Care 2011;20:119–28.
12. Balfour-Lynn IM, Abrahamson E, Cohen G, Hartley J, King S, Parikh D, et al. BTS guidelines for the management of pleural infection in children. Thorax 2005;60:1–21.
13. Hacimustafaoglu M, Celebi S, Sarimehmet H, Gurpinar A, Ercan I. The evaluation and cluster analysis of parapneumonic effusion in childhood. J Trop Pediatr 2006;52:52–5.
14. Gayretli-Aydın ZG, Tanır G, Bayhan Gİ, Aydın-Teke T, Öz FN, Metin-Akcan Ö, et al. Evaluation of complicated and uncomplicated parapneumonic effusion in children. Turk J Pediatr 2017;58:623–31.
15. Collins TR, Sahn SA. Thoracocentesis. Clinical value, complications, technical problems, and patient experience. Chest 1987;91:817–22.
16. Light RW. Pleural effusions. Med Clin North Am 2011;95:1055–70.
17. St. Peter SD, Tsao K, Harrison C, Jackson MA, Spilde TL, Keckler SJ, et al. Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. J Pediatr Surg 2009;44:106–11.
18. Sonnappa S, Cohen G, Owens CM, Van Doorn C, Cairns J, Stanojevic S, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. Am J Respir Crit Care Med 2006;174:221–7.
19. Alkrinawi S, Chernick V. Pleural fluid in hospitalized pediatric patients. Clin Pediatr (Phila) 1996;35:5–9.

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

Kuruyemiş Alerjisi Olan Çocuklarda Klinik Bulgular ve Doğal Seyrin Değerlendirilmesi

Ezgi HASBEK[1], Ilknur KULHAS CELIK[2], Emine DIBEK MISIRLIOGLU[3], Ersoy CIVELEK[3], Tayfur GINIS[2], Murat CAPANOGLU[4], Can Naci KOCABAS[5], Muge TOYRAN[3]

[1]Ankara City Hospital, Division of Pediatric Cardiology, Ankara, Turkey
[2]Ankara City Hospital, Division of Pediatric Allergy and Immunology, Ankara, Turkey
[3]University of Health Sciences, Ankara City Hospital, Division of Pediatric Allergy and Immunology, Ankara, Turkey
[4]Mersin Medical Park Hospital, Division of Pediatric Allergy and Immunology, Mersin, Turkey
[5]Division of Pediatric Allergy and Immunology, Department of Children's Health and Diseases, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey

ABSTRACT

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

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

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

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

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

HASBEK E : 0000-0002-0113-1761
KULHAS I : 0000-0003-3812-9654
DIBEK MISIRLIOGLU E : 0000-0002-3241-2005
CIVELEK E : 0000-0002-1780-4801
GINIS T : 0000-0003-1939-3951
CAPANOGLU M : 0000-0001-5864-9054
KOCABAS CN : 0000-0001-8859-7187
TOYRAN M : 0000-0002-2490-0551

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

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

How to cite / *Atıf yazım şekli* : Hasbek E, Kulhas Celik I, Dibek Mısırlıoglu E, Civelek E, Ginis T, Capanoglu M, et al. Evaluation of Clinical Symptoms and Clinical Course in Pediatric Patients with Tree Nut Allergy. Turkish J Pediatr Dis 2022; 16: 42-48.

Correspondence Address / Yazışma Adresi:
Muge TOYRAN
University of Health Sciences, Ankara City Hospital,
Division of Pediatric Allergy and Immunology, Ankara, Turkey
E-posta: mugetoyran@yahoo.com

Received / Geliş tarihi : 21.12.2020
Accepted / Kabul tarihi : 12.02.2021
Online published : 07.04.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.840929

ÖZ

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

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

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

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

Anahtar Sözcükler: Çocuklar, Prognoz, Semptomlar, Kuruyemiş alerjisi

INTRODUCTION

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

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

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

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

MATERIALS and METHODS

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

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

Patients with primary immunodeficiency were excluded from the study.

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

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

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

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

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

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

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated by Kolmogorov-Smirnov test. Numerical variables without normal distribution were shown as median (min-max). Categorical variables were expressed as numbers and percentages. Mann Whitney U test was used for comparison of numerical variables between two groups, and Kruskal Wallis H test (posthoc: Dunn tests test) was used for comparison between three groups.

RESULTS

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

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

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

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

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

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

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

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

***:**n (%)*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

Anaphylaxis is the most critical symptom of TNA. Couch et al.(11) reported that anaphylaxis was the first presenting symptom in 28% of patients with TNA. In our study, 47 patients (36.7%) were admitted with anaphylaxis symptoms and it was most common for chestnut allergic patients (68.3%). Among patients whose first symptom was anaphylaxis, concomitant allergic disease (p=0.01) and aeroallergen sensitization (p=0.02) were higher than patients presenting with other symptoms. In a recent study from our country, 48.9% of 184 children with TNA were reported to have anaphylaxis as presenting symptom and female gender, having concomitant egg allergy and asthma were defined as risk factors (12). When patients have accompanying food allergies and allergic diseases, higher risk of anaphylaxis should be kept in mind.

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

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

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

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

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

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

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

REFERENCES

1. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007;119:1016–8.
2. Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, Fox AT, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. Clin Exp Allergy 2017;47:719–39.
3. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson H. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010;25:1322-6.
4. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of FA on the daily activities of children and their families. Ann Allergy Asthma Immunol 2006; 96: 415-21.
5. amar Weinberger, Scott Sicherer. Current perspectives on tree nut allergy: a review. J Asthma Allergy 2018;11:41-51.
6. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods–position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;59: 690– 7.
7. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS; Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123:365-83.
8. McWilliam V, Koplin J, Lodge C, Tang M, Dharmage S, Allen K. Prevalence of Tree Nut Allergy: A Systematic Review. Curr Allergy Asthma Rep 2015;15:54.
9. Senol HD, Köksal BT. The Clinical Characteristics of Children with Food Allergy in Van. Van Medical Journal 2015;22:266-72.
10. Barlık F, Güner, Ş, Barlık M, Söğüt A, Sancak R .Prevalence of food allergy in nursery and kindergarten children in Samsun. Turk Arch Ped 2013;4: 288-93.
11. Couch C, Franxman T, Greenhawt M. Characteristics of tree nut challenges in tree nut allergic and tree nut sensitized individuals. Ann Allergy Asthma Immunol 2017;118:591-6.
12. Cetinkaya PG, Buyuktiryaki B, Soyer O, Sahiner UM, Sekerel BE. Factors predicting anaphylaxis in children with tree nut allergies. Allergy Asthma Proc 2019;10:180-6.
13. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. J Allergy Clin Immunol 2005;116:1087-93.

Clinical Spectrum of Acute Chlorine Poisoning in Children

Çocuklarda Akut Klor Zehirlenmesinin Klinik Spektrumu

Serkan TURSUN[1], Aysegul ALPCAN[1], Yasar KANDUR[2]

[1]Kırıkkale University Faculty of Medicine, Department of Pediatrics, Kırıkkale,Turkey
[2]Kırıkkale University Faculty of Medicine, Department of Pediatric Nephrology, Kırıkkale,Turkey

ABSTRACT

Objective: Chlorine gas (Cl_2) is a common substance used in industry, which causes toxic inhalation as a potent pulmonary irritant. Herein, we aimed to investigate the findings of pediatric cases accidentally exposed to Cl_2 gas.

Material and Methods: In October 2017, an accident involving Cl_2 gas exposure occurred in a school where 650 students were trained.

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

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

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

ÖZ

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

Gereç ve Yöntemler: Ekim 2017'de, 650 öğrencinin eğitim aldığı bir okulda Cl_2 gazına maruz kalmayı içeren bir kaza meydana geldi.

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

TURSUN S : 0000-0003-3354-6360
ALPCAN A : 0000-0001-9447-4263
KANDUR Y : 0000-0002-8361-5558

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

Contribution of the Authors / Yazarların katkısı*: *TURSUN S: 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. ***ALPCAN A:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions. ***KANDUR Y:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study.

How to cite / *Atıf yazım şekli* : Tursun S, Alpcan A, Kandur Y. Clinical Spectrum of Acute Chlorine Poisoning in Children. Turkish J Pediatr Dis 2022; 16: 49-52.

Correspondence Address / Yazışma Adresi:
Aysegul ALPCAN
Kırıkkale University Faculty of Medicine, Department of Pediatrics, Kırıkkale, Turkey
E-posta: ozcalk@yahoo.com

Received / Geliş tarihi : 04.12.2020
Accepted / Kabul tarihi : 12.02.2021
Online published : 08.04.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.835355

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

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

INTRODUCTION

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

MATERIAL and METHODS

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

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

Statistical Analyses

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

RESULTS

The mean age of the patients was 11.2±1.5 years (range 2–18 years); 62% of the children were male. Among patients evaluated at the emergency department, 21 (42%) patients were discharged within 4-6 hours after the initial examination; symptomatic treatment was administered to relieve upper respiratory tract symptoms mimicking a mild croup attack. These patients were treated with humidified oxygen via a mask. The remaining 29 patients were hospitalized. The presenting symptoms of the participant were only cough (n=23, 46%), cough plus dyspnea (n=30, 60%), nausea plus vomiting (n=6, 12%), headache (n=7, 14%), and sore throat (n=3, 6%). None of the patients was diagnosed with respiratory failure or acute pulmonary edema. Invasive or non-invasive airway support was not required. Seven patients were discharged on day 1, 21 patients on day 2, and 1 patient on day 3.

Regarding investigations performed at the hospital, 19 (38%) patients with respiratory distress were evaluated with a chest X-ray (CXR) which showed no pathology. They were also evaluated with an electrocardiogram (ECG) and arterial blood gas (ABG) analysis. .Five patients (M/F= ¼) had sinus tachycardia on ECG. CK-MB levels of these patients were above normal range (mean:78 U/L, range:46-278). The presenting symptoms of these patients were only cough (n=1), cough plus dyspnea (n=3) and sore throat (n=2). During the follow-up period, CK-MB levels returned to normal levels.

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

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

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

DISCUSSION

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

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

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

A baseline CXR should be obtained if a patient is symptomatic; additionally, respiratory functions should be monitored with ABG and pulse oximetry (14). Chest radiograms can show diffuse nodular opacities, patchy consolidation, pulmonary edema, and signs of vascular congestion. Radiologically, air trapping can be seen in cases with persistent hyper reactivity and airflow obstruction. Our patients had no pathological sign on CXR. Cardiotoxicity is another important complication of Cl_2 toxicity. Chlorine inhalation attenuates myocardial contractile force, reduces systolic and diastolic blood pressures, and may cause cardiac failure and even death. The most common electrocardiographic finding is sinus tachycardia (15). Guloglu et al. (4) detected ST depression and sinus tachycardia in one patient and premature beats in another (only a total of 2 patients with ECG abnormalities were reported) among 18 cases. In our study, five patients had sinus tachycardia , however their troponin levels were normal at the time of admission. During the follow-up period, sinus tachycardia disappeared .

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

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

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

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

Table I: Haddon matrix applied to acute chlorine poisoning.

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

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

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

The authors declare that there is no conflict of interest. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

REFERENCES

1. White CW, Martin JG. Chlorine gas inhalation: human clinical evidence of toxicity and experience in animal models. Proc Am Thorac Soc 2010; 7:257–63.
2. Deschamps D, Soler P, Rosenberg N, Baud F, Gervais P. Persistent asthma after inhalation of a mixture of sodium hypochlorite and hydrochloric acid. Chest 1994;105:1895-6.
3. Slaughter RJ, Watts M, Vale JA, Grieve JR, Schep LJ. The clinical toxicology of sodium hypochlorite. Clin Toxicol (Phila) 2019; 57: 303-11.
4. Guloglu C, Kara IH, Erten PG. Acute accidental exposure to chlorine gas in the Southeast of Turkey: a study of 106 cases. Environ Res 2002;88:89-93.
5. Agabiti N, Ancona C, Forastiere F, Di Napoli A, Lo Presti effects of acute exposure to chlorine due to a swimming pool accident. Occup Environ Med 2001;58:399-404.
6. Mrvos R, Dean BS, Krenzelok EP. Home exposures to chlorine/ chloramine gas: review of 216 cases. South Med J 1993;86:654-7.
7. Gunnarsson M, Walther SM, Seidal T, Lennquist S. Effects of inhalation of corticosteroids immediately after experimental chlorine gas lung injury. J Trauma 2000;48:101-7.
8. Martinez TT, Long C. Explosion risk from swimming pool chlorinators and review of chlorine toxicity. J Toxicol Clin Toxicol 1995;33:349-54.
9. Fleta J, Calvo C, Zuniga J, Castellano M, Bueno M. Intoxication of 76 children by chlorine gas. Hum Toxicol 1986;5:99-100.
10. Squadrito GL, Postlethwait EM, Matalon S. Elucidating mechanisms of chlorine toxicity: reaction kinetics, thermodynamics, and physiological implications. Am J Physiol Lung Cell Mol Physiol 2010; 299:L289–300.
11. Hawkins CL, Pattison DI, Davies MJ. Hypochlorite-induced oxidation of amino acids, peptides and proteins. Amino Acids 2003; 25:259–74.
12. Evans RB. Chlorine: state of the art. Lung 2005;183:151-67.
13. Donnelly SC, FitzGerald MX. Reactive airways dysfunction syndrome (RADS) due to chlorine gas exposure. Ir J Med Sci 1990;159:275-6.
14. Howard C, Ducre B, Burda AM, Kubic A. Management of chlorine gas exposure. J Emerg Nurs 2007;33:402- 4.
15. den Hartog GJ, Haenen GRMM, Vegt E, van der Vijgh WJF, Bast A. Efficacy of HOCl scavenging by sulfur-containing compounds: antioxidant activity of glutathione disulfide? Biol Chem 2002; 383:709–13.
16. Mohapatra S, Agarwal V, Sitholey P. Pediatric anxiety disorders. Asian J Psychiatr 2013; 6:356-63.
17. Szerlip HM, I Singer I. Hyperchloremic metabolic acidosis after chlorine inhalation. Am J Med 1984; 77:581-2.
18. Vengust M. Hypercapnic respiratory acidosis: A protective or harmful strategy for critically ill newborn foals? Can J Vet Res 2012; 76:275–80.
19. Krapf R, Beeler I, Hertner D, Hulter HN. Chronic respiratory alkalosis. The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 1991; 324:1394-401.
20. Runyan C. Using the Haddon Matrix: Introducing the third dimension. Injury Prevention 1998; 4:302–7.

Kistik Fibrozis Hastalarında Akciğer Tutulumunun Manyetik Rezonans Görüntüleme ile Değerlendirilmesi

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

Gökçen Dilşa TUĞCU[1], Sanem ERYILMAZ POLAT[1], Mina GARİBZADEH HIZAL[1], Beste KARAKAYA ÖZSEZEN[1], Altan GÜNEŞ[4], Güzin CİNEL[1]

[1]Ankara Şehir Hastanesi Çocuk Hastanesi, Çocuk Göğüs Hastalıkları Kliniği, Ankara, Türkiye
[4]Ankara Şehir Hastanesi Hastanesi, Radyoloji Kliniği, Ankara, Türkiye

ÖZ

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

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

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

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

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

TUĞCU GD : 0000-0002-9804-1200
ERYILMAZ POLAT S : 0000-0003-2309-7952
GARİBZADEH HIZAL M : 0000-0002-6922-4948
KARAKAYA ÖZSEZEN B : 0000-0002-0052-8361
GÜNEŞ A : 0000-0002-0365-1218
CİNEL G : 0000-0002-6209-196X

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

Etik Kurul Onayı / *Ethics Committee Approval*: Bu çalışmada ulusal ve uluslararası etik kurallara uyulmuştur. Çalışmamız için Ankara Çocuk sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu'ndan 16.04.2019 tarih ve 2019-090 karar numarası ile onay alınmıştır.

Yazarların katkısı / *Contribution of the Authors*: *TUĞCU GD:* Araştırma ve/veya makalenin hipotezini veya fikrini oluşturan, Sonuçlara ulaşmak için planlama/metodoloji belirleme, Araştırma/çalışmanın sorumluluğunu üstlenmek, ilerlemenin seyrini denetlemek, 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. ***ERYILMAZ POLAT S:*** Sonuçlara ulaşmak için planlama/metodoloji belirleme, Hasta takibinde sorumluluk almak, ilgili biyolojik malzemelerin toplanması, veri yönetimi ve raporlama, deneylerin yürütülmesi. ***HIZAL M:*** Sonuçlara ulaşmak için planlama/metodoloji belirleme, Hasta takibinde sorumluluk almak, ilgili biyolojik malzemelerin toplanması, veri yönetimi ve raporlama, deneylerin yürütülmesi. ***KARAKAYA ÖZSEZEN B:*** Hasta takibinde sorumluluk almak, ilgili biyolojik malzemelerin toplanması, veri yönetimi ve raporlama, deneylerin yürütülmesi. ***GÜNEŞ A:*** Araştırma ve/veya makalenin hipotezini veya fikrini oluşturan, Sonuçların mantıksal olarak Yorumlanması ve sonuçlandırılması, Çalışma için gerekli literatür taramasında sorumluluk almak, Yazım ve dilbilgisi dışında bilimsel olarak gönderilmeden önce makaleyi gözden geçirme.***CİNEL G:*** Araştırma/çalışmanın sorumluluğunu üstlenmek, ilerlemenin seyrini denetlemek, Sonuçların mantıksal olarak Yorumlanması ve sonuçlandırılması, Çalışma için gerekli literatür taramasında sorumluluk almak, Yazım ve dilbilgisi dışında bilimsel olarak gönderilmeden önce makaleyi gözden geçirme.

Atıf yazım şekli / *How to cite* : Tuğcu GD, Eryılmaz Polat S, Garibzadeh Hızal M, Özsezen Karakaya B, Güneş A, Cinel G. Kistik Fibrozis Hastalarında Akciğer Tutulumunun Manyetik Rezonans Görüntüleme ile Değerlendirilmesi. Türkiye Çocuk Hast Derg 2022; 16: 53-59.

Ek bilgi / *Additional information*: Bu çalışma 2019 yılında Türk Toraks Derneği 22. Yıllık Kongresinde sözel bildiri olarak sunulmuştur.

Yazışma Adresi / Correspondence Address:
Gökçen Dilşa TUĞCU
Ankara Şehir Hastanesi Çocuk Hastanesi,
Çocuk Göğüs Hastalıkları Kliniği, Ankara, Türkiye
E-posta: gokcendtugcu@gmail.com

Geliş tarihi / Received : 06.01.2021
Kabul tarihi / Accepted : 15.02.2021
Elektronik yayın tarihi : 28.05.2021
Online published
DOI: 10.12956/tchd.854953

ABSTRACT

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

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

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

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

Key Words: Cystic Fibrosis, Computed Tomography, Magnetic Resonance İmaging, Lung İnvolvement

GİRİŞ

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

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

Tablo I: BT ve MRG için Helbich skorlama sistemi.

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

***** *(maksimum skor = 27)*

Tablo II: MRG için Eichinger skorlama sistemi.

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

*****(maksimum skor = 60)

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

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

GEREÇ ve YÖNTEMLER

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

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

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

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

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

Tüm BT görüntülemesi, 16 kesitli cihaz ile (Toshiba America Medical Systems), (100–120 kV; kesit kalınlığı ≤2 mm; matriks 512×512 piksel; gantry açısı 0°) intravenöz kontrast madde kullanılmadan, hasta yaşına uygun kV (<2 yaş: 100 kV, >2 yaş: 120 kV) seçilerek gerçekleştirildi. Tüm MR görüntülemeleri 1.5T cihaz ile (GE Healthcare, Milwaukee, WI) çok kanallı sarmal kullanılarak, aksiyel ve koronal T2 ağırlıklı (TR/TE:4500–6000/90–110 ms) sekansları kullanılarak solunum tetiklemeli olarak elde edildi. Görüntülerin kesit kalınlığı 3–4 mm, ortalama çekim süresi 7 dakikadı. MR görüntülemeler, küçük çocuklarda yüzeyel sedasyonlu (klorohidrat) veya sedasyon kullanılmadan kendi uykusu altında gerçekleştirildi.

İstatistiksel Analiz

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

BULGULAR

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

Tablo III: Hastaların klinik ve laboratuar bulguları.

	n=14	%
Yaş ortancası	3.9 (1-18 yaş)	
E/K	10/4	71.4/28.6
Malnütrisyon	2	14.2
Yenidoğan tarama programı ile tanı	2	14.2
Dornaz Alfa kullanımı	13	92.8
P. aeruginosa ile kronik kolonizasyon	5	35.7
Normal spirometri[a]	3/4	75
NIMV	1	7.1
KFTR DNA Sekans Analizi	14	100
F508del homozigot	4	28.5
Q220X / 2789+5G->A	1	7.1
R334Q / p.Phel152	1	7.1
R1070Q Homozigot	1	7.1
457TAT->G Homozigot	1	7.1
S466X Homozigot	1	7.1
G314E Homozigot	1	7.1
2184delA / 3878 delG	1	7.1
G542 / D58N	1	7.1
G85E Homozigot	1	7.1
c.2657+5G>A Homozigot	1	7.1

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

Tablo IV: KF hastalarının BT ve MRG bulgularının karşılaştırılması.

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

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

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

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

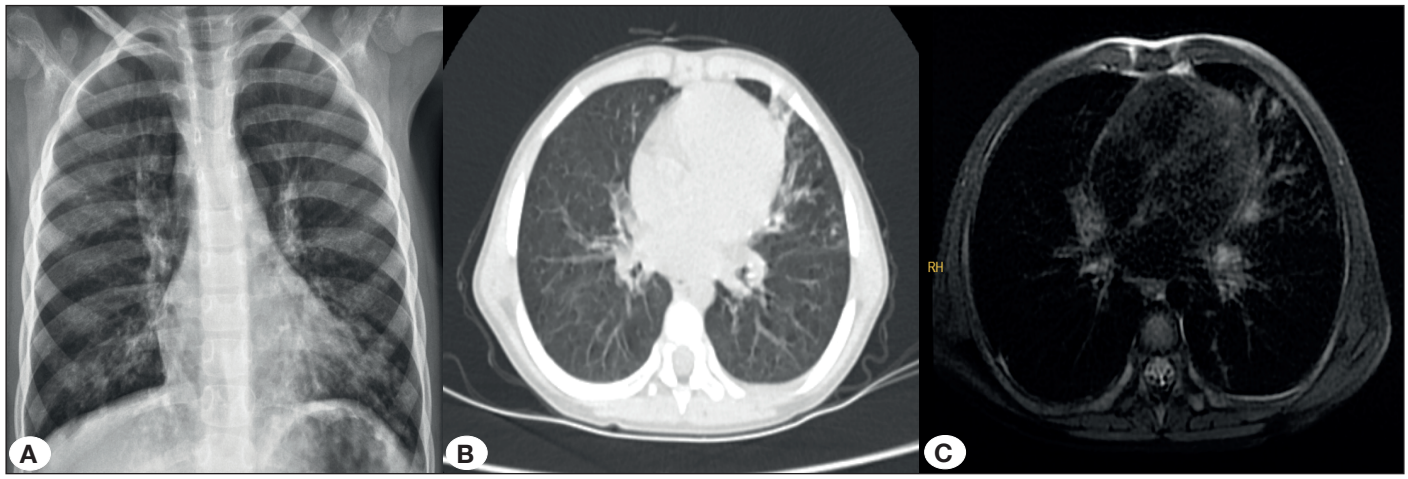
Hastaların klinik ve demografik bulguları karşılaştırıldığında F508 delesyonu homozigot mutasyonu olup *P. aeruginosa* ile kronik kolonize olan dört (%28.5) hastanın yaş ortancası 8.9 (6.5 en küçük-20 en büyük)'tü. Bu hastaların BT ve MRG skorları, yaş ortancası 3.9 (1-20 yaş) olan diğer hastalara göre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

TARTIŞMA

Bu retrospektif kesitsel çalışmada klinik olarak stabil iken çekilen BT ve MRG' de mozaik atenüasyon dışındaki akciğer bulgularında istatistiksel olarak anlamlı fark olmadığı saptandı. KF'de erken dönemde periferal hava yolu inflamasyonu, enfeksiyonlar ve bozulmuş mukosiliyer klirens ile başlayan akciğer hasarı, geri dönüşümsüz yaygın bronşektaziler ve son dönemde kronik solunum yetmezliği nedeni olabilir (13,14). Akut pulmoner alevlenmede solunum fonksiyon testleri etkilenmeden önce BT'de de klinik ile korele değişiklikler görüldüğü, uzun dönem izlemde de pulmoner alevlenme sayısı arttıkça BT bulgularının da belirginleştiği gösterilmiştir (8,15).

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

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



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

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

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

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

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

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

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

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

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

SONUÇ

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

KAYNAKLAR

1. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. Nat Rev Dis Primers 201;1:15010.
2. Paranjape SM, Mogayzel PJ Jr. Cystic fibrosis. Pediatr Rev 2014;35:194-205.
3. Horsley A. Book review: Hodson and Geddes' Cystic Fibrosis. Breathe 2016;12:91–2.
4. Cystic Fibrosis Lung Disease: An OvervieW Nelson L Turcios Respiratory Care Feb 2020;65:233-51.
5. Kołodziej M, de Veer MJ, Cholewa M, Egan GF, Thompson BR. Lung function imaging methods in Cystic Fibrosis pulmonary disease. Respir Res 2017;18:96.
6. Villanueva G, Marceniuk G, Murphy MS, Walshaw M, Cosulich R; Guideline Committee. Diagnosis and management of cystic fibrosis: summary of NICE guidance. BMJ 2017;359:j4574.
7. Newbegin K, Pilkington K, Shanthikumar S, Ranganathan S. Clinical utility of surveillance computed tomography scans in infants with cystic fibrosis. Pediatr Pulmonol 2018;53:1387-90.
8. Sanders DB, Li Z, Brody AS. Chest computed tomography predicts the frequency of pulmonary exacerbations in children with cystic fibrosis. Ann Am Thorac Soc 2015;12:64-9.
9. Wielpütz MO, Puderbach M, Kopp-Schneider A, Stahl M, Fritzsching E, Sommerburg O, ve ark. Magnetic resonance imaging detects changes in structure and perfusion, and response to therapy in early cystic fibrosis lung disease. Am J Respir Crit Care Med 2014;189:956-65.
10. Theilmann RJ, Darquenne C, Elliott AR, Bailey BA, Conrad DJ. Characterizing Lung Disease in Cystic Fibrosis with Magnetic Resonance Imaging and Airway Physiology. PLoS One 2016;11:e0157177.
11. Anjorin A, Schmidt H, Posselt HG, Smaczny C, Ackermann H, Deimling M, ve ark. Comparative evaluation of chest radiography, low-field MRI, the Shwachman-Kulczycki score and pulmonary function tests in patients with cystic fibrosis. Eur Radiol 2008;18:1153-61.
12. Thia LP, Calder A, Stocks J, Bush A, Owens CM, Wallis C, ve ark. London Cystic Fibrosis Collaboration. Is chest CT useful in newborn screened infants with cystic fibrosis at 1 year of age? Thorax 2014;69:320-7.
13. Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, ve ark. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009;64:876-82.
14. Loeve M, Hop WC, de Bruijne M, van Hal PT, Robinson P, Aitken ML, ve ark. Computed Tomography Cystic Fibrosis Survival Study Group. Chest computed tomography scores are predictive of survival in patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med 2012;185:1096-103.
15. Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, Quan J. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005;172:1128-32.
16. Jacobsen LE, Houston CS, Habbick BF, Genereux GP, Howie JL. Cystic fibrosis: a comparison of computed tomography and plain chest radiographs. Can Assoc Radiol J 1986;37:17-21.
17. Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, ve ark. Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF). Bronchiectasis in infants and

preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 ;155:623-8.e1.

18. Mott LS, Park J, Murray CP, Gangell CL, Klerk NH, Robinson PJ, ve ark. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012;67:509-16.
19. Wainwright CE, Vidmar S, Armstrong DS, Byrnes CA, Carlin JB, Cheney J, ve ark. ACFBAL Study Investigators. Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial. JAMA 2011;306:163-71.
20. Tepper LA, Utens EM, Caudri D, Bos AC, Gonzalez-Graniel K, Duivenvoorden HJ, ve ark. Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis. Eur Respir J 2013;42:371-9.
21. Yang C, Montgomery M. Dornase alfa for cystic fibrosis. Cochrane Database Syst Rev 2018;9:CD001127.
22. Kerem E, Conway S, Elborn S, Heijerman H; Consensus Committee. Standards of care for patients with cystic fibrosis: a European consensus. J Cyst Fibros 2005;4:7-26.
23. Hansell DM, Strickland B. High-resolution computed tomography in pulmonary cystic fibrosis. Br J Radiol 1989;62:1-5.
24. Hansell DM. Bronchiectasis. Radiol Clin North Am 1998;36:107-28.
25. Arakawa H, Webb WR. Air trapping on expiratory high-resolution CT scans in the absence of inspiratory scan abnormalities: correlation with pulmonary function tests and differential diagnosis. AJR Am J Roentgenol 1998;170:1349-53.
26. Gilchrist FJ, Buka R, Jones M, Ho SA, Lenney W, Carroll WD. Clinical indications and scanning protocols for chest CT in children with cystic fibrosis: a survey of UK tertiary centres. BMJ Paediatr Open 2018;2:e000367.
27. de González AB, Kim KP, Samet JM. Radiation-induced cancer risk from annual computed tomography for patients with cystic fibrosis. Am J Respir Crit Care Med 2007;176:970-3.
28. Ferris H, Twomey M, Moloney F, O'Neill SB, Murphy K, O'Connor OJ, ve ark. Computed tomography dose optimisation in cystic fibrosis: A review. World J Radiol 2016;8:331-41.
29. Roach DJ, Crémillieux Y, Fleck RJ, Brody AS, Serai SD, Szczesniak RD, ve ark. Ultrashort Echo-Time Magnetic Resonance Imaging Is a Sensitive Method for the Evaluation of Early Cystic Fibrosis Lung Disease. Ann Am Thorac Soc 2016;13:1923-31.
30. Walkup LL, Thomen RP, Akinyi TG, Watters E, Ruppert K, Clancy JP, ve ark. Feasibility, tolerability and safety of pediatric hyperpolarized 129Xe magnetic resonance imaging in healthy volunteers and children with cystic fibrosis. Pediatr Radiol 2016;46:1651-62.
31. Thomen RP, Walkup LL, Roach DJ, Cleveland ZI, Clancy JP, Woods JC. Hyperpolarized 129Xe for investigation of mild cystic fibrosis lung disease in pediatric patients. J Cyst Fibros 2017;16:275-82.
32. Sileo C, Corvol H, Boelle PY, Blondiaux E, Clement A, Ducou Le Pointe H. HRCT and MRI of the lung in children with cystic fibrosis: comparison of different scoring systems. J Cyst Fibros. 2014;13:198-204.
33. Davis SD, Fordham LA, Brody AS, Noah TL, Retsch-Bogart GZ, Qaqish BF, ve ark. Computed tomography reflects lower airway inflammation and tracks changes in early cystic fibrosis. Am J Respir Crit Care Med 2007;175:943-50.
34. Amin R, Charron M, Grinblat L, Shammas A, Grasemann H, Graniel K, ve ark. Cystic fibrosis: detecting changes in airway inflammation with FDG PET/CT. Radiology 2012;264:868-75.
35. Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, ve ark. AREST CF Investigators. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med 2013;368:1963-70.
36. Failo R, Wielopolski PA, Tiddens HA, Hop WC, Mucelli RP, Lequin MH. Lung morphology assessment using MRI: a robust ultra-short TR/TE 2D steady state free precession sequence used in cystic fibrosis patients. Magn Reson Med 2009;61:299-306.
37. Stahl M, Wielpütz MO, Graeber SY, Joachim C, Sommerburg O, Kauczor HU, ve ark. Comparison of Lung Clearance Index and Magnetic Resonance Imaging for Assessment of Lung Disease in Children with Cystic Fibrosis. Am J Respir Crit Care Med 2017;195:349-59.
38. Couch MJ, Munidasa S, Rayment JH, Voskrebenzev A, Seethamraju RT, Vogel-Claussen J, ve ark. Comparison of Functional Free-Breathing Pulmonary 1H and Hyperpolarized 129Xe Magnetic Resonance Imaging in Pediatric Cystic Fibrosis. Acad Radiol 2020:S1076-6332(20)30284-1.
39. Couch MJ, Thomen R, Kanhere N, Hu R, Ratjen F, Woods J, ve ark. A two-center analysis of hyperpolarized 129Xe lung MRI in stable pediatric cystic fibrosis: Potential as a biomarker for multi-site trials. J Cyst Fibros 2019;18:728-33.
40. Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA; Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Early Lung Disease in Infants and Preschool Children with Cystic Fibrosis. What Have We Learned and What Should We Do about It? Am J Respir Crit Care Med 2017;195:1567-75.
41. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. J Pediatr 2004 ;144:154-61.

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

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

Mehmet Ali NARSAT[1], Ayse YILMAZ[2], Eren YILDIZ[3]

[1]Department of Pediatric Surgery, Kastamonu Training and Research Hospital, Kastamonu, Turkey
[2]Department of Anesthesiology and Reanimation, Kastamonu Training and Research Hospital, Kastamonu, Turkey
[3]Department of Pediatrics, Kastamonu Training and Research Hospital, Kastamonu, Turkey

ABSTRACT

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

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

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

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

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

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

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

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

ÖZ

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

NARSAT MA : 0000-0002-6496-1965
YILMAZ A : 0000-0001-7635-0830
YILDIZ E : 0000-0002-8056-5727

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*: The approval of the Kastamonu University Clinical Research Ethics Committee, dated 26.11.2020 and numbered 2020-KAEK-143-02.01.

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

How to cite / *Atıf yazım şekli* : Narsat MA, Yilmaz A, Yildiz E. Inguinal Hernia Repair with Laparoscopic-Supported Percutaneous Internal Ring Suturing Technique in Children - One Center Experience. Turkish J Pediatr Dis 2022; 16: 60-64.

Correspondence Address / Yazışma Adresi:
Mehmet Ali NARSAT
Department of Pediatric Surgery,
Kastamonu Training and Research Hospital, Kastamonu, Turkey
E-posta: malinarsat@gmail.com

Received / Geliş tarihi : 08.02.2021
Accepted / Kabul tarihi : 05.04.2021
Online published : 18.06.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.876778

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

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

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

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

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

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

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

INTRODUCTION

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

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

MATERIAL and METHOD

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

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

Operation steps

Under general anesthesia, 5 mm and 30^0 laparoscopy optic was advanced through the umbilical incision with the aid of a reusable trocar under 5 mmHg intraabdominal pressure setting. The appearance of the inguinal canals and their openness were evaluated (Figure 1-A). The 21G injection needle, used as a guide, was advanced from the lateral of the inguinal canal to the preperitoneal area carrying the carrier loop suture material (Figure 1-B, C). The guide needle was advanced between the carrier loop suture material, taking care not to take it into the spermatic cord from the medial of the inguinal canal, and the carrier loop suture material was placed on the guide needle (Figure 1-D). The ligature suture material, which was advanced through the guide needle, was released and was taken out of the body with the help of loop suture material (Figure 1-E, F). As the binding material, 3/0 non-absorbable mono-fiber suture material was used in children under the age of three, and 2/0 non-absorbable monofilament suture material was used in children over the age of three. The closure of the internal inguinal ring was checked and the intervention in the groin area was terminated when it was observed that it was closed (Figure 1-G). In the case of accompanying umbilical hernias, umbilical hernia repair was also performed.

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

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

RESULTS

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

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

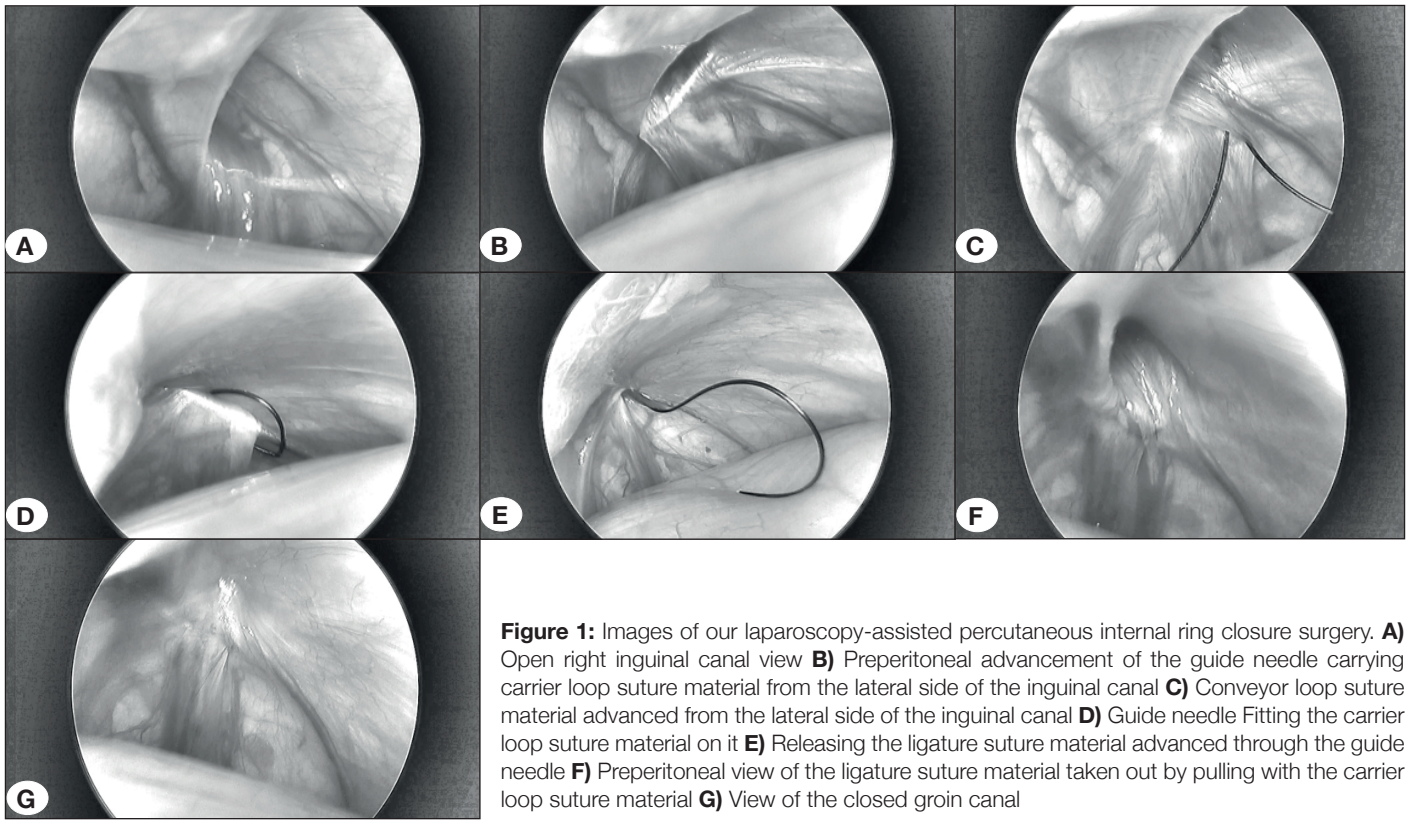


Figure 1: Images of our laparoscopy-assisted percutaneous internal ring closure surgery. **A)** Open right inguinal canal view **B)** Preperitoneal advancement of the guide needle carrying carrier loop suture material from the lateral side of the inguinal canal **C)** Conveyor loop suture material advanced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

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

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

During the follow-up of the patients, no recurrence, intraabdominal complication, or inguinal complication was detected. Skin infection developed in the umbilical incision in one patient. None of the patients had skin scar in the groin area in the control examination performed in the sixth month. In six patients, it was found that the prolene knot material could be palpated subcutaneously. In the examination of the male patients, the testicles were in an age-appropriate size and the scrotum. The visual assessment of the umbilical incision was scored as an average of 4.74±0.12 by the patient's relative and 4.0±0.12 by the doctor whose opinion was taken.

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

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

DISCUSSION

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

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

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

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

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

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

After the previously described and applied laparoscopic inguinal hernia repair method, the average length of stay stated in the studies is higher than the open method; however, there was no difference in operative time between the two methods (12, 13). We did not compare the operation time, length of stay, and treatment cost with any other laparoscopic or open method that we determined in our series. However, both the operation time, the duration of stay, and the treatment cost were within acceptable limits and the morbidity rate did not increase significantly. Since the average length of stay of the patients in the hospital is calculated as days, the hospital stay of the patients who are followed up overnight appears to be two days. The follow-up of pediatric patients operated under general anesthesia by staying in the hospital for 24 hours is a routine approach in our hospital. Even if we do not apply it, patients who are operated under general anesthesia can be discharged on the same day. If this method is preferred, the duration of hospital stay will be shorter.

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

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

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

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

CONCLUSION

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

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

REFERENCES

1. Lau WY: History of treatment of groin hernia. World J Surg 2002;26:748-59.
2. Sachs M, Damm M, Encke A: Historical evolution of inguinal hernia repair. World J Sur 1997;1:218-23.
3. Schier F, Montupet P, Esposito C: Laparoscopic inguinal herniorrhaphy in children: a three-center experience with 933 repairs. J Pediatr Surg 2002;37:395-7.
4. Patkowski D, Czernik J, Chrzan R, Jaworski W, Apoznański W. Percutaneous internal ring suturing: a simple minimally invasive technique for inguinal hernia repair in children. J Laparoendosc Adv Surg Tech A 2006;6:513-7.
5. Wolak PK, Patkowski D. Laparoscopic inguinal hernia repair in children using the percutaneous internal ring suturing technique–own experience. Wideochir Inne Tech Maloinwazyjne 2014;9:53-8
6. Danielson J, Pakkasjärvi N, Högberg N. Percutaneous Hernia Repair in Children: Safe to introduce. Scand J Surg 2020:1457496920918151.
7. Dreuning K, Maat S, Twisk J, van Heurn E, Derikx J. Laparoscopic versus open pediatric inguinal hernia repair: state-of-the-art comparison and future perspectives from a meta-analysis. Surg Endosc 2019;1:3177-91.
8. Thomas DT, Göcmen KB, Tulgar S, Boga I: Percutaneous internal ring suturing is a safe and effective method for the minimal invasive treatment of pediatric inguinal hernia: experience with 250 cases. J Pediatr Surg 2016;51:1330-5.
9. Tanger R, Singh AP, Gupta AK, Mathur V. Laparoscopic inguinal hernia repair in girls using the percutaneous internal ring suturing technique–our own experience. Menoufia Med J 2020;33:713-6.
10. Miyake H, Fukumoto K, Yamoto M, Nakajima H, Sekioka A, Yamada Y, et al. Risk factors for recurrence and contralateral inguinal hernia after laparoscopic percutaneous extraperitoneal closure for pediatric inguinal hernia. J Pediatr Surg 2017;52:317-21.
11. Frýbová B, Trčka J, Dotlačil V, Poš L, Patkowski D, Rygl M. Laparoscopic inguinal hernia repair in children via PIRS (percutaneous internal ring suturing). Řešení tříselné kýly u dětí technikou PIRS (percutaneous internal ring suturing). Rozhl Chir 2020;99:277-81.
12. Takehara H, Yakabe S, Kameoka K. Laparoscopic percutaneous extraperitoneal closure for inguinal hernia in children: clinical outcome of 972 repairs done in 3 pediatric surgical institutions. J Pediatr Surg 2006;41:1999-2003.
13. Timberlake MD, Herbst KW, Rasmussen S, Corbett ST. Laparoscopic percutaneous inguinal hernia repair in children: review of technique and comparison with open surgery. J Pediatr Urol 2015;11: 262.e1-262.e6
14. Pogorelić Z. Effects of laparascopic hernia repair by PIRS (percutaneous internal ring suturing) technique on testicular artery blood supply. J Investig Surg 2018;12:348-9.
15. Oral A, Karaca L, Ahiskalioglu A, Yildiz A, Yigiter M, Celikkaya ME, et al. Effects of laparoscopic hernia repair by PIRS (Percutan Internal Ring Suturing) technique on testicular artery blood supply. J Invest Surg 2019;32: 343-7.
16. Chen JC, Zhang QL, Chen L, Wang YJ, Huang WH, Zhou CM Single-port laparoscopic percutaneous closure of the internal ring for scarless repair of inguinal hernias in girls. Minim Invasive Ther Allied Technol 2020:1-7. doi: 10.1080/13645706.2020.1768124.

Upper Gastrointestinal Endoscopy in Pediatric Surgical Practice

Pediatrik Cerrahi Pratiğinde Üst Gastrointestinal Endoskopi

Lutfi Hakan GUNEY, Ender FAKIOĞLU, Tugba ACER DEMIR

Başkent University Ankara Hospital, Department of Pediatric Surgery, Ankara, Turkey

ABSTRACT

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

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

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

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

Key Words: Children, Endoscopy, Esophagus

ÖZ

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

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

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

GUNEY LH : 0000-0002-2500-5401
FAKIOGLU E : 0000-0002-7437-2734
ACER DEMIR T : 0000-0001-5391-9094

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

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

How to cite / *Atıf yazım şekli* : Guney LH, Fakioglu and Acer Demir T. Upper Gastrointestinal Endoscopy in Pediatric Surgical Practice . Turkish J Pediatr Dis 2022; 16: 65-69.

Correspondence Address / Yazışma Adresi:

L. Hakan GUNEY
Başkent University Ankara Hospital,
Department of Pediatric Surgery, Ankara, Turkey
E-posta: dr.guney@gmail.com

Received / Geliş tarihi : 02.03.2021
Accepted / Kabul tarihi : 16.04.2021
Online published : 23.09.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.889666

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

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

Anahtar Sözcükler: Çocuk, Endoskopi, Özofagus

INTRODUCTION

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

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

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

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

MATERIAL and METHOD

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

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

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

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

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

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

RESULTS

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

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

Endoscopy for Foreign body ingestion:

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

Endoscopy for Caustic Agents Ingestion:

Out of 89 children with caustic ingestion, 55.1% (49) were females and 44.9% (40), males. The age group who most commonly ingested a caustic agent corresponded to children younger than 3 years, who accounted for 77.5% (69) of cases (mean age 30.4±27.5 months). Thirty five (39.31%) patients underwent RE, 41 (46.1%) underwent FE in the first 24 to 48 hours after ingestion and 13 (14.6%) patients were observed conservatively. The ingested corrosives were alkaline substances in 60 cases (67.5%) and acidic substances in 29 (32.5%). Sodium hypochloride was the most commonly ingested alkaline agent; while hydrochloric acid was the most common acidic substance ingested. Figure 1 demonstrates an example for the chemical esophageal injury via FE.

Table I: Demographics of the study group.

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

***:** *Mean ±SD (min.- max. months),* **†:** *n(%)*

Table II: Type and location of esophageal foreign bodies.

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

Endoscopy for dilatation of the esophageal strictures:

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

Endoscopy for rare esophageal conditions:

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

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

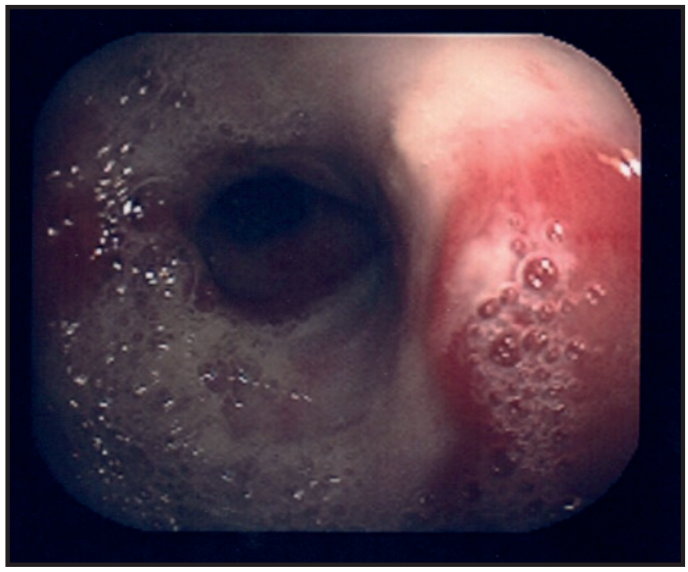


Figure 1: Chemical esophagitis.

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

DISCUSSION

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

Most frequent indication of endoscopy in our study is corrosive substance ingestion. Accidental ingestion of corrosive compounds is reported to be more frequently observed in young children, especially those younger than the age of five (4). Our results are consistent with that, with the far lower mean age detected (30 months). Early esophageal endoscopy (during the first 24 to 48 hours) is considered a safe procedure (5). Bıçakçı et al.(6) state that they avoid from early esophagoscopy as the early esophagoscopy requires unnecessarily general anesthesia administration and this is the most fragile period of esophagus. In our clinic endoscopy is performed only if symptoms persist. Eighty five percent of our patients underwent the procedure. Thirty five patients underwent RE. We converted the RE procedure to flexible in two patients because of the insufficient visualisation of both esophagus and the stomach mucosa. Most of patients (n=41) were evaluted with FE without any complications but the patients who were evaluted with RE had minor complications (two of them were dental injuries one of them was mucosal bleeding that caused insufficient visualisation). Niedzielski et al.(7) presented their study including 150 patients who were evaluted due to caustic ingestion between 1967 -2018. They performed FE for all of their patients without any complication. They suggest performing endoscopy for all patients and point out 'endoscopy is the most effective and widely used method for determining the degree of injury and planning treatment'. Similarly Balderas et al. (8) report in their retrospective study with 133 patients that all of their patients underwent fiberobtic endoscopy with no complications.

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

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

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

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

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

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

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

CONCLUSIONS

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

REFERENCES

1. Gmeiner D, von Rahden BH, Meco C, Hutter J, Oberascher G, Stein HJ. Flexible versus rigid endoscopy for treatment of foreign body impaction in the esophagus. Surg Endosc 2007;21:2026–9.
2. Popel J, El-Hakim H, El-Matary W. Esophageal foreign body extraction in children: flexible versus rigid endoscopy. Surg Endosc 2011;25:919–22.
3. Hoffman RS, Burns MM, Gosselin S. Ingestion of Caustic Substances. N Engl J Med 2020;382:1739-48.
4. Fallahi S, Hosseini SMV, Fallahi S, Salimi M, Hesam AA, Hoseini SH. Extent of injury of gastrointestinal tract due to accidental ingestion of chemicals among children at Bandar Abbass Children Hospital 2009-2011. Life Sci J 2012;9:2054-8.
5. Temiz A, Oguzkurt P, Ezer SS, Ince E, Hicsonmez A. Long-term management of corrosive esophageal stricture with balloon dilation in children. Surg Endosc Other Interv Tech. 2010;24: 2287-92.
6. Bicakci U, Tander B, Deveci G, Rizalar R, Ariturk E, Bernay F, et al. Minimally invasive management of children with caustic ingestion: less pain for patients. Pediatr Surg Int 2010; 26: 251-5.
7. Niedzielski A, Schwartz SG, Partycka-Pietrzyk K, Mielnik-Niedzielska G. Caustic Agents Ingestion in Children: A 51-Year Retrospective Cohort Study Ear Nose Throat J 2020;99:52-7.
8. Barrón Balderas A, Robledo Aceves M, Coello Ramírez P, García Rodríguez E, Barriga Marín JA. Endoscopic findings of the digestive tract secondary to caustic ingestion in children seen at the Emergency Department. Arch Argent Pediatr 2018;116:409-14.
9. Kramer RE, Lerner DG, Lin T, Manfredi M, Shah M, Stephen TC, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN endoscopy committee. J Pediatr Gastroenterol Nutr 2015;60:562–74.
10. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF,et al. Guideline for the management of ingested foreign bodies. Gastrointest Endosc 2002; 55:802–6.
11. Russell RT, Cohen M, Billmire DF. Tracheoesophageal fistula following button battery ingestion: successful non-operative management. J Pediatr Surg 2013; 48:441–4.
12. Litovitz T, Whitaker N, Clark L, White NC, Marsolek M. Emerging battery-ingestion hazard: clinical implications. Pediatrics 2010;125:1168–77.
13. Tiryaki T, Akbıyık F, Şenel E, Mambet E, Livanelioğu Z, Atayurt H. Foreign Body Ingestion in Childhood. Turkish J Pediatr Dis 2010; 4: 94-9.
14. Russell R, Lucas A, Johnson J, Yannam G, Griffin R, Beierle E, et al. Extraction of esophageal foreign bodies in children: rigid versus flexible endoscopy Pediatr Surg Int 2014;30:417–22.
15. Sink JR, Kitsko DJ, Mehta DK, Georg MW, Simons JP. Diagnosis of Pediatric Foreign Body Ingestion: Clinical Presentation, Physical Examination, and Radiologic Findings. Ann Otol Rhinol Laryngol 2016;125:342-50.
16. Yan XE, Zhou LY, Lin SR, Wang Y, Wang YC. Therapeutic Effect of Esophageal Foreign Body Extraction Management: Flexible versus Rigid Endoscopy in 216 Adults of Beijing. Med Sci Monit 2014;20:2054-60.
17. Ferrari D, Aiolfi A, Bonitta G, Riva CG, Rausa E, Siboni S, et al. Flexible versus rigid endoscopy in the management of esophageal foreign body impaction: systematic review and metaanalysis. World J Emerg Surg 2018;13:42.
18. ASGE Standards of Practice Committee, Ikenberry SO, Jue TL, Anderson MA, Appalaneni V, Banerjee S, et al. Management of ingested foreign bodies and food impactions. Gastrointest Endosc 2011;73:1085-91.
19. Wennervaldt K, Melchiors J. Risk of perforation using rigid oesophagoscopy in the distal part of oesophagus. Dan Med J 2012; 59: A4528.
20. Gu Z, Wang Y, Lin K, Wang X, Cheng W, Wang L, et al.Magnetically Controlled Capsule Endoscopy in Children: A Single-center, Retrospective Cohort Study J Pediatr Gastroenterol Nutr 2019;69:13-17.

Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

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

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

Azize Pınar METBULUT[1], Ayse METIN[1], Omer GUNES[2], Gulsum Iclal BAYHAN[2], Guzin CINEL[3], Gulsah BAYRAM ILIKAN[4], Abdurrahman KARA[5]

[1] Ankara City Hospital, Children's Hospital, Pediatric Immunology and Allergy Clinic, Ankara, Turkey
[2] Ankara City Hospital, Children's Hospital, Pediatric Infectious Diseases Clinic, Ankara, Turkey
[3]Ankara City Hospital, Children's Hospital, Pediatric Chest Diseases Clinic, Ankara, Turkey
[4]Ankara City Hospital, Clinic of Radiology, Ankara, Turkey
[5] Ankara City Hospital, Children's Hospital, Pediatric Hematology Clinic, Ankara, Turkey

ABSTRACT

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

Key Words: Child, Granulomatous disease, Liver abscess

ÖZ

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

Anahtar Kelimeler: Çocuk, Granulomatöz hastalık, Karaciğer absesi

METBULUT AP : 0000-0001-8823-5960
METIN A : 0000-0002-0731-5799
GUNES O : 0000-0001-7121-3810
BAYHAN GI : 0000-0002-1423-4348
CINEL G : 0000-0002-6209-196X
BAYRAM ILIKAN G : 0000-0001-5833-022X
KARA A : 0000-0001-6156-3219

Conflict of Interest /*Çıkar Çatışması:* *On behalf of all authors, the corresponding author states that there is no conflict of interest.*
Financial Disclosure / *Finansal Destek*: The authors declared that this case has received no financial support.
***Confirmation / Onay*:** The written consent was received from the patient who was presented in this study.
How to cite / *Atıf Yazım Şekli* : Metbulut AP, Metin A, Gunes O, Bayhan GI, Cinel G, Bayram Ilikhan G, Kara A. Rapid Resolution of Multiple Liver Abscesses in A Chronic Granulomatous Disease Patient with Granulocyte Transfusions. Turkish J Pediatr Dis 2022;16: 70-74.
Additional information / *Ek Bilgi*: Thanks to Dr. Yavuz Koker from Erciyes University for dihidro-rhodamine 123 test.

Correspondence Address / Yazışma Adresi :
Azize Pınar METBULUT
Ankara City Hospital, Children's Hospital,
Pediatric Immunology and Allergy Clinic, Ankara, Turkey
E-posta: pinar298@yahoo.com

Received / Geliş tarihi : 14.01.2021
Accepted / Kabul Tarihi : 20.04.2021
Online published : 23.09.2021
Elektronik yayın tarihi
DOI:10.12956/tchd.858827

INTRODUCTION

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

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

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

The use of life-long antibacterial prophylaxis with trimethoprim-sulfamethoxazole is recommended. Pulmonary Aspergillus infections are the leading cause of mortality. Anti-fungal prophylaxis mainly with itraconazole can reduce the incidence of fungal infections (1-3). One of the most serious errors in the management of CGD patients is the failure to treat potentially serious infections early and to continue therapy long enough to eradicate them.

Although neutrophil absolute numbers are normal in CGD patients, it can be considered functional neutropenia because the killing function is impaired. Granulocyte transfusions have been used to treat infections in neutropenic patients for nearly 30 years (8-10) (Table II). The data from recent systematic reviews suggest that properly collected and promptly infused granulocytes are active against bacterial and fungal infections in the patient. The most important question is in which patients the administration of granulocytes will be necessary. Prominent evidence suggests that granulocyte transfusions should be used in selected cases, as a final measure to control an infection that is expected to be refractory to optimal antimicrobial treatment.

In this regard, CGD patients who do not have their neutrophil response to the infection are good candidates for granulocyte transfusions (Table II).

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

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

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

Table II. Indications of granulocyte transfusions.

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

CASE REPORT

A 3 y old male patient from a Syrian immigrant family, admitted first when he was 18 mo old, to the Republic of Turkey, Ministry of Health, Ankara City Hospital, Children's Hospital, Emergency Department with a complaint of scrotal swelling. On admission, there was a left apical cervical, 1.5x1.5 cm diameter lymphadenopathy, submandibular pigmented scars left due to previous suppurative lymphadenitis, hepatomegaly 1 cm below the costal margin, palpable left inguinal lymphadenopathy, multiple micro epididymal, and scrotal abscess. His weight was 10 kg. The patient consulted the Pediatric Immunology Unit for primary immunodeficiency diseases and especially for congenital defects of phagocyte number and functional defects due to the skin and soft tissue infections of the patient. Parents were first-degree relatives (cousins). The patient was the 1st child of the family, and 2nd child was 7 mo old and healthy. There was a perianal abscess in the newborn period in his history. He was hospitalized and the biopsy of the cervical lymph node was reported as necrotizing granulomatous inflammation by the pathologist. The patient was evaluated with the immunological screening tests as seen in Table III. Nitroblue tetrazolium test showed the killing defect of the neutrophils of the patient and the Dihidro-rhodamine 123 test showed that the patient's probable mutant NADPH-oxidase component is p67 phox protein according to the stimulation index found. Mutation analysis results are pending for the precise diagnosis. After antimicrobial treatment, he was given the drug reports and prescriptions of prophylactic TMP-SMX 5mg/kg/d, 3 days/week, per oral.; itraconazole 5mg/kg/d, every day, per oral., and interferon-gamma (Imukin® -1b 100mcg flacon) 3 days/week, sc. and called for Pediatric Immunology outpatient clinic controls. Since the patient had a routine BCG vaccine, no history of BCGitis, a PPD test was applied. Since the result was 18 mm, chest radiography and CT were taken due to the possibility of active TB infection. It was normal; prophylactic Isoniazid and Rifampicin treatments (both 10 mg/kg/d dose) were started for latent TB. The family belonged to a low socio-cultural level and could bring the child 12 months later for the new complaints of the child. They stated that they could not give the TMP-SMX, itraconazole continuously and regularly, except prophylactic TB drugs. Since the family was a Sirian immigrant, we contacted Sirian Social Aid Organisations in Turkey but Imukin could not be provided. His current complaints were >38° C fever of 5 days, abdominal pain, severe weakness, and pallor. The patient was hospitalized again in 2020 October. Physical examination revealed oral moniliasis, abdominal distention, bilateral suppurative cervical lymphadenitis with 3x3 cm diameter. Laboratuary tests were given in Table III. Abdominal USG and abdominal MRI revealed multiple (nearly 8-9) subcapsular and scattered abscesses the biggest ones sized 42x48, 28x20, and 34x27 mm diameter at the right lobe of the liver. There were another abscess sized 23x17 adjacent to the upper part of the right kidney with an undetectable capsular border. There were also multiple reactive mesentery lymphadenopathies and minimal free liquid collection. Computed tomography of the thorax showed no appearance in favor of pulmonary TB and Aspergillus pneumonia when compared with previous MR, but 18 mm right pleural effusion. Cranial MRI was normal. Treatment began with meropenem, vancomycin, teicoplanin, amikacin, and caspofungin. IVIG was added as a single dose to support the treatment in a 0.5g/kg/dose. Subcapsular hepatic abscesses drained percutaneously. Despite these treatments, fever, blood, and abscess culture yields of *S.capitis* in the blood; *Aspergillus spp*. and *Staphylococcus spp* in the hepatic abscess respectively, and the high number of the abscesses led us to decide to give granulocyte transfusion (GTX) to the patient. After the 14th day, vancomycin and caspofungin stopped and voriconazole was begun. After GTXs and multiple (3 times) interventional abscess drainages until they solidify, he remained afebrile, imaging showed improvement of all the abscesses, and the return of the erythrocyte sedimentation rate to its normal baseline (<20mm/h), the patient could be discharged after 1.5 months of antibiotic and antifungal treatment, returning to the routine CGD prophylaxis and increasing the awareness of the family about CGD, the decision was made to prepare for bone marrow transplantation. The patient was also discharged with continuing voriconazole treatment.

DISCUSSION

Recurrent cutaneous abscesses and lymphadenitis represent the earliest and common types of infection in CGD as seen in our patient. İmpetigo, froncules frequently in the perianal area due to feces contamination as well as recurrent perirectal abscess are seen (Table I). These require prolonged courses of oral and topical antibiotics to clear and once formed can persist for years despite aggressive antimicrobial treatment.

Hepatic and perihepatic abscesses were also quite common in CGD as seen in our patient, mostly caused by the hematogenous spread of *S.aureus* in patients who are incompatible with

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

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

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

In recent years the prognosis of these organ abscesses has dramatically improved with the use of GTX. In cases of severe fungal and bacterial infections that fail to respond to medical and surgical approaches, GTX is necessary to shorten the healing process.

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

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

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

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

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

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

REFERENCES

1. Segal BH,Leto TL, Gallin JI, malech HI, holland SM. genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine 2000; 79:170-200.
2. Ahlin A, Fasth A. Chronic granulomatous disease- conventional treatment vs. hematopoietic stem cell transplantation: an update. Curr Opin Hematol 2015; 22:41–5.
3. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine. 2000; 79:155–69.
4. T Turul-Özgür, G Türkkani-Asal, I Tezcan, MY Köker, A Metin, L Yel, et al. Clinical features of chronic granulomatous disease: a series of 26 patients from a single center. Turk J Pediatr 2010;52: 576-81.
5. Köker MY, Camcıoğlu Y, van Leeuwen K, Kılıç SŞ, Barlan I, Yılmaz M, et al. Clinical, functional, and genetic characterization of chronic granulomatous disease in 89 Turkish patients. J Allergy Clin Immunol 2013;132;1156-63.
6. Köker MY, Sanal O, De Boer M, Tezcan I, Metin A, Ersoy F, Roos D. Mutations of chronic granulomatous disease in Turkish families. Eur J Clin Invest 2007; 37: 589-95.
7. MY Köker, Ö Sanal, M De Boer, I Tezcan, A Metin, C Tan, F Ersoy, D Roos. Skewing of X-chromosome inactivation in three generations of carriers with X-linked chronic granulomatous disease within one family. Eur J Clin Invest 2006; 36: 257-64.
8. Lublin M, Bartlett DL, Danforth DN, Kauffman H, Gallin JI,Malech HL et al. Hepatic abscess in patient with chronic granulomatous disease. Annals of Surgery 2002;235:383-91.
9. Straughan DM, McLoughlin KC, Mullinax JE, Marciano BE, Freeman AF, Anderson VL et al. The changing paradigm of management of liver abscesses in chronic granulomatous disease. Clin Infect Dis 2018;66:1427-34.
10. Price TH, Boeckh M, Harrison RW, McCullough J, Ness PM,Strauss RG, et al .Efficacy of transfusion with granulocytes from G-CSF/dexamethasone treated donors in neutropenic patients with infection. Blood 2015;126: 2153-61.
11. Gea-Banacloche. Granulocyte transfusions: A concise review for practitioners. Cytotherapy 2017;19: 1256-69.
12. Stroncek DF, Leonard K, Eiber G, Malech HL, Gallin JI, Leitman SF. Alloimmunization after granulocyte transfusions. Transfusion 1996;36:1009-15.

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

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

Emine Gülşah TORUN[1], Mutlu UYSAL YAZICI[2], Ebru AZAPAĞASI[2], Fatih Mehmet Akif ÖZDEMİR[3], Nesrin CEYLAN[3]

[1]Sağlık Bilimleri Üniversitesi Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı, Hastalıkları Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği, Ankara, Türkiye
[2]Sağlık Bilimleri Üniversitesi Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı, Hastalıkları Eğitim ve Araştırma Hastanesi, Pediatri Yoğun Bakım Kliniği Ankara, Türkiye
[3]Sağlık Bilimleri Üniversitesi Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı, Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Nöroloji Kliniği, Ankara, Türkiye

ÖZ

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

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

ABSTRACT

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

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

GİRİŞ

Kafa içi basınç artışı sendromu (KİBAS), intrakranial yer kaplayan bir kitlenin (tümör, hematom, abse gibi) gelişmesi; ekstra veya intrasellüler sıvı miktarının artması (beyin ödemi); beyin kan akımının artması, beyin omurilik sıvı miktarının artması nedeniyle oluşabilir (1). Hayatı tehdit eden, hızlı değerlendirme ve tedavi gerektiren acil bir durumdur. Çocuklarda KİBAS'ın erken tanı ve doğru yönetimi ile kalıcı beyin hasarı gelişimi engellenebilir.

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

TORUN EG : 0000-0003-2005-7082
UYSAL YAZICI M : 0000-0001-7377-4718
AZAPĞASI E : 0000-0002-0684-8219
ÖZDEMİR FMA : 0000-0003-4820-1234
CEYLAN N : 0000-0001-5844-1261

Çıkar Çatışması / *Conflict of Interest:* : Tüm yazarlar adına, ilgili yazar çıkar çatışması olmadığını belirtir.
Finansal Destek / *Financial Disclosure*: Yazarlar bu olgu için finansal destek almadıklarını beyan etmişlerdir.
Onay / *Confirmation*: Kayıt sırasında veliler tarafından araştırmaya katılım için bilgilendirilmiş bir onay imzalanmıştır.
Atıf yazım şekli / *How to cite* : Torun EG, Uysal Yazıcı M, Azapğası E, Özdemir FMA, Ceylan N. Kafa İçi Basınç Artışı Sendromundan Beyin Ölümü ve Organ Donasyonuna Giden Bir Adölesan Olgu Sunumu. Türkiye Çocuk Hast Derg 2022; 16;75-78.

Yazışma Adresi / Correspondence Address:
Emine Gülşah TORUN
Sağlık Bilimleri Üniversitesi Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı, Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, Ankara, Türkiye
E-posta: drgtorun@gmail.com

Geliş tarihi / Received : 25.02.2021
Kabul tarihi / Accepted : 20.04.2021
Elektronik yayın tarihi : 14.09.2021
Online published
DOI: 10.12956/tchd.885694

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

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

OLGU

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

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

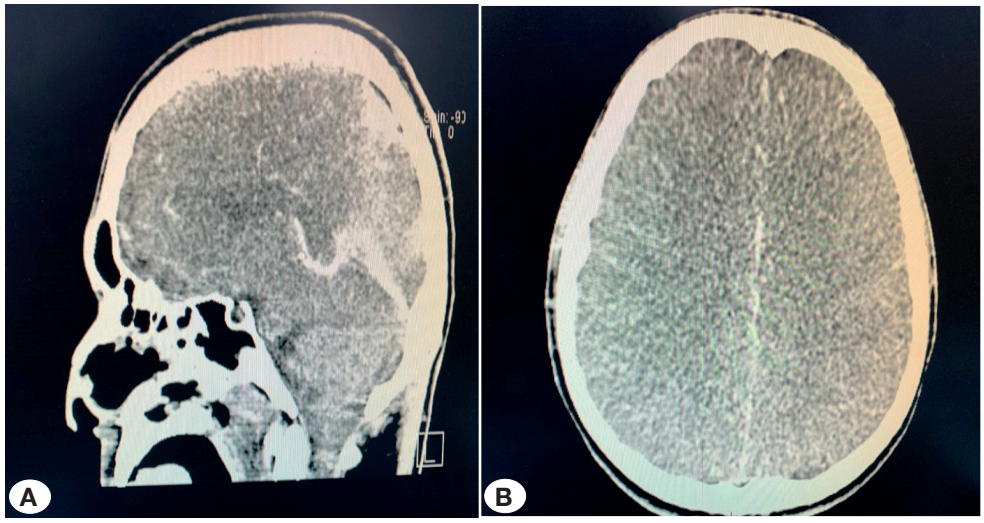
Geliş fizik muayenesinde; genel durumu kötü, bilinç kapalı, GKS 3, tansiyon 76/43 mmHg, kalp tepe atımı 85/dk, oksijen saturasyonu %90'dı. Bilateral ışık refleksi ve beyin sapı refleksleri alınamadı, pupilleri sabit dilateydi, spontan solunumu yoktu. Hastanın ense sertliği vardı. Diğer sistem muayeneleri normaldi. Hastanın başvurduğu merkezde sevk edilmeden önce GKS'sı 9 ve kranial BT'sinin normal olduğu öğrenilmişti. Fakat hastanın merkezimize başvurusunda GKS'sı 3'dü ve beyin ölümü bulguları (derin koma durumu, beyin sapı areflexisi) mevcuttu.

Hastanın tetkiklerinde: hemoglobin: 15.8 gr/dl, beyaz küre: 8450/mm^3 (%87.9 nötrofil), trombosit: 105000/mm^3, CRP: 234,5 mg/L, kreatinin: 1.01 mg/dL, kreatin kinaz: 1656 IU/L, troponin I: 2.55 ng/mL, kan gazı; pH: 7.29, pCO2: 31 mmHg, pO2: 70 mmHg, HCO-3: 15 mmol/lt, BE: -10 mmol/lt, laktat: 20 mg/dL olarak saptandı. Elektrolit dengesizliği yoktu ve karaciğer fonksiyon testleri normaldi. Olası intoksikasyon açısından serum ve idrardan ilaç düzeyleri gönderildi.

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

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

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



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

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

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

TARTIŞMA

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

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

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

Ülkemiz beyin ölümü teşhisi konan donörlerden organ nakli yapılmasına izin veren ilk ülkelerden olmasına (7) ve gerekli olanaklara sahip olmasına rağmen, beyin ölüm bildirimlerinin sayısı ve organ nakli oranı düşüktür (4,8). Ülkemizde 2019 verilerine göre; 28 bin 272 hasta nakil için sıradadır (8). Türkiye'de 1975'ten beri böbrek nakli yapılmaktadır ve ülkemizde en çok nakil yapılan organ da böbrektir (9). Akciğer nakli, tüm organ nakilleri içinde en komplike organ naklidir. Ülkemizde. ise ilk başarılı akciğer nakli 2009 yılında yapılmıştır (10). Ülkemizde organ nakli bekleyen hasta sayısı her yıl yaklaşık %20 civarında artmaktadır ve organ bekleyen hastaların %10 undan fazlasının bu süreçte hayatını kaybetmektedir. Organ nakli bekleyen hasta sayısı her yıl yaklaşık yüzde 20 civarında artmaktadır ve hastaların yüzde 10'undan fazlasının organ beklerken hayatını kaybetmektedir. 2019 verilerine göre; 2 bin 309 beyin ölümü bildiriminden 256'sı 0-19 yaş arasındadır ve bu hastalardan yalnızca 52 hasta organ donörü olmuştur (8). Bu nedenle, beyin ölümü erken tanısı ve donör organların bakımı son derece önemlidir.

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

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

KAYNAKLAR

1. Rangel-Castilla L, Gopinath S, Robertson CS. Management of intracranial hypertension [published correction appears in Neurol Clin 2008;26: xvii.
2. Türk Nöroloji Derneği Beyin Ölümü Tanı Klavuzu 2014; 20: 101-4.
3. Şantaş G, Şantaş F. Türkiye'de organ bağışının mevcut durumu ve organ bağışında stratejik iletişimin önemi. Süleyman Demirel Üniversitesi Sağlık Bilimleri Dergisi 2018;9:163-8.
4. Gündüz RC, Sahin S, Uysal-Yazici M, Ayar G, Yakut HI, ve ark. Brain death and organ donation of children. The Turkish journal of pediatrics 2014;56:597-603.
5. Sagarin MJ, Chiang V, Sales JC, Barton ED, Wolfe RE, Vissers RMW, ve ark. Rapid sequence intubation for pediatric emergency airway management. Pediatr Emerg Care 2002;18:417-23.
6. Gerardi MJ, Sacchetti AD, Cantor RM, Santamaria JP, Gauche M, Lucid W, ve ark. Rapid-sequence intubation of the pediatric patient. Pediatric Emergency Medicine Committee of the American College of Emergency Physicians. Ann Emerge Med 1996;28:55-74.

7. Yasa no. 2238 29 Mayıs 1979 Organ ve Doku Alınması, Saklanması, Aşılanması ve Nakli Hakkında Kanun. TC Resmi Gazete 3 June 1979; 16655: 1-4.
8. Doku, Organ Nakli ve Diyaliz Hizmetleri Dairesi Başkanlığı, Türkiye Transplantasyon, Diyaliz İzlem Sistemleri, erişim 19.04.2020 https://organkds.saglik.gov.tr/dss/PUBLIC/Public Default2.aspx
9. Haberal M. Historical evolution of kidney and liver transplantation in Turkey. Transplant Proc1995;27:2771-4.
10. Türk Toraks Derneği, Ülkemizde Akciğer Nakli, erişim 19.04.2020, https://www.toraks.org.tr/halk/News.aspx? detail=3810
11. https://www.aa.com.tr/tr/saglik/turkiye-genelinde-gecen-yil-9-bin-477-organ-ve-doku-nakli-yapildi/1690942 erişim tarihi 18 ocak 2021.
12. Bayrakcı B, Çocuk Yoğun Bakım Ünitesinde Organ Donörünün Tıbbi Bakımı. Yoğun Bakım Dergisi 2004;4:186-9.
13. Kotloff RM, Blosser S, Fulda GJ, Malinoski D, Ahya, VN, ve ark. Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/ Association of Organ Procurement Organizations Consensus Statement. Crit Care Med 2015; 43: 1291–325.
14. Park J, Yang NR, Lee YJ, Hong KS. A Single-Center Experience with an Intensivist-Led Brain-Dead Donor Management Program. Ann Transplant 2018;23:828-35
15. Friedman AL, Marquez E, Lewis JA. Organ Donation is an Indication for Renal Replacement Therapy (RRT). Am J Transplant. 2019; 19 (suppl 3). https://atcmeetingabstracts.com/abstract/organ-donation-is-an-indication-for-renal-replacement-therapy-rrt/. Accessed June 12, 2020.

COVİD-19 ve Nörolojik Bulgular

Neurologic Manifestations of COVID-19

Esra GÜRKAŞ, Deniz YILMAZ, Ayşegül Neşe ÇITAK KURT

Ankara Şehir Hastanesi, Çocuk Hastanesi, Çocuk Nöroloji Kliniği, Ankara, Türkiye

ÖZ

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

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

ABSTRACT

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

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

GİRİŞ

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

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

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

0000-0003-3942-5105 : GÜRKAŞ E
0000-0002-0789-8955 : YILMAZ D
0000-0002-7277-3550 : ÇITAK KURT AN

Çıkar Çatışması: Tüm yazarlar adına, ilgili yazar çıkar çatışması olmadığını belirtir.
Conflict of Interest: *On behalf of all authors, the corresponding author states that there is no conflict of interest.*

Atıf yazım şekli / *How to cite* : Gürkaş E, Yılmaz D, Çıtak Kurt AN. COVID-19 ve Nörolojik Bulgular. Türkiye Çocuk Hast Derg 2022;16:79-82.

Yazışma Adresi / Correspondence Address:
Esra GÜRKAŞ
Ankara Şehir Hastanesi, Çocuk Hastanesi,
Çocuk Nöroloji Kliniği, Ankara, Türkiye
E-posta: esragurkas@yahoo.com

Geliş tarihi / Received : 04.02.2021
Kabul tarihi / Accepted : 29.03.2021
Elektronik yayın tarihi :16.11.2021
Online published
DOI: 10.12956/tchd.874225

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

Santral Sinir Sistemi ile ilişkili Bulgular

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

Tablo I: COVİD-19 enfeksiyonunda görülen nörolojik bulgular.

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

Periferik Sinir Sistemi ile ilişkili Bulgular

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

Kas-İskelet Sistemi ile ilişkili Bulgular

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

Çocuklarda Görülen Nörolojik Bulgular

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

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

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

Nörolojik Bulguların Gelişiminde Öngörülen Mekanizmalar

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

SONUÇ

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

KAYNAKLAR

1. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. JAMA Neurol 2020;77:1018-27.
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, ve ark. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:1-9.
3. Pinna P, Grewal P, Hall JP, Tavarez T, Dafer RM, Garg R, ve ark. Neurological manifestations and COVID-19: experiences from a tertiary care center at the frontline. J Neurol Sci 2020;415:116969.
4. Pezzini, A., Padovani, A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol 2020;16:636-44.
5. Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, ve ark. New onset neurologic events in people with COVID-19 in 3 regions in China. Neurology 2020;95:e1479-e87.
6. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci 2020;77:8-12.
7. Chen X, Laurent S, Onur OA, Kleineberg NN, Fink GR, Schweitzer F, ve ark. A systematic review of neurological symptoms and complications of COVID-19. J Neurol. 2021;268:392-402.
8. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, ve ark. Comorbidity and its impact on 1,590 patients with COVID–19 in China: A Nationwide Analysis. Eur Respir J 2020;55:2000547.
9. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, ve ark. Neurologic Features in Severe SARS-CoV–2 Infection. N Engl J Med 2020;382:2268-70.
10. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, ve ark. A first case of meningitis/encephalitis associated with SARS-Coronavirus–2. Int J Infect Dis 2020; 94:55-8.
11. Ye M, Ren Y, Lv T. Encephalitis as a Clinical Manifestation of COVID–19. Brain Behav Immun. 2020;88: 945-6.
12. Pilotto A, Odolini S, Masciocchi S, Comellia A, Volonghi I, Gazzina S, ve ark. Steroid-responsive severe encephalopathy in Coronovirus disease 2019. Ann Neurol 2020;88:423-7.
13. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Grith B. COVID–19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology 2020;292:E119-E120.
14. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, ve ark. Neurological associations of COVID-19 Lancet Neurol 2020;19:767-83.
15. Khatoon F, Prasad K, Kumar V. Neurological manifestations of COVID-19: available evidences and a new paradigm. J Neurovirol 2020;26:619-30.
16. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, ve ark. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID–19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277:2251-61.
17. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, ve ark. Guillain-Barré Syndrome Associated with SARS-CoV-2. N Engl J Med 2020;382:2574-6.
18. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, ve ark. Neurologic manifestations of COVID 19. Crit Care 2020;24: 421.
19. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas, ve ark. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. Neurology 2020;95:e601-5.
20. Lima MA, Silva MTT, Soares CN, Coutinho R, Oliveira HS, Afonso L, ve ark. Peripheral facial nerve palsy associated with COVID-19 J Neurovirol 2020;26:941-4.

21. Wei H, Yin H, Huang M, Guo Z. The 2019 novel cornoavirus pneumonia with onset of oculomotor nerve palsy: a case study. J Neurol 2020;267:1550–3.
22. Román GC, Spencer PS, Reis J, Buguet A, Faris MEA, Katrak SM, ve ark. The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. J Neurol Sci 2020;414: 116884.
23. Jin M, Tong Q. Rhabdomyolysis as Potential Late Complication Associated with COVID-19. Emerg Infect Dis 2020; 6:1618-20.
24. Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. Pediatr Infect Dis J 2020;39:355-68.
25. Stafstrom CE, Jantzie LL. COVID-19: Neurological Considerations in Neonates and Children. Children (Basel) 2020;7: 133.
26. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20:689-96.
27. X Lu, L Zhang, H Du, Zhang J, Li Y, Qu J, ve ark, Chinese pediatric novel coronavirus study, SARS-CoV-2 infection in children, N Engl J Med 2020;382:1663-5.
28. Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L. Neurological Complications of SARS-CoV-2 Infection in Children: A Systematic Review and Meta-Analysis. J Trop Pediatr 2020;fmaa070.
29. McAbee GN, Brosgol Y, Pavlakis S, Agha Rabia, Gaffoor. Encephalitis associated with COVID-19 infection in an 11-year-old child. Pediatr Neurol 2020;109:94.
30. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, ve ark. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill 2020;25:2000600.
31. Cura Yayla BC, Özsürekçi Y, Aykaç K, Derin Oygar P, Laçinel Gürlevik S, İlbay S, ve ark. Characteristics and Management of Children with COVID-19 in Turkey. Balkan Med J 2020;37:341-7.
32. Chen TH. Neurological involvement associated with COVID-19 infection in children. J Neurol Sci 2020;418:117096.
33. Serdaroğlu E, Serdaroğlu A. COVID-19 and neurologic manifestations. Turkiye Klinikleri J Med Sci 2020;40:269-71.
34. Wenting A, Gruters A, van Os Y, Verstraeten S, Valentijn S, Ponds R, ve ark. COVID-19 Neurological Manifestations and Underlying Mechanisms: A Scoping Review. Front Psychiatry 2020;11:860.

Use of Phenytoin in Vertigo/Dizziness

Vertigoda Fenitoin Kullanımı

Hilal AYDIN[1], Demet CAN[2]

[1]Department of Pediatric Neurology, Balikesir University, Faculty of Medicine, Balikesir, Turkey
[2]Department of Pediatric Allergy and Immunology, Balikesir University, Faculty of Medicine, Balikesir, Turkey

ABSTRACT

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

Key Words: Phenytoin, Treatment, Vertigo

ÖZ

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

Anahtar Kelimeler: Fenitoin, Tedavi, Vertigo

INTRODUCTION

We have read the article by Dilber et al. (1) titled, “Neurological Manifestations of Pediatric Acute COVID Infections: A Single Center Experience?” with interest. The second most common non-specific symptom reported in patients followed-up with Covid-19 was dizziness, observed in 14.3% of patients, 0.7% of whom were hospitalized. Diphenylhydantoin has been used in the treatment of patients hospitalized with dizziness, and a good clinical response has been reported. The use of diphenylhydantoin with this indication attracted our attention. However, it was stated that 25% of Covid-19 patients had central nervous system findings and 2% of them had at least one seizure during the treatment process (2). Firat et al. (3), mentioned drug-drug interactions of clinical importance between anti-Covid-19 treatments (antiviral and immune therapies) and antiepileptic drugs. It has been emphasized that phenytoin reduces lopinavir/ritonavir serum levels by 30%. For this reason, it was emphasized that attention should be paid the dose of antiviral treatment in COVID-19 patients with epilepsy receiving phenytoin (3).

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

0000-0002-2448-1270: AYDIN H
0000-0002-1258-9348: CAN D

Conflict of Interest/ *Çıkar Çatışması:* *On behalf of all authors, the corresponding author states that there is no conflict of interest.*
How to cite / *Atıf yazım şekli* : Aydin H and Can D. Use of Phenytoin in Vertigo/Dizziness. Turkish J Pediatr Dis 2022; 16: 83-84.

Correspondence Address / *Yazışma Adresi*:
Hilal AYDIN
Department of Pediatric Neurology,
Balikesir University, Faculty of Medicine, Balikesir, Turkey
E-posta: drhilalaydin@gmail.com

Received / Geliş tarihi : 02.10.2021
Accepted / Kabul tarihi : 17.12.2021
Online published : 10.01.2022
Elektronik Yayın Tarihi
DOI:10.12956/tchd.1002338

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

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

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

REFERENCES

1. Dilber B, Aydın ZGG, Yeşilbaş O, Sağ E, Aksoy NK, Gündoğmuş F, et al. Neurological Manifestations of Pediatric Acute COVID Infections: A Single Center Experience. J Trop Pediatr 2021;67: fmab062.
2. Asadi Pooya AA. Seizures associated with coronavirus infections. Seizure 2020;79:49–52.
3. Fırat O, Yalçın N, Demirkan K. COVID-19 & antiepileptic drugs: Should we pay attention? Seizure 2020;80:240-1.
4. Abou-Khalil BW. Antiepileptic Drugs. Continuum (Minneap Minn) 2016;22:132-56.
5. Yaari Y, Selzer ME, Pincus JH. Phenytoin: mechanisms of its anticonvulsant action. Ann Neurol 1986;20:171-84.
6. Patocka J, Wu Q, Nepovimova E, Kuca K. Phenytoin - An anti-seizure drug: Overview of its chemistry, pharmacology and toxicology. Food Chem Toxicol 2020;142:111393.
7. Keppel Hesselink JM, Kopsky DJ. Phenytoin: 80 years young, from epilepsy to breast cancer, a remarkable molecule with multiple modes of action. J Neurol 201;264617-21.
8. Keppel Hesselink JM, Kopsky DJ. Phenytoin: neuroprotection or neurotoxicity? Neurol Sci 2017;38:1137-41.
9. Keppel Hesselink JM. Phenytoin repositioned in wound healing: clinical experience spanning 60 years. Drug Discov Today 2018;23:402-8.
10. Russel G, Abu-Arafeh I. Paroxysmal vertigo in children- an epidemiological study. Int J Pediatr Otorhinolaryngol 1999;49:105–7.
11. Various Vertigo Syndromes. In: Vertigo and Dizziness. Springer, London 2005: 123-38. https://doi.org/10.1007/1-84628-081-8_6.