Tip 1 Diyabet Hastalarının Glisemik Kontrolleri, Etkileyen Faktörler ve Tip 1 Diyabet ile Enfeksiyon Sıklığı İlişkisi

Glycemic Controls of Patients with Type 1 Diabetes, Affecting Factors and Relationship Between Type 1 Diabetes and Infection Frequency

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ÖZ

Amaç: Tip 1 diabetes mellitus (Tip 1 DM), çocukluk ve ergenlikte en sık görülen endokrin-metabolik bozukluktur. Bu çalışmada, Tip 1 DM'de kötü metabolik kontrol için risk faktörleri, olgularda enfeksiyon sıklığı, eşlik eden otoimmün hastalık sıklığı, Tip 1 DM'un final boyuna ve vücut kitle indeksine (VKİ) etkisinin saptanması planlanarak tedavi ve izlemlerinin tekrar gözden geçirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya Tip 1 DM'li 184 çocuk ve ergen dahil edilmiştir. Hasta dosyaları retrospektif olarak incelenmiştir ve hastaların sosyodemografik özelliklerini ve enfeksiyon öyküsünü içeren bir anket uygulanmıştır.

Bulgular: Dahil edilen vakaların%53.5'i kız,%46.7'si erkek olup yaş ortalaması 12.71±0.31 yıldı. Ortalama tanı yaşı 7.71±0.29 yıl iken ortalama Hb1ac değeri 8.45±1.78'di. Ortalama HbA1c değeri ile tip 1 DM için aile öyküsü, ev halkı büyüklüğü, ikametgah ve aylık gelir arasında bir korelasyon bulunmadı. Tip 1 DM kronik bir hastalık olması nedeni ile hastalarda nihai boya etkisi, hedef boy ile nihai boy karşılaştırılarak yapıldı. Nihai boya ulaşan 29 hastanın hedef boylarını geçtiği görüldü. Metabolik kontrolün bir göstergesi olan ortalama HbA1c değeri arttıkça mikroalbüminüri ve nöropatinin arttığı saptandı. Olgularda hastanede yatış gerektirecek ciddi enfeksiyon olmadığı ve yıllık ortalama enfeksiyon sayısı 2,3 olduğu görüldü. Enfeksiyon sıklığında artış saptanmadı.

Sonuç: Sonuç olarak, Tip 1 DM'li hastalarda kötü metabolik kontrol için risk faktörü olarak hastalık süresi ve artmış yaş, ergenlik, sosyoekonomik durum, diyet önerilerine uyumsuzluk ve kontrol ziyaretlerine gelememe tespit edilmiştir. Geliştirilmiş metabolik kontrol ile hastaların hedef boya ulaştığı görülmüştür. Hastalarımızda enfeksiyon oranında artış veya hastanede yatmayı gerektirecek ciddi enfeksiyon görülmemiştir. Literatür ile benzer otoimmün hastalık sıklığı izlenmiştir.

Anahtar Sözcükler: Hemoglobin A1C, Enfeksiyon, Metabolik, Tip 1 Diyabetes Mellitus

ABSTRACT

Objective: Type 1 diabetes mellitus (Type 1 DM) is the most common endocrine-metabolic disorder at childhood and adolescence. In this study, it was aimed to determine the risk factors for poor metabolic control in Type 1 DM, the frequency of infection in the cases, the frequency of accompanying autoimmune diseases, the effect of Type 1 DM on the final height and body mass index (BMI) and to review the treatment and follow-up.

Material and Methods: The present study included 184 children and adolescent with Type 1 DM. The patient charts were retrospectively reviewed and a questionnaire was applied including sociodemographic characteristics of the patients, and history of infection.

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Results: Of the cases included, 53.5% were girl whereas 46.7% were boy with a mean age of 12.71±0.31 years. Mean age at diagnosis was 7.71±0.29 years while mean Hb1ac value was 8.45±1.78. No correlation was found between mean HbA1c value and family history for diabetes mellitus, household size, residency and monthly income. Since type 1 DM is a chronic disease, the final dye effect in patients was made by comparing the target height with the final height. It was observed that 29 patients who reached to final height passed over their target height. It was determined that as the mean HbA1c value, which is an indicator of metabolic control, increased, microalbuminuria and neuropathy increased. There was no severe infection requiring hospitalization. The mean number of infection per year was 2.3 and there was no increase in the frequency of infection.

Conclusion: In conclusion, duration of disease and increased age, puberty, socioeconomic status, incompliance to dietary recommendation and failure in attending control visits were identified as risk factor for poor metabolic control in patients with Type 1 DM. It was found that patients reached to target height by improved metabolic control. No increase in infection rate or severe infection requiring hospitalization was observed in our patients. The frequency of autoimmune diseases was similar to the literature.

Key Words: Hemoglobin A1C, Infection, Metabolic, Type 1 Diabetes Mellitus

GİRİŞ

Diyabetes mellitus tek bir hastalık tablosu olmayıp etiyoloji, patogenez ve genetik yönden farklılıklar gösteren hastalıklar grubudur. Çocukluk ve adölesan döneminin en sık görülen endokrin-metabolik bozukluğu olan Tip 1 DM insülinin eksikliği sonucu gelişen karbonhidrat, yağ ve protein metabolizmalarında bozukluklarla karakterizedir (1).

Glikozile hemoglobin (HbA1c), diyabetin başlangıç tanısı ve daha sonraki takibinde metabolik kontrolün iyi bir göstergesidir. HbA1c, İSPAD'a göre <%7.5 optimal, %7.5-9 arasında suboptimal ve >%9 kötü metabolik kontrol olarak sınıflandırılmıştır. İyi bir metabolik kontrol ile diyabetin mikro ve makrovasküler komplikasyonlarının önlenebileceği veya geciktirilebileceği bilinmektedir (2).

Tip 1 DM'de iyi metabolik kontrolün sağlanması için multidisipliner bir ekip çalışması gerekmektedir. Bu ekipte, pediatrik endokrinolog, diyabet hemşiresi, diyetisyen ve psikolog bulunmalıdır. Sosyoekonomik durumun kötü olması, diyabet süresinin (yaşı) uzaması, diyabetik ketoasidoz (DKA) atak sıklığı, düzensiz poliklinik kontrolü, ailedeki birey sayısının fazla olması, psikolojik durum bozukluğu ile HbA1c arasında anlamlı ilişki olduğu bildirilmiştir (2,3).

Bazı epidemiyolojik çalışmalarda, diyabetes mellitus (DM) (Tip 1 DM ve Tip 2 DM'li tüm hastalar) hastalarının enfeksiyonlar için DM hastası olmayanlara göre daha sık tedavi gördüğünü gösterilmesine rağmen, DM enfeksiyon riski üzerindeki etkisinin büyüklüğü aktif bir araştırma sorusu olmaya devam etmektedir. Çoğu çalışma, genel popülasyonla karşılaştırıldığında DM'lu hastalar arasında enfeksiyon riskinin arttığını desteklemektedir, ancak bu riskin büyüklüğü belirsizdir (4-6). Özellikle DM, deri ve yumuşak doku enfeksiyonları ve ardından genitoüriner, gastrointestinal malign eksternal otit ve solunum yolu enfeksiyonları ile ilişkilendirilmiştir (4).

Bu çalışmada, Tip 1 DM'de kötü metabolik kontrol için risk faktörleri, olgularda enfeksiyon sıklığı, eşlik eden otoimmün hastalık sıklığı, Tip 1 DM'un final boyuna ve vücut kitle indeksine (VKİ) etkisinin saptanması planlanarak tedavi ve izlemlerinin tekrar gözden geçirilmesi amaçlanmıştır.

GEREÇ ve YÖNTEMLER

Bu çalışma, Akdeniz Üniversitesi Hastanesi Çocuk Endokrin Kliniği'nde takip edilen son bir yılda en az bir poliklinik başvurusu olan ve en az bir yıldır Tip 1 DM tanısı ile takipli olan 184 Tip 1 DM tanılı olgu incele

nerek yapılmıştır. Bu çalışmada olgulara ait dosyalar retrospektif olarak değerlendirilip, hastalara bir anket uygulanmıştır. Olguların dosyalarında, anamnez, sistemik muayene, eşlik eden hastalıklar hastalıkla ilgili komplikasyon ve tedavi bilgileri ayrıntılı olarak incelenmiştir.

Ankette hastaların, yaşı, cinsiyeti, boyu, kilosu, hedef boyu, anne ve baba mesleği, anne ve babanın eğitim durumu, ailenin aylık geliri, evdeki birey sayısı, yaşanılan yer, hastanın tanı aldığı tarih, tanı mevsimi, insülin rejimi, hastanın diyet ve egzersiz yapıp yapmadığı, poliklinik kontrol sıklığı, kan şekeri profili tutup tutmadığı, ailede diyabet tanılı birey varlığı, insülin dozlarının kim tarafından yapıldığı, hipoglisemisi olup olmadığı, son bir yıl içinde diyabetik ketoasidoz veya ek bir neden ile hastane yatışı olup olmadığı, son bir yıl içinde enfeksiyon öyküsü sorgulanmıştır.

Hastaların metabolik kontrol ve komplikasyonları İSPAD konsensus kriterlerine göre değerlendirildi. Hastaların son bir yıllık ortalama glikozile hemoglobin (HbA1c) düzeylerine göre metabolik kontrolleri belirlendi. Ortalama HbA1c <%7 ise iyi metabolik kontrol, %7-9 arasında ise orta metabolik kontrol ve >%9 ise kötü metabolik kontrol olarak değerlendirildi (2). Diyabetik ketoasidoz, venöz kan gazı değerlerinde pH <7.30-HCO3<15 mcq/l olması ve kan şekeri >300 mg/dl, idrarda keton çıkması olarak tanımlandı (7). Tüm olguların tanıdaki ve son muayenelerindeki VKİ'leri [VKİ=Ağırlık (kg)/(boy =m)^2] hesaplandı. Olguların VKİ, Neyzi ve ark.'nın (8) Türk toplumu standartlarına göre değerlendirildi. Hastaların dosyalardan alınan vücut ağırlıkları büyük terazi ile, boyları ise ayakkabıları çıkarılmış olarak Harpenden Stadiometre ile aynı kişi tarafından ölçülmüştür. DM yaşı; DM tanısının konulduğu tarihten son muayene tarihine kadar geçen süre hesaplandı. Olguların ilk tanı esnasında anti-glutamik asit dekarboksilaz antikoru (Anti-GAD) insülin (İAA) ve adacık hücre (İCA) antikorları değerleri varsa kaydedildi. Tüm olguların kullandığı insülin rejimleri, günlük dozu

(ünite/kg) kaydedildi. Olguların 3 aylık aralıklarla son bir yıl içinde bakılmış olan HbA1c değerinin ortalaması alındı. Tip 1 DM'e eşlik eden otoimmun hastalıklar kaydedildi. Otoimmun tiroidit tanısı, serbest tiroksin (sT4) düşük, tiroid stimulan hormon (TSH) ve tiroid otoantikor (anti-hTG ve anti-TPO) yüksekliği ile konuldu. Diyabetik mikrovasküler komplikasyonlardan; mikroalbuminüri, en az iki kez albumin ekskresyonunun (30-300 mg/gün) üzeri olması kabul edildi. Retinopati tanısı, fundoskopi ve gerekirse renkli fundus fotografi ile tanı konuldu. Nöropati tanısı ise, fizik muayene (el ve ayaklarda ağrı, uyuşma, iğnelenme ve geceleri olan ağrı, kaslarda güçsüzlük, dokularda beslenme bozuklukları, ciltte renk değişiklikleri) ve EMG bulguları ile konuldu. Çölyak hastalığı tanısı, antigliadin IgA, doku transglutaminaz IgA ve kolonoskopi bulguları ile konuldu.

Hastalarda enfeksiyon görülme sıklığı anket ile sorgulandı. Son bir yılda sekizden fazla enfeksiyon, ikiden fazla ciddi sinüs enfeksiyonu, ikiden fazla pnömoni ve ikiden fazla derin doku enfeksiyonu geçirme, primer immun yetmezlik açısından uyarıcı sıklıkta kabul edildi (9).

Biyokimyasal Analiz Metodları

Biyokimyasal testler olarak; glukoz, olgulara ait serumlar bekletilmeden, Roche COBAS 8000 otoanalizör cihazı ile hekzokinaz yöntemiyle mg/dl olarak ölçüldü. TSH, s-T3, s-T4'ün her biri için ayrı roche ticari kiti kullanılarak Roche COBAS 8000 otoanalizöründe elektrokemilüminesans immunoassay (ECLIA) yöntemi ile çalışıldı. Test kitinde normal referans aralıkları; s-T3 için 1.8-4.6 pg/ml, s-T4 için 0.93-1.7 ng/dl, TSH için ise 0.27-4.2 µlU/ml. HbA1c, Roche COBAS 8000 otoanalizöründe Roche ticari kitleri kullanılarak turbidimetrik yöntem ile ölçüldü. Sonuçlar yüzde HbA1c (normal aralık %4.8-5.9) ve aynı zamanda mmol/mol olarak değerlendirildi. Roche COBAS 8000 otoanalizöründe kolorimetrik yöntem ile Roche ticari kiti kullanılarak idrarda albumin miktarına bakıldı. Beklenen referans aralıkları: Yenidoğan (0-4 günlük) 2.8-4.4 g/dl, çocuk (4 gün-14 yaş), 3.8-5.4 g/dl, çocuk (14-18 yaş) 3.2-4.5 g/dl (Bu referans aralıkları kullanılan kittin referans aralıklarıdır).

Akdeniz Üniversitesi Tıp Fakültesi, Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır (15.03.2013/107). Ailelerinden yazılı onam alınarak 184 olgu çalışmaya dahil edildi. Onam alınamayan hastalar çalışma dışında bırakıldı.

İstatistiksel Değerlendirme

Veriler SPSS 18.0 (Chicago) kullanılarak analiz edildi. Örneklemi tanımlamak için frekans dağılımı, ortalama, standart sapma gibi tanımlayıcı istatistikler kullanıldı. İki grubun sürekli dağılımların analizinde test varsayımlarına göre Student-t testi ya da Mann-Whitney U testi yapıldı. Çok grubun sürekli dağılımlarının analizinde test varsayımlarına göre Kruskal-Wallis analizi yapıldı. Fark bulunan grupların belirlenmesinde ikişerli karşılaştırmalar için Mann-Whitney U testi kullanıldı. Gruplara göre kategorik verilerin analizinde Ki-kare testi kullanıldı. Ölçüm değişkenlerin ilişki analizinde test varsayımlarına göre Spearmann korelasyon analizi kullanıldı. Analizlerde farklılıkların belirlenmesi için %95 anlamlılık düzeyi (ya da α=0.05 hata payı) kullanılmıştır.

BULGULAR

Bu çalışma Akdeniz Üniversitesi Tıp Fakültesi Hastanesi Çocuk Endokrin Kliniği'nde takip edilen Tip 1 DM tanılı 0-18 yaş arasında 184 olgu üzerinde gerçekleştirildi.

Olguların %53.3'ü (98) kız, %46.7'si (86) erkek olarak saptandı. Olguların cinsiyetleri arasında anlamlı bir fark saptanmadı. Olguların ortalama yaşı 12.73±0.31'di. Olguların %11.4'ü (21) 0-6 yaş arasında, %31.6'sı (58) 6-12 yaş arasında, %57' si (105) 12 yaşından büyüktü. Tedavi sonrası vücut kitle indeksi ortalamaları 19.98±0.30, tanı yaşı 7.71±0.29, ortalama diyabet yaşı 4.93±0.26 ve ortalama insülin dozu (ünite/kg/gün) 0.88±0.02 olarak hesaplandı (Tablo I).

Tanı anında, olguların %34.8'i (64) 6 yaşından küçük, %49.5' i (91) 6-12 yaş arasında, %15.7'si (29) 12 yaşından büyüktü. Olgular en sık 6-12 yaş aralığında tanı almıştı.

İnsülin tedavisi olguların %34.2'sinde (63) anne, %0.5'inde (1) baba, %1.6'sında (3) bakıcı, %63.6'sında (117) kendisi tarafından uygulanmaktaydı. Olguların %32 (59) ailede Tip 1 veya Tip 2 diyabet öyküsü mevcut olduğu saptandı.

Olguların ortalama HbA1c değerleri 8.45±1.78'di. Olguların cinsiyetine göre HbA1c değerleri arasında anlamlı farklılık saptanmadı. Altı yaşından küçük olguların ortalama HbA1c değerleri 7.61±0.26, 6-12 yaş arasındaki olguların ortalama HbA1c değerleri 7.98±0.18, 12 yaşından büyük olguların ortalama HbA1c değerleri 8.89±0.19'du. Olguların yaşı arttıkça HbA1c değerlerinde artış saptandı (p: 0.001). Yaş ile HbA1c arasında pozitif ancak güçsüz korelasyon saptandı (r:0.30, p : 0.0001).

Tablo I: Çalışmadaki olguların genel özellikleri.

	Ortalama	Standart Deviasyon
Yaş	12.73	0.31
Tedavi sonrası VKİ	19.82	0.30
Tanı yaşı	7.71	0.29
Diyabet yaşı	4.93	0.26
HbA1c	8.45	1.78
Ortalama insülin dozu	0.88	0.02

VKİ: *Vücut kitle indeksi*

Tablo II: Olguların otoantikor verileri.

	Anti GAD	Anti İnsülin Ab	İslet cell Ab	Anti-TPO/ anti-HTG
Pozitif (%)	89.5	52.8	59.1	10.3
Negatif (%)	10.5	48.2	41.9	89.7
n	68	123	44	184

n: *Tetkik edilen hasta sayısı*

Tablo III: Olguların son bir yılda enfeksiyon verileri.

	Nezle n (%)	Orta kulak iltihabı n (%)	Sinüzit n (%)	Boğaz iltihabı n (%)	Zatüre n (%)	Ağızda yara n (%)	Ciltte yara n (%)	İYE n (%)	İshal n (%)
0	50 (27)	171 (93)	158 (86)	144 (78)	184 (100)	175 (95)	176 (96)	164 (89)	153 (83)
1	73 (40)	10 (5.4)	18 (9.8)	21 (11)	0	9 (4.9)	4 (2.2)	13 (7.1)	23 (13)
2	39 (21)	2 (1.1)	6 (3.3)	7 (3.8)	0	0	3 (1.6)	2 (1.1)	3 (1.6)
3	14 (7.6)	1 (0.5)	2 (1.1)	10 (5.4)	0	0	0	5 (2.7)	5 (2.7)
4	3 (1.6)	0	0	2 (1.1)	0	0	0	0	0
5	5 (2.7)	0	0	0	0	0	0	0	0

İYE: *İdrar yolu enfeksiyonu*

Tablo IV: HbA1c ve diyabet yaşı ile komplikasyonların ilişkisi.

	Yok	Var	p
Mikroalbuminüri			
HbA1c (Ort)	8.23	9.13	**0.009**
Diyabet yaşı (Ort)	4.42	6.68	**0.004**
Nöropati			
HbA1c (Ort)	8.23	11.33	**0.004**
Diyabet yaşı (Ort)	4.65	5.66	0.358

Olguların diyetleri sorgulandı. Diyetine uymayan olguların ortalama HbA1c değerleri 8.77±1.63'di, ara ara diyete uyan olguların ortalama HbA1c değerleri 8.63±1.74'dü,düzenli diyet yapan olguların ortalama HbA1c değerleri 8.15±1.85di. Diyetine dikkat eden olguların HbA1c değerleri daha düşük saptandı (p: 0.030). Olguların %44'ü düzenli diyetine uyarken, %15.2'si hiç diyetine uymamaktaydı, %40.8'i ise ara ara uymaktaydı.

Olguların egzersiz bilgileri ve egzersiz yapmaları ile HbA1c değeri arasında ilişki değerlendirildi. Grupların egzersiz yapması ile HbA1c değerleri arasında ilişki saptanmadı (p: 0.330). Olguların %10.9' u egzersiz yapmıyor, %59.8'i ara ara yapıyor, %29.3' ü düzenli egzersiz yapıyordu.

Ailede diyabeti olan hastaların ortalama HbA1c değeri 8.49±1.62, ailede diyabeti olmayan hastaların ortalama HbA1c değeri 8.43±1.86 bulundu. İki grup arasında anlamlı fark bulunmadı (p: 0.720).

Olguların kendisi dışında ailede yaşayan birey sayısı sorgulandı. Evde kendi dışında iki kişi olan olguların ortalama HbA1c değeri 8.00±1.14, üç kişi olan olguların ortalama HbA1c değeri 8.17±1.72, dört kişi olan olguların ortalama HbA1c değeri 8.53±1.87, dört kişiden fazla olan olguların ortalama HbA1c değeri 8.75±1.84 olarak saptandı. Ailedeki birey sayısının artmasıyla olguların HbA1c değerlerinde artış olduğu saptandı (p:0.410)

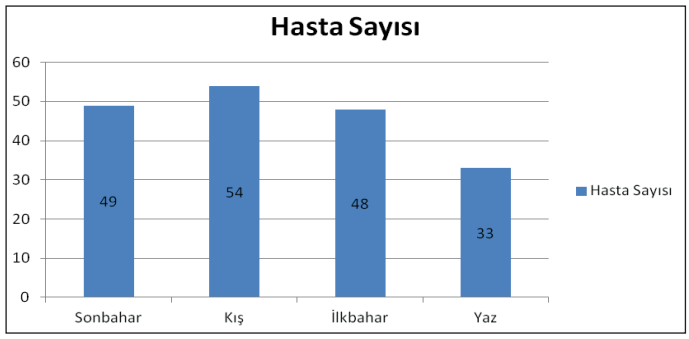
Olgular il, ilçe ve köyde yaşamalarına göre gruplandı. Olguların %48.4'ü (89) il merkezinde, %34.8'i (64) ilçede, %16.8'si (31) köyde yaşamaktaydı. İl merkezinde yaşayanları ortalama HbA1c'si 8.26±1.71, ilçede yaşayanların ortalama HbA1c'si 8.51±1.66, köyde yaşayanların ortalama HbA1c'si 8.84±2.17'dü. İl merkezinde yaşayan olguların HbA1c ortalaması daha düşük saptanmasına rağmen istatistiksel açıdan anlamlı ilişki saptanmadı (p: 0.480). Olguların gelir dağılımı sorgulanmış olup gelir grupları ile HbA1c değerleri arasında anlamlı fark bulunamadı (p: 0.580).

Uzun etkili + üç doz kısa etkili kullanan grup ile iki doz orta etkili + üç doz kısa etkili insülin kullanan grup karşılaştırıldı. Gruplar arasında anlamlı fark bulunamadı (p: 0.160). Olguların %83'ü kan şeker profili tutmaktaydı. Kan şeker profili tutma ile HbA1c değerleri arasında anlamlı farklılık saptanmadı (p: 0.080). Olguların %15.8'i günde iki kez kan şekerini ölçerken, %49.5'i günde dört kez, %23.4'ü günde altı kez ve %11.3'ü günde altıdan fazla kan şekeri ölçümü yapmaktaydı Günlük kan şekeri ölçüm sayısı ile HbA1c düzeyi değerlendirildi. Aralarında anlamlı ilişki saptanmadı (p: 0.210).

Hastaların HbA1c değeri poliklinik kontrol sıklığına göre değerlendirildi. Olguların büyük çoğunluğu üç ayda bir kontrole gelmekteydi. Düzenli kontrole gelen hastaların ortalama HbA1c değeri 8.28±0.13 diğerlerine göre daha düşük saptandı (p: 0.001).

Olguların tanı anında ve son poliklinik kontrollerinde kaydedilen VKİ ortalamaları incelendiğinde tedavi sonrasında hem kız hem erkek olgular için istatistiksel açıdan anlamlı olarak VKİ' nde artış gözlendi (p:0.000). Hastaların tanı anında DKA varlığı değerlendirildi. Kız hastaların %57.1'inde, erkek hastaların %46.5'inde tanı anında DKA vardı. İstatistiksel olarak anlamlı farklılık yoktu (p:0.150). Hastaların başvuru sırasında, toplam %52.2'sinde DKA tablosu vardı. Tanı anında kız hastaların %24.5'inde (24), erkek hastaların ise %16.3'ünde (14) enfeksiyon olduğu saptandı. Olguların cinsiyeti ile tanıda enfeksiyon tanıda arasında anlamlı ilişki saptanmadı (p: 0.070). Olguların %26.6'sı (49) sonbaharda, %29.3'ü (54) kışın, %26.1'i (48) ilkbaharda ve %17.9'u (33) yazın tanı almıştı (Şekil 1). Olguların son bir yılda DKA geçirme sıklıkları incelenmiştir. Hastaların 27' si son bir yılda DKA atağı geçirmiştir. Hastaların %2.1'inde tekrarlayan DKA atağı mevcuttur.

Antikor bakılabilen 68 olgunun %89.5'inde anti-GAD, 123 olgunun %52.8'inde anti-insulin antikor, 44 olgunun %59.1'inde islet cell antikoru ve tüm olguların %10.3'ünde tiroid otoantikorları pozitif olarak saptandı (Tablo II). Merkezimizde



Şekil 1: Olguların tanı mevsimleri.

Anti-GAD, anti-insülin antikor ve islet cell antikoru olguların tanı aldığı dönemde çalışılamadığından ve bazı olguların dosyalarına kaydedilmediğinden sadece bilgilerine ulaşılan olgular değerlendirmeye alınmıştır.

Hastalarda enfeksiyon sıklığı anket ile geriye yönelik olarak sorgulanmıştır. Son bir yılda olguların %78.8'i en az bir kez enfeksiyon geçirmişti %21.2 enfeksiyon geçirmemiştir. Yıllık ortalama enfeksiyon sayısı 2.3 olarak saptandı. Olgularda sekizden fazla enfeksiyon geçiren olgu mevcut değildi. Ayrıca hastaneye yatış gerektirecek ağır enfeksiyon olgusu yoktu.

Hastalara hangi hastalığı kaç kez geçirdikleri soruldu. 73 olgu bir kez, 39 olgu iki kez, 14 olgu üç kez, üç olgu dört kez, beş olgu beş kez nezle olduğunu belirtti. On olgu bir kez, iki olgu iki kez, bir olgu üç kez orta kulak enfeksiyonu geçirdiğini belirtti. 18 olgu bir kez, altı olgu iki kez, iki olgu üç kez sinüzit geçirmiş. 21 olgu bir kez, yedi olgu iki kez, 10 olgu üç kez, iki olgu dört kez boğaz iltihabı geçirmiş. Dokuz hastanın bir kez ağızda yarası olmuş. Dört olgunun bir kez, üç olgunun iki kez cilt yarası olmuş. 13 olgu bir kez olgu iki kez, beş olgu üç kez idrar yolu enfeksiyonu geçirmiş. 23 olgu bir kez, üç olgu iki kez, beş olgu üç kez ishal olmuş (Tablo III).

Son bir yılda olguların %11.4'ünde (21) bir kez ağır hipoglisemi olurken, %2.2'sinde (4) iki kez, %0.5'inde (1) ise üç kez ağır hipoglisemi olmuştu. Son bir yılda olguların %3.3'üne (6) bir kez glukagon uygulandığı, %1.1 olguya (2) ise iki kez glukagon uygulandığı saptandı.

Olguların diyabetik komplikasyonları açısından bakıldığında 16'sında mikroalbuminüri, altısında nöropati, bir olguda retinopati saptandı (34). Olguların komplikasyonları, HbA1c ortalaması ve diyabet yaşı ile birlikte değerlendirildi. Mikroalbuminüri gelişmesi, HbA1c ortalaması ve diyabet yaşı arttıkça arttığı saptandı. Nöropati gelişmesi, HbA1c ortalaması arttıkça artarken diyabet yaşı ile değerlendirildiğinde istatistiksel açıdan anlamlı bulunmadı.

Hastalarda mikroalbuminüri saptanmayan grubun HbA1c ortalaması 8.23 iken, mikroalbuminüri saptanan hasta grubunun HbA1c ortalaması 9.13'dü. Aradaki fark istatistiksel olarak anlamlı bulundu (p:0.009). Mikroalbuminüri saptanmayan grubun ortalama diyabet yaşı 4.42 iken, mikroalbuminüri saptanan grubun ortalama diyabet yaşı 6.68 bulundu. Aradaki fark istatistiksel olarak anlamlı bulundu (p:0.004). Nöropati saptanmayan hastaların ortalama HbA1c değeri 8.23 iken, nöropati saptanan olguların ortalama HbA1c değeri 11.33 olarak bulundu. Aradaki fark istatistiksel olarak anlamlı bulundu (p:0.004). Nöropati saptanmayan olguların ortalama diyabet yaşı 4.65 iken nöropati saptanan olguların ortalama diyabet yaşı 5.66 bulundu. Aralarında istatistiksel olarak anlamlı fark bulunmadı (p:0.350) (Tablo IV).

Puberte gelişimini tamamlamış olan toplam 29 hastanın hedef boy ortalamaları (168 cm±0.08) ve son poliklinik kontrolündeki boy ortalamaları (170 cm±0.09) karşılaştırıldı. Ortalamaya göre değerlendirildiğinde hastaların hedef boylarını yakaladığı saptandı.

TARTIŞMA

Diyabetes mellitus tek bi r hastalık tablosu olmayıp etiyoloji, patogenez ve genetik yönden farklılıklar gösteren hastalıklar grubudur. Çocukluk ve adölesan döneminin en sık görülen endokrin-metabolik bozukluğu olan Tip 1 DM, insülinin salgılanmasında ya da etkisinde yetersizlik sonucu gelişen karbonhidrat, yağ ve protein metabolizmalarında bozukluklarla karakterizedir (1). Diyabetik hastalarda iyi metabolik kontrol sağlanması ile mikrovasküler ve makrovasküler komplikasyonların önlenebileceği veya geciktirilebileceği bilinmektedir. Metabolik kontrolün en önemli göstergesi HbA1c olup, İSPAD'a göre <%7.5 iyi, %7.5-9 arasında orta ve >%9 kötü olarak sınıflandırılmıştır (10). Çalışmamızda ortalama HbA1c değeri %8.45 olarak bulundu, bu diğer çalışmalar ile benzerdi (11,12).

Tip 1 DM'de olguların metabolik kontrolü ile yaş ve diyabet süresi arasında ilişki olduğu bildirilmiştir. Birçok çalışma diyabet süresinin uzamasıyla metabolik kontrolün zorlaşacağını ve diyabet süresi 10 yılı aşan olgularda komplikasyon riskinde artışın olacağını bu yüzden diyabet süresi uzayan hastalarda metabolik kontrol için daha dikkatli olunması gerektiğini bildirmiştir (11,13,14). "Scottish Study Group for the Care of the Young Diabetic (DIABAUD2)" yaptığı çalışmada 1609 tip 1 DM'lu çocukta, bulgularımıza benzer şekilde ortalama HbA1c düzeyini, %8.9 olarak saptamış, özellikle 12 yaşın üstünde olanlarda anlamlı olarak yüksek (%9.5) bulmuşlardır (11). Olgularımızın HbA1c değeri ortalaması %8.45 olup, suboptimal metabolik kontrol sınırlarında yer almaktadır. Adölesan yaş grubundaki olgularımızın HbA1c ortalaması %8.89 olarak saptandı. Adölesan döneminin psikolojik durumu, yaşın artmasıyla ailenin hasta üzerindeki denetimin zayıflaması, okula başlama ve beraberinde sık enfeksiyon gibi çevresel faktörlerin devreye girmesi, puberte ve hastalığın kronik karakteri, HbA1c değerlerinin yüksek olmasını açıklayabilir.

Tip 1 diyabetteki cinsiyet dağılımının farklılık gösterdiği bildirilmiştir. Örneğin hastalığın sık görüldüğü Finlandiya ve Norveç gibi ülkelerde erkeklerde daha sık, İsrail ve Polonya gibi insidansın düşük olduğu ülkelerde kızlarda daha sık olduğu bildirilmiştir (15). Kandemir

ve ark.(16) yaptığı çalışmada cinsiyetler arasında farklılık saptanmamıştır. Bizim çalışmamızda da olguların cinsiyet dağılımı benzerdir, %53.3'ü kız, %46.7'si erkektir.

Tip 1 DM' nin sık görülme yaşı 5-7 yaş ve pubertenin başladığı adolesan yaş grubudur. 5-7 yaş grubu çocuklarda, okula başlamayla infeksiyonlara daha fazla maruz kalma suçlanırken, pubertal dönemde ise pubertenin etkisi ile artan seks steroidleri, büyüme hormonu ve dönemin ruhsal stres faktörlerinin rolü düşünülmektedir (1). Tip 1 DM'un giderek 5 yaş altında daha sık görüldüğü bildirilmiştir (17,18). Taşkın ve ark.'nın Bursa'da yaptığı çalışmada diyabet tanı yaşı 1-6 yaş ve 10-16 yaş arasında pik yapmaktadır (19). Kandemir ve ark. (16) Ankara'da 477 hastayı kapsayan çalışmada, diyabet tanı pik yaşı 12-14 yaş grubu arası olarak bildirmişlerdir (16). Çalışmamızda ortalama tanı yaşı 7.71 olarak bulundu. Olguların %35.2'si 6 yaş altında, %49.5'i 6-12 yaş arasında tanı almıştır. Tanı yaşı olgularımızın büyük çoğunluğunda 12 yaş altında olup (%84.7), pik yaşı 6-12 yaş aralığı olarak saptanmıştır.

Diyabetik ketoasidoz (DKA), insulin eksikliğinin ciddi bir sonucu olup Tip1 DM'lu çocuklarda önemli ölçüde mortalite ve morbiditeye neden olan bir durumdur (20). Çocuklarda DKA insidansı, dünyanın değişik bölgelerinde farklı olup, genellikle %25-30 oranında olduğu bildirilmiştir (21). Bideci ve ark.(22) 1995-1999 yılları arası tip 1 DM tanısı alan hastalarda DKA ile başvuru oranını %50 olarak bulmuşken, 2000-2004 yılları arasında başvuranlarda %34.1'e kadar düştüğünü görmüşlerdir. DKA sıklığındaki bu azalmanın söz konusu faktörlerin düzelmesiyle ilşkili olduğu düşünülmüştür. Taşkın ve ark.'nın (19) Elazığ ilinde yaptıkları çalışma DKA tablosu ile başvuru oranını %59.5 olarak gösterirken, Kocabaş ve ark. (23) Akdeniz yöresinde başvuru anında DKA tablosunu hastaların yaklaşık 1/3'ünde saptamışlardır. Çalışmamızda hastaların %52.2'si DKA tablosu ile başvurmuştur. Hastanemizin Antalya ve çevresindeki il ve ilçeler için bölge hastanesi olması, bu oranın yüksek olmasına neden olmuş olabilir. Çalışmamızda, 23 (%12.5) hasta bir kez, dört (%2.1) hasta birden fazla DKA nedeniyle hastaneye yatmıştır. Eğitim, sosyal iletişim araçlarıyla sağlık bilinci geliştirilmesi ve çocuk endokrinoloji hizmetlerinin ülkede yaygınlaşması ile erken tanı ve daha iyi metabolik kontrolün sağlanması, tekrarlayan DKA oranının düşmesini sağlayacaktır.

Birçok çalışmada düşük sosyoekonomik durumun, kötü metabolik kontrol ile ilişkili olduğu bildirilmiştir. Gallegos-Maceas ve ark. (24) yaptığı 184 tip 1 diyabet tanılı hastanın sosyoekonomik durumu değerlendirildiğinde, düşük aile geliri olan hastalarda metabolik kontrolün kötü olduğu saptanmıştır. Anne – baba eğitimi ile metabolik kontrol arasında ilişki saptanmamıştır (24). Hassan ve ark.(25) yaptığı çalışmada HbA1c düzeyi ile sosyoekonomik düzey arasında ilişki saptanmıştır. Çalışmamızda da, ailelerin aylık geliri, evde yaşayan birey sayısı, yaşadıkları yer ile kötü metabolik arasında ilişki saptanmamıştır. Sosyoekonomik olarak olguların büyük çoğunluğunun ekonomik olarak düşük düzeyde olmasına rağmen metabolik kontrol ile ilişkisinin anlamlı olmaması anket doldurulurken hastaların ekonomik durumlarının yeterli değerlendirmemiş olabileceğini akla getirmektedir. Ayrıca anlamlı ilişki saptanmaması olguların büyük çoğunluğunun (%64.1) düşük gelire sahip olmasına da bağlanabilir.

Yapılan çalışmalarda, Tip 1 DM'un en fazla sonbahar ve kış aylarında tanı aldığı bildirilmiştir (26). İtalya'da yapılan çalışmada kışın daha sık iken, Güven ve ark. (28) yaptığı bir çalışmada, Samsun'da Tip 1 DM'lu çocukların en fazla sonbahar ve kış aylarında başvuru yaptığı bildirilmiştir (27). Elazığ'da yapılan çalışmada ise tip 1 diyabet tanısının en fazla kış ayında olduğu, en az ise sonbahar ve ilkbahar aylarında olduğu görülmüştür (19). Bala ve ark. (29) yaptığı bir çalışmada ise en çok sonbahar ve kış aylarında başvuru olduğu bildirilmiştir. Bizim çalışmamızda da yazın en az başvuru mevcut iken kış, ilkbahar ve sonbahar mevsimleri arasında anlamlı bir farklılık saptanmamıştır.

Tip 1 DM' lu hastalarda insülinin kullanıma girdiği yıllarda büyüme gelişme geriliği bildirilmiştir. Orta, uzun ve hızlı insülinlerin kullanılması ile normal büyüme ve gelişmenin sağlandığı bildirilmektedir (30). Çalışmamızda pubertelerini tamamlamış 29 hastanın final boyu ortalamasının (170 cm) hedef boyu ortalamasını (168 cm) geçtiği görülmüştür. Oldukça iyi metabolik kontrollü olguların normal büyüme ve gelişme gösterdikleri saptanmıştır. Uygun insülin tedavisi ve iyi metabolik kontrol ile Tip 1 DM'lu hastaların normal büyüme gelişme sağladığı görülmektedir.

Hastalarımızın, tanı sırasında ve son poliklinik kontrolündeki VKİ skorları karşılaştırıldığında; tedaviyle VKİ skorunun belirgin olarak arttığı gözlenmiştir. Bu artış istatistiksel olarak anlamlı bulunmuştur. Belçika ve Fransa çalışmalarında benzer olarak takipte hastaların VKİ anlamlı olarak arttığı bildirilmiştir (14,31). Ancak hastalarımızın VKİ skoru ile HbA1c arasında anlamlı ilişki saptanmamıştır. İyi metabolik kontrol için suprafizyolojik dozlarda insülin uygulanması, bazen de hastaların kendi uygulamaları ile örneğin fazla yemek yediklerinde insülin dozlarını yükseltmeleri neden olmaktadır. Ancak insülin ve kilo ilişkisi bir kısır döngüye dönüşebilir. Bu nedenle sağlıklı beslenme ve düzenli egzersizin Tip 1 DM' li çocuklarda bir hayat tarzı olarak benimsenmesi metabolik kontrol düzeyine çok olumlu etki yapmaktadır (23).

Pediatrik hastalarda diyabet yönetimi, insülin tedavisi dışında, hasta ve ailelerinin eğitimi diyetisyen ve psikolojik desteği içermelidir. İnsülin tedavisinin yanında hastaların diyetlerine dikkat etmesi ve egzersiz yapmayı ihmal etmemesi gereklidir. Bunun yanında hastaların poliklinik kontrollerine düzenli gelmesi metabolik kontrolleri açısından çok önemlidir. Fransa'da Pediatri Diyabet Grubu tarafından yapılan çalışmada diyetini ve egzersizlerini tam uygulayan, gün içinde daha fazla glukoz ölçümü yapan hastalarda daha iyi metabolik kontrolün sağlandığı görülmüştür (14). ABD'de yapılan başka bir çalışmada adölesan hastalar kan şekeri ölçüm sayısı açısından değerlendirilmiştir. Kan şekeri ölçüm sayısı arttıkça HbA1c seviyesinde anlamlı

düşme gösterdiğini bildirmiştir (3). Çalışmamızda diyete uyma ve sık poliklinik kontrolü ile hastaların HbA1c düzeyleri daha düşük saptanmıştır. Egzersiz ve kan şeker ölçüm sayısı ile HbA1c arasında anlamlı ilişki saptanmamıştır.

Tip 1 DM' de tanıda Anti GAD %60-80, İCA %70 ve İAA%35-60 oranında pozitif olabileceği bildirilmiştir (16). Karjaleinen ve ark'nın(32) çalışmasında %34.7 oranında otoantikor pozitifliği saptandığı bildirilmiştir. Bizim çalışmamızda antikor bakılabilen 68 olgunun %89.5'inde Anti-GAD, 123 olgunun %52.8'inde İAA, 44 olgunun %59.1'inde İCA pozitif saptanmıştır. Merkezimizde Anti-GAD, İAA ve İCA hastaların tanı aldığı dönemde zaman zaman çalışılamaması, ailelerin maddi veya başka nedenlerle bu tetkikleri yaptırmaması ve/veya bazı hastalarda kayıtların dosyaya işlenmemesi nedeniyle veriler tüm hastaları kapsamamaktadır.

Tip 1 DM' de uzun dönemde görülen mikrovasküler komplikasyonları nefropati, retinopati ve nöropati oluşturmaktadır. Prepubertal dönemde, özellikle 12 yaş altında görülme sıklığı düşük iken, puberte döneminden sonra ve tanı anından beş yıl sonra metabolik kontrol ile ilişkili olarak mikrovaskuler komplikasyonların görülme sıklığının arttığı bildirilmektedir (33). Hiperglisemi komplikasyonlar için başlıca etkendir ve iyi glisemik kontrol diyabetin mikrovasküler ve nörolojik komplikasyonlarını engellemekte veya geciktirmektedir (13). Şimşek ve ark. (34) Türkiye'de yaptıkları 1032 hastayı kapsayan çok merkezli çalışmada, nöropati %2.6, retinopati %1.4, persistant mikroalbuminüri %5.4 oranında görüldüğü bildirilmiştir. Çalışmamızda hastaların %8.7'sinde mikroalbuminüri, %3.5'inde nöropati, %0.6'sında retinopati saptanmıştır, hiçbir olguda kardiyomiyopati saptanmamıştır. Hastalarda mikroalbuminüri ve nöropati ile HbA1c düzeyi arasında anlamlı ilişki bulunmuştur. Hastalarda nöropati ile ortalama HbA1c düzeyi arasında anlamlı ilişki bulunmamıştır. Diyabet yaşı ile mikroalbuminüri arasında anlamlı ilişki mevcut iken nöropati ile arasında anlamlı ilişki saptanmamıştır. HbA1c düzeyi ve diyabet yaşı ile komplikasyonlar arasındaki ilişki Şimşek ve ark'nın (34) yaptığı çok merkezli çalışma sonuçları ile benzerdir.

Tip 1 DM' lu hastalarda hipoglisemi korkulan komplikasyonlardandır. Çocuklarda yapılan çalışmalarda ağır hipoglisemi ile metabolik kontrol arasında ilişki olmadığı bildirilmiştir (35). Bizim çalışmamızda hastaların HbA1c değerleri ile ağır hipoglisemi arasında anlamlı ilişki saptanmamıştır. Hafif hipoglisemiler ile HbA1c değerleri arasında pozitif korelasyon saptanmıştır. Fransa'da Pediatri Diyabet Grubu yapılan 2579 hastayı kapsayan çalışmada ise HbA1c değerleri ile ağır hipoglisemi arasında anlamlı ilişki bildirilmiştir. Bu çalışmada HbA1c değeri daha düşük olan hastalarda daha sık ağır hipoglisemi geliştiği ve ağır hipoglisemisi olan hastaların insülin dozu ortalamasının daha yüksek olduğu bildirilmiştir (14). Belçika çalışmasında farklı olarak HbA1c değeri daha yüksek olan olgularda ağır hipoglisemi daha fazla görüldüğü ve hipoglisemilerin diyabet süresi ve insülin dozunun yüksek olması ile ilişkisi olduğu bildirilmiştir (31).

Tip 1 DM'da hashimato troiditi en sık görülen otoimmun hastalıktır. Antikorlarının pozitifliği prevalansı %12.1-23.4 iken, hipotiroidi sıklığı %4-18 olduğu bildirilmektedir (36). Şimşek ve ark. (34) otoimmun tiroid hastalığı sıklığını %12 olarak bildirmiştir. Karagüzel ve ark. (37) çalışmalarında %38.6 oranında tiroid otoantikor pozitif bulunduğunu bildirmiştir. Bala ve ark. (23) çalışmalarında %5.9, Kocabaş ve ark. (29) %12.2 oranında otoimmun troidit saptadıklarını bildirmişlerdir. Bizim de olgularımızın %8.7'sinde hipotroidi, %10.3'ünde de tiroid otoantikor pozitifliği saptanmıştır.

Tip 1 DM tanılı hastalara çölyak hastalığı da eşlik edebilmektedir. Tip 1 diyabet tanılı çocuklarda yapılan çalışmalarda %3.1 ile %7.4 arasında değişen sıklıkta çölyak hastalığı olduğu belirlenmiştir (38). Şimşek ve ark. (34) çok merkezli çalışmalarında Tip 1 DM'li hastaların %4.3'üne çölyak hastalığı eşlik ettiğini bildirmiştir. Çalışmamızda bir hastada (%0.5) çölyak hastalığı mevcuttur. Addison hastalığı, pernisyöz anemi gibi diğer otoimmün hastalıklarla birliktelik gözlenmemiştir.

Hastalarımızın çoğunluğu yoğun insülin tedavisi almaktadır. İnsülin dozu (ünite/kg) ve insülin doz sayısı ile HbA1c düzeyi arasında istatistiksel açıdan anlamlı ilişki saptanmamıştır. Hastalarımızdan 0.5 ünite/kg ve daha düşük dozda alanlar ile 0.5 ünite/kg'dan yüksek dozda tedavi alan hastalar HbA1c düzeyi açısından değerlendirildiğinde anlamlı bir farklılık saptanmamıştır. İskoçya'da yapılan çalışmada da benzer sonuçlar bildirilmiştir (11).

Tip 1 DM etyopatogenezinde enfeksiyonların rolü olduğu bildirilmiştir. Olguların takibinde enfeksiyon sıklığı olduğu bildirilmektedir. Yetişkinlerde yapılan bir çalışmada diyabet ile asemptomik bakteriüri, piyelonefrit, deri, tırnak ve mükoz membran infeksiyonları, peridontal hastalıklar ile ilişkisi olduğu bildirilmiştir (39). Çocuk hastalarda yeterli çalışma mevcut olmayıp erişkin hastalarla yapılan birçok çalışma, diyabet ile enfeksiyon sıklığının arttığı bildirilmektedir. Jeffrey Model Vakfı immun yetmezlik kriterlerine göre; son bir yılda sekizden fazla enfeksiyon, son bir yılda ikiden fazla ciddi sinüs enfeksiyonu, son bir yılda ikiden fazla pnömoni, ikiden fazla derin doku enfeksiyonu geçirme primer immun yetmezlik açısından uyarıcı olması gerektiği bildirilmiştir (9). Hollanda'da bir çalışmada, iki yıllık süre boyunca tip 2 diyabet hastalarında görülen enfeksiyonların sayısını değerlendirilmiştir. Hasta başına ortalama 2.4 enfeksiyon (±1.9) ile 193 hastada dört yüz elli sekiz enfeksiyon meydana gelmiştir (6). Çalışmamızda da benzer olarak hastalarımızın son bir yılda geçirdikleri enfeksiyon sıklıkları incelendiğinde yıllık ortalama enfeksiyon sayısı 2.3 olarak saptanmıştır. Ayrıca ağır ve hastaneye yatış gerektirecek enfeksiyon yoktur. Sık enfeksiyon kriterine uyan hasta yoktur. Bu nedenle enfeksiyon sıklığında artış gösterilememiştir.

SONUÇ

Sonuç olarak; çalışmamızda Tip1 DM'lü hastalarda, diyabet süresi ve yaşının artması, puberte, sosyoekonomik durum,

diyete uymama ve poliklinik kontrolüne gelmeme, kötü metabolik kontrol için risk faktörü olarak saptanmıştır. İyi metabolik kontrol ile hastaların hedef boyunu yakaladıkları saptanmıştır. Hastaların VKİ' lerinin artması dikkati çekmiştir. Buna iyi metabolik kontrol için, suprafizyolojik dozlarda insülin uygulanması veya hastaların insülin dozlarını hekim kontrolü dışında yükseltmeleri neden olmuş olabilir. Hastalarımızda enfeksiyon artışı ve hastaneye yatmayı gerektirecek ağır enfeksiyon gözlenmemiştir.

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Comparison of Tuberculin Skin Test and QuantiFERON-TB Gold Test in Children

Çocuklarda Tüberkülin Deri Testi ve QuantiFERON-TB Gold testinin Karşılaştırılması

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ABSTRACT

Objective: Interferon-γ release tests (IGRAs) and tuberculin skin testing (TST) are important helpful tests for diagnosing tuberculosis (TB) disease in children. It was aimed to compare the sensitivity and compatibility of QuantiFERON-TB Gold In-tube test (QFT) and TST used in children with TB and Latent tuberculosis infection (LTBI).

Material and Methods: A total of 118 patients between September 2018 and January 2020 were included in the study prospectively to determine the case characteristics related to the performance of the tests, and to measure the sensitivity of these tests.

Results: A total of 118 patients were included in the study; and 13 (11%) patients presented with pneumonia symptoms and 7 (6%) patients were diagnosed with TB in active TB Contact Screening. TB diagnosis was made 20% microbiologically. *Mycobacterium tuberculosis* culture positivity was found to be 10%. None of the patients had acid-resistant bacilli positivity. The male / female rate was 74/44 in our study (p = 0.006). The median age was found to be 14 (1.17-19.2 years) in males, and 12 (0.33 -17.9 years) in females. The mean age of the LTBI Group was higher than the TB Group at significant levels (p <0.05), and was similar to the non-infected group (p>0.05). A total of 53.5% of the patients had a history of meeting someone with tuberculosis, and 97 children were vaccinated with BCG (82.2%). TST and QFT positivities were 19.5% and 22%, respectively. The most common radiological finding that was detected was consolidation areas. While there was moderate compliance between TST and IGRA test in patients with TB diagnosis (kappa =0.50, p=0.025), no compliance was found between tests in LTBI patients. In patients who were diagnosed with TB and LTBI, the sensitivity of TST was found to be 51.1%, and the sensitivity of QFT was found to be 60.4%.

Conclusion: TST seems to continue as the most preferred method of diagnosis in rural areas with limited resources and poor laboratory infrastructure due to the costs and technical considerations.

Key Words: Interferon Gamma Release Test, Latent Tuberculosis, Tuberculin Skin Test, Tuberculosis

ÖZ

Amaç: İnterferon-γ salınım testleri (IGRA'lar) ve tüberkülin deri testi (TST) çocuklarda tüberküloz (TB) hastalığının teşhisi için önemli yardımcı testlerdir. Bu çalışmada, TB ve latent tüberküloz enfeksiyonu (LTBI) olan çocuklarda kullanılan QuantiFERON-TB Gold In-tube testi (QFT) ile tüberkülin deri testinin (TST) duyarlılığının ve uyumunun karşılaştırılması amaçlandı.

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Gereç ve Yöntemler: Eylül 2018-Ocak 2020 tarihleri arasında testlerin performansıyla ilişkili vaka özelliklerini belirlemek ve testlerin duyarlılığını ölçmek için 118 hasta prospektif olarak çalışmaya dahil edildi. TST ve QFT testleri eşzamanlı yapıldı.

Bulgular: Çalışmaya 118 hasta dahil edildi. Pnömoni semptom ve bulguları ile başvuran 13 (%11), aktif TB temaslı taramasında 7 (%6) hasta TB tanısı aldı. TB tanısı %20 mikrobiyolojik, %80 klinik olarak konuldu. Semptomatik hastalık nedeniyle 50 (%42.3) çocuktan açlık mide sıvısında tüberküloz belirteçleri çalışıldı. *Mycobacterium tuberculosis* kültür pozitifliği ise %10'du. Hiçbir hastamızda asidorezistan basil pozitifliği saptanmadı. Çalışmamızda erkek / kadın oranı 74/44'dı. Ortanca hasta yaşı erkeklerde 14 yıl (1.17-19.2 yıl), kızlarda ise 12 yıl (0.33 -17.9 yıl)'dı. LTBI grubunun yaş ortalaması TB grubundan anlamlı olarak yüksekken ($p<0.05$) enfekte olmayan grup ile benzerdi ($p>0.05$). Hastaların % 53.5'inde tüberkülozlu biriyle karşılaşma öyküsü vardı ve % 82.2'sinde BCG aşısı yapılmıştı. Saptanan en sık radyolojik bulgu konsolidasyondu. TB tanılı hastalarda TST ile IGRA testi arasında orta düzeyde (kappa =0.50, $p=0.025$) uyum saptanırken LTBI hastalarında testler arasında uyum saptanamadı. TB ve LTBI tanılı hastalarda TST'nin sensitivitesi %51.1 (%95 CI,36.7-65.3), QFT'nın sensitivitesi %60.4 (%95 CI,45.5-73.6)'dı.

Sonuç: Maliyet ve teknik hususlar, sınırlı kaynaklara ve zayıf laboratuvar altyapısına sahip kırsal bölgelerde tanıda TST en çok tercih edilen yöntem olarak devam edecek gibi gözükmektedir.

Anahtar Sözcükler: İnterferon gama salım testi, Latent tüberküloz, Tüberkülin deri testi, Tüberküloz

INTRODUCTION

The definitive diagnosis of tuberculosis (TB) disease in children is made by demonstrating the bacillus microbiologically. The diagnosis is called "bacteriological diagnosis" in case the bacillus is shown, and "clinical diagnosis" when it cannot be shown. Unlike in adults, the rate of showing bacillus is very low in children. In case the bacillus cannot be shown, the contact history of the child with infectious TB patients, clinical and radiological findings, Tuberculin Skin Test (TST), and Interferon-γ Release Test (IGRA) positivity are evaluated together, and the diagnosis is made in this way. For this reason, TST and IGRA play important roles in the decision to initiate the treatment for pediatric TB (1-3).

TST has been employed in supporting the diagnosis when TB is suspected. However, the sensitivity of TST is limited in severe forms of TB. For example, TST-positive results are detected only in 60% of patients with proven TB meningitis. The specificity of TST is also insufficient as non-tuberculosis mycobacterial infection and Bacille Calmette-Guerin (BCG) vaccination may yield false positive TST results (4).

IGRAs have superior test specificity compared to TSTs; however, the data on their sensitivity in children with TB, especially in those <5 years old, are limited (2).

In the present study, the purpose was to compare the performance of IGRA and TST in patients with active TB contacts, those who had tuberculosis symptoms, those who admitted to a tertiary pediatric hospital, and those referred to detect possible Mycobacterium Tuberculosis infection before using immunosuppressive drugs.

MATERIAL and METHODS

A total of 118 patients who were examined for TB between September 2018 and January 2020 were included in the study prospectively. The patients were divided into 3 groups. Patients who had TB symptoms and / or abnormal radiological imaging results, those who had active TB contact, and those who admitted with other reasons (e.g., before using biological agents) were examined for TB. The IGRA and TST were performed for all patients. Patients for whom the tests were not applied simultaneously were excluded from the study. We examined the medical records of patients, and collected the data on their demographic, clinical, microbiological and radiological examinations, and on the presence of BCG Scar and BCG vaccination history. Complete clinical evaluations were performed for all patients.

TST (Mantoux Test). In the Tuberculosis Dispensary or in our hospital, 0.1 ml (5 IU) Tuberculin Solution (PPD-S Tween 80) was applied with a 26-No needle to the dry skin in the 1/3 upper front area of the left forearm. The diameter of the induration that appeared at the test site 72 hours after injection was measured as millimeter (mm). Interpretation of the tuberculin test; in children who are not vaccinated with BCG; TST reaction positive if ≥10 mm, negative if <10 mm; children with BCG vaccine were considered positive if ≥ 15 mm and negative if < 15 mm (5).

IGRA Test. This test was done according to the manufacturer's recommendations, and the results were evaluated as summarized below. One ml venous blood sample was taken from the patients into Nil Control, Mitogen Control, and TB Antigen Tubes that were included in the kit. The tubes were shaken gently 10 times and were then incubated at 37°C for 16-24 hours. After the incubation, the RCF was centrifuged at 2200 to 2300 g for 15 minutes, the plasmas were taken, and the amount of IFN-γ (IU / ml) was measured with ELISA. The analyzes of the optical density values were made by using the "QuantiFERON-TB Feron Analysis Software"; and the results of the analyses were evaluated as positive, negative, or undetermined (6).

Latent TB Infection (LTBI) was defined as an asymptomatic child who had a positive TST and / or IGRA result but with a chest

X-ray not suggesting TB. Active TB was defined as symptoms suggesting TB, abnormal chest X-ray results consistent with TB, acid-resistant bacilli stain(ARB) from clinical samples, Nucleic Acid Amplification Test (NAAT), or Mycobacterium tuberculosis positivity in culture.

Symptoms suggesting TB were identified as a cough that lasted more than two weeks, persistent fever, night sweating, weight loss, lymphadenopathy, hydrocephalus, seizure, and cranial nerve involvement.

According to the disease site, the definitions were made as Pulmonary, Central Nervous System (CNS), Extrapulmonary, and Multifocal (> 1 region) TB.

Laboratory verified disease included children with ARB, NAAT, or Mycobacterium tuberculosis culture positivity. All cases who did not meet bacteriological confirmation criteria, but had pathological images in chest X-rays and who had a positive response to specific anti-tuberculosis treatment were accepted as clinical TB.

All contacted children were followed-up at home with 3-month intervals for 12 months by trained field employees, repeated symptom screenings were done, and clinical visits were paid if the child became ill.

Children who were diagnosed with active TB were followed-up clinically with 2-month intervals and at the end of TB treatment to evaluate their response to treatment.

Informed consent forms were obtained from the families for the study.

Approval was obtained from Adıyaman University, Faculty of Medicine, Ethics Board with the decision number 2018/6-10.

Statistical Analyses

The Statistical Package for the Social Sciences 15.0 program (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The One-Sample Kolmogorov-Smirnov test was used to determine whether the continuous data were distributed normally. Groups were compared using the One-Way ANOVA or the Kruskal Wallis H test whichever one was appropriate. As a result of these analyses, the groups which were found significant were compared with the Tukey's Multiple Range Test or Mann Whitney U test (Bonferroni Correction was applied for p values <0.0167 (i.e., and 0.05/3 comparisons). The results were reported as Mean±SD or median (Min-Max). Categorical variables were compared using the Chi-Square Test or Fisher's Exact Chi-Square Test whichever was appropriate, and were expressed as numbers and percentages. The Cohen's Kappa Statistic was used for the agreement test. p value < 0.05 was considered statistically significant.

RESULTS

The flow diagram of the study is given in Figure 1. A total of 13 (11%) patients who admitted with pneumonia symptoms and findings, and 7 (6%) patients in active TB contact screening were diagnosed with TB. LTBI was detected in 23 (19.5%) patients; and 75 (63.5%) children were not infected.

Clinical and demographic details are given in Table I.

The male / female rate was 74/44 in our study (p=0.006). The median age was found to be 14 (1.17-19.2 years) in males, and 12 (0.33 -17.9 years) in females.

When the 3 groups were compared in terms of age, it was found that there were significant differences (p <0.01). The mean age of the LTBI Group was higher than that of the TB Group at significant levels (p<0.05), and was similar to that of the non-infected group (p>0.05) (Table II).

When the 3 groups were compared in terms of TST, it was found that there were significant differences (p <0.001). The median TST of the LTBI and TB Groups were higher than that of the non-infected group at significant levels (p< 0.0167), and was similar to that of the median TST of the LTBI and TB Groups (p>0.05) (Table II).

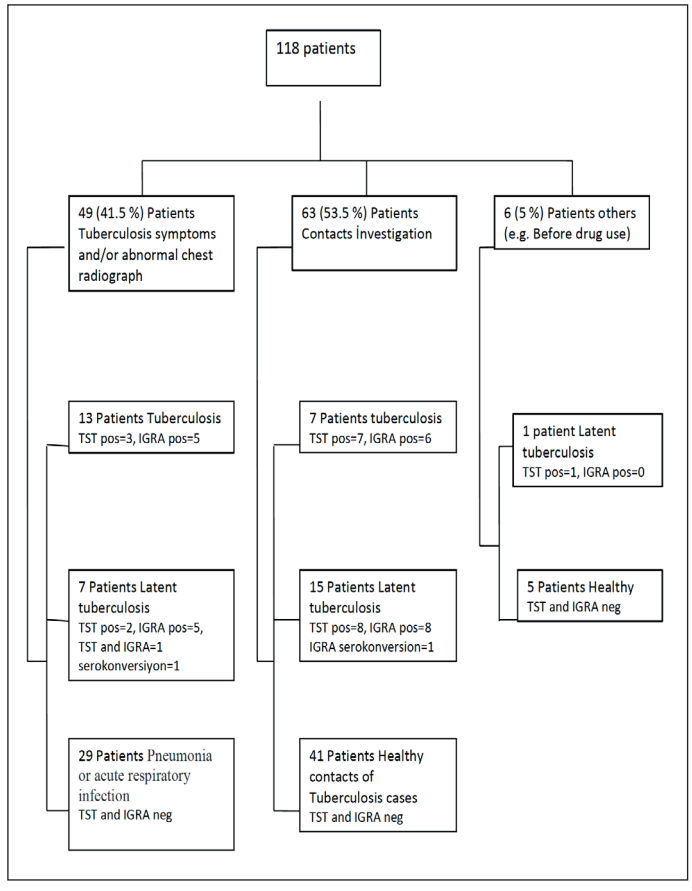

Figure 1: The outline of the study design.

Table I: Characteristics of children enrolled in the study (n = 118).

Characteristic	n (%)
Male	74 (62.7%)
Age (yrs), median (min-max)	13.4 (1.1-19.2)
BCG vaccinated	97 (82.2%)
BCG non-vaccinated	21 (17.8%)
TST/IGRA test performed	118 (100%)
Culture or/and Nucleic acid amplification (NAAT) method performed (n=20)	
Acid fast staining positive	-
Culture positive (M. tuberculosis)	2 (10%)
NAAT positive	1 (5%)
Pathology positive	1 (5%)
Site of disease	
Pulmonary TB only	11 (55%)
CNS disease	1 (5%)
Extrapulmonary only	3 (15%)
>1 site	5 (25%)
Pulmonary and extrapulmonary	4 (75%)
Pulmonary and CNS disease	1 (25%)
Radiological examination performed	
Radiological findings	
Consolidation	13 (13.5%)
Cavitary lesion	3 (3.1%)
Mediastinal lymphadenopathy	4 (4.1%)
Consolidation and bronchiectasis	2 (2%)
Pleural effusion	2 (2%)
Abdominal mesenteric lymphadenopathy	1 (1%)
Disease confirmation criteria (n=20)	
Laboratory	4 (20%)
Clinical	16 (80%)

BCG: *Bacille Calmette-Guerin,* ***TST:*** *Tuberculin Skin Test,* ***IGRA:*** *Interferon-γ release tests,* ***TB:*** *Tuberculosis,* ***CNS:*** *Central Nervous System.*

A total of 97 children were vaccinated with BCG (82.2%). Because of symptomatic disease, ARB, Mycobacterium tuberculosis culture, and / or NAAT were examined in fasting gastric fluid of 50 (42.3%) children. A total of 20 children were diagnosed with TB; 11 had pulmonary TB, and only one of these had positive culture, TST was negative, and IGRA was positive; CNS TB was detected in 1, TST and IGRA were negative, and NAAT was positive; extra-pulmonary TB was detected in 3; and 5 were diagnosed with multifocal TB. Culture, TST and IGRA were positive in 2 patients diagnosed with Multifocal TB.

The IGRA and TST tests were performed together on 118 patients. Positive TST was recorded in 23 (19.5%) patients who were tested, and the induration size ranged between 10 and 20 mm. IGRA positivity rate was 26 (22%). When two patients who had a history of domestic contact were evaluated again, immunological transformations were detected in IGRA and TST (from zero to 16 mm) in one patient, and only in IGRA in the other patient.

The first-line radiological imaging results were evaluated with postero-anterior Chest X-rays. Computed Tomography was performed on 29 (24.5%) patients who had abnormal radiological imaging results. Although the most common radiological finding was consolidation areas in patients diagnosed with pulmonary TB, cavitary lesions were detected in the lungs of 3 patients.

While there was moderate compliance between TST and IGRA test in patients with TB diagnosis (kappa =0.50, P=0.025), no compliance was found between tests in LTBI patients.

The sensitivity of TST was found to be 51.1% (95% CI, 36.7-65.3), and the sensitivity of IGRA was 60.4% (95% CI, 45.5-73.6) in patients diagnosed with TB and LTBI.

Table II: Age and Sex Distribution of Study Patients.

	Patient number n (%)	Mean age (years)	Std. deviation	Minimum age (years)	Maximum age (years)	Median age (years)	p*
Boys	74 (62.7%)	13.2	3.56	1.17	19.2	14	0.033
Girls	44 (37.3%)	11.7	4.11	3.33	17.9	12	0.033
Total	118 (100%)	12.6	3.83	1.17	19.2	13.41	

Mann-Whitney U test

Table III: Three Intragroup Comparison in terms of Age, Gender, Presence of BCG Scar, and Tuberculin Skin Test Measurements.

	Non-Infected (n=75)	LTBI (n=23)	TB (n=20)	p
Age*	12.58^{ab}±3.47	14.52^{a}±2.91	10.93^{b}±4.95	0.002
Gender† (E/K)	51/24	14/9	9/11	0.164
BCG Scar † (Yes/No)	16/59	4/19	1/19	0.237
TST (mm)‡	0 (0-14)^{c}	13 (0-20)^{d}	12.5 (0-20)^{d}	<0.001

: *One Way ANOVA test,* ^{ab}*: Means within the same row with different superscripts are significantly different (p <0.05, Tukey's test),* **†:** *Chi square testi yapıldı.* **‡:** *Kruskal Wallis H test,* ^{cd}*: Medians within the same row with different superscripts are significantly different Mann Whitney U test was used for multiple comparison (Bonferroni correction was applied for which p-values <0.0167 (i.e., 0.05/3 comparisons).* ***LTBI****: Latent Tuberculosis,* ***TB****: Active Tuberculosis,* ***BCG****: Bacille Calmette-Guerin,* ***TST****: Tuberculin Skin Test.*

Table IV: Comparison of the Results of QuantiFERON-TB gold In-Tube and TST.

		QuantiFERON-TB gold In-Tube		Kappa	p
		positive	negative		
TST					
TB patients (n=20)	positive	8 (40%)	2 (10%)	0.50	0.025
	negative	3 (15%)	7 (35%)		
LTBI (n=23)	positive	5 (21.7%)	8 (34.7%)	-0.63	0.002
	negative	10 (43.5%)	0 (0%)		
TB and LTBI (n=43)	positive	13 (30%)	10 (23.2%)	-0.086	0.571
	negative	13 (30%)	7 (16.3%)		

TST: *Tuberculin Skin Test,* ***TB:*** *Tuberculosis,* ***LTBI****: Latent Tuberculosis,* ***TB****: Active Tuberculosis .*

DISCUSSION

The low rate of bacteriological confirmation and test positivity in pediatrics continues to be a problem in active TB disease due to the paucibacillary nature of the disease and the relative difficulties in collecting sufficient specimens for microbiology (7). Many children who have clinical TB do not have microbiologically proven TB. In many studies, clinical TB diagnosis, which is a less reliable method, is employed (4, 8). In our study, although we had 20% patients with microbiological evidence, we could not detect ARB positivity in any of our cases. We believe that this was because of the lack of our laboratory experiences or the patient group's being a pediatric age group, and perhaps due to insufficient samples.

Although IGRA tests yielded promising results in many studies, there are few published articles on their performance in children. Current studies suggest that these tests may be used and may also be clinically useful in evaluating TB in children in some cases. Kay et al. (2) found in their study that IGRA sensitivity was similar to that of TST in children under 5 years of age, but the sensitivity of these tests decreased in children who were younger than 2 years of age, undetermined results were higher in children who were younger than 1 year of age and in the presence of a Central Nervous System disease. It was also reported in the same study that IGRA had more sensitivity than TST in children who were ≥5 years old and who had laboratory-approved TB and must be considered as the preferred immunodiagnostic test (2). In the study conducted by Ahmed et al. (9), the sensitivity of TST and IGRA were reported as 50% and 75%, respectively. Connell et al. (10) reported that although high-level compliance was detected between IGRAs in their study, there was no compliance between IGRAs and TST. It was found in another study that the sensitivity of the QuantiFERON-TB Gold In-tube Test was 92%, the compliance between IGRAs was high, and IGRAs were also compatible with TST (11). In our study, the sensitivity of TST was 51%, and that of IGRA was 60% in patients diagnosed with TB and LTBI. Eight of our 10 TST-positive TB patients were also found to be IGRA positivity, and cohen-kappa analysis between the tests showed moderate agreement. We think that the small number of patients with a diagnosis of TB in our study population and the small number of patients with microbiological evidence may affect this result and this is a limitation of our study. However, there was no agreement between TST and IGRA tests in our LTBI patients. In only 5 of our 23 LTBI patients, both tests were positive at the same time. TST was positive in 13 patients, while IGRA was positive in 15 patients. IGRAs are increasingly being recommended as a replacement for TST. Is the reason for this discrepancy in our study, false positive TST or false negative IGRA? Considering the disadvantages of both tests, it seems to be an important question that may affect the practical use of the tests.

Studies speculated that IFN-γ may be required to predict active TB in countries where the TB burden is high and where the combination of other risk factors with IGRA results has a much higher predictive value than IFN-γ response alone, but is not sufficient on its own (11-13). Based on the current data, a negative IGRA does not exclude active TB, and it is not recommended that IGRA is used as a single tool to confirm or exclude active TB in children. IGRA positivity was 55%, TST positivity was 50%, and the positivity of both tests was 40% in our patients diagnosed with TB. Also, some authors argue that IGRA, which is initially negative, must be repeated in patients if clinicians plan to start TB treatment. When the tests were evaluated again in our 2 patients who had a history of domestic contact, the immunological transformation was detected in both IGRA and TST (from 0 to 16 mm) in one patient, and only in IGRA in the other patient (14). If one of the tests is positive, it is considered in favor of LTBI. If the target of requesting the test is sensitivity, one of these tests can be employed. We believe that the diagnosis can be continued to be made with TST under the conditions of our country, except for the cases for whom sensitivity is very important, who have a high suspicion of TB, for children with risk factors for TB, and for patients who will receive immunomodulatory biological agents in a short time.

Studies show the importance of even one single case in detecting the disease and the contact in TB (15,16). In the present study, 7 patients (11%) were diagnosed with TB in active tuberculosis contact screening, and 13 patients (20%) were detected to have LTBI. Programs to fight against tuberculosis must be continued

without interruptions. We believe that finding active cases and contacts should be considered among the close contacts of infectious TB cases in countries with moderate and high TB burden, and careful follow-ups are needed to detect additional tuberculosis and latent tuberculosis cases that may progress to tuberculosis in childhood.

Our study had limitations that deserve discussion. The most important limitation was that only 4 (20%) patients could be diagnosed with TB based on microbiological evidence in the sampling size that consisted of 118 patients. We could not predict the sensitivity of the QFT and TST Tests because of the small number of TB cases that were microbiologically confirmed. We analyzed the sensitivity of the tests in children with TB and LTBI to overcome this limitation partially. Also, we could not measure important covariates (e.g., nontuberculous mycobacterium infection, HIV infection, and malnutrition), which would enable us to evaluate the performance of these tests better.

When compared with TST, IGRA had higher sensitivity. IGRAs have the advantage of not having cross-reactions with BCG vaccine or non-TB mycobacterial proteins. However, problems that occur due to the production of the test, collection of samples, delay in the isolation and incubation of cells, improper shaking of the test tubes, problems that occur due to the laboratory, or immunological problems caused by possible booster response of the recently performed TST still remain as the disadvantages (17).

As a conclusion, cost and technical considerations might support the selection of TST in rural areas that have limited resources and poor laboratory infrastructure. Multicentric, prospective, and large-scale studies are required with microbiologically proven patient groups to determine our test priority in the conditions of our country.

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Evaluation of Infants with Retinopathy of Prematurity Treated with Intravitreal Bevacizumab

İntravitreal Bevacizumab Uygulanan Prematüre Retinopatisi Olan Bebeklerin Değerlendirilmesi

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ABSTRACT

Objective: To evaluate the systemic and local effects and side effects of intravitreal bevacizumab injection in preterm infants with aggressive posterior retinopathy of prematurity.

Material and Methods: A total of 16 patients were included in this single-center observational cohort study between June 2020 and March 2021. The clinical, laboratory, and radiological findings before and after intravitreal injection of 0.3 mg bevacizumab were recorded for a total of 32 eyes.

Results: The patients' mean gestational age at birth was 25±0.38 weeks and their mean birth weight was 695±119.2 g. None of the patients developed complications such as local vitreous hemorrhage or endophthalmitis secondary to intravitreal injection administered at a postmenstrual age of 34 weeks, and none required repeated injections. There was no increase in the rate of intraventricular hemorrhage after injection. There was no statistically significant difference in the patients' laboratory parameters, blood pressure values, or systemic findings before and after treatment.

Conclusion: Although no systemic or local side effects were observed in patients treated with intravitreal bevacizumab injection in this study, patients should be monitored closely for systemic hypertension, intraventricular hemorrhage, and hypotension. More detailed studies are needed to evaluate later neurodevelopmental outcomes compared to other treatment options.

Key Words: Bevacizumab, Hypertension, Hypotension, Intracranial Hemorrhage, Retinopathy of Prematurity

ÖZ

Amaç: Agresif posterior prematüre retinopatisi olan prematüre bebeklerde intravitreal bevacizumab enjeksiyonunun sistemik, lokal etkilerini ve yan etkilerini değerlendirmek.

Gereç ve Yöntemler: Haziran 2020 ile Mart 2021 arasında tek merkezli gözlemsel kohort çalışmasına toplam 16 hasta dahil edildi. Toplam 32 göz için intravitreal 0.3 mg bevacizumab enjeksiyonu öncesi ve sonrası klinik, laboratuvar ve radyolojik bulgular kaydedildi.

Bulgular: Hastaların doğumdaki ortalama gestasyonel yaşı 25±0.38 hafta ve ortalama doğum ağırlığı 695±119.2 gr'dı. Hiçbir hastada postmenstrüel 34 haftalıkken intravitreal enjeksiyona sekonder lokal vitreus kanaması veya endoftalmit gibi komplikasyonlar gelişmedi, hiçbirinde tekrarlanan enjeksiyon gerekmedi. Enjeksiyondan sonra intraventriküler

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Ethics Committee Approval / *Etik Kurul Onayı*: The observational cohort study was approved by the Ankara City Hospital, Clinical Research No. 1 ethics committee (11.06.2020, E1-748).

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

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kanama oranında artış olmadı. Tedavi öncesi ve sonrası hastaların laboratuvar parametreleri, kan basıncı değerleri veya sistemik bulguları arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Bu çalışmada intravitreal bevacizumab enjeksiyonu ile tedavi edilen hastalarda sistemik veya lokal yan etki görülmemekle birlikte hastalar sistemik hipertansiyon, intraventriküler kanama ve hipotansiyon açısından yakından izlenmelidir. Diğer tedavi seçeneklerine kıyasla daha sonraki nörogelişimsel sonuçları değerlendirmek için daha ayrıntılı çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Bevacizumab, Hipertansiyon, Hipotansiyon, İntrakraniyal Kanama, Prematüre Retinopatisi

INTRODUCTION

Retinopathy of prematurity (ROP) occurs secondary to abnormal vasoproliferation in the retina of preterm infants and is among the leading causes of blindness. The Turkish ROP Neonatal Study Group reported the incidence of ROP in Turkey as 8.1% in infants with low birth weight (LBW) and 19.4% in infants with extremely low birth weight (ELBW) (1). In the TR-ROP study, birth weight, gestational age, duration of oxygen therapy, and relative weight gain at postnatal 28 days were found to be independent risk factors for ROP (2). Although the incidence of ROP is gradually decreasing due to well-planned screening programs, clinical studies investigating new risk groups and different treatment modalities are needed.

Aggressive posterior ROP (APROP) is a form characterized by plus disease in zone I and posterior zone II disproportionate to peripheral disease findings, and it can lead to retinal detachment without early diagnosis and treatment (3). Laser photocoagulation and intravitreal anti-vascular endothelial growth factor (VEGF) agents (bevacizumab, ranibizumab) are commonly used in its treatment. There are publications suggesting that anti-VEGF agents provide better visual outcomes than laser photocoagulation in the treatment of APROP involving zone I (4,5). However, anti-VEGF agents have also been reported to cause adverse effects such as hypotension, hypertension, and intracranial hemorrhage (ICH) (6,7). In this single-center study, the clinical, radiological, and laboratory results of patients with APROP who required intravitreal bevacizumab injection (IVI) were examined for possible side effects after the procedure.

MATERIAL and METHODS

The ROP Diagnosis, Treatment, and Education Center, which operated within the Dr. Zekai Tahir Burak Women's Health Training and Research Hospital from 2004 until becoming affiliated with Ankara City Hospital, is one of the first centers in Turkey to implement a monitoring program for ROP. It continues to serve as the highest volume diagnosis and treatment center. The center provides ROP screening and treatment for infants born in and/or followed up in the neonatal intensive care unit (NICU) of the same hospital, as well as infants at-risk infants from the province and by the national emergency call center.

This study included patients diagnosed as having APROP and treated with intravitreal bevacizumab between June 2020 and March 2021. The observational cohort study was approved by the local ethics committee in the institution where the clinical study was conducted (date 11.06.2020, E1-20-748).

Retinal examination:

Ophthalmologists qualified and competent in the area of ROP performed retinal examinations using 20- and 28-diopter lenses after placing a lid speculum. The infants were placed in supine position for the examinations, which were performed at bedside in the NICU under appropriate monitoring. To visualize the retina and vitreous, mydriasis was induced with 2.5% phenylephrine and 0.5% tropicamide 2 to 3 times at 5-minute intervals, starting 1 hour before the examination. Patients with ideal pupil dilation were examined 45 to 60 minutes after the last instillation. ROP was classified according to the ICROP (International Classification of Retinopathy of Prematurity) (1,2).

Intravitreal Injections:

The advantages, disadvantages, and expected benefits of laser photocoagulation and intravitreal bevacizumab injection in the treatment of ROP were explained in detail to the parents and their informed consent was obtained. Intravitreal injections were administered 1.5 mm from the limbus under appropriate sedation and sterile conditions. Bevacizumab 0.3 mg/0.0125 ml was used as the anti-VEGF agent. All injections were performed by the same specialist ophthalmologist (O.O.). Moxifloxacin eye drops were used 4 times a day for 5 days as post-procedure endophthalmitis prophylaxis.

Data regarding the preterm infants' demographic characteristics (gestational age, birth weight, sex, mode of delivery, need for resuscitation in the delivery room) and antenatal/postnatal risk factors (clinical chorioamnionitis, prelabor rupture of membranes at term [PROM] or preterm [PPROM], preeclampsia, antenatal corticosteroid therapy) were obtained from medical records.

Additionally, the following were also recorded:

- Respiratory distress syndrome (RDS) requiring surfactant (8),
- Hemodynamically significant patent ductus arteriosus (hsPDA) requiring treatment (echocardiographically documented with continuous murmur, hyperdynamic

precordium, left-to-right shunt, pulsatile pulse and wide pulse pressure, increased oxygen requirement, cardiomegaly, and congestive heart failure) (9),

- Early neonatal sepsis (within first 72 hours in very low birth weight infants) and late neonatal sepsis (after 3 days) (10),
- Time to oral intake, necrotizing enterocolitis (NEC) higher than stage IIb according to Bell staging (11),
- Oxygen requirement at postnatal 7, 14, 21, and 28 days and duration of invasive and non-invasive mechanical ventilation (MV),
- Intraventricular hemorrhage (IVH; ventricular enlargement and periventricular infarction stage 3 according to Volpe staging) (12), concomitant diseases, and late morbidities.

Hematological and biochemical parameters, IVH presence and stage, systolic, diastolic, and mean arterial blood pressure (BP) values measured using an appropriate sleeve, and ocular findings 48 hours before and 96 hours after intravitreal bevacizumab injection were obtained from patient records and the hospital database.

Statistical analysis:

Statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY). p values < 0.05 were accepted as statistically significant. Normal distribution of measured values were analyzed graphically and with Shapiro-Wilk test. Results were presented as mean and standard deviation or median, minimum, and maximum values. Paired-samples t test was used to compare patients' pre- and post-treatment values.

RESULTS

The patients' mean gestational age at birth was 25±0.38 weeks and their mean birth weight was 695±119.2 g. Of the 16 infants in the study, 11 (68.8%) were female, 13 (81%) were born by cesarean section, 14 (87.5%) underwent advanced resuscitation in the delivery room, and all received endotracheal surfactant therapy. Ten (62.5%) of the preterm infants had received a complete course of antenatal steroid, while 4 (25%) received no antenatal corticosteroid therapy. Other risk factors and diseases are summarized in Table I.

Intravitreal bevacizumab injection was administered to a total of 32 eyes at a mean postmenstrual age of 34±0 weeks. Stage I-II ROP and plus disease were detected in 12 infants (75%) and APROP in zone I was detected in 10 infants (62.5%). None of the patients required repeated injections and none developed complications associated with the procedure. There was no increase in the rate of IVH after injection. There were no statistically significant differences in the patients' laboratory parameters, blood pressure values, or systemic findings before and after treatment (Table II).

Table I: Summary of the antenatal and clinical characteristics of preterm infants with ROP (n=16). Data presented as mean ± standard deviation or number and percentage.

Birth weight, g	695±119.2
Gestational age, weeks	25±0.38
Sex (F), n (%)	11 (68.8)
Mode of birth (C/S), n (%)	13 (81.0)
Complete course of antenatal corticosteroid	10 (62.5)
No antenatal corticosteroid	4 (25.0)
Preeclampsia	1 (6.3)
Chorioamnionitis	2 (12.5)
PPROM	4 (25.0)
Resuscitation in the delivery room	14 (87.5)
Early neonatal sepsis	8 (50.0)
Late neonatal sepsis	15 (93.8)
hsPDA	11 (68.8)
Day 7 Invasive ventilation	5 (33.3)
Day 14 Invasive ventilation	9 (56.3)
Day 21 Invasive ventilation	8 (50.0)
Day 28 Invasive ventilation	4 (25.0)
MV duration, (days)	37.4±22.3
NIV duration, (days)	24.1±13.0
BPD mild/moderate	6 (37.5)
BPD severe	10 (62.5)
Oral intake start time, (days)	3±0.3 (2-4)
Rate of weight gain, (g/day)	13.3±4.4
Necrotizing enterocolitis	7 (43.8)
Intraventricular hemorrhage	5 (31.3)
Stage I-II ROP/APROP	12 (75.0)
Stage III APROP	4 (25.0)
Zone I APROP	10 (62.5)
Zone II APROP	6 (37.5)
Pre-treatment systolic BP, (mmHg)	88±8.8 (81-93)
Post-treatment systolic BP, (mmHg)	91±7.7 (83.2-95.7)
Pre-treatment diastolic BP, (mmHg)	52.5±7.5 (47.7-60)
Post-treatment diastolic BP, (mmHg)	54.5±5.6 (51-57)
Pre-treatment mean BP, (mmHg)	63.5±7.6 (57-70.7)
Post-treatment mean BP, (mmHg)	65.5±7.2 (60-69.7)

***F:** Female, **C/S:** Cesarean section, **PPROM:** Preterm prelabor rupture of membranes, **hsPDA:** Hemodynamically significant patent ductus arteriosus, **MV:** Mechanical ventilation, **NIV:** Noninvasive mechanical ventilation, **BPD:** Bronchopulmonary dysplasia, **ROP:** Retinopathy of prematurity, **APROP:** Aggressive posterior ROP, **BP:** Blood pressure*

Table II: Comparison of blood and blood pressure parameters before and after intravitreal bevacizumab therapy.

	Pre-treatment	Post-treatment	p
CRP, (mg/dL)	3.6 (1.15-25)	3.2 (1.0-10.9)	0.160
WBC, (x10^9/L)	7655.0±675.5	7720.6±664.9	0.870
Hb, (g/dL)	9.7±0.5	9.8±0.5	0.490
PLT (x10^9/L)	340562±53740	349812±53133	0.710
Systolic BP (highest), mmHg	93	95	0.460
Diastolic BP (highest), mmHg	60	57	0.880
Mean BP (highest), mmHg	70	69	0.950
Systolic BP (lowest), mmHg	81	83	0.840
Diastolic BP (lowest), mmHg	47	51	0.130
Mean BP (lowest), mmHg	57	60	0.250

CRP: *C-reactive protein,* ***WBC:*** *White blood cells,* ***Hb:*** *Hemoglobin,* ***PLT:*** *Platelets,* ***BP:*** *Blood pressure*

DISCUSSION

The results of this study indicate that intravitreal bevacizumab therapy can be safely used in very low birth weight preterm infants, has no effect on vital signs and blood parameters, and is not associated with important morbidities of prematurity. As ethical considerations preclude randomized controlled or placebo-controlled studies in critical, sight-threatening diseases that require urgent treatment such as APROP, sharing drug side effects and observed complications through retrospective cohort studies and case reports is more valuable scientifically.

In 2013, the American Academy of Pediatrics and American Academy of Ophthalmology recommended ROP screening for all infants with birth weight ≤ 1500 g and/or gestational age ≤ 30 weeks and those infants born after 30 weeks of gestation with birth weight of 1500-2000 g and clinical problems requiring cardiopulmonary support (13). In Turkey, it is generally recommended to screen all infants born at or before 32 weeks of gestation. The first eye examination is performed at 30-31 weeks of postmenstrual age for all infants born before 27 weeks of gestation and at postnatal 4 weeks for infants born after 27 weeks of gestation (2).

The pathogenesis of ROP is explained by the development of abnormal neovascularization due to elevated VEGF and insulin-like growth factor-1 (IGF-1) levels, and the most important risk factors are prematurity and low birth weight (14). Elevated inflammatory markers secondary to complement activation have been shown to be useful in the prediction of ROP and early intervention (15). In a meta-analysis of ROP risk factors, prenatal steroid use, gestational age, MV duration, and RDS were associated with ROP development, while gestational age, bronchopulmonary dysplasia (BPD), erythrocyte suspension transfusion count, ICH, and periventricular leukomalacia were associated with ROP progression (16). In the present study, 62.5% of the infants received a complete course and 12.5% received a half course of prenatal corticosteroid, the mean gestational age was 25 weeks, the mean duration of MV was 37 days, 93.8% received surfactant, 62.5% had severe BPD, and 31.3% had ICH. Lee et al. (17) and Anaya-Alaminos et al. (18) determined that the preterm infants of mothers with PROM had a lower risk of severe ROP, whereas preterm infants with bacteremia and postnatal hyperoxemia were at higher risk of severe ROP. The prevalence of PPROM was 25% in this study. In a meta-analysis investigating the association between sepsis and ROP, sepsis was found to be directly associated with all stages of ROP (19). Late neonatal sepsis was observed in nearly all of the patients in the present study. There are also studies demonstrating a direct association with chorioamnionitis and funisitis (20).

As ROP is a preventable disease, preterm infants weighing less than 1500 g should receive oxygen therapy with saturation monitoring in accordance with established guidelines (21). For the conditions in Turkey, it is recommended to monitor infants with gestational age ≤ 34 weeks and birth weight < 1700 g according to the routine screening program (2). A model incorporating postnatal growth into ROP screening (G-ROP) has recently been developed for preterm infants who do not meet conventional birth weight and gestational age criteria, and gestational age < 28 weeks, birth weight < 1051 g, weight gain <120 g during postnatal days 10-19, weight gain <180 g during days 20-29, weight gain <170 g during days 30-39, and hydrocephalus were reported as poor prognostic factors (22). Treatment tment modalities commonly used for ROP include cryotherapy, laser photocoagulation, IVI, and retinal surgery (23).

APROP is the most aggressive form of ROP and its treatment is more challenging compared to classical ROP (3). A study investigating APROP risk factors found that maternal chorioamnionitis and intrauterine growth restriction (IUGR) were directly associated with APROP (24). Only two of the patients in this study had chorioamnionitis, and none had IUGR. In a routine ROP screening program, APROP was detected in a series of 3 infants born at gestational ages of 27 weeks, 305/7 weeks, and 31 weeks, and the authors emphasized the potentially aggressive course of this disease

and the importance of close monitoring and follow-up of risk groups (25).

Anti-VEGF agents are frequently used together with laser photocoagulation in the treatment of APROP (26). In some studies, anti-VEGF injection is recommended as rescue therapy in cases of laser photocoagulation failure (27). However, in a small number of series, it was shown that laser photocoagulation can be used if the disease progresses after IVI (28). Although uncommon, some complications such as cataract, vitreous hemorrhage, corneal abrasion/opacity, endophthalmitis, hyphema, and thromboembolic events may develop after bevacizumab injection (29). As in our study, there are publications reporting no complications after IVI (30, 31). A recent meta-analysis by Popovic et al. (32) comparing IVI and laser photocoagulation showed that the need for repeat treatment was less common after laser photocoagulation, astigmatism and the need for surgery were lower after IVI, and there was no significant difference between IVI and laser photocoagulation in terms of vision, safety, and disease regression times. In a study showing that IVI therapy was at least as effective as laser photocoagulation and that the risk of complications and retreatment was lower, the degree of myopia was found to be higher in APROP patients compared to type 1 ROP patients (33-35).

Intravitreal bevacizumab injection is also frequently used in our clinic. As in this study, Nicoara et al. (36) administered intravitreal bevacizumab to patients with APROP and stage 3 ROP and observed significant regression of ROP findings, with no complications or retinal detachment. There are publications demonstrating a greater need for laser photocoagulation and retinal surgery in the APROP group after bevacizumab treatment for APROP and type 1 ROP (37). APROP has a high risk of recurrence and was found to be correlated with intravitreal hemorrhage, low birth weight, postmenstrual age, and low neutrophil count in one study (38).

Opinions are divided regarding bevacizumab dosing for the treatment of APROP. In a study comparing doses of 0.5 mg and 0.625 mg, no difference in complications was observed between the groups (39). The patients in the present study were administered 0.3 mg intravitreal bevacizumab with no complications. Systemic hypotension, hypertension, and ICH after bevacizumab treatment have been reported in small cases series (6,7). The patients in this study had no increase in ICH and no change in systemic blood pressure values after injection.

Limitations of this study is small number of cases due to the inclusion of high-risk infants with low gestational age.

CONCLUSION

Although intravitreal bevacizumab therapy is widely used in the treatment of APROP, side effects such as systemic hypertension, hypotension, and ICH risk have been reported. However, no systemic or local side effects were observed in the injected eyes in this study. Additionally, none of the treated eyes required a second injection or laser treatment during follow-up. Nevertheless, ROP patients who receive intravitreal injections should be monitored closely for possible short-term drug side effects. More extensive studies are needed to determine the dose with highest efficacy and lowest side effects, and later neurodevelopmental outcomes should be investigated in comparison with other treatment options.

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Evaluation of Patients with Juvenile Idiopathic Arthritis-Associated Uveitis from Rheumatology Perspective

Juvenil İdiyopatik Artrit ile İlişkili Üveitli Hastaların Romatolojik Açıdan Değerlendirilmesi

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ABSTRACT

Objective: Uveitis, the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA), is most commonly found in children with oligoarticular type and polyarticular rheumatoid factor (-) JIA. Close follow-up of these children by pediatric rheumatologists and ophthalmologists is important because of the risk of blindness if these cases are untreated. This study aims to evaluate the frequency of uveitis, demographic characteristics, and complications in children with JIA.

Material and Methods: Among the patients with JIA who were followed up at the Pediatric Rheumatology Clinic of Dr Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital between January 2017 and July 2021, those with uveitis were included in the study. Location of uveitis, laterality, age at onset of uveitis, complications of uveitis, duration of follow up, laboratory findings, medications used, and status of uveitis at the time of data collection were obtained from the patients' files.

Results: Uveitis was observed in 34 (7.1%) of the 473 children with JIA included in the present study. Twenty three patients were female (67.6%). The age at diagnosis of JIA was 5.9±5.1 years, and the age at diagnosis of uveitis was 7.5±4.2 years. The most common form of JIA was the persistent oligoarticular form. Compared with the age of onset of arthritis in all JIA patients, the age of onset of arthritis was lower in patients with JIA-associated uveitis (7.8±4.6 years vs. 5.9±5.1 years). Anatomically, all patients had anterior uveitis. Antinuclear antibody positivity was more common in children with JIA-associated uveitis (47.1%) than all of our patients with JIA (19%). In one of the patients, arthritis and uveitis were diagnosed simultaneously. Posterior synechia was found in three patients (8.8%). Arthritis was the first symptom in 27 patients (79.4%) and uveitis in six patients (17.6%), cataract in five patients (14.7%), glaucoma in two patients (5.9%), and blindness in one eye (2.9%).

Conclusion: Uveitis is the most common extra-articular complication of JIA and has sight-threatening complications which may lead to irreversible visual loss. The findings of this study suggest that the joint effort of pediatric rheumatologists and ophthalmologists is needed to diagnose these children promptly and treat them appropriately.

Key Words: Eye diseases, Juvenile Idiopathic Arthritis, Uveitis

ÖZ

Amaç: Jüvenil idiyopatik artritin (JİA) en yaygın eklem dışı bulgusu olan üveit, en sık olarak oligoartiküler tip ve poliartiküler romatoid faktör (RF) negatif JİA'lı çocuklarda bulunur. Bu çocukların pediatrik romatologlar ve oftalmologlar tarafından

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by Ankara Keçiören Training and Research Hospital, Clinical Research Ethics Committee, numbered 22.07.2020/15-2153.

Contribution of the Authors / Yazarların katkısı*: *BAGLAN E: 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 the writing of the whole or important parts of the study. ***OZDEL S:*** Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***OZDEMIR K:*** 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. ***CAKAR OZDAL MP:*** Reviewing the article before submission scientifically besides spelling and grammar. ***BULBUL M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results.

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yakın takibi, tedavisiz kalan vakalarda körlük riski nedeniyle önemlidir. Bu çalışmanın amacı JİA'lı çocuklarda üveit sıklığını, demografik özelliklerini ve komplikasyonlarını değerlendirmektir.

Gereç ve Yöntemler: Ocak 2017-Temmuz 2021 tarihleri arasında SBÜ Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi hastane bilgi veri tabanından elde edilen hastaların demografik, klinik ve sonuç verileri geriye dönük olarak incelendi. Çocukların yaşı ve cinsiyeti, takip süresi, artrit başlangıç yaşı, JİA alt tiplerinin dağılımı, üveit başlangıç yaşı, tanı yaşı, üveit lokalizasyonu, özellikleri, semptomları, laboratuvar parametreleri ve kullanılan ilaçlar değerlendirildi.

Bulgular: Çalışmaya alınan 473 JİA'lı çocuğun 34'ünde (%7.1) üveit görüldü. JIA'nın en yaygın formu, kalıcı oligoartiküler formdu. Tüm JIA hastalarında artrit başlangıç yaşı ile karşılaştırıldığında, JIA ile ilişkili üveiti olan hastalarda artrit başlangıç yaşı daha düşüktü (5.94±5.143 ve 7.83±4.62 yıl). Antinükleer antikor pozitifliği, JIA ile ilişkili üveiti olan çocuklarda tüm JIA hastalarımıza kıyasla daha yaygındı (%19'a karşı %47.1). Bir hastada artrit ve üveit aynı anda teşhis edildi. 3 hastada (%8.8) posterior sineşi, 5 hastada (%14.7) katarakt, 2 hastada (%5.9) glokom ve bir gözde (%2.9) körlük saptandı.

Sonuç: Üveit, JİA'nın en sık görülen eklem dışı komplikasyonudur ve geri dönüşü olmayan görme kaybına yol açabilen komplikasyonlara sahiptir. Bu çalışmada JİA hasta popülasyonumuzda üveit tanısı alan hastalarımızı değerlendirmeyi amaçladık. Bu çocuklara bir an önce teşhis koymak ve uygun şekilde tedavi etmek; hem pediatrik romatologların hem de oftalmologların ortak çabasını gerektirmektedir.

Anahtar Sözcükler: Göz bozuklukları, Jüvenil idiopatik artriti, Üveiti

INTRODUCTION

Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA). The incidence of uveitis in children with JIA is between 12-38%. Chronic anterior uveitis, which is usually asymptomatic, is the most common type of JIA-associated uveitis. Acute anterior uveitis usually presents with a painful, red eye. It is generally associated with enthesitis-related arthritis (ERA) and HLA-B27 positivity (1).

If JIA-associated uveitis is treated inadequately, it may lead to ocular complications, such as cataracts, glaucoma, band keratopathy and persistent macular edema, ultimately resulting in visual impairment and blindness (2). According to the 2019 American College of Rheumatology (ACR) recommendations, patients with JIA should be screened regularly (every 3-12 months) for uveitis depending on the risk factors (3) (Figure 1). It is more commonly observed in girls with oligoarticular JIA who have positive antinuclear antibodies (ANA) (2).

In approximately 10% of children, uveitis may be present before the onset of arthritis, while in nearly half of affected children, it occurs at the time of or soon after the diagnosis of arthritis. In a significant number of children, it develops within seven years of onset (2,4,5). Treatment of JIA-associated uveitis includes the use of both topical and systemic medications. In resistant cases, the use of biological agents may be required. Approximately 51% develop synechia and 34% develop band keratopathy. Cataract is found in 20% of affected children, while glaucoma develops in approximately 17% of children (4,6,7). In some children, some of the structural complications are already present at the time of uveitis (1,6-8). This study aims to evaluate the frequency and complications of JIA- associated uveitis.

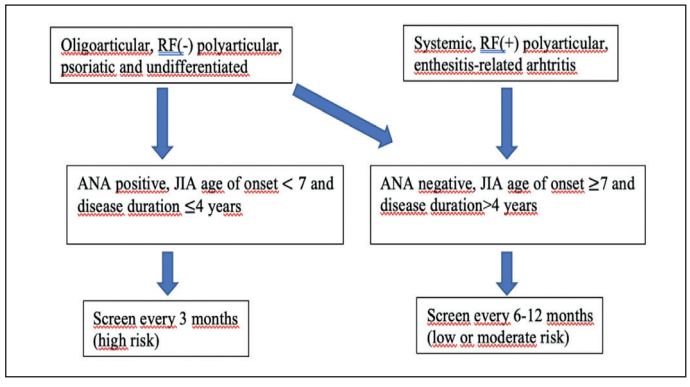

Figure 1: 2019 American College of Rheumatology/Arthritis Foundation Guideline for Juvenile Idiopathic Arthritis-Associated Uveitis opthamologic screening examination.

RF:*Rheumatoid factor,* ***ANA:*** *Antinuclear antibody,* ***JIA****: juvenile idiopathic arthritis.*

MATERIAL and METHODS

This retrospective study was conducted by analyzing the medical records of 473 children with JIA who were followed up for at least three months in the Pediatric Rheumatology Clinic of Dr Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital between January 2017 and July 2021. Diagnosis and classification of subtypes of JIA were made in accordance with the International League of Associations for Rheumatology (ILAR). In the present study, demographic, clinical and outcome data of the patients from the hospital information database were examined retrospectively. Child's age and sex, duration of follow-up, age of onset of arthritis, distribution of subtypes of JIA, age of onset of uveitis, localization, symptoms (eye redness and pain, photophobia, vision changes), laboratory parameters at the time of diagnosis, rheumatoid factor (RF), ANA, HLA-B27 results and the drugs they used were evaluated. An ANA titer of ≥1:80 by fluorescent antibody testing was designated positive. This study was approved by Ankara Keçiören Training and Research Hospital, Clinical Research Ethics Committee, numbered 22.07.2020/15-2153.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). The

Shapiro-Wilk test was used to determine the variables whether or not they are normally distributed. Results are given as mean ±SD. Categorical variables were evaluated using the chi-square test. Comparisons of continuous variables between the two grupsa were performed using the T-test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Of the 473 patients with JIA who were followed up at Dr Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital between 2017-2021, 34 patients with JIA-associated uveitis were included in the present study. Twenty three patients were female (67.6%). The female/male ratio was 2:1. At the time the patient data were collected, their age was 12.8±5.4 years. The age at first diagnosis of uveitis was 7.5±4.2 years, and the age at first diagnosis of arthritis was 5.9±5.1 years. Arthritis was the first symptom in 27 patients (79.4%) and uveitis in six patients (17.6%). In one patient, uveitis and arthritis were diagnosed at the same time. Compared with the age of onset of arthritis in all our patients with JIA, the age of onset of arthritis was lower in patients with JIA-associated uveitis (13.3±5.1 years vs. 5.9±5.1 years) ($p<0.05$). Considering the subtypes of JIA, persistent oligoarticular JIA was the most common type associated with JIA-associated uveitis in 19 patients (55.9%). Eleven patients (32.4%) had ERA, 3 patients (8.8%) had RF (-) polyarticular JIA and 1 patient (2.9%) had extended oligoarticular JIA. Anatomically, all patients had anterior uveitis. Considering the laterality of uveitis, 5 patients (14.7%) had right, 3 patients (8.8%) had left, and 26 patients (76.5%) had bilateral involvement. Although not statistically significant, bilateral involvement was more frequent in female patients (76.9%) than males (23.1%) ($p= 0.11$). While ANA positivity was 19% in our JIA patients, it was 47.1% with JIA-associated uveitis. ($p<0.05$). Although ANA positivity was higher in girls (52.2%) than in boys (36.4%), it was not statistically significant ($p= 0.38$).

Topical treatment was administered to all patients with uveitis. Systemic steroid treatment was administered to 25 patients (73.5%) and methotrexate treatment was administered to 29 (85.2%) patients. Biological agent treatment was administered to 24 patients (70.5%) who were resistant to systemic steroid and methotrexate treatment. Twenty patients (58.8%) received adalimumab, 3 patients (8.8%) received infliximab after adalimumab. Tocilizumab treatment was administered in one patient after adalimumab and infliximab (2.9%). The need for biological therapy for ocular complications was higher in our female patients, but it was not statistically significant ($p=0.53$). No patient received intraocular steroid injection. Considering the eye complications, posterior synechia were observed in 3 patients (8.8%), cataracts in 5 patients (14.7%), glaucoma in 2 patients (5.9%), and blindness in one patient (2.9%). Ocular complications were higher in female patients, but they were not statistically significant ($p= 0.92$). The main characteristics of patients are given in Table I.

Table I: Main characteristics of patients.

Number of patients	34
Gender (girls %)*	23 (67.6)
Arthritis onset age	5.9± 5.1years
Age of onset of uveitis	7.5± 4.2 years
Bilateral uveitis*	26 (76.5)
Antinuclear antibody positivity*	16 (47.1)
Number of patients given biologic therapy*	24 (70.5)

***** *n(%)*

DISCUSSION

Uveitis is the most common extra-articular manifestation of JIA, with a potential risk of visual impairment. We aimed to evaluate the frequency of uveitis in our patient population with JIA, the demographic data of our patients with uveitis, and eye complications. The prevalence of uveitis in children with JIA varies widely between 10-38% (8-10). The frequency of uveitis in JIA was reported as 12% by Heiligenhaus et al (8). In our patient cohort, uveitis was detected in 7.1% of JIA patients.

The previous studies have shown that frequency of uveitis in JIA varies with the JIA subtype. According to Paroli et al. (10) reported that 87.3% of joint involvement in patients with JIA-associated uveitis was compatible with oligoarticular JIA. Angeles-Han et al. (11) reported that 41% JIA patients had a persistent oligoarticular form of JIA. They concluded that having oligoarticular type of JIA is one of the most important determinants in the development of uveitis. Oligoarticular JIA was the most common JIA category (38.8%) in the JUPITER study cohort, which included four centers from Turkey. Other JIA subgroups and percentages in the JUPITER study were ERA, 23.2%; RF (-) polyarthritis, 15.6%; systemic arthritis, 12.2%; juvenile psoriatic arthritis, 5.2%; undifferentiated arthritis, 2.8%; and RF-positive polyarthritis, 2.2% (12). In our report, the most common type of JIA associated with uveitis was the persistent oligoarticular JIA with a rate of 55.9% and ERA was the second most common JIA subtype category with 32.4%.

Another important risk factor for JIA-associated uveitis is the age at onset of JIA. In early-onset disease, the risk of accompanying uveitis increases accordingly (5). Paroli et al. (10) reported that the mean age of children with JIA-associated uveitis was 3 years in their study. The age at first diagnosis of uveitis was older (7.5±4.2 years) in our study. The high mean age of our ERA patients may have increased the mean age of uveitis.

The role of ANA in the pathogenesis remains unclear. Angeles-Han et al. (11) found ANA positivity more frequently in children with JIA-associated uveitis than in children without uveitis (16.7% vs. 66.7%). Kasapçopur et al.(13) found ANA positivity in 25 of 37 children with oligoarticular JIA and reported that

uveitis developed in 10 of them. A study conducted in Italy revealed that ANA positivity was the biggest risk factor for the development of uveitis and that 30% of ANA-positive JIA patients develop uveitis regardless of the age and gender of the child (14). In 2017, Çakan et al. (15). found the frequency of uveitis to be 4.5% in 265 JIA patients. ANA positivity was present in 27.2% of these patients. In our JIA cohort, ANA positivity was 19%.

Uveitis may develop before the diagnosis of JIA, so eye-related inflammatory conditions may progress in the meantime, remain undetected for a while and cause complications. Studies show that 50% to 70% of eyes have at least one complication at the initial ophthalmology exam. The biggest risk of having all these complications is blindness (1,2,5). Angeles- Han et al. (11) reported that cataracts and synechiae were frequently present in 31% of children, while keratopathy was less common in 25% and glaucoma in 17%. Ocular complications were found in 32.3% of our cohort. This rate is similar to the complication risk in JIA-associated uveitis in the literature. We think that the close cooperation between the ophthalmology and the pediatric rheumatology clinics will reduce the risks of these complications. In this respect, a multidisciplinary team approach is essential.

In Angeles- Hans' report the need for methotrexate treatment was 76.8%, and the need for biological treatment was 55.7% in JIA-associated uveitis (11). These were 85.2% and 70.5%, respectively, in our patient cohort. The reason for the high number of patients using biological agents in our study is the early detection of treatment-resistant cases and early initiation of biological treatments for complicated cases.

The limitations of the study are that it is retrospective and the number of patients is small. The asymptomatic course of the disease may complicate the diagnosis and cause the number of patients to appear less.

CONCLUSION

Uveitis is one of the most important long-term complications of patients with JIA. In this respect, a multidisciplinary team approach is essential. Also families should be warned about the risks of JIA uveitis and to take their children for eye check-ups even if they do not have any complaints.

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Ebeveynlerin Antiepileptik İlaç Kullanımıyla İlgili Bilgi, Tutum, Davranışları ve Antiepileptik İlaçların Sık Gözlenen Yan Etkileri; Tek Merkezli Gözlemsel Deneyim

Parents' Knowledge, Attitudes, Behaviors Towards Use of Antiepileptic Drugs and Common Adverse Effects of Antiepileptic Drugs; Single Center Observational Experience

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ÖZ

Amaç: Antiepileptik ilaçlar çocukluk çağında erişkinlere göre farmakokinetik ve farmakodinamik süreçlerinde farklılıklar gösterebilir; bu nedenle ilaçların etki ve yan etki profilleri değişebilmektedir. Çalışmamızda epilepsi tanısı konulan çocukların ebeveynlerinin antiepileptik ilaçlara karşı bilgi, tutum ve davranışları ile çocuklarda antiepileptik ilaç kullanımına bağlı sık gözlenen olası yan etkileri değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamız, ebeveynlere anket uygulanarak yapıldı. Ağustos 2019-Mart 2020 tarihleri arasında Çocuk Nöroloji Polikliniği'nde epilepsi tanısı konulmuş 110 hasta ebeveyni çalışmaya dahil edildi.

Bulgular: Katılımcıların çoğunluğunu anneler (n=68, %61.8) oluşturmaktaydı. Katılımcıların yaş ortalamaları 38.4±7.78 yaştı. %70 olgu monoterapi, %30 olgu politerapi kullanmaktaydı. Monoterapiden en sık kullanılan ilaçlar; levetirasetam (%22.7), valproik asit (%21.8) ve karbamazepin (%13.6)'dı. %34.5 olguda antiepileptik ilaçlara karşı yan etki gözlenmedi. En sık görülen yan etkiler; sinirlilik (%35.5), kilo alma (%18.2), yorgunluk (%14.5) ve davranış problemleri (%11.8)'di. Politerapi uygulanan hastalarda yan etki görülme oranı (%72.7), monoterapi uygulanan hastalara göre istatistiksel olarak anlamlı olmasa da daha yüksek bulundu (%62.3).

Sonuç: Çalışmamızın çocuklarda antiepileptik ilaç tedavisi sırasında karşılaşılabilecek yan etki profilinin aydınlatılmasına ve ebeveynlere verilecek eğitimlere katkıda bulunacağını düşünmekteyiz.

Anahtar Sözcükler: Yan Etki, Antiepileptik İlaçlar, Ebeveynler, Epilepsi, Pediatri

ABSTRACT

Objective: The use of antiepileptic drugs in childhood may differ in their pharmacokinetic and pharmacodynamic processes compared to adults and therefore, the effect and adverse effect profiles of drugs may change. We aimed to evaluate the knowledge, attitudes and behaviors of parents of children diagnosed with epilepsy towards antiepileptic drugs and possible adverse effects related to the use of antiepileptic drugs in children.

Material and Methods: Our study was conducted by applying a questionnaire to parents. August 2019 and March 2020, 110 parents of patients who were diagnosed with epilepsy in pediatric neurology outpatient clinic were included in the study.

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

***Etik Kurul Onayı / Ethics Committee Approval*:** Bu çalışma Helsinki Deklarasyonu İlkelerine uygun olarak yapılmıştır. Balıkesir Üniversitesi Klinik Araştırmalar Etik Kurulu'ndandan onay (14.10.2020/220/175) alınmıştır.

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

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Results: The majority of the participants were mothers (n=68, 61.8%). The mean age of the participants was 38.4±7.78 years. 70% of cases were using monotherapy, 30% of cases were using polytherapy. The most commonly used drugs from monotherapy; levetiracetam (22.7%), valproic acid (21.8%) and carbamazepine (13.6%). No side effects were observed against antiepileptic drugs in 34.5% of the cases. The most common side effects were irritability (35.5%), weight gain (18.2%), fatigue (14.5%) and behavioral problems (11.8%). The incidence of adverse effects in patients treated with polytherapy (72.7%) was found to be higher (62.3%) than in patients treated with monotherapy, although it was not statistically significant.

Conclusion: We hope that our study will contribute to the enlightenment of the adverse effect profile that may be encountered during antiepileptic drug treatment in children and to the education to be given to parents.

Key Words: Advers Effect, Antiepileptic Drugs, Parents, Epilepsy, Pediatrics

GİRİŞ

Epilepsi nöbetlerle karakterize, sık görülen bir nörolojik hastalık olup, hastaların ve ailelerin sosyal hayatlarını ve yaşam kalitelerini olumsuz etkileyebilmektedir (1). Tedavide temel hedef, nöbetlerin baskılanması, sıklığının azaltılması ve hastanın yaşam kalitesini iyileştirmektir (2).

Farmakoterapi, epilepsi tedavisinin bel kemiğini oluşturur (3). Bu amaçla epilepsi tedavisinde antiepileptik ilaçlar kullanılır. Epilepsi tedavisinde kullanılmak üzere pek çok ilaç geliştirilmiş olup, bu ilaçlar nöbet sıklığı ve şiddetinin azalmasını sağlamakla birlikte, kullanımları sırasında bazı yan etkiler gözlemlenebilmektedir (4). Epileptik hastaların yaklaşık 1/3'ünün nöbet başlangıcından önce depresyon, anksiyete, somatik şikayetler ve dikkatsizlik gibi semptomlar yaşayabildiği de düşünüldüğünde klinik tablo daha karmaşık hale gelebilmektedir (5-7).

Çocukluk çağında ilaç kullanımı erişkinlerle kıyaslandığında birtakım farklılıklar içermektedir. Çocukluk çağının yetişkinlere göre fizyolojik, psikolojik ve mental olarak değişken dinamik doğası nedeniyle, ilaçların farmakokinetik ve farmakodinamik süreçlerinde farklılıklar görülebilmekte, ilaçların etki ve yan etki profilleri değişebilmektedir (8). Günümüzde antiepileptik ilaçlarla ilişkili olduğu bilinen yan ilaç reaksiyonlarının çoğu, yetişkin popülasyonda yürütülen çalışmalardan elde edilmiştir (9). Literatürde pediatrik hastalarda antiepileptik ilaç güvenlik profilini araştıran kısıtlı sayıda çalışma mevcuttur. Çocukluk çağının dinamik doğası ve ilaç güvenlik verilerindeki kısıtlılıklar çocuklarda antiepileptik ilaç kullanımını daha hassas hale getirmektedir (9).

Hastaların ve ebeveynlerin hastalık ve tedavileri ile ilgili bilgi düzeyleri, tedavilerine güvenleri ve uyumları tüm hastalıklarda olduğu gibi epilepsi tedavisinin de başarısını ve güvenliğini etkileyebilmektedir. Bu nedenle ilaçların kullanımında, etki ve kullanım sırasında ortaya çıkabilecek yan etkilerin tespiti ve takibinde ebeveynlere büyük sorumluluklar düşmektedir. Bir diğer ifadeyle çocuklardaki antiepileptik ilaç tedavisinin başarısı ve tedavi güvenliği ebeveynlerin antiepileptik ilaçlar hakındaki bilgi, tutum ve davranışlarıyla yakından ilişkilidir.

Biz bu çalışmazda hastanemizde epilepsi tanısı konulan çocukların ebeveynlerinin antiepileptik ilaçlara karşı bilgi, tutum ve davranışlarını ile çocuklarda antiepileptik ilaç kullanımına bağlı olası yan etkileri değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER

Çalışmamıza Ağustos 2019-Mart 2020 tarihleri arasında Balıkesir Üniversitesi Sağlık Uygulama ve Araştırma Hastanesi Çocuk Nöroloji Polikliniğimiz'e başvuran ve epilepsi tanısı konulmuş 110 hasta ebeveyni dahil edildi. Hasta ebeveynleri ile yüz yüze görüşme sağlanarak yazılı onamları alındıktan sonra anket uygulaması yapıldı. Anket formu konu ile ilgili literatürdeki makalelerdeki soruların revizyonu ve yeni soruların eklenmesiyle hazırlandı (9,11,13). Katılımcıların 3 ayrı bölümden oluşan anket formlarını poliklinikte, aynı araştırmacının gözetiminde doldurmaları istendi.

Anket formunda;

1. Bölüm: Ebeveynlere ait demografik verilerin (ebeveynleri cinsiyeti, yaşı, çocuğa yakınlık derecesi, sağlık güvencesi, eğitim ve çalışma durumları, ailelerin gelir düzeyi, nerede yaşadıkları, kardeş sayısı).

2. Bölüm: Epilesi tanılı çocuklar ve hastalıkları ile ilgili genel özellikleri (yaş, nöbet sıklığı, tetikleyen faktörler komorbid durumlar, ailede epilepsy hastalığı varlığı, tedavi, yan etki).

3. Bölüm: Ebeveynlerin antiepileptik ilaçlar ve epilepsi tedavisiyle ilgili bilgi, tutum ve davranışlarının değerlendirilmesine yönelik boşluk doldurma, evet/hayır, soruyla ilgili bir ya da daha fazla işaretlenebilecek seçenekler ve ifade seçeneklerini içeren 36 soru bulunmaktaydı.

Çocuklar ile ilgili herhangi bir tanısal ve laboratuvar verisi kullanılmamıştır. Çalışmamız için Balıkesir Üniversitesi Klinik Araştırmalar Etik Kurulu'ndandan onay (14.10.2020/220/175) alınmıştır.

İstatiksel Analiz

Çalışmada anket uygulaması ile elde edilen verilerin analizi için SPSS 23 istatiksel yazılım paket programı kullanıldı. Tanımlayıcı verilerin elde edilmesinin ardından, ki-kare testi ile ikili karşılaştırmaların istatistiksel olarak anlamlı olup olmadığı değerlendirildi.

BULGULAR

Çalışmamıza 110 ebeveyn katıldı. Katılımcıların çoğunluğunu anneler (n=68, %61.8) oluşturmaktaydı. Katılımcıların yaş ortalamaları 38.4±7.78 yaştı. Hastaların çoğunluğunun sağlık güvencelerinin olduğu görüldü (n=103, %93.6). Sağlık güvenceleri olarak en sık Sigorta Sağlık Kurumunu (SSK) (n=70, %63.6) olduklarını belirttiler.

Ebeveynlerin eğitim düzeyleri değerlendirildiğinde annelerin (%40, n=44) ve babaların (n=43, %39.1) çoğunluğunun ilkokul mezunu oldukları, ayrıca annelerin bir kısmının okuma yazma bilmediği görüldü (n=4, %3.6). Çalışma durumları değerlendirildiğinde; annelerin çoğunlukla ev hanımı olduğu (n=88, %80), babaların ise çoğunlukla çalıştıkları (n=100, %90.9) öğrenildi. Ebeveynlerden kendi gelir düzeylerini tarif etmeleri istendiğinde, sıklıkla orta gelir düzeyinde olduklarını (n=81, %73.6) belirttiler. Katılımcıların 108'inin (%98.2) Türkiye Cumhuriyeti (TC) uyruklu olduğu, yabancı uyruklu katılımcı sayısının yalnızca 2 (%1.8) olduğu görüldü. Katılımcıların %43.6'sı il merkezinde (n=48), %56.4'ü ilçe (n=32) ve köylerde (n=30) ikamet ettiklerini belirtti. Epilepsi hastalarının çoğunun kardeşi (n=94, %85.5) vardı ve çoğu anne-babalarıyla birlikte yaşamaktaydı (n=94, %85.5) (Tablo I).

Epilepsi tanısı ile izlediğimiz hastaların yaş ortalaması 9.79 ±5.05 yaş (10 ay-17 yaş) olup, çoğunun adolesan dönemde oldukları (n=59, %53.6) görüldü. Süt çocukluğu döneminde (0-2 yaş) 10, okul öncesi dönemde (>2-5 yaş) 14, okul çağında (>5-10 yaş) 27 hasta bulunmaktaydı. Hastaların çoğunluğu erkekti (n=58,%52.7) (Tablo II). Hastaların %60.9'unda (n=67) son bir yılda nöbet aktivitesine hiç rastlanılmazken, ayda birden fazla nöbet geçirenlerin oranı %13.6 (n=15)'di. Katılımcılardan çocıklarındaki nöbeti tetikleyici faktör yada faktörleri belirtmeleri istendiğinde; belirtilen nöbet tetikleyici faktörler arasında arasında en sık gürültü (n=27, %44.3), ikinci sıklıkla uykusuzluğun (n=19, %31.1) olduğu görüldü.

Olguların 34'ünde (%30.9) epilepsi hastalığına eşlik eden ko-morbid durumlara rastlandı. En sık eşlik eden ko-morbid durumların mental gerilik (n=7), otizm (n=5), öğrenme güçlüğü (n=4) ve fiziksel yetersizlik (n=4) olduğu görüldü. 82 (%74.5) olgunun ailesinde epilepsi hastalığı bulunmazken, 28 (%25.5) olgunun ailesinde epilepsi hastalığı bulunmaktaydı.

Epilepsi tedavisi amacıyla %70 olgunun (n=77) tek bir ilaç kullandığı, %30 olgunun (n=33) birden fazla ilaç kullandığı görüldü. Monoterapide kullanılan antiepileptik ilaçlar levetirasetam (n=25, %22.7), valproik asit (n=24, %21.8), karbamazepin (n=15, %13.6) ve topiramat (n=8, %7.3) ve lamotrijindi (n=5, %4.5) (Tablo III).

38 (%34.5) olguda antiepileptik ilaçlara karşı yan etki gözlenmezken, çoğunlukla birden fazla yan etkinin gözlemlendiği, en sık görülen yan etkilerin sinirlilik (n=39, %35.5), kilo alma (n=20, %18.2), yorgunluk (n=16, %14.5), davranış problemleri (n=13, %11.8), uykusuzluk (n=12,%10.9) ve huzursuzluk (n=12,% 10.9) olduğu görüldü. Tek başına en sık görülen yan etki ise sinirlilikti (n=6, %5.5) (Tablo IV).

Ebeveynlerin çoğu çocuklarıyla ilgili olarak sağlık hizmetlerine erişimlerinin iyi ve çok iyi olduğunu belirtmiş olup (n=88, %80),

Tablo I: Ebeveynlerin demografik veriler (n=110).

	n (%)
Kadın (Anne)	68 (61.8)
Erkek (Baba)	42 (38.2)
Ebeveynlerin Ortalama Yaşı*	38.4 (21-70 yaş)
Kardeş varlığı	
Var	94 (85.5)
Aile Gelir Düzeyi	
Çok iyi-iyi	20 (18.2)
Orta	81 (73.6)
Kötü-Çok Kötü	9 (8.2)
Sağlık Sigortası	103 (93.6)
Var	7 (6.4)
Yok	
Anne Eğitim Durumu	
İlkokul	44 (40)
Ortaokul	37 (33.6)
Lise	21 (19.1)
Üniversite	8 (7.3)
Baba eğitim durumu	
İlkokul	43 (39.1)
Ortaokul	19 (17.3)
Lise	25 (22.7)
Üniversite	23 (20.9)
Yaşanılan yer	
İl	48 (43.6)
İlçe	62 (56.4)

* *Ortalama (min-max)*

Tablo II: Epilesi tanılı çocuklara ait demografik veriler (n=110).

	n (%)
Kız	68 (61.8)
Erkek	42 (38.2)
Ortalama Yaş	9.79±5.05 (10 ay-17 yaş)
Süt çocukluğu (0-2 yaş)	10 (9.1)
Okul öncesi dönem (>2 yaş-5 yaş)	14 (12.7)
Okul çağında (>5 yaş-10 yaş)	27 (24.5)
Adolesan dönem (>10 yaş-17 yaş)	59 (53.6)

Tablo III: Çocuklara uygulanan antiepileptik tedaviler (n=110).

	n (%)
Politerapi	33 (30)
Monoterapi	77 (70)
Levetirasetam	25 (22.7)
Valproik asit	24 (21.8)
Karbamazepin	15 (13.6)
Topiramat	8 (7.3)
Lamotrijin	5 (4.5)

Tablo IV: Yan etkiler ve görülme sıklığı

Yan Etki	n (%)
Sinirlilik	39 (35.5)
Kilo artışı	20 (18.2)
Yorgunluk	16 (14.5)
Davranış problemleri	13 (11.8)
Uykusuzluk	12 (10.9)
Huzursuzluk	12 (10.9)
Konsantrasyon azalması	11 (10.0)
Hiperaktivite	11 (10.0)
Konuşma bozukluğu	10 (9.1)
Mide. bağırsak şikayetleri	10 (9.1)
Kilo kaybı	10 (9.1)
Unutkanlık	9 (8.2)
Yürüyüş bozukluğu	8 (7.3)
Baş ağrısı	7 (6.4)
Diş eti kanaması	7 (6.4)
Titreme	7 (6.4)
Cilt problemleri	7 (6.4)
Görme bozukluğu	6 (5.5)
Baş dönmesi	4 (3.6)
Adet düzensizliği	2 (1.8)

Tablo V: Ebeveynlerin bilgi, tutum ve davranışları (n=110).

	Kesinlikle Katılıyorum/ Katılıyorum n (%)	Kararsızım n (%)	Katılmıyorum / Kesinlikle Katılmıyorum n (%)
Epilepsi hastalığı ilaçlarla etkin bir biçimde tedavi edilebilir.	91 (82.7)	13 (11.8)	6 (5.5)
Epilepsi ilaçlarının yaşam boyu alınması gerekir	33 (30)	37 (33.6)	40 (36.4)
Nöbetler durduktan sonra epilepsi ilaçlarının kullanımına gerek yoktur.	26 (23.7)	18 (16.4)	65.9 (60)
Epilepsi tedavisinin başarılı olabilmesi için ilaçlar düzenli alınması gerekir.	109 (99.1)	-	1 (0.9)
Bazı epilepsi ilaçları için belli aralıklarla ilacın kan seviyesinin saptanması önemlidir	94 (85.5)	13 (11.8)	3 (2.7

doktorlarıyla ilişkilerinin profesyonel anlamda olduğunu (n=103, %93.6) ve epilepsi hastalığı hakkında sahip oldukları bilgiyi sadece doktorlardan öğrenendiğini belirten katılımcı sayısı yüksekti (n=58, %52.7). Ebeveynlerin %36.4'ü (n=40) doktor ile birlikte internet, televizyon, radyo, gazete, dergi, arkadaş, aile ve akrabalar gibi ilave kaynaklardan da hastalık hakkında bilgi edindiklerini belirtirken, %10.9'unun (n=12) ise hastalık hakkında bilgi sahibi oldukları kaynak olarak doktorları belirtmediği, diğer kaynakları belirttiği görüldü.

Epilepsi hastalığının antiepileptik ilaçlarla tedavi edileceğine inanan katılımcı sayısı 91 (%82.7) iken, 13 (%11.8) katılımcı kararsız ve 6 (%5.4) katılımcı epilepsinin ilaçlarla tedavi edilebileceğine inanmamaktaydı. Ancak katılımcıların 109'u (%99.1) tedavisinin başarılı olabilmesi için antiepileptik ilaçların düzenli olarak kullanılması gerektiğini belirttiler. 103 hasta (%93.6) ilaçlarını düzenli kullanırken, 3 olgunun (%2.7) sosyoekonomik yetersizlik, 3 (%2.7) olgunun unutkanlık ve 1 olgunun da (%0.9) nöbet sıklığınının azalması nedeni ile ilaçlarını düzenli kullanmadığı görüldü. Antiepileptik ilaçların ömür boyu alınması gerektiğine inanan katılımcı sayısı 33 (%30), kararsız katılımcı 37 (%33.6) ve inanmayan katılımcı 40 (%36.4) iken katılımcıların çoğu ilaç tedavisi sonrası nöbetlerin kesilmesinin, ilaçların kullanılmasına gerek kalmadığı anlamına gelmeyeceğini belirtti (n=66, %60).

Ayrıca 106 (%96.4) hastanın tedavide sadece antiepileptik ilaç kullandığı, başka bir tedavi yöntemi denemedikleri saptandı. 4 (%3.6) katılımcı çocuklarının hastalığının tedavisinde ilaca ilave olarak hacemat, balık yağı, sirke ve soğuk su kullandıklarını belirtti.

Ebeveynlerin büyük bir bölümü kullanılan ilaçlarla ilgili olarak ilk defa yada yeni bir yan etki ile karşılaştıklarında doktorlarına başvuracaklarını (n=100, %90.9) belirttiler. Epilepsi tedavisi sırasında belli periyodlarla hastanın poliklinik ve ilaç kan düzeylerinin kontrolünün gerektiğini bildiren katılımcı sayısı 94 (%85.5)'di (Tablo V).

TARTIŞMA

Epilepsi, tüm dünyada 70 milyondan fazla insanı etkileyen, en sık görülen kronik hastalıklardan biridir (10). Epilepsi tedavisinde temel hedef, hastalık sırasında görülen nöbetlerin baskılanması, sıklığının azaltılması ve hastanın yaşam kalitesini iyileştirmektir (2). Epilepsinin esas tedavisi farmakoterapi olup, bu amaçla antiepileptik ilaçlar kullanılmaktadır.

Hastaların ve ebeveynlerin hastalık ve tedavileri ile ilgili bilgi düzeyleri, tedavilerine güvenleri ve uyumları tüm hastalıklarda olduğu gibi epilepsi tedavisinin başarısını etkileyebilmektedir. Bizim çalışmamıza katılan ebeveynlerin %99.1'i tedavinin başarılı olabilmesi için antiepileptik ilaçların düzenli olarak kullanılması gerektiğini belirttiler. Yine ebeveynlerin çoğu ilaç tedavisi sonrası

nöbetlerin kesilmesinin, ilaçların kullanılmasına gerek kalmadığı anlamına gelmeyeceğini belirtti (n=66, % 60). Ancak katılımcıların büyük bir bölümü epilepsi hastalığının antiepileptik ilaçlarla tedavi edileceğine inanırken (n=91, %82.7), ilaçların ömür boyu alınması gerektiğine inanan katılımcı sayısının 33 (%30), kararsız katılımcı sayısının 37 (%33.6) ve inanmayan katılımcı sayısının 40 (%36.4) olduğu görüldü. Ayrıca 106 (%96.4) hastanın tedavide sadece antiepileptik ilaç kullandığı belirlendi. Kurt tarafından yapılan çalışmada ebeveynlerin %45.7'si epilepsinin ilaçlarla tedavi edilebilir olduğunu belirtmiş, Zainy ve ark. (12); ebeveynlerin %29'unun non-farmakolojik tedavi yöntemlerini kullandıklarını bildirmiştir (11). Çalışmamızda ebeveynlerin antiepileptik ilaç tedavisine daha yüksek oranda inandıkları ve non-farmakolojik tedavi yöntemlerin daha az kullandıkları görülmüş olup; bu durumun poliklinik kontrollerine geldiklerinde kendilerine verilen epilepsi ve tedavisiyle ilgili eğitimlere bağlı olabileceğini düşünmekteyiz.

Epilepsi tedavisinde kullanılmak üzere pek çok ilaç geliştirilmiş olup, bu ilaçlar nöbet sıklığı ve şiddetinin azalmasını sağlamakla birlikte, kullanımları sırasında bazı yan etkiler gözlemlenebilmektedir (4). Bu yan etkiler hastanın tedaviye uyumunu ve klinik tabloyu olumsuz etkileyebilmektedir Çocukluk çağında antiepileptik ilaç kullanımı ile ilgili yapılan bazı çalışmalarda, Bansal ve ark. (9) hastaların %63.2'sinde, Kaushik ve ark. (15) hastaların %48.5'inde, Anderson ve ark. (13) %31'inde, Mistry ve ark. (14) ise hastaların %26'sında yan etki geliştiğini gözlemlemişlerdir. Bizim çalışmamızda da, Bansal ve ark. (9) yaptığı çalışmaya benzer şekilde, antiepileptik ilaçlara bağlı yan etki görülen olguların oranı %63.5 olarak bulundu. Bununla birlikte literatürde yan etki insidansının çok düşük bulunduğu (%5.3) çalışmalar da mevcuttur (16). Bu farklılıkların nedeni, farklı çalışma popülasyonu, bölgesel olarak farklı ilaçların kullanımı ve/veya farklı çalışma metodolojisinin benimsenmesi olabilir.

Kaushik ve ark. (15), pediatrik epilepsili hastaların büyük çoğunluğunda bilişsel yan etkilerin görüldüğünü, bunu nörolojik etkilerin, kilo değişikliklerinin, davranışsal ve motor yan etkilerin izlediğini belirtmişlerdir. Junger ve ark. (17) ise epileptik olgularının çoğunluğunun davranışsal ardından genel nörolojik ve bilişsel yan etkilerle karşılaştıklarını ortaya koymuşlardır. Anderson ve ark. (13) yan etki olarak en sık davranış problemleri (%19.3) ve somnolans (%15.8) ile, Mistry ve ark. (14) irritabilite ve sonrasında uyuşukluk (%18.6) ile karşılaştıklarını belirtmişlerdir. Kaushik ve ark. (15)ise karşılaştıkları en yaygın yan ilaç etkisinin okul başarısının olumsuz etkilenmesi (%33.8), ikinci etkinin uykuya meğil (%25.9) olduğunu bildirmişlerdir (14). Bizim çalışmamızda ise hastalarda genellikle birden fazla yan etkinin gözlemlendiği, çoğunlukla gözlemlenen yan etkilerin sinirlilik (n=39, %35.5), kilo alımı (n=20, %18.2), yorgunluk (n=16, %14.5), davranış problemleri (n=13, %11.8), uykusuzluk (n=12,%10.9) ve huzursuzluk (n=12,%10.9) olduğu, tek başına en sık görülen advers etkinin ise sinirlilik (n=6, %5.5) olduğu görüldü (Tablo IV).

Yapılan çalışmalarda çocuklarda antiepileptik ilaç kullanımına bağlı yan etki görülme sıklığının yaş grubuna ve cinsiyete göre farklılık gösterebildiği belirtilmiştir. Kaushik ve ark. (15) yaptıkları çalışmada yan etki gelişen çocukların çoğunun 10 yaşından büyük olduğunu, Bansal ve ark. (9) yan etki gelişen çocukların daha büyük yaşlarda olduklarını saptamışlardır (9). Her iki çalışmada da kız çocuklarında daha fazla yan etki görüldüğü gözlemlenirken (%55.4, %71.3), bazı çalışmalarda yan reaksiyonların erkek çocuklarında daha fazla gözlendiği belirtilmiştir (14,16,18-20). Bizim çalışmamızda ise yan reaksiyonların %70.4 oranıyla en fazla okul çocukluk çağında (5-10 yaş), en az süt çocukluğu döneminde (0-2 yaş) gözlemlendiği (%50) görüldü. Ancak yan etki görülme sıklığı açısından çocukluk çağı yaş grupları arasında istatistiksel olarak anlamlı bir fark olmadığı görüldü (p>0.05). Cinsiyete göre yan etki görülme sıklığını değerlendirdiğimizde kız çocuklarında (n=52,%71.2) erkek çocuklarından (n=58,%60.3) daha sık gözlemlendiği görüldü. Ancak bu sıklık farkı da istatistiksel olarak anlamlı değildi (p>0.05).

Günümüzde epilepsi tedavisinde kullanılmak üzere piyasaya sunulmuş pek çok ilaç olup, etki ve güvenlik profilleri daha iyi ilaçların geliştirilmesi için çalışmalar devam etmektedir. Tarihsel süreç içinde ortaya çıkan; klonazepam, karbamazepin, etosuksimid, fenobarbital, primidon, fenitoin ve valproik asit birinci nesil, gabapentin, lamotrijin, levetirasetam, okskarbazepin, topiramat ve zonisamid ikinci nesil, brivarasetam, klobazam, kannabidiol, cenobamat, eslikarbazepin asetat, lakozamid, perampenel ve rufinamid ise üçüncü nesil antiepileptik ilaçlar olarak ifade edilmektedir (21-23).

Genel olarak yeni nesil antiepileptik ilaçlarda, eski ilaçlara kıyasla daha az yan etki görüldüğü belirtilmektedir (24). Anderson ve ark. (13) yan reaksiyonlara en sık neden olan antiepileptik ilaçların valproik asit (%33) ve karbamazepin (%25) olduğunu bildirmişlerdir (16). Kaushik ve ark.(15), okul başarısında düşüklüğe en fazla yol açan antiepileptik ilacın valproik asit olduğunu, bunu sırası ile fenitoin ve karbamazepin izlediğini belirtmişlerdir. Benzer durum Bansal ve ark. (9) çalışmasında da görülmüştür. Bizim çalışmamızda monoterapide kullanılan ilaçlardan karbamazepinde %73.3 (n=11/15), valproik asitte %66.7 (n=16/24), levetirasetamda %60 (n=15/25), topiramatta %50 (n=4/8) ve lamotrijinde %40 (n=2/5) yan etki oranı bulundu. Bu oranların yapılan diğer çalışmalara göre daha yüksek bulunmasının, hastanemizin ilimizdeki tek üçüncü basmak sağlık kurumu olması nedeniyle, tedaviye dirençli hasta sayımızın yüksekliği ile ilişkili olabileceğini düşünmekteyiz.

Farmakoterapinin başarısı açısından, kullanılan ilaçlar kadar, kullanılan ilaç sayısı da önem arz etmektedir. Bu durum gerek hastanın tedaviye uyuncu gerekse yan etkilerin sıklığı, takibi

ve değerlendirilmesi açısından önemlidir. Pediatrik epilepsi tedavisinde tercih edilen yöntem; tek ilaçla tedavi, monoterapidir. Ancak nöbet tipine ve nöbetlerin tedaviye direncine bağlı olarak, hastalarda birden fazla ilaçla tedavi, politerapi gerekebilmektedir (25,26).

Kaushik ve ark. (15) yaptıkları çalışmada monoterapi oranı %87 iken, politerapi oranı %13 olarak bulunmuştur. Kaushik ve ark. (15) çalışmalarında monoterapide en sık kullanılan antiepileptik ilacın sodyum valproik asit (%49) olduğunu, 2. sıklıkla feniotin kullanıldığını, benzer şekilde Kousalya ve ark. da (16) en yaygın olarak sodyum valproik asitin (%37.02) ardından fenitoinin (%23.83) kullanıldığını bildirmişlerdir. Bansal ve ark. (9) ile Mathur ve ark. (18) en sık kullanılan ilacın fenitoin olduğunu, George ve ark. (19) ise en sık kullanılan antiepileptik ilaçların klobazam (%37) ve fenitoin (%25.5) olduğunu belirtmişlerdir (15). Bizim çalışmamızda da hastaların çoğunda monoterapi uygulandığı (%70), politerapi uygulanma oranının %30 olduğu görüldü. Politerapi oranın diğer çalışmalara göre yüksek olmasının nedeni Covid-19 pandemisi nedeni ile çalışmaya dahil edilen olgu sayısının az olması ve tedaviye dirençli hasta sayımızın yüksekliği ile ilişkili olabileceği düşünüldü. Politerapi uygulanan hastalarda yan etki görülme oranı (n=24/33, %72.7), monoterapi uygulanan hastalara göre istatistiksel olarak anlamlı olmasa da (p>0.05) daha yüksek bulundu (n=48/77, %62.3).

Literatürden farklı olarak bizim çalışmamızda monoterapide kullanılan antiepileptik ilaçlar sırasıyla levetirasetam (n=25, %22.7), valproik asit (n=24, %21.8), karbamazepin (n=15, %13.6) ve topiramat (n=8, %7.3) ve lamotrijin (n=5, %4.5) olarak bulundu. Çalışmamıza dahil olan monoterapi yada politerapi gören tüm hastalar birlikte değerlendirildiğinde ise en sık kullanılan kullanılan antiepileptik ilacın levetirasetam (n=31, %28.2) olduğu, bunu valproik asitin (n=28, 25.5) izlediği görüldü.

Kronik hastalıklarda hastanın kliniğinin, kullandığı ilaçların etkinliğinin, olası yan etkilerin belirli aralıklarla takibi ve gerektiğinde ilaç yada doz değişikliğine gidilmesi tedavinin başarısını ve güvenliğini etkileyen en önemli faktörlerden biridir. İlaca ve hastaya bağlı bazı faktörler nedeniyle bazen de ilacın kan ilaç düzeyi izlemi de gerekebilmektedir. Bu durum özellikle terapötik aralığı dar olan antiepileptik ilaçların kullanımı sırasında, ilaç etkinliliğinin sürdürülebilmesi ve toksik etki olasılığının azaltılması açısından gereklidir. Bu anlamda hastaların sağlık hizmetlerine kolay erişebilir olması önem arzetmektedir. Çalışmamıza katılan ebeveynlerin çoğunluğu (n= 94, %85.5) epilepsi tedavisi sırasında belli periyodlarla hastanın poliklinik ve ilaç kan düzeylerinin kontrolünün gerektiğini belirtti. Sağlık hizmetlerine ulaşılabilirlik açısından ise çoğu sağlık güvencelerinin olduğunu (n=103, %93.6) ve çocuklarıyla ilgili olarak sağlık hizmetlerine erişimlerinin iyi ve çok iyi olduğunu ifade ettiler (n=88, %80).

Sonuç olarak; çalışmamızda elde edilen verilerin çocuklarda antiepileptik ilaç tedavisi sırasında karşılaşılabilecek yan etki profilinin aydınlatılmasına ve ebeveynlerin epilepsi hastalığı, tedavisi ve çocuklarının kullandığı ilaçlar hakkında eğitim ve bilgilendirilmelerinde katkı sağlayacağını düşünmekteyiz. Benzer çalışmaların ülkemizde ve dünya genelinde yapılmaya devam etmesi gerektiği ve elde edilecek verilere bağlı olarak sağlık hizmeti sunucuları tarafından yapılacak düzenleme ve planlamaların halk sağlığı açısından önemli olduğu kanaatindeyiz.

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Konjenital Nazolakrimal Kanal Tıkanıklığının Doğum Şekliyle İlişkisi

The Relationship Between Congenital Nasolacrimal Duct Obstruction and Mode of Delivery

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ÖZ

Amaç: Konjenital nazolakrimal kanal tıkanıklığı (KNLKT) görülme insidansı ile doğum şekli arasındaki ilişkiyi incelemektir.

Gereç ve Yöntemler: Çalışmaya 2014-2017 yılları arasında epifora şikayetiyle başvuran KNLKT tanısı alan hastalar dahil edildi. Hastaların demografik ve klinik özellikleri belirlendi ve hastalar doğum şekline göre sezaryen doğum (SD) veya normal vajinal yolla doğum (NVD) olarak iki gruba ayrıldı. KNLKT görülme sıklığı, cinsiyet ve lateralite özellikleri gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya başvuru yaşı ortalama 5.5±4.6 ay olan 62 hastanın 75 gözü dahil edildi. Çalışmaya dahil edilen hastaların doğum şekli %59.7'sinde NVD iken %40.3'ünde sezaryendi doğumdu. Hastaneye başvuru yaşı ve lateralite açısından gruplar arasında istatistiksel olarak anlamlı fark bulunmamaktaydı (p=0.501 ve p=0.624). Doğum şeklinin NVD ya da SD olması ile KNLKT görülme sıklığı arasında farklılık yoktu (p=0.128).

Sonuç: Çalışmamızda doğum şekli ile KNLKT görülme sıklığı arasında farklılık tespit edilmemiştir ancak sezaryen doğumun KNLKT için artmış bir risk faktörü olarak etyopatogenezdeki rolü literatürde tartışmalı olarak devam etmektedir.

Anahtar Sözcükler: Doğum şekli, Epifora, Konjenital nazolakrimal kanal tıkanıklığı, Konjenital dakriyostenoz

ABSTRACT

Objective: To investigate relationship between incidence of congenital nasolacrimal duct obstruction (CNLDO) and mode of delivery.

Material and Methods: Patients with epiphora, diagnosed as CNLDO in 2014-2017 years were enrolled the study. Demographic and clinical properties of the patients were identified and patients were divided into two groups according to mode of delivery, as cesarean section delivery (CSD) and normal vaginal delivery (NVD). Frequency of CNLDO, gender and laterality were compared between groups.

Results: Seventy five eyes of sixty two patients with mean age 5.5±4.6 months were included in the study. Of the patients included in the study; mode of delivery was NVD in 59.7% of the patients and CSD in 40.3% of the patients. There was no statistically significant difference between two groups according to age and laterality (p=0.501 and p=0.624). There was no difference between mode of delivery (CSD or NVD) and incidence of CNLDO (p=0.128).

Conclusion: There was no difference between mode of delivery and frequency of CNLDO in our study, however the role of CSD in the etiopathogenesis of CNLDO is still controversial according to the literature.

Key Words: Mode of delivery, Epiphora, Congenital nasolacrimal duct obstruction, Congenital dacryostenosis

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Yazarların katkısı / Contribution of the Authors*: *DAĞ ŞEKER E: 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. ***ERBAHÇECİ TİMUR İE:*** 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.

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GİRİŞ

Konjenital nazolakrimal kanal tıkanıklığı (KNLKT), yaşamın ilk yılındaki epiforanın en sık sebebidir (1). İnsidansı %11 ile %20 arasında bildirilmiştir (1-3).

Genellikle yaşamın ilk haftalarından sonra, tek ya da iki taraflı olarak, sulanma, kapak kenarlarında mukoid sekresyon birikmesi, kirpiklerde ıslanma ile başlayıp, staza sekonder enfeksiyon eklenmesiyle sekresyonun mukopurülan karakter kazanması ve tekrarlayıcı konjonktivit tablosuyla prezente olmakta, persistan vakalar dakriyosistit, preseptal selülit, orbital selülit ve menenjit ile komplike olabilmektedir (4-6). Gerek sulanma ve çapaklanmanın deprivasyon etkisiyle, gerek KNLKT olan çocuklardaki artmış hipermetropi görülme sıklığı sebebiyle, ambliyopi riski de taşımaktadır (7,8).

Nazolakrimal kanal doğumda henüz olgunlaşmamıştır. Tıkanıklığın en sık nedeni Hasner valvinde veya nazolakrimal kanalın meatus nazi inferiora açıldığı distal uçta gelişen membranöz tıkanıklıktır (9,10). Belirtiler genellikle yaşamın ilk birkaç haftasında ortaya çıkar (1,10). Yaşamın ilk aylarında genellikle kendiliğinden açılan bu tıkanıklık, gerektiğinde hidrostatik basıncı artıracak şekilde yapılan masaj ile, olguların %96 kadarında, yaşamın ilk yılında açılabilmektedir (11-14).

Bu çalışmanın amacı son yıllarda artan sezaryen doğum (SD) oranlarının, yaşamın ilk yıllarında sık hastane ziyareti, takip ve tedavi gerektiren, ambliyopi riski de taşıyan KNLKT sıklığıyla ilişkisini değerlendirmektir.

GEREÇ ve YÖNTEMLER

Mart 2014- Şubat 2017 tarihleri arasında 1 yaş altında epifora ve/veya çapaklanma şikayeti ile polikliniğe başvuran hastalar nazolakrimal kanal tıkanıklığı açısından değerlendirildi. Çalışma için Ankara Şehir Hastanesi 1 Nolu Klinik Araştırmalar Etik Kurulu'ndan E1-21-2042/22.09.2021 numaralı onay alındı ve çalışma Helsinki Deklarasyonu prensiplerine uygun olarak yapıldı.

Şikayetlerin doğumun 1. ayından sonra başlamış olması, rekürren karakterde olması, kese bölgesine bastırılınca sekresyon gelmesi bulgularıyla konjenital dakriyositenozdan şüphelenilmiş ve tanıyı kesinleştirmek için fluoresein boya kaybolma testi yapılarak pozitif sonuçlanan hastalar çalışmaya dahil edilmiştir. Hasta grubunu zamanında doğan (>38 hafta), normal gelişim gösteren, KNLKT dışında sağlık problemi olmayan bebekler oluşturmaktaydı. Ayrıca preterm doğan, yenidoğan yoğun bakım ihtiyacı olan, ek hastalığı olan hastalar çalışma dışı bırakıldı. Çalışmaya dahil edilen hastaların yaş, cinsiyet, lateralite ve doğum şekli bilgileri takip dosyalarından elde edildi.

Verilerin analizi SPSS version 20 programı ile yapıldı. SD ile normal vajinal yolla doğum (NVD) arasında tanımlayıcı ve sayısal parametrelerin karşılaştırılmasında Mann-Whitney U testi kullanıldı. Çalışmaya 62 hastanın 75 gözü dahil edildi. Ancak aynı bireyin iki gözü arası korelasyondan kaynaklanabilecek istatistiksel hata riski nedeniyle, gruplar arası analizler 62 hasta üzerinden yapıldı. Testlerin değerlendirilmesinde "p" değerinin 0.05'den küçük olması ($p<0.05$) istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya dahil edilen 62 hastanın 35'i (%56.5) erkek, 27'si (%43.5) kızdı. Doğum şekli 37 hastada (%59.7) NVD iken 25 hastada (%40.3) SD'di. Çalışmamızda doğum şeklinin NVD ya da SD olması ile KNLKT görülme sıklığı arasında ilişki saptanmadı ($p<0.128$).

Toplam 62 hastanın 75 gözüne KNLKT tanısı kondu. Tıkanıklık hastaların 30'unda (%48.4) sağda, 19'unda (%30.6) solda ve 13'ünde (%21) bilateraldi. Hastane başvuru yaşı ortalaması 5.5±4.6 aydı (Tablo I).

NVD grubunda hastaneye başvuru yaşı 5.1±4.1 ay iken SD grubunda 6.2±5.5 aydı ve iki grup arasında hastaneye başvuru yaşı istatistiksel olarak anlamlı farklılık göstermemekteydi ($p=0.501$). NVD grubunda KNLKT hastaların 20'sinde (%54.1) sağ gözde, 8'inde (%21.6) sol gözde ve 9'unda (%24.3) her iki gözde iken SD olan grupta hastaların 10'unda (%40) sağ gözde, 11'inde (%44) sol gözde ve 4'ünde (%16) her iki gözdeydi ve gruplar arasındaki KNLKT lateralitesindeki farklılık istatistiksel olarak anlamlı değildi ($p=0.624$). NVD grubunda hastaların 17'si (%45.9) erkek iken SD grubunda hastaların 18'i (%72) erkekti ve gruplar arasındaki cinsiyet farklılığı istatistiksel olarak anlamlıydı ($p=0.044$) (Tablo II).

2014-2016 yılları arasında Türkiye'deki sezaryen doğum oranı %38'di ve çalışmamızdaki SD oranı ise %40.2 bulundu. Çalışmamızdaki SD oranını Türkiye'deki SD oranı ile karşılaştırmak için kullanılan binomial test ile yapılan istatistiksel analizde, çalışmamızdaki SD oranı Türkiye'deki SD oranı ile benzer bulundu ($p=0.399$) (Şekil 1).

Tablo I: Hastaların demografik ve klinik özellikleri.

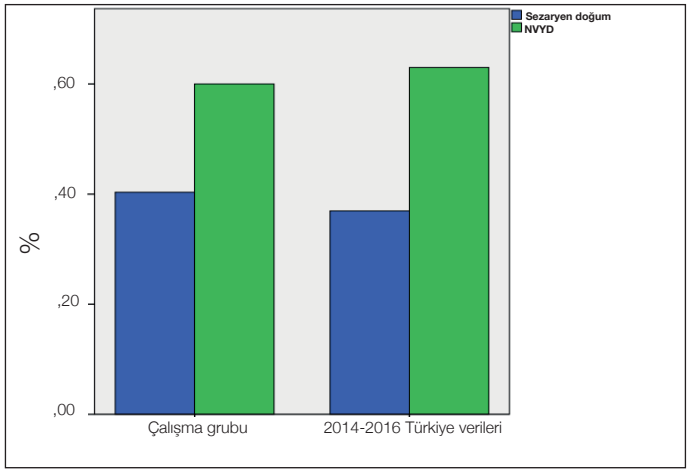
Parametre	
Cinsiyet*	
Kız	27 (43.5)
Erkek	35 (56.5)
Hastane başvuru yaşı (ay, ort±SS)	5.5±4.6
Doğum şekli*	
NVD	37 (59.7)
SD	25 (40.3)
Lateralite*	
Sağ	30 (48.4)
Sol	19 (30.6)
Bilateral	13 (21)

NVD: *Normal vajinal yolla doğum,* ***SD:*** *sezaryen doğum,* ******* *n(%)*

Tablo II. Hastaların demografik ve klinik özelliklerinin doğum şekline göre karşılaştırılması.

	NVD n (%)	SD n (%)	p
Sayı	37 (59.8)	25 (40.2)	0.128
Hastane başvuru yaşı (ay, ort±SS)	5.1±4.1	6.2±5.5	0.501
Cinsiyet (n, K/E)	20/17 (54.1/45.9)	7/18	0.044*
Lateralite			
Sağ	20 (54.1)	10 (40)	
Sol	8 (21.6)	11 (44)	0.624
Bilateral	9 (24.3)	4 (16)	

E: *Erkek,* ***K:*** *Kız,* ***NVD:*** *Normal vajinal yolla doğum,* ***SD:*** *Sezaryen doğum*



Şekil 1: 2014-2016 Türkiye doğum verileri ile çalışma grubunun karşılaştırılması.
NVYD: *Normal vajinal yolla doğum*

TARTIŞMA

Konjenital nazolakrimal kanal tıkanıklığının bilinen risk faktörleri, prematürite, kraniofasial hastalıklar, Down Sendromu, maternal enfeksiyonlar, genetik yatkınlıktır (2,3,15). Ancak son yıllarda artan SD oranları göz önünde bulundurulduğunda doğum şeklinin KNLKT etyopatogenezinde rol alabileceği öngörülmüş ve yapılan çalışmalarda farklı sonuçlar bildirilmiştir. Bazı çalışmalarda SD ile KNLKT arasında ilişki bulunurken, bazı çalışmalarda sadece ilk doğumun SD olması ya da kompleks doğumların KNLKT ile ilişkili olduğu bildirilmiştir (16-21).

Spaniol ve ark. (19) yaptığı bir çalışmada ilk doğumun SD olmasının KNLKT için artmış bir risk faktörü olduğunu göstermişlerdir. Alakuş ve ark. (20) ilk doğumun SD olmasının ve ailede KNLKT hikayesi olmasının KNLKT etyopatogenezinde önemli bir risk faktörü olabileceğini bildirmişlerdir. Bu iki çalışmada da ilk ve tekrarlayan SD'ler ayrı ayrı olarak incelenmiş ve ilk doğum SD olanlarda KNLKT görülme sıklığı artmış olarak bulunmuştur. Literatürde yapılan çalışmalar göz önüne alındığında SD ile KNLKT görülme sıklığı arasındaki ilişkiyi araştırırken, yalnızca ilk doğumları değil, tüm doğumların dikkate alınması gerektiği vurgulanmaktadır. Ancak bizim çalışmamızda bu ayrımın yapılmamış olması çalışmamızın bir kısıtlılığıdır.

İlk doğum NVD olanlarda ilk doğum SD olanlara kıyasla KNLKT görülme sıklığının daha az bulunduğu çalışmalarda doğum sırasındaki yüksek dış basınç ve kollajenolitik aktivitenin Hasner membranında açılmaya neden olabileceği ileri sürülmüştür (16,17). Ancak bu çalışmalara dahil edilen hasta sayılarının azlığı ve bu çalışmalarda kendiliğinden rezolüsyon oranlarının düşük bildirilmiş olması da çalışmaya dahil edilme kriterlerinde güvenilirliğin sağlanamamış olabileceği fikrini desteklemektedir.

KNLKT tespit ettiğimiz hastalarda SD oranı %40.2 iken aynı dönemde Türkiye'de SD oranı %38'di. Çalışmamızda SD oranı Türkiye ortalamasından fazla olsa da bu farklılık istatistiksel olarak anlamlı değildi. Daha geniş hasta sayılarını içeren çalışmalarla KNLKT etyopatogenezinde doğum şeklinin KNLKT ile ilişkisi aydınlatılabilecektir.

Yaptığımız çalışmada doğum şeklinin NVD ya da SD olmasının KNLKT görülme sıklığı arasında ilişki tespit edilmedi. Bu yönü ile Yıldız ve ark.'nın (22) ülkemizde yaptığı 40 olguyu içeren çalışmada ve Amerika'da yapılmış 17.713 yenidoğanın dahil edildiği 1998 KNLKT tanısı ile takip edilmiş on yıllık verileri içeren geniş kohort çalışmasında SD oranı ile KNLKT görülme sıklığı arasında bir ilişki saptanmamış olması bizim çalışma sonuçlarımızla benzerlik göstermektedir (2).

Literatürde KNLKT çoğunlukla tek taraflı görünürken olguların %20'sinde iki taraflı olduğu bildirilmiştir. Bizim çalışmamızda da hastaların %21'inde KNLKT iki taraflıydı ve literatürle uyumluydu (23). Çalışmamızda SD ile doğan erkek bebeklerde kız bebeklere göre KNLKT daha sık tespit edilmiştir. Ancak literatürde bu sonuçla uyumlu herhangi bir veriye rastlanmamıştır. Çalışmaya dahil edilen hasta sayısının azlığı bu sonucun anlamlılığını düşürmekle birlikte daha geniş hasta sayılarının dahil edileceği çalışmalara ihtiyaç vardır.

Sonuç olarak; bizim çalışmamızda doğum şekli ile KNLKT görülme sıklığı arasında ilişki tespit edilmemiştir. KNLKT çok faktörlü etyopatogeneze sahiptir ve doğum şeklinin bu etyopatogenezdeki rolü tartışmalı olarak devam etmektedir.

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The Presence of Atopic March in Patients Diagnosed with Atopic Dermatitis

Atopik Dermatit Tanılı Hastalarda Atopik Yürüyüşün Varlığı

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ABSTRACT

Objective: Atopic march is a model that explains the progression of allergic diseases from atopic dermatitis (AD) to allergic asthma and rhinitis. In our study, while evaluating the presence of allergen sensitivity and allergic diseases in patients who were diagnosed with AD and followed up until the age of at least 5 years, we wanted to investigate how much the definition of classical atopic gait responded to expectations.

Material and Methods: We retrospectively reviewed the file records of patients diagnosed with atopic dermatitis, whose ages were 2 years and under at the time of application and followed up regularly until at least 5 years of age. We recorded the clinical and laboratory findings. We noted the allergic disease status and allergen sensitivity of the patients when they were 5 years old.

Results: Forty-one patients with a diagnosis of AD who met the criteria were identified. During the application, we found food sensitivity in 28 (68.3%) patients. When 41 patients reached the age of 5, 13 (31.7%) were diagnosed with asthma and 12 (29.2%) were diagnosed with allergic rhinitis.

Conclusion: We found the frequency of asthma and allergic rhinitis higher in patients with AD than in the normal population. However, we could not show a relationship between food sensitivity and the development of asthma and/or allergic rhinitis. Effective skin care in AD can be protective for developing of allergic diseases. In order for clinicians to understand the heterogeneity of atopic disease models in children and to eliminate this variability, infants with AD should be followed up in later life.

Key Words: Allergic rhinitis, Allergy, Asthma, Atopic dermatitis, Food allergy

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ÖZ

Amaç: Atopik yürüyüş, alerjik hastalıkların atopik dermatitten (AD) alerjik astım ve rinite ilerlemesini açıklayan bir modeldir. Çalışmamızda AD tanısı konan ve en az 5 yaşına kadar takip edilen hastalarda alerjen duyarlılığı ve alerjik hastalık varlığını değerlendirirken, klasik atopik yürüyüş tanımının beklentilere ne kadar cevap verdiğini araştırmak amaçlanmıştır.

Gereç ve Yöntemler: Başvuru sırasında yaşları 2 yaş ve altında olan, AD tanılı, ve en az 5 yaşına kadar düzenli olarak takip edilen hastaların dosya kayıtları geriye dönük olarak incelendi. Klinik ve laboratuvar bulguları kaydedildi. Hastaların 5 yaşında iken alerjik hastalık varlığı ve alerjen duyarlılık durumları not edildi.

Bulgular: Kriterleri karşılayan AD tanılı 41 hasta belirlendi. Başvuru sırasında 28 (%68.3) hastada besin duyarlılığı saptandı. Hastaların 5 yaşına geldiğinde 13 (%31.7)'ünde astım, 12 (%29.2)' sinde alerjik rinit tanısı saptandı.

Sonuç: AD'li hastalarda astım ve alerjik rinit sıklığı normal popülasyon verilerine göre daha yüksek bulundu. Ancak gıda duyarlılığı ile astım ve/veya alerjik rinit gelişimi arasında bir ilişki gösterilemedi. AD'de etkili cilt bakımının, alerjik hastalıkların gelişmesine karşı koruyucu olabileceği düşünüldü. Klinisyenlerin çocuklarda atopik hastalık modellerinin heterojenliğini anlamaları ve bu değişkenliği ortadan kaldırabilmeleri için AD'li bebeklerin sonraki yaşamlarında takip edilmeleri faydalı olacaktır.

Anahtar Sözcükler: Alerjik rinit, Alerji, Astım, Atopik dermatit, Besin alerjisi

INTRODUCTION

Atopic dermatitis (AD) is a chronic, itchy, recurrent inflammatory skin disease that affects 2-20% of the general population (1). Studies show that having AD is associated with the later development of other atopic diseases known as "atopic march" (2,3). Today, food allergy and AD are the early steps of atopic march, while allergic rhinitis and asthma are the late steps. It is believed that the concept of atopic march helps to recognize allergic patients that may develop in the future and to provide their treatment or prevention. However, instead of focusing on the classical atopic march, studies have stated that it would be beneficial to develop this concept today (4,5). In our study, while evaluating allergen sensitivity and the presence of allergic diseases in patients diagnosed with AD and followed up up to the age of at least 5 years, we also wanted to investigate how well the classical atopic march responds to the expectations for predicting allergic diseases.

MATERIALS and METHODS

Based on the Hanifin-Rajka Criteria, we analyzed the file records of patients who were diagnosed with atopic dermatitis and 2 years of age or younger at the time of admission, followed up regularly until at least 5 years of age, and without any additional chronic disease (6). We recorded the following parameters and identified the groups.

We retrospectively reviewed the file records of patients diagnosed with atopic dermatitis whose, ages were 2 years and under at the time of application and followed up regularly until at least 5 years of age.

We recorded the application dates of the patients. We divided it into 2 groups according to the age of diagnosis of AD, diagnosed in the first 6 months and diagnosed over 6 months. We recorded total IgE and blood eosinophil levels in peripheral blood at admission, 3 years old and 5 years old. According to previous studies, we considered 470 eosinophils / µL and higher values for eosinophilia and 45 IU/ml and higher concentrations at Total IgE level as high (7).We recorded the results of the skin prick test (SPT) at the time of admission and at the age of five. SPT results were considered positive if a wheal size was >3 mm compared with the negative control. In the application; grasses/cereals, trees I-II mixture, mushrooms I-II mixture, Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat-dog epithelium, cow's milk, chicken egg white-yolk, wheat flour commercial extracts (Allergovit, Allergopharma, Germany) were used. Age of five and over, pollens (Grasses (herbs), Artemisia vulgaris (wormwood), Alnus glutinosa (alder), Populus alba (poplar tree), Betula alba (birch), Fagus silvatica (beech), Parietaria officinalis (sticky grass), Olea europaea (olive tree)]; mites (Dermatophagoides pteronysinus, Dermatophagoides farinae); animal epithelium [Felis domesticus (cat), Canis familiaris (dog), Blatella germanica (cockroach)]; Commercial extracts of fungi (Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus) (Alk-Abello®, Hørsholm, Denmark) were used. We noted specific IgE levels on house dust mite, cat and dog hair, grasses / cereals pollen, cow's milk, chicken egg whites and yolks, and wheat allergens operated by the ImmunoCAP (Phadia AB®, Uppsala, Sweden) method. We accepted 0.35 kU/L and above as positive for allergen-specific IgE value. We considered the patient atopic in case of positivity to at least one allergen according to SPT and/or allergen specific IgE results at the time of application.We recorded the SCORAD scores of patients with mild atopic dermatitis below 20 points, moderate between 20 and 40 points, and severe atopic dermatitis above 40 (8). We considered the detection of more than 2 positivity in SPT and/or allergen specific IgE values as multiple sensitivity to allergens. According to the IgA levels of Turkish children, we classified the IgA levels of our patients as low, normal and high at the time of admission and between the ages of 5-6 (9).Although the use of skin moisturizing creams or emollients was recommended to all patients, topical corticosteroids and topical Calcineurin Inhibitors were used for.

Ethics committee approval was received for this study from the Local Ethics Committee of Dokuz Eylül University, School of Medicine (approval number: 2021/03-34).

Statistical analysis

Kolmogorov Smirnov normality test was performed to select the statistical methods to be used. If any group did not meet the normality assumption, nonparametric test methods were chosen. The chi-square and Fisher's exact tests were used to analyze the relations between categorical variables or differences between groups. Logistic regression analysis was performed to determine the risk factors thought to affect the development of asthma and allergic rhinitis, and correlation analysis was performed to determine related factors. Statistical analysis of the study was performed using IBM SPSS Statistics for Windows, Version 25 and the statistical significance limit was determined as $p \leq 0.05$.

RESULTS

We identified 645 patients, but we included 41 patients with a diagnosis of AD who met our criteria. The median age of diagnosis of AD was 7 (min-max: 2-11) months. When the patients were classified according to AD diagnosis age, 19 (46.3%) were in the range of 0-6 months and 22 (53.7%) were older than 6 months. We found a relationship between the increase in the age of diagnosis of AD and the development of asthma at the age of 5 years ($p = 0.040$; $r = 1.00$).

Twenty (48.8%) of the 21 patients who went to daycare were between the ages of 2-5. It was observed that AD often improved in the first 24 months in patients who went to daycare ($p = 0.010$). The demographic characteristics and laboratory findings of the patients are summarized in Table I.

Table I: Demographic Characteristics and Laboratory Findings of the Cases.

Category	n (%)
Gender	
Female	10 (24.4)
Male	31 (75.6)
Presence of atopy in parents	
Yes	22 (53.7)
No	19 (46.3)
Bronchiolitis attack in the first 3 years	
Yes	30 (73.2)
No	11 (26.8)
Bronchiolitis attack in the last 12 months	
<3	26 (63.4)
≥3	15 (36.6)
Scorad score	
Mild	15 (36.6)
Moderate/Severe	26 (%63.4)
AD recovery age	
<24 months	20 (48.8)
>24 months	21 (51.2)

AD: *Atopic dermatitis*

Table II: Allergen Sensitivity Of Patients At Age 5 According To Skin Prick Tests.

Allergen sensitivity	n (%)
Egg	2 (4.9)
Egg+ grasses / grains	1 (2.4)
Egg+Fungi	4 (9.8)
Cow milk+Cat epithelium / hair	1 (2.4)
Wheat+Mites	1 (2.4)
Grasses / grains	4 (9.8)
Mites	2 (4.9)
Cat epithelium / hair	2 (4.9)
Fungi	1 (2.4)
Grasses / grains+Mites	1 (2.4)

Table III: Presence of an allergic disease at age 5 in patients.

Allergic disease	n (%)
No	21 (51.2)
Food allergy	9 (21.9)
Asthma	7 (17.1)
Allergic Rhinitis	6 (14.6)
Urticaria	1 (2.4)
Atopic dermatitis	0 (0)
Asthma + Allergic Rhinitis	6 (14.6)

During the application, we found food sensitivity in 31 (75.6%) patients according to allergen-specific IgE results and 28 (68.3%) patients according to SPT. 19 (46.3%) of the patients had egg sensitivity, 6 (14.6%) had cow milk sensitivity, and 3 (7.3%) had both cow milk and egg sensitivity. We did not detect aeroallergen sensitivity in any of our patients. However, when the patients reached the age of 5, according to SPT, aeroallergen sensitivity developed in 17 (41.4%). When they were 5 years old, 2 (4.9%) patients were sensitive to only food, 10 (24.4%) patients to only aeroallergens, 7 (17.1%) patients to both food and aeroallergens. However, all patients could consume the foods they were sensitive to without any problems. We found that the most common aeroallergen sensitivity in grasses/grains 6 (14.6%). When 41 patients reached the age of 5, 13 (31.7%) were diagnosed with asthma and 12 (29.2%) were diagnosed with allergic rhinitis. Of the 31 patients who were found to have food sensitivity at the time of application, 10 (32%) were diagnosed with asthma and 8 (25%) were diagnosed allergic rhinitis at the age of 5. However, there is no significant relationship between the presence of food allergy and the development of asthma ($p = 0.900$) or allergic rhinitis ($p = 0.250$). The allergen sensitive of the patients at the age of 5 is shown in Table II, and the development of allergic diseases in Table III.

The median Scorad score of the patients was 22 (min-max: 12-48). According to this scoring system, 15 (36.6%) of the

Table IV: Patients' total ige level, absolute eosinophil count, scorad score, age at admission and differences between gender.

Category	Female Median (Min-Max)	Male Median (Min-Max)	p	Total Median (Min-Max)
AD Diagnosis Age (Months)	4.5 (2-9)	7 (2-11)	0.180	7 (2-11)
Application Age (Months)	9 (2-23)	9 (3-21)	0.980	9 (2-23)
Scorad score	22.5 (15-38)	21 (12-48)	0.960	22 (12-48)
AEC in application (/uL)	200 (10-800)	400 (100-2200)	0.030	400 (10-2200)
Total IgE in application (IU/ml)	28.5 (10.6-158)	25.8 (1.1-322)	0.840	25.8 (1.1-322)
Total IgE at age 3 (IU/ml)	71.5 (20.7-303)	57.5 (9.8-568)	0.440	60.5 (9.8-568)
Total IgE at age 5 (IU/ml)	92.8 (17.1-350)	75 (14.6-818)	0.770	84 (14.6-818)
AEC at age 5 (/uL)	200 (0-400)	300 (100-900)	0.009	300 (0-900)
IgA at age 5 (mg/dl)	78.5 (41-100)	89 (48-317)	0.010	87 (41-317)

AD: *Atopic dermatitis,* ***AEC:*** *Absolute eosinophil count*

patients were in the mild, 22 (53.7%) were in the moderate and 4 (9.8%) were in the severe.

Total IgE level was 45 IU/ml and above in 17 patients (41.5%) at admission and in 27 patients (65.9%) aged 5 years. Total IgE level evaluated at admission, it was higher in patients with food sensitivity (p = 0.040). Additionally, the Total IgE level at the time of admission was higher in patients with AD recovery age greater than 24 months (p = 0.030). Total IgE levels of 5-year-old patients with positive SPT were also significantly higher (p = 0.003).

While eosinophilia was detected in 16 (39%) patients at the time of admission, it was found in 11 (26.8%) patients when they were 5 years old. In patients with eosinophilia at the time of admission, had more allergic diseases at the age of 5 years (p = 0.040). Also, we observed eosinophilia more frequently in male patients when they were 5 years old (p = 0.020). At the time of diagnosis, we found a positive correlation between high eosinophil count and Scorad scores (p = 0.030; r = 0.36).

Of the 21 (51.2) patients whose IgA levels were found to be low for age at the time of admission, only 8 (19.5%) of them were still low in the 5 years old. However, in all patients over 5 years of age, IgA level was above 40 mg/dl. The incidence of asthma was higher in patients with still low IgA levels at the age of 5 years (p = 0.030).

There were 32 (78%) patients who regularly used moisturizers during the active dermatitis period. Between the patients who used skin moisturizer and those who did not, we found a significant difference between the development of asthma (p <0.001).

In Table IV, the total IgE level of the patients, absolute eosinophil count, scorad score, distribution of age at presentation and diagnosis of AD and the difference between genders are shown.

We found that 30 (73.2%) of all patients had bronchiolitis attacks in the first 3 years of their lives. 24 of these 30 patients had food sensitive. However, we did not find a significant relationship between the presence of food allergy and having a bronchiolitis attack (p = 0.610). Of the 15 patients who had 3 or more episodes of bronchiolitis in the last 12 months, 8 were receiving regular low-dose inhaled corticosteroids, 4 were receiving montelukast, and 3 were receiving intermittent low-dose inhaled corticosteroid therapy.

The distribution of patients by the age of AD recovery; 20 (48.8%) in the first 2 years, 11 (26.8) in 25-48 months, 9 (22%) in 49-60 months, 1 (2.4%) above 60 months. The rate of bronchiolitis attack was higher in the group who received a diagnosis of AD over the age of 6 months. (p = 0.040). We found that 5-year-old IgA levels of patients diagnosed with AD in the first 6 months were lower (p = 0.040). Aeroallergen sensitivity more frequently in patients diagnosed with AD in the first 6 months (p = 0.020). However, we could not show its relationship with the presence of allergic diseases at the age of 5 (p = 0.150).

We did not find a relationship between the presence of atopy and scorad severity (p = 0.310) at the time of admission. However, we found that the Total IgE levels of patients who were atopic at admission were significantly higher at the time of admission (p = 0.005), 3 years old (p = 0.006), and 5 years old (p = 0.007).

Factors affecting the patients' risk of developing asthma and allergic rhinitis at 5 years of age were analyzed using univariate

Table V: Risk Factors For Developing Asthma And Allergic Rhinitis

	Asthma		AR	
	OR (CI 95%)	p	OR (CI 95%)	p
AD Diagnosis Age (Months)	0.93 (0.63-1.37)	0.720	1.20 (0.90-1.60)	0.200
Scorad score	1.00 (0.88-1.12)	0.990	1.04 (0.94-1.14)	0.390
Total IgE in application (IU/ml)	0.99 (0.97-1.02)	0.900	1.01 (0.99-1.04)	0.100
AEC^{c} in application (/uL)	0.99 (0.99-1.00)	0.740	1.00 (0.99-1.00)	0.480
Total IgE at age 3 (IU/ml)	1.01 (0.99-1.02)	0.280	0.99 (0.97-1.00)	0.380
Total IgE at age 5 (IU/ml)	0.99 (0.98-1.00)	0.590	1.00 (0.99-1.00)	0.900
IgA at age 5 (mg/dl)	1.08 (1.01-1.16)	0.010	1 (0,97-1,02)	0.880
Gender	5.73 (0.63-52.06)	0.120	0.81 (0.13-5.07)	0.820
Presence of atopy in parents	1.64 (0.39-6.84)	0.490	2.71 (0.54-13.51)	0.220
Food sensitivity at application	0.89 (0.15-5.04)	0.890	0.54 (0.08-3.37)	0.510
Aeroallergen sensitivity at age 5	0.95 (0.20-4.43)	0.950	0.163 (0.02-1.09)	0.060

AR: *Allergic Rhinitis,* ***AD:*** *Atopic dermatitis,* ***AEC:*** *Absolute eosinophil count*

logistic regression analysis. The age of onset of AD, gender, presence of food allergy and presence of atopy in the family were evaluated, but no significant risk factor was found on its own. The data are shown in Table V.

DISCUSSION

Atopic dermatitis most often begins between three and six months, and 60% of patients are diagnosed by the age of one (1). Nineteen (% 46.3) of our patients were diagnosed with AD in the first 6 months and all of them were diagnosed before the age of 2. Additionally, AD improved in about half of our patients in the first 2 years of age and almost all by the age of 5.

Food allergy (most commonly cow's milk and eggs) is present in 30% of patients with atopic dermatitis (10). In the Danish Allergy Research Cohort (DARC) study in which children from three months to six years of age were followed, food sensitivity was observed in 52% of 122 patients with AD, and food allergy confirmed by food provocation test was found in only 15% (11). In our study, we found food sensitivity in 28 (68.3%) of the patients, the most common being egg. There were 7 (17%) patients whose diagnosis was confirmed by food provocation test.

Especially, 35% of patients with early onset, severe and persistent AD have accompanying food allergy (1). Tsakok et al. (12), in the meta-analysis, the frequency of food sensitivity was found six times higher in those who had AD at the age of three months compared to those who had not. In our study, we found food sensitivity in 17 (41.4%) of 19 patients diagnosed with AD in the first 6 months. We did not find a relationship between the Scorad scores and food sensitivity of our patients.

In the TUCSON cohort, the development of AD in the first year of life has been shown to be a risk factor for persistent wheezing (1). Additionally, studies have shown that correcting the skin barrier can prevent subsequent atopic disorders (10). The rate of bronchiolitis attack was higher in our patients who were diagnosed with AD after the 6th month. We thought that the delay in diagnosis and treatment of AD might be effective in this situation.

In a study evaluating children diagnosed with AD in the first three months of life, it was reported that 69% were sensitized to aeroallergens until the age of five (13). In a different study in which 2270 children diagnosed with AD were evaluated, it was shown that 66% of the children developed asthma and/or allergic rhinitis at the age of three and these diseases were associated with poor AD control (14). In studies conducted with normal population; the frequency of asthma is 4-17.8% and the frequency of allergic rhinitis is 6.3-17.6% (15). When our patients are over the age of 5; aeroallergen sensitivity was developed in 17 (41.4%), asthma in 10 (31.7%) and allergic rhinitis (AR) in 12 (29.2%) patients. We did not find any correlation between food sensitivity and the development of asthma and / or AR at the age of 5 years. Therefore, we think that atopic dermatitis has

a more important risk in terms of respiratory allergic diseases than food sensitivity.

In studies, early-onset AD, male gender, presence of eosinophilia, food and aeroallergen sensitivity have been shown as risk factors for the development of asthma (4,16-19). In our study, we could not find a significant risk factor for the development of asthma or allergic rhinitis. This situation reminds us of the fact that asthma is a complex disease that occurs under the influence of genetic, environmental and epigenetic factors.

Mechanically, the questions of whether skin barrier defects will encourage allergen entry and whether this will contribute to allergic diseases afterward have been questioned in studies (5). However, the effect of early control of AD on atopic march is still unclear (20). We saw less asthma development in patients who regularly used moisturizers. We thought this might be related to the contribution of moisturizers to the skin barrier.

In a study conducted in our region; Asthma, past wheezing, atopic dermatitis, food allergy, and atopic sensitization were found to be higher in individuals with Ig A deficiency compared to studies conducted in a normal population (15). Similarly, we found that the frequency of asthma was higher in patients with still low IgA levels when they were 5 years old.

As a result, compared to the studies conducted in the normal population, we found the frequency of asthma and allergic rhinitis more in patients with AD. However, we could not show the relationship between food sensitivity and the development of asthma and/or allergic rhinitis. It should be kept in mind that the treatment of AD, especially the measures to protect the integrity of the skin, can help prevent the development of asthma. In order for clinicians to understand the heterogeneity of atopic disease models in children and to eliminate this variability, patients should be followed up in later life. This is also critical for the prognosis of allergic diseases.

The small sample size of the study, the absence of a control group, and the retrospective design of the study are the limitations of our study.

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Decreased Pediatric Viral Burden and Increased Rhinovirus Infection During The COVID-19 Pandemic

COVİD-19 Pandemisi Sırasında Azalan Pediatrik Viral Yük ve Artan Rinovirüs Enfeksiyonu

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ABSTRACT

Objective: Primary preventive nonpharmaceutical interventions were introduced to reduce viral transmission and disease spread at the beginning of the COVID-19 pandemic. Therefore, herein, we aimed to determine and assess the impact of the nonpharmaceutical interventions on bronchiolitis and varicella infection rates in the pediatric population during the pandemic compared to the previous four years. We also aimed to evaluate which viruses cause viral respiratory tract infections during the pandemic period.

Material and Methods: Diagnosis and laboratory data of the patients who were one month to 18 years of age were retrospectively retrieved from hospital records. The distribution of the number of patients with bronchiolitis and chickenpox diagnoses was shown monthly between January 2016 and December 2020. Viral agents detected by polymerase chain reaction (PCR) in the nasopharyngeal aspirate samples obtained at the first application of the patients during the pandemic period were investigated.

Results: The data of 2.254.877 pediatric patients admitted to our hospital from January 2016 to December 2020 were examined. There were 38.458 bronchiolitis and 954 chickenpox cases reported both as inpatients and outpatients. There was a 85.6% decrease in the rate of bronchiolitis compared to previous years, and chickenpox peak was not observed in the pandemic period. Rhinovirus was found to be the most common etiologic agent of bronchiolitis during the pandemic period and Respiratory Syncytial Virus (RSV) came second. A significant decrease in the frequency of influenza was also observed.

Conclusion: Our study reveals that the measures which curtail social life and prioritize social distancing prevent the spread of viral infections. It has also shown that there is an increase in the frequency of Rhinovirus infection during the pandemic period.

Key Words: Bronchiolitis, Chickenpox, COVID-19, Rhinovirus

ÖZ

Amaç: COVİD-19 pandemisinin başlangıcından itibaren viral bulaşı ve hastalık yayılmasını azaltmak ve engellemek amacıyla dünya genelinde olduğu gibi ülkemizde de medikal olmayan birincil önlemler alındı. Çalışmamızda bu önlemlerin çocuk hastalarda önceki dört yıla göre bronşiolit ve suçiçeği oranlarına etkisini belirlemeyi ve değerlendirmeyi, ayrıca pandemi döneminde viral solunum yolu enfeksiyonlarına hangi etkenlerin sebep olduğunu değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bir ay ile 18 yaş arasındaki hastaların tanı ve laboratuvar verileri geriye dönük olarak hastane bilgi sisteminden alındı. Bronşiolit ve suçiçeği tanılı hasta sayılarının Ocak 2016' dan Aralık 2020' ye kadar olan aylara göre

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara City Hospital No. 2 Clinical Research Ethics Committee (E2-20-66/16.12.2020).

Contribution of the Authors / Yazarların katkısı*: *YIGIT M: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in 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. ***OZKAYA PARLAKAY A:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar.

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dağılımı gösterildi. Pandemi döneminde, hastaların ilk başvurusunda alınan nazofaringeal aspirat örneklerinde polimeraz zincir reaksiyonu (polymerase chain reaction, PCR) yöntemiyle saptanan viral etkenler araştırıldı.

Bulgular: Ocak 2016-Aralık 2020 tarihleri arasında hastanemize başvuran 2.254.877 çocuk hastanın verileri incelendi. Toplamda 38.458 bronşiolit ve 954 suçiçeği tanılı hasta vardı. Pandemi döneminde bronşiolit vakalarında önceki yıllara göre %85.6 oranında azalma görüldü ve önceki yıllarda görülen suçiçeği piklerinin hiçbiri görülmedi. Pandemi döneminde bronşiolit hastalarında en sık etkenin Rhinovirüs olduğu bulundu. Respiratuvar Sinsitiyal Virüs (RSV) ikinci sırada yer aldı. İnfluenza sıklığında da önemli bir azalma gözlendi.

Sonuç: Çalışmamız, sosyal hayatı kısıtlayan ve sosyal mesafeyi ön planda tutan önlemlerin viral enfeksiyonların yayılmasını engellediğini ortaya koymuştur. Ayrıca pandemi döneminde Rhinovirüs enfeksiyonu sıklığında artış olduğunu göstermiştir.

Anahtar Sözcükler: Bronşiolit, Suçiçeği, COVİD-19, Rhinovirus

INTRODUCTION

The novel coronavirus disease (COVID-19), first described in December 2019, has affected a large number of people of all age groups worldwide (1). Current evidence suggests that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) mainly transmits through respiratory droplets among people who are in close contact with each other. Aerosol transmission can occur in specific settings, particularly in indoor, crowded, and inadequately ventilated spaces (1,2). Since preventive vaccines for COVID-19 or effective drugs to treat the disease have not yet been found, primary preventive nonpharmaceutical interventions, including physical distancing, wearing masks, stay-at-home orders, school closures, strict hand hygiene, and travel restrictions, were introduced to reduce viral transmission and disease spread at the very beginning of the pandemic. These measures are not just specific to reducing the spread of SARSCoV-2 and may impact the epidemiology and transmission of other viruses as well. When COVID-19 infection was first seen in March 2020 in Turkey, we feared that it would put a huge burden on the healthcare system as the clinical manifestations would be confused with other respiratory diseases and viral infections. Surprisingly, according to our observations, the interventions dramatically reduced the burden of pediatric infectious diseases, including influenza, varicella, bronchiolitis, gastroenteritis, common cold, acute otitis media, and urinary tract infections. Therefore, herein, we aimed to determine and assess the impact of the nonpharmaceutical interventions on bronchiolitis and varicella rates of infection in the pediatric population during the pandemic compared to the previous four years.

MATERIALS and METHODS

We conducted this retrospective cross-sectional study at the Children's Hospital of the Ankara City Hospital, which is a tertiary pediatric hospital in Ankara, the Turkish capital, and among the biggest pediatric hospitals in Europe. About 500.000 patients under the age of 18 years visit our hospital annually. Approximately 40.000 suspected COVID-19 pediatric patients have been followed up and treated as inpatients and outpatients in our hospital since the first case of COVID-19 was documented in Turkey in March 2020.

Patients' diagnosis and laboratory data were retrospectively retrieved from computerized hospital records. The number of the outpatients and inpatients who were admitted to our hospital monthly from January 2016 till January 2021 were analyzed. According to the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic system, the patients diagnosed with bronchiolitis and chickenpox, were determined. The distribution of the number of patients with these diagnoses was shown by month. The bronchiolitis and chickenpox patients were included. All of the bronchiolitis patients were COVID-19 polymerase chain reaction (PCR) negative. Because bronchiolitis and chickenpox are clinical diagnoses, we did not stipulate whether the serology or PCR results were available when including patients with these diagnoses (3,4).

The detection of the respiratory viruses from the patients with bronchiolitis who have undergone PCR testing was performed by the multiplex real-time PCR assay (Rotor-Gene Q, QIAGEN, Germantown, MD) that is capable of identifying viral pathogens including influenza viruses (influenza A, influenza A H1N1, and influenza B), human rhinovirus, human coronaviruses (HCoV) (NL63, 229E, OC43 and HKU1), human parainfluenza viruses (PIV) (PIV-1, PIV-2, PIV-3 and PIV-4), human metapneumoviruses A/B (hMPV), human respiratory synctial viruses A/B (RSV), enterovirus, bocavirus, human adenovirus, and human parechovirus.

A z-test for two proportions (e-picos, 2021) was used to compare the difference between pre-pandemic (2016 and 2019) months' means and pandemic months. The level of statistical significance was established as $p < 0.05$. The data were anonymous. Patient-informed consent was not required according to the current dispositions.

The study conformed with the principles of the Declaration of Helsinki and was approved by the local ethics committee and the Institutional Review Board of the Children's Hospital of the Ankara City Hospital (E2-20-66/16.12.2020).

RESULTS

We examined the data and diagnosis of 2.254.877 pediatric patients who were admitted to our hospital from January 2016 to December 2020. There were 38.458 bronchiolitis and 954 chickenpox cases reported as both inpatients and outpatients.

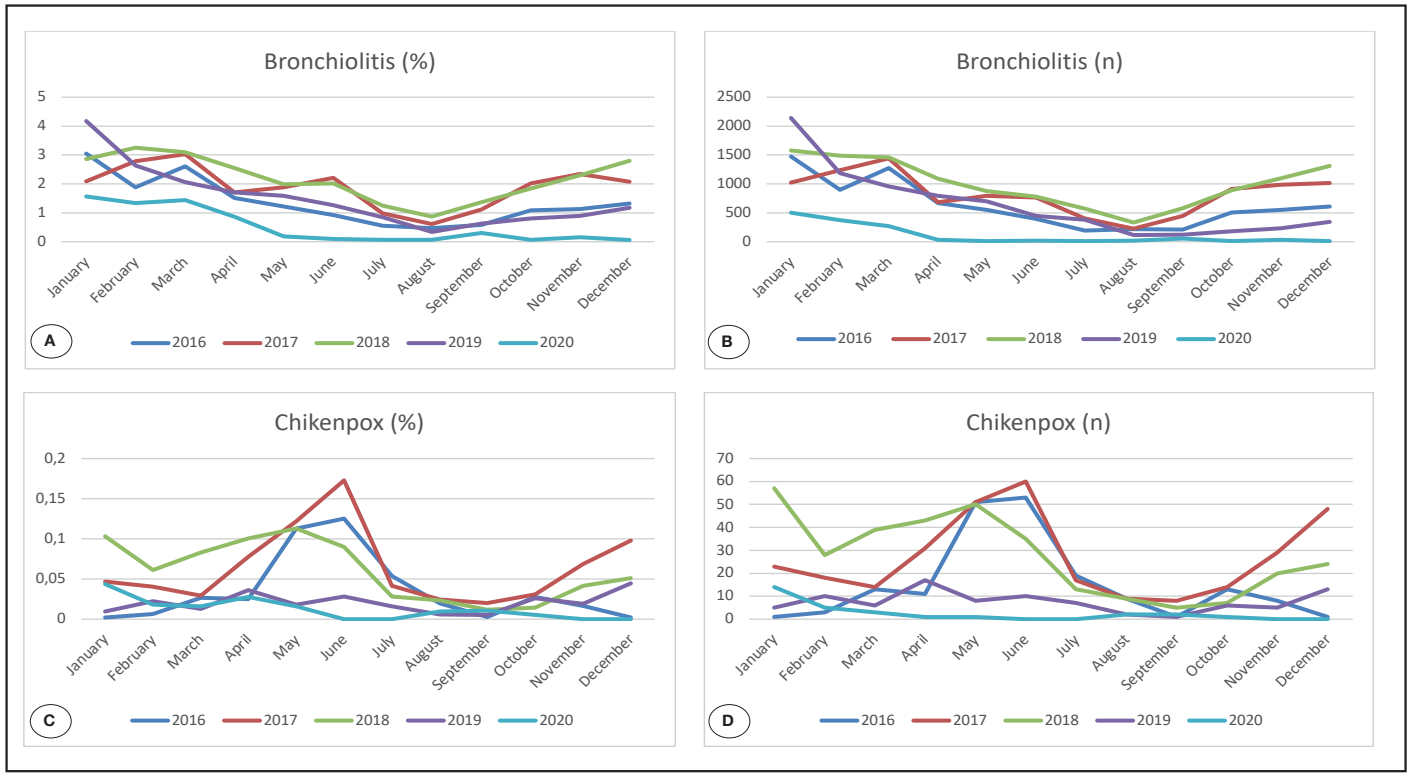

Figure 1: Distribution of the percentage of bronchiolitis (**A**) and chickenpox (**C**) cases by years, and distribution of the number of bronchiolitis (**B**) and chickenpox (**D**) cases by years.

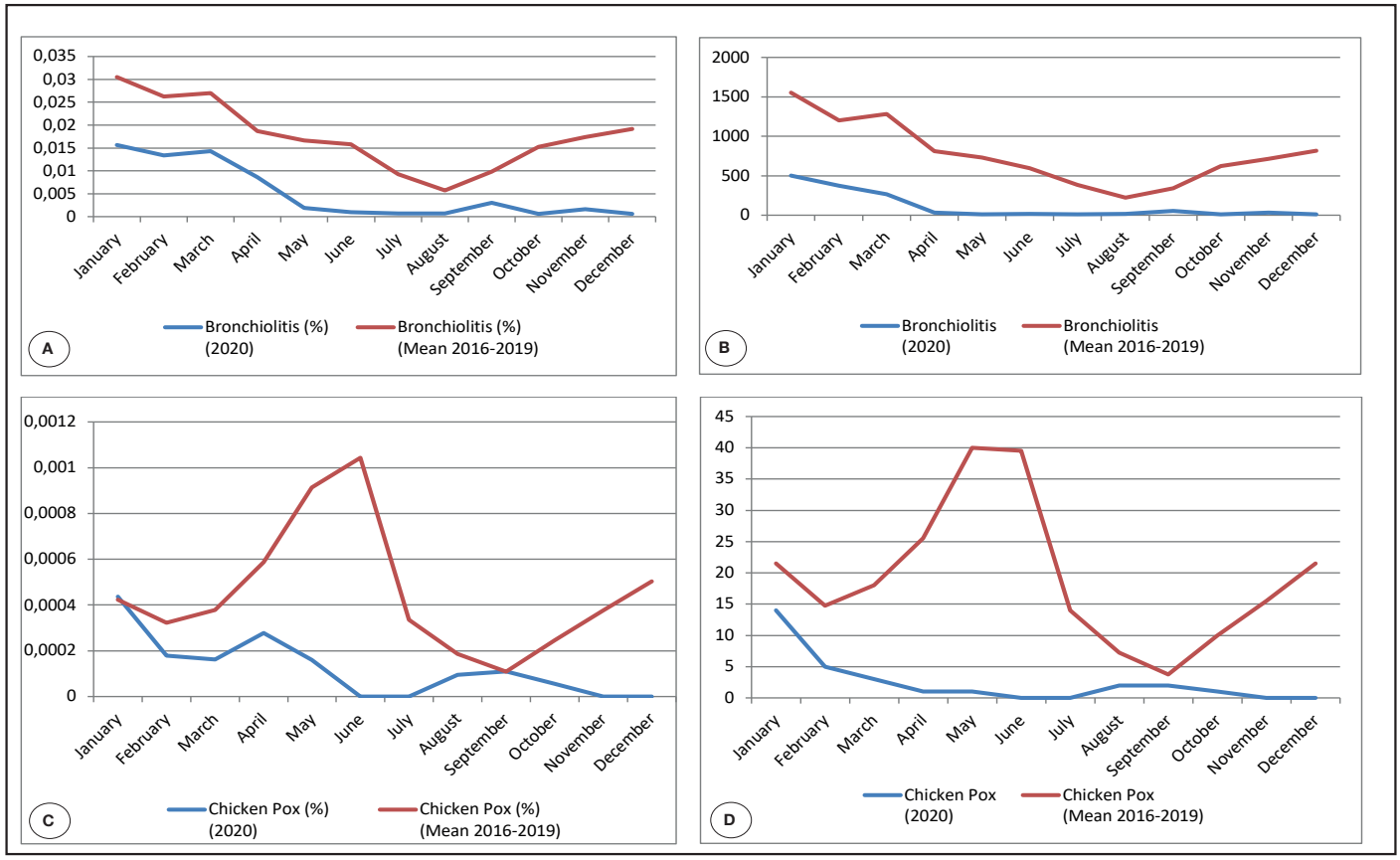

Figure 2: Distribution of the percentage of bronchiolitis (**A**) and chickenpox (**C**) cases in 2020 and 2016-2019, and distribution of the number of bronchiolitis (**B**) and chickenpox (**D**) cases in 2020 and 2016-2019.

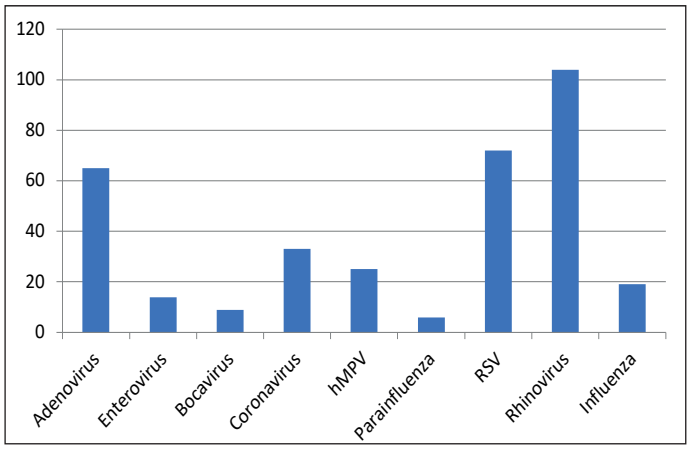

Figure 3: The distribution of the viral pathogens of the bronchiolitis patients in 2020.

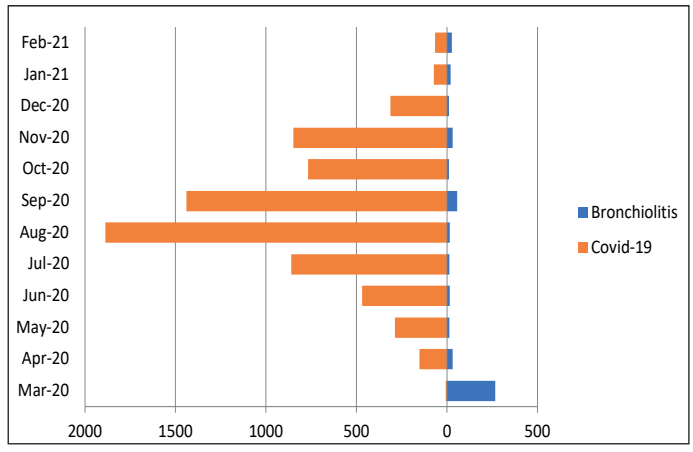

Figure 4: Number of bronchiolitis and COVID-19 cases in 2020.

Table I: Comparation of bronchiolitis admissions in 2020 and 2016-2019.

	Bronchiolitis (2020)	Total Admission (2020)	Bronchiolitis (Mean 2016-2019)	Total Admission (Mean 2016-2019)	Z*	p
January	502	32075	1553	50916	-13.406	<0.001
February	374	27915	1201	45671	-11.731	<0.001
March	267	18605	1284	47467	-9.697	<0.001
April	31	3609	810	43381	-4.39	<0.001
May	12	6279	729	43828	-9.039	<0.001
June	16	15996	597	37857	-14.764	<0.001
July	14	19843	386	41628	-12.351	<0.001
August	15	21052	223	38825	-9.342	<0.001
September	55	18316	340	34494	-8.701	<0.001
October	11	18216	623	40826	-15.959	<0.001
November	32	19897	717	41118	-16.646	<0.001
December	11	18267	819	42692	-18.136	<0.001

*****Z-test for two proportions (e-picos,2021)*

The mean number of bronchiolitis per year in the pre-pandemic and pandemic periods was 9282±399.4 and 1340±170.3, respectively. The mean number of chickenpox per year in the pre-pandemic and pandemic periods was 232 and 29, respectively. The monthly distribution and the ratio to the overall number of bronchiolitis and chickenpox cases are shown in Figure 1. Over the pre-pandemic period, between 2016 and 2019, the monthly averages of bronchiolitis and chickenpox cases were calculated, and the monthly distribution of each disease was parallel (Figure 2). The mean was compared with the data of the post-pandemic period, and the difference was statistically evaluated (Tables I, II). It was observed that there was a significant decrease in the number and rate of bronchiolitis compared to previous years ($p < 0.001$). A nearly 85% decrease was observed in bronchiolitis cases in 2020 compared to the previous years. In 2020, the number of bronchiolitis cases did not exceed 30% of the average of the previous four years. In addition a comparison of monthly bronchiolitis and COVID-19 patient numbers since March 2020, when COVID-19 infection was first seen in Turkey, is shown in Figure 3.

We analyzed the PCR results of bronchiolitis patients who were followed up in our hospital after January 2020. 1191 of 1340 bronchiolitis patients were tested with PCR and 844 were negative. Rhinovirus was found to be the most common etiologic agent in bronchiolitis patients who were negative for COVID-19 during the pandemic period. RSV was in second place. A significant decrease in the frequency of influenza was also observed. The distribution of pathogens detected in 347 positive tests is shown in Figure 4.

The chickenpox vaccine was included in the mandatory vaccination schedule in Turkey in February 2013; therefore, the incidence was low. However, as shown in the graphs, the number of reported chickenpox cases did fluctuate to

Table II: Comparation of Chicken Pox Admissions in 2020 and 2016-2019.

	Chicken Pox (2020)	Total Admission (2020)	Chicken Pox (Mean 2016-2019)	Total Admission (Mean 2016-2019)	Z *	p
January	14	32075	21.5	50916	0.03	0.97
February	5	27915	14.75	45671	-1.192	0.23
March	3	18605	18	47467	-1.414	0.15
April	1	3609	25.5	43381	-0.776	0.43
May	1	6279	40	43828	-1.953	0.05
June	0	15996	39.5	37857	-4.113	<0.001
July	0	19843	14	41628	-2.584	<0.001
August	2	21052	7.25	38825	-0.813	0.42
September	2	18316	3.75	34494	-0.069	0.94
October	1	18216	10	40826	-1.563	0.12
November	0	19897	15.5	41118	-2.782	<0.001
December	0	18267	21.5	42692	-3.069	<0.001

**Z-test for two proportions (e-picos,2021)*

some extent between 2016-2019: the lowest incidence was in September–October and the highest was in June–July and November–December.

DISCUSSION

Our study is one of the first and most extensive studies on this subject in our country. This study, which was carried out in the largest and most visited children's hospital in Turkey, has shown strikingly and clearly the impact of COVID-19 measures on the spread of other viral diseases, such as bronchiolitis and chickenpox.

In the five-year course of the bronchiolitis cases we examined in our study, the cases of bronchiolitis, which peaked every year in January, reached its highest value in January 2020 but did not reach a peak value as in previous years. A serious decrease was observed in the number of bronchiolitis cases even before the first COVID-19 case in Turkey was reported in March 2020.

The first COVID-19 case in our country was seen on March 11th, 2020. With the restriction measures implemented throughout the country as of March 12nd, a nearly 85% decrease was observed in bronchiolitis cases in 2020 compared to the previous years. The restrictions, wearing masks, physical distancing, and school closures during the pandemic were essential precautions that caused this remarkable reduction. The decrease in the transmission in the community as a result of the measures was also reflected in the number of cases. Because the majority of bronchiolitis agents—parainfluenza virus, respiratory syncytial virus, and human rhinoviruses are the most common agents in Turkey—are transmitted by droplets, close contact in community settings, such as schools and day-care centers, is ideal for the spread of viral infections (5-7).

In a multicenter study conducted in France in which the infectious diseases of 2020 and the previous three years were compared, a decrease of more than 70% was observed, especially in bronchiolitis, the common cold, and acute otitis media (8). In a similar study, it was reported that the most significant decrease in admissions and hospitalizations due to lower respiratory tract infection in the last five years was observed in the 0–2 year age group, among whom acute bronchiolitis is most prevalent (9). In support of this, a study conducted in the United States showed similar results (10).

In the pre-pandemic years, although it was included in the routine vaccination schedule, at least one chickenpox case was observed every month and the highest monthly number of chickenpox cases diagnosed in our center was 60. During the post-March 2020 period, a total of seven cases were detected, and no chickenpox cases were found in several months. In a study conducted in Italy, chickenpox cases decreased by 80% in 2020 compared to the previous years (11). In a study conducted in the Guangzhou province of China, chickenpox cases in the pediatric and adult populations decreased significantly in 2020 compared to the previous three years (12). In this study, more than half of the cases were found in individuals under the age of 10. The relationship between the decrease in the number of cases of chickenpox (which is highly contagious) and physical distancing and the closure of indoor public spaces may be stronger than its relationship with the decrease in bronchiolitis cases.

In different studies conducted in different years in our country before the pandemic, when the viral agents of bronchiolitis were examined, the most common cause was RSV, and the second most common cause was Rhinovirus. Influenza and parainfluenza viruses were also among the common causes of bronchiolitis in children in our country (13–15). Kıymet et

al. (16) found in their study which was conducted in Turkey during pandemic period, that the most common detected viral pathogen was rhinovirus on nasopharyngeal swabs for SARS-CoV-2 and other common human respiratory tract pathogens. In a study conducted in Japan with 2244 respiratory specimens, it was found that the frequency of influenza and other respiratory viruses was appreciably reduced among all patients during the COVID-19 pandemic except for that of rhinovirus in children younger than 10 years, which was appreciably increased. COVID-19 has not spread among this age group, suggesting an increased risk of rhinovirus infection in children (17). Similar to these studies, in our study, Rhinovirus was found to be the most common agent in bronchiolitis patients who were negative for COVID-19 during the pandemic period. RSV was in second place. A significant decrease in the frequency of influenza was also observed. Rhinovirus is partially resistant to ethanol based disinfectant, and it can survive on environmental surfaces for a prolonged period of time because it is a nonenveloped virüs. These viral properties may be the underlying cause of the relatively increased frequency of rhinovirus (17–19).

Our study attributes the decreases in the rate of bronchiolitis and chickenpox cases to hygiene and social distancing measures taken to control the pandemic. Undoubtfully, these measures must have contributed to the reduction of the transmission of respiratory infectious diseases. In addition, other factors should be taken into account as possible modifiers of epidemiology. Among them, one of the main theories ascribes this epidemiological change to the competition between viruses, in which SARS-CoV-2 would have occupied the ecological niche of other viruses, colonizing the nasopharynx and preventing other viral infections (20,21). These theories should be taken into consideration.

Our study had some limitations. Firstly, it was designed as a retrospective study. Secondly, it was conducted in a single center. In addition, since pre-pandemic respiratory tract PCR results were not available, we could not compare the pre-pandemic and pandemic PCR results and their changes in our center.

CONCLUSION

Our study reveals that the measures that curtail social life and prioritize social distancing prevent the spread of infectious diseases other than COVID-19. The effects of the measures implemented across the country on infectious diseases have produced unique results that support the theories of modern medicine. On the other hand, care should be taken in the new-normal period after the pandemic with the spread of vaccination, especially to prevent rebound peaks of viral infections. Patients with diagnoses such as immunodeficiency, malignancy, and chronic lung disease and those in a risk group should continue to take personal precautions for a certain period of time. Comprehensive studies examining this period more closely will be illuminating to the medicine of today and the future.

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Neurological Manifestations of *Mycoplasma pneumoniae* Infection in Hospitalized Children: A Single-Center Experience

Hastanede Yatan Çocuklarda *Mikoplazma pnömoni* Enfeksiyonunun Nörolojik Belirtileri: Tek Merkezli Bir Deneyim

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ABSTRACT

Objective: *Mycoplasma pneumoniae* is one of the major causes of upper and lower respiratory tract infection in childhood. Neurological diseases are among the most common extrapulmonary manifestations.This study aimed to share our center's experience regarding the treatment characteristics and clinical and radiological course of patients with *M. pneumoniae*-related neurological symptoms in light of the available evidence.

Material and Methods: The study included in hospitalized patients with positive primary *M. pneumoniae* serology *M. pneumoniae* serology was examined in serum from the acute period and, if possible, convalescent serum (1-4 weeks after disease onset) using *M. pneumoniae*-specific immunoglobulin M (IgM) and IgG enzyme-linked immunoassay. A 4-fold or greater increase in IgG titer between acute and convalescent serum samples was considered diagnostic for *M. pneumoniae* infection. The clinical, laboratory, and imaging results and demographic data of patients with CNS involvement were evaluated.

Results: Review of the patients' charts showed that 13 (25%) of the 52 patients with confirmed *M. pneumoniae* infection had neurological symptoms and findings. When evaluated together with clinical, laboratory, and imaging results, 6 patients were diagnosed with acute cerebellar ataxia, 4 patients with encephalitis, and 1 patient each with GBS, optic neuritis, and longitudinally extensive transverse myelitis.

Conclusion: Although *M. pneumoniae* is known as mainly a respiratory pathogen, it also causes various neurological disorders. Although all of our patients had symptoms of respiratory tract infection, it has been shown that that *M. pneumoniae* can also cause neurological disease without respiratory symptoms. Further studies are needed to evaluate the most appropriate methods for early diagnosis and treatment of neurological involvement, considering the long-term burden of the disease.

Key Words: Childhood, *Mycoplasma pneumonia*, Neurological signs and symptoms

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Contribution of the Authors / Yazarların katkısı*: *CELIK H: 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 the writing of the whole or important parts of the study. ***AKSOY E:*** 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 necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***OZTOPRAK U:*** Planning methodology to reach the Conclusions, Taking responsibility in necessary literature review for the study. ***AKCABOY M:*** 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. ***UYSAL YAZICI M:*** 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. ***SAVAS SEN Z:*** Taking responsibility in necessary literature review for the study. ***YUKSEL D:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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ÖZ

Amaç: *Mikoplazma pnömoni*, çocukluk çağında üst ve alt solunum yolu enfeksiyonlarının başlıca nedenlerinden biridir. Nörolojik hastalıklar en sık görülen ekstrapulmoner belirtiler arasındadır. Bu çalışma, *M. pnömoni* ile ilişkili nörolojik semptomları olan hastaların tedavi özellikleri, klinik ve radyolojik seyri ile ilgili merkezimizin deneyimlerini mevcut kanıtlar ışığında paylaşmayı amaçlamıştır.

Gereç ve Yöntemler: Hastanede yatan ve primer *M. Pnömoni* serolojisi pozitif çıkan pediatrik hastalar dahil edilmiştir. *M. Pnömoni* serolojisi akut dönemde serumda ve mümkünse konvalesan serumda *M. Pnömoni* spesifik IgM ve immünglobulin G (IgG) enzim immün assay yöntemi kullanılarak bakıldı. Akut dönemde ve hastalık başladıktan 7 gün-4 hafta sonra, konvalesan dönemde alınan serumlarda IgG titresinde dört kat ve üzeri artış *M. Pnömoni* enfeksiyonu için tanısal kabul edildi. SSS tutulumu olan hastalar demografik, klinik, labarotuvar ve görüntüleme sonuçları eşliğinde değerlendirildi.

Bulgular: Çeşitli nedenlerle Ocak 2019- Aralık 2020 tarihleri arasında hastanemizde yatan 52 hasta primer *M. Pnömoni* enfeksiyonu doğrulanmıştı. *Mikoplazma pnömoni* enfeksiyonu doğrulan 52 hastanın 13'ünde (%25) nörolojik semptom ve bulgular olduğu tespit edildi. Klinik, laboratuar ve görüntüleme sonuçları ile birlikte değerlendirildiğinde; 6 olgu (%46) Akut serebellar ataksi, 4 olgu (%30) ensefalit, bir olgu Guillain barre sendromu (GBS), bir olgu optik nörit bir olgu da Longitudinal ekstensif transvers miyelit (LETM) tanısı almıştı.

Sonuç: *Mikoplazma pnömoni* başlıca solunum yolu patojeni olarak bilinmesine rağmen çeşitli nörolojik rahatsızlıklara da neden olur. Nörolojik tutulumun erken tanı ve tedavisine yönelik en uygun yöntemlerin değerlendirilmesi için hastalığın uzun dönemli yükünü de göz önünde bulundurarak daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Çocukluk çağı, *Mikoplazma pnömonisi*, Nörolojik belirti ve semptomlar

INTRODUCTION

Mycoplasma pneumoniae is one of the major causes of upper and lower respiratory tract infection in childhood. Besides respiratory tract infection, *M. pneumoniae* also causes various extrapulmonary diseases such as hemolytic anemia, polyarthritis, erythema multiforme, and hepatic, cardiac, and neurological diseases in 25% of cases. Neurological diseases are among the most common extrapulmonary manifestations (1,2).

M. pneumoniae-related neurological disorders are the most difficult to diagnose and treat, and may represent a true medical emergency. Neurological symptoms have been demonstrated in approximately 7% to 10% of patients hospitalized with *M. pneumoniae* infection (3-5). Encephalitis and meningoencephalitis are the most common neurological diseases caused by *M. pneumoniae*, although there have also been reports of cerebellitis, polyneuropathy, acute disseminated encephalomyelitis (ADEM), stroke, transverse myelitis (TM), Guillain-Barré syndrome (GBS), myasthenia gravis (MG), peripheral neuropathy, and optic neuritis (6-9).

The time between the onset of respiratory symptoms and the onset of neurological symptoms ranges from 2 to 14 days (10). More than 80% of patients with central nervous system (CNS) symptoms also have a respiratory tract infection (11). The etiopathogenesis of these neurological manifestations is still unknown, although three different mechanisms have been proposed: direct CNS invasion by *M. pneumoniae*, indirect autoimmune mechanisms, and vasculitis or thrombotic vascular occlusions that occur by a direct and indirect mechanism (12).

This study aimed to share our center's experience regarding the treatment characteristics and clinical and radiological course of patients with *M. pneumoniae*-related neurological symptoms in light of the available evidence.

MATERIALS and METHODS

The study included pediatric patients hospitalized in the Dr. Sami Ulus Maternity and Pediatrics Training and Research Hospital between January 2019 and December 2020 and whose primary *M. pneumoniae* serology was positive. *M. pneumoniae* serology was examined in serum from the acute period and, if possible, convalescent serum (1-4 weeks after disease onset) using *M. pneumoniae*-specific immunoglobulin M (IgM) and IgG enzyme-linked immunoassay. A 4-fold or greater increase in IgG titer between acute and convalescent serum samples was considered diagnostic for *M. pneumoniae* infection. The study was approved by the Clinical Research Ethics Committee of Ankara Dr Sami Ulus Gynecology and Childhood Health and Diseases Training and Research Hospital (07.04.2021/ E-21-04-147)

The clinical, laboratory, and imaging results and demographic data of patients with CNS involvement were evaluated. The patients' neurological signs and symptoms were categorized as seizure, ataxia, muscle weakness, confusion or coma, altered mental status, visual disturbance, and speech disturbance. Detection of enterovirus, parechovirus, herpes simplex virus (HSV) 1 and 2, and varicella zoster virus (VZV) in cerebrospinal fluid (CSF) specimens was performed using multiplex real-time polymerase chain reaction (RT-PCR) kits in an RT-PCR device.

According to the consensus statement of the International Encephalitis Consortium (13), *M. pneumoniae*-related encephalitis was defined as encephalopathy (altered consciousness, lethargy, irritability, or personality change) lasting at least 24 hours and at least two of the following criteria: fever, seizures, focal neurological findings, CSF pleocytosis, and electroencephalography or imaging findings suggestive of encephalitis. According to the 2002 diagnostic criteria report of the Transverse Myelitis Consortium Working Group (14), GBS was diagnosed based on clinical and neurological examination findings, presence of albuminocytologic dissociation in CSF, and electromyography

(EMG) findings; cerebellitis was diagnosed based on clinical, examination, and radiological imaging findings; postinfectious cerebellar ataxia was diagnosed based on history, the nature of cerebellar ataxia, the patient's clinical findings, CSF findings, and convalescent characteristics.

RESULTS

Serum *M. pneumoniae*-specific IgM was detected in 158 patients hospitalized in our center for various reasons between January 2019 and December 2020. Of these, 52 patients exhibited an increase in IgG titer in the acute period and/or at an average of 2 weeks after disease onset that was consistent with the diagnostic criteria and confirmed primary *M. pneumoniae* infection. In the other 106 patients, primary *M. pneumoniae* infection could not be confirmed.

Review of the patients' charts showed that 13 (25%) of the 52 patients with confirmed *M. pneumoniae* infection and 21 (19.8%) of the 106 unconfirmed patients had neurological symptoms and findings (Figure 1). Of the 13 patients with confirmed infection and neurological symptoms, 12 (92%) were female and 1 (8%) was male, and the mean age was 10.1 years (range, 5-16).

In addition to neurological symptoms, 11 (84.4%) of the patients had upper respiratory tract infection symptoms and 2 (15.6%) had lower respiratory tract infection symptoms. Neurological symptoms included ataxia (n = 6), confusion (n = 4), visual impairment (n = 1), myasthenia/paralysis (n = 2), and seizure (n = 2). The patients' mean Glasgow Coma Score at admission was 14.

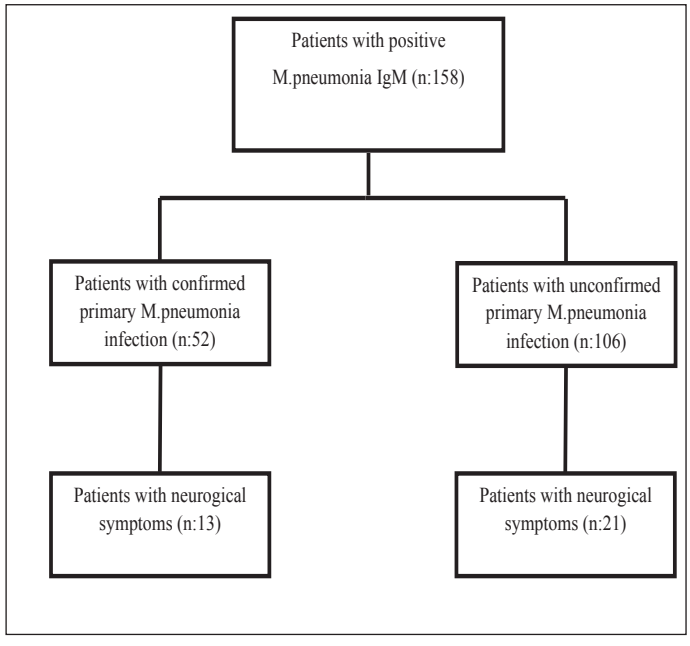

Figure 1: Algorithm of study.

The patients' reported neurological signs and symptoms as well as their CSF, electroencephalography, brain magnetic resonance imaging (MRI), and EMG findings were evaluated to establish a definitive diagnosis. CSF analysis revealed increased protein in 3 patients (21.4%) and cells on direct examination in 2 patients (14%). The detailed laboratory and imaging findings are presented in Table I.

RT-PCR tests for enterovirus, HSV 1 and 2, and VZV in CSF and tests for viral (EBV, cytomegalovirus [CMV], VZV) and bacterial (Borrelia burgdorferi, Brucella) pathogens in serum were performed for differential diagnosis and resulted negative in all patients. CSF culture was also negative in all cases. When evaluated together with clinical, laboratory, and imaging results, 6 patients (46%) were diagnosed with acute cerebellar ataxia, 4 patients (30%) with encephalitis, and 1 patient (8%) each with GBS, optic neuritis, and longitudinally extensive transverse myelitis (LETM).

The patients' mean length of hospital stay was 13 days, and 3 patients required admission to the intensive care unit due to isolated neurological symptoms. All patients were treated with clarithromycin starting a mean of 2 days after admission. In addition, 10 patients received intravenous immunoglobulin (IVIg) therapy (6 patients with cerebellitis, 2 with encephalitis, 1 with GBS, 1 with LETM), 4 patients received high-dose methylprednisolone (2 with encephalitis, 1 with LETM, 1 with optic neuritis), and the patient with LETM underwent plasma exchange. In 11 patients, empiric acyclovir therapy was initiated and discontinued when CSF HSV-PCR resulted negative.

The mean follow-up time after discharge was 13.4 months (range, 6-24). The patient with LETM exhibited moderate sequelae during follow-up, while the other patients had no sequelae.

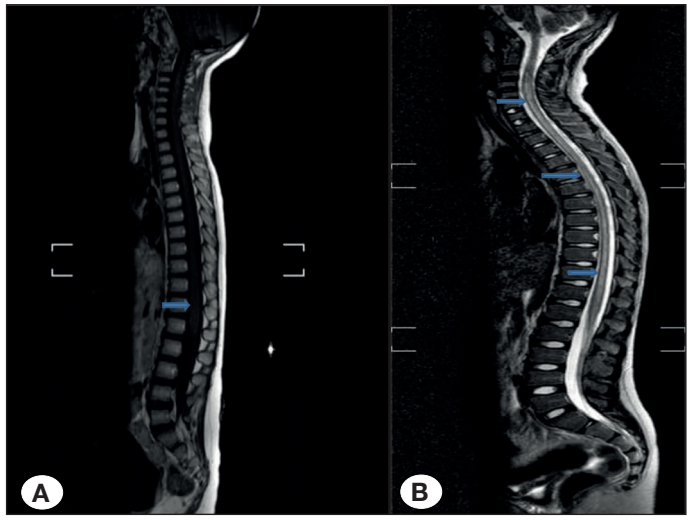

Figure 2: A) Pial enhancement in the distal thoracic plane. **B)** Sagittal longutidinal MR image showed increased signal in the gray matter starting from the C2 inferior end plate level to the subject in the whole spinal cord and expansion due to edema in the cervical.

Table I: The clinical findings in the pediatric patients presenting with *M. pneumoniae*-related neurological disorders.

Case	Age (y)/ Gender	Res. Findings	Neurological manifestation	GCS	CSF examination cell count (10^6/L)	CSF protein (g/L)	EEG	MRI findings	Diagnosis	Treatment	Hospital stay interval (days)	Prognosis
1	5/F	+	Ataxia, vomiting	15	-	22	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	10	CR
2	14/F	+	Ataxia, vomiting, dizziness	15	-	34	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	14	CR
3	5/F	+	Ataxia, dizziness	15	-	32	N	N	Postinfectious Cerebellar Ataxia	IVIg, Antibiotic (macrolide) Acyclovir	8	CR
4	12/F	+	Ataxia, vomiting, dizziness	15	-	130	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	10	CR
5	6/F	+	Ataxia, vomiting	15	-	120	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	14	CR
6	11/F	+	Ataxia, Dizziness	15	-	24	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	10	CR
7	6/F	+	Confusion, drowsiness, seizure	10	-	34	Generalized hypersynchronous discharges	Leptomeningeal enhancement Supratentorial white matter Basal ganglia	Encephalitis	High-dose methylprednisolone, IVIg, macrolide Acyclovir,	28	CR
8	12/F	+	Fever, confusion, drowsiness,	12	80	103	N	N	Encephalitis	IVIg, macrolide Acyclovir	20	CR
9	11/F	+	Confusion, drowsiness, seziure	12	-	55	N	N	Encephalitis	Antibiotic (macrolide) Acyclovir	14	CR
10	12/M	+	Confusion, drowsiness, seizure	12	120	50	Generalized slowing	N	Encephalitis	High-dose methylprednisolone, IVIg, macrolide Acyclovir,	28	CR
11	17/M	+	Blurred vision, painful eye movements	15	-	45	-	right optic nerve thickening	Optic neuritis	High-dose methylprednisolone, macrolide	7	CR
12	5/F	+	Pain in the legs, inability to walk	15	-	57	-	pial enhancement in the thoracic regionand filume terminale	Guillain-Barre syndrome	IVIg, macrolide	10	CR
13	16/F	+	Inability to walk, urinary incontinence	15	-	28	-	Spinal MRI T2 cervical, dorsal, lumbar patchy hyperintensities	Transvers myelitis	High-dose methylprednisolone, Macrolide, IVIg,PLX	26	Paraparesis

***F:** Female, **M:** Male, **GCS:** Glasgow coma scale, **CSF:** Cerebrespinal fluid, **IVIg:** Intravenous immunoglobulin, **PLX:** plasma exchange, **CR:** Complete remission, **N:** Normal*

DISCUSSION

Mycoplasma pneumoniae infection has been associated with various neurological diseases in children. Other than the many case reports and reviews, a few studies have systematically examined this relationship, but studies reporting the frequency and detailed analysis of neurological symptoms and predicting neurological involvement in children are rare (7,15,16). While neurological complications are observed in approximately 5% of patients hospitalized for *M. pneumoniae* infection, this pathogen has been detected in approximately 10% of patients presenting with acute, febrile CNS findings (3-5). In our study, 52

patients with primary *M. pneumoniae* infection were identified and neurological involvement was detected in 13 (25%) of them during hospitalization and treatment. Similarly, Kammer et al. (15) reported neurological involvement associated with *M. pneumoniae* in 22 (24.7%) of 89 patients in their study.

Approximately 80% of patients with neurological involvement have signs and symptoms of respiratory tract infection during or beforehand (2,10,17,18). All of our patients had respiratory signs and symptoms, but they were not severe enough to require hospitalization, and all were admitted because of neurological involvement.

Previous studies have shown encephalitis to be the most common extrapulmonary neurological disease caused by *M. pneumoniae* (7,8,15). In our study, the most common neurological involvement was acute cerebellar ataxia (6 patients), followed by encephalitis in 4 patients (30%), and GBS, optic neuritis, and LETM in 1 patient each (8%), which suggests that *M. pneumoniae* can be considered as a trigger in acute and otherwise unexplained neurological disorders.

Acute cerebellar ataxia often occurs after infections or appears suddenly during an infection, and usually causes only cerebellar signs and symptoms. Acute cerebellar ataxia is a diagnosis of exclusion; history, physical examination, laboratory, and imaging findings must be used to rule out conditions that should be considered in the differential diagnosis, including posterior fossa tumors, neuroblastoma (opsoclonus-myoclonus syndrome), acute bleeding, drug intoxications, acute labyrinthitis and metabolic diseases (Hartnup disease, maple syrup urine disease) (10,19). *M. pneumoniae*-related ataxia may occur in the early or late stages of infection. It is believed to occur due to direct invasion during the early period or the effect of immune complexes in the late period (20). Because acute cerebellar ataxia is generally associated with certain infections, especially VZV, all of our patients had serology and CSF PCR analysis for differential diagnosis from VZV, EBV, and CMV. Brain and spinal MRI were normal in all of our patients, and all were discharged without sequelae after a mean hospital stay of 8 days (range, 7-14).

Encephalitis is the most common extrapulmonary neurological disease caused by *M. pneumoniae* (21). In our study, it was the second most common neurological involvement (n = 4) after acute cerebellar ataxia. It has been suggested that *M. pneumoniae*-related encephalitis occurs as a result of both direct and autoimmune mechanisms. In previous studies, the low detection rates of *M. pneumoniae* DNA in the CSF of patients with *M. pneumoniae* encephalitis and the presence of a latent period after respiratory symptoms suggest indirect mechanisms in the pathogenesis of encephalitis (6,22). In our study, *M. pneumoniae* infection was demonstrated serologically in the serum of 4 patients with encephalitis. As all other causative factors were ruled out, we believe *M. pneumoniae* caused encephalitis as a result of indirect invasion.

Conjunctivitis is the most common ocular finding in *M. pneumoniae* infection, although others such as nystagmus, uveitis, and ocular motor nerve paralysis have been reported (23). *M. pneumoniae*-associated optic neuritis has rarely been described (24). In our study, optic neuritis was detected in 1 patient. This previously healthy patient presented with decreased vision and pain in the right eye after an upper respiratory infection. Their extraocular eye movements and other neurological examination were normal, but hyperemia and optic disc edema were observed on fundus examination and orbital MRI revealed thickening of the right optic nerve. In terms of all other causative factors, CSF analysis was normal, serology and PCR were negative for EBV, CMV, and VZV, serum anti-aquaporin 4 antibody (NMO IgG) and anti-MOG antibody were negative, and brain MRI was unremarkable. Based on these findings, optic neuritis associated with *M. pneumoniae* was suspected. Most cases of *M. pneumoniae*-related optic neuritis reported in the literature have been in children and young adults (24-27). *M. pneumoniae* should be considered in children diagnosed with isolated optic neuritis, even if they have no symptoms of respiratory tract infection.

GBS is an acute inflammatory polyneuropathy that is characterized by rapidly progressing symmetrical muscle weakness and loss of deep tendon reflexes, and can affect individuals of all ages. Symptoms of GBS usually occur after a viral or bacterial infection. *M. pneumoniae* is the second most commonly reported cause, after Campylobacter jejuni (28). The one GBS patient in our study developed weakness of the legs and gradual inability to walk starting 6 days after the onset of respiratory tract infection symptoms. On physical examination, the patient's vital signs were normal, there was loss of strength in the legs that was more pronounced distally, deep tendon reflexes were absent, while sensory and other system examinations were normal. CSF and spinal MRI findings (figure-2) were consistent with GBS and a pre-treatment serum sample was positive for *M. pneumoniae* IgM and IgG. The patient received IVIg therapy and serology performed 4 weeks after treatment was negative for *M. pneumoniae* IgM while IgG titer was increased. Serology and PCR are still the most accurate methods to determine the role of *M. pneumoniae* in GBS (29). Although PCR analysis could not be performed for our patient, the diagnosis of *M. pneumoniae*-associated GBS was based on the presence of respiratory tract infection findings, *M. pneumoniae* IgM and IgG positivity in serum before treatment, and the increase in *M. pneumoniae* IgG titer and lack of IgM at 4 weeks after treatment. *M. pneumoniae* should be considered as a common and treatable cause of GBS in childhood.

TM is one of the rare neurological diseases caused by *M. pneumoniae*. In a study evaluating 365 children with *M. pneumoniae* detected by PCR analysis of CSF or respiratory

swab sample, 42 patients were diagnosed as having *M. pneumoniae*-related neurological disease. TM was observed in 12% of those 42 patients, while in another study by Kammer et al. (15), LETM was observed in only 1 of 22 patients with *M. pneumoniae*-related neurological disease (7). In our study, a patient who presented with complaints of bilateral lower extremity weakness and urinary incontinence 7 days after respiratory tract infection was found to have spinal MRI findings consistent with LETM, but etiological studies of serum anti-aquaporin 4 antibody (NMO IgG) and anti-MOG antibody were negative (Figure 2). The results of CSF analysis, serology and PCR for EBV, CMV, VZV serology, and brain MRI also suggested no other causative factor, and *M. pneumoniae* IgM and IgG were detected in the patient's pre-treatment serum sample. When the desired response was not seen after high-dose methylprednisolone therapy, the patient was treated with IVIg and plasma exchange therapy. In serology performed 4 weeks after treatment, *M. pneumoniae* IgM was negative and IgG titer was increased. Based on the clinical and laboratory findings, the patient was diagnosed as having M. pneumonia-related LETM.

There is a lack of consensus regarding how to treat neurological diseases associated with *M. pneumoniae*. In most studies, it is suggested that administering systemic antibiotherapy is necessary independent of disease type and pathogenesis. Patients with suspected or confirmed cases of disease characterized by acute severe inflammation are treated with steroids and/or IVIg (22). All patients in our study received clarithromycin, 10 patients were treated with IVIg (4 with cerebellitis, 2 with encephalitis, 1 with GBS, and 1 with LETM), 4 patients received high-dose methylprednisolone (2 with encephalitis, 1 with LETM, 1 with optic neuritis), and 1 patient with LETM underwent plasma exchange therapy. The patients were followed for a mean of 13.4 months (range, 6-24) after discharge and only the patient with LETM had moderate sequelae, while no sequelae were observed in the other patients.

In conclusion, although *M. pneumoniae* is known as mainly a respiratory pathogen, it also causes various neurological disorders. Although all of our patients had symptoms of respiratory tract infection, it has been shown that that *M. pneumoniae* can also cause neurological disease without respiratory symptoms. Further studies are needed to evaluate the most appropriate methods for early diagnosis and treatment of neurological involvement, considering the long-term burden of the disease.

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Evaluation of Clinical Differences of Newly Diagnosed and Formerly Diagnosed Pediatric Diabetic Ketoacidosis Patients

Eski ve Yeni Tanı Pediatrik Diyabetik Ketoasidoz Hastalarının Klinik Farklılıkların Değerlendirilmesi

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ABSTRACT

Objective: Our aim is to determine the severity, clinical features, presence of complications and outcome differences in previously diagnosed and newly diagnosed Type 1 Diabetes Mellitus (T1DM) patients followed up with diabetic ketoacidosis (DKA) in the pediatric intensive care unit.

Material and Methods: This study was conducted retrospectively in a 32-bed tertiary pediatric intensive care unit. The patients were divided into newly diagnosed and previously diagnosed T1DM. All collected data were compared between groups.

Results: 107 patients were included into the study. Most of the patients were male (51.4%). Most of the newly diagnosed patients were in the 6-10 age group (49.2%). When patient complaints were evaluated before admission, the complaint of nausea was statistically higher in previously diagnosed DM patients (p=0.041). The complaints of fatigue, polyuria, polydipsia, and weight loss were statistically higher in newly diagnosed Type-1 DM (p value 0.001, 0.001, 0.001, 0.001, respectively). Hypokalemia was statistically higher in the newly diagnosed DM group during diabetic ketoacidosis treatment (p=0.015). Although there was no difference between intensive care durations, total hospitalization days were statistically longer in newly diagnosed DM patients (p values 0.145, 0.007, respectively). All patients survived.

Conclusion: The school age group was the most common age group in newly diagnosed T1DM. While polyuria, polydipsia and weight loss are common in newly diagnosed Diabetic Ketoacidosis patients; Vomiting was common in diabetic ketoacidosis patients with previous diagnosis. Trainings, national advertisements, etc. should be done to increase the knowledge level of patients and families about these symptoms and the disease.

Key Words: Children, Diabetic Ketoacidosis, Intensive Care

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ÖZ

Amaç: Amacımız, çocuk yoğun bakım ünitesinde diyabetik ketoasidoz (DKA) ile takip edilen daha önce tanı almış ve yeni tanı almış Tip 1 Diabetes Mellitus (T1DM) hastalarının şiddeti, klinik özellikleri, komplikasyon varlığı ve sonuç farklılıklarını belirlemektir.

Gereç ve Yöntemler: Bu çalışma, 32 yataklı üçüncü basamak çocuk yoğun bakım ünitesinde geriye dönük olarak yapıldı. Hastalar yeni tanı almış ve önceden tanı almış T1DM olarak ayrıldı. Toplanan tüm veriler gruplar arasında karşılaştırıldı.

Bulgular: 107 hasta çalışmaya dahil edildi. Hastaların çoğu erkekti (%51.4). Yeni tanı alan hastaların çoğu 6-10 yaş grubundaydı (%49.2). Başvuru öncesi hasta şikâyetleri değerlendirildiğinde kusma şikayeti, daha önce tanı almış DM hastalarında istatistiksel olarak anlamlı derecede yüksekti (p=0.041). Yeni tanı alan Tip-1 DM'de halsizlik, poliüri, polidipsi, kilo kaybı şikâyetleri istatistiksel olarak anlamlı derecede yüksekti (p değeri sırasıyla 0.001, 0.001, 0.001, 0.001). Diyabetik ketoasidoz tedavisi sırasında yeni tanı almış DM grubunda hipokalemi istatistiksel olarak daha yüksekti (p=0.015). Yoğun bakım süreleri arasında fark olmamasına rağmen yeni tanı konmuş DM hastalarında toplam yatış günleri istatistiksel olarak daha uzundu (p değerleri sırasıyla 0.145, 0.007). Hastalarda mortalite görülmedi.

Sonuç: Okul yaş grubu, yeni tanı konan T1DM'de en sık görülen yaş grubuydu. Yeni tanı Diyabetik Ketoasidoz hastalarında poliüri, polidipsi, kilo kaybı sık iken; eski tanılı diyabetik ketoasidoz hastalarında kusma yaygın olarak saptandı. Hastalar ve ailelerin bu semptomlar ve hastalık hakkında bilgi düzeyini artırıcı eğitimler, ulusal reklamlar vb uygulamalar yapılmalıdır.

Anahtar Sözcükler: Çocuk, Diyabetik Ketoasidoz, Yoğun Bakım

INTRODUCTION

Diabetic Ketoacidosis (DKA) is one of the major reasons of hospitalizations into pediatric intensive care (1). DKA is a life-treating complication of Type 1 Diabetes Mellitus (T1DM) (2). DKA has several complications like hyponatremia, hypokalemia and hypoglycemia. DKA is also cause activation of inflammatory pathways, disruption of coagulation cascade and increase the risk for thrombosis and stroke (3). Cerebral edema is most important and fatal complication of DKA (4). Incidence of cerebral edema was 0.5-0.9%, but associated with mortality (4). Like incidence of T1DM, mortality rate of DKA vary between countries. In developing countries DKA-related mortality rate ranges from 6%-24% (4). In developed countries mortality rate was 0.15%-0.30% (4).

Presence of family history, geographic location, age and socioecomic status affects DKA progression in T1DM patients (2). DKA was more common in at the time of T1DM diagnosis in newly diagnosed T1DM (2). Formerly diagnosed T1DM patients are less suffers from DKA (2). Insulin negligence, insulin pump failure, or insufficient insulin dose affects DKA progression in formerly type T1DM (2).

Aim of our study was to identify severity, clinical characteristics, complication presence and outcomes differences of formerly diagnosed and newly diagnosed T1DM patients presented as DKA followed-up in pediatric intensive care unit. We also evaluate interventions before and during admission of patients.

MATERIAL and METHODS

Our study was conducted in a 32 bed third-level pediatric intensive care unit retrospectively. Study period was planned as 24 months dates between 01-August-2019/31-August-2021. All patients between one month old eighteen years were included into study followed as diabetic ketoacidosis. First admission was recorded in recurrent admissions of DKA. Patients without acidosis but had hyperglycemia or diabetic ketosis was excluded.

Diabetic ketoacidosis was diagnosed according to criteria of International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 guideline: 1)Serum glucose >200 mg/dl, 2) Venous pH<7.30, 3)Ketonemia or ketonuria presence (5).

Diabetic ketoasidosis severity was classified according to venous pH level as <7.30 mild DKA, <7.20 moderate DKA, <7.10 severe DKA (5).

Demographic data, presence of co-morbidity, presence of family history with DM variables were collected.

Duration of complaints, symptoms (fever, nausea, vomiting, diarrhea, malaise, tachypnea, polyuria, polydipsia, polyphagia and weight loss), interventions before Pediatric Intensive Care Unit (PICU) and family history were pre-intensive care variables.

In intensive care follow-up Glasgow Coma Score (GCS) at admission, DKA severity, laboratory parameters (blood count, electrolytes, corrected sodium level, blood gas parameters, liver functions tests, kidney function tests, serum glucose level, blood ketone), respiratory support therapies, complications during DKA treatment (hyponatremia, hypokalemia, hypophosphatemia, hypoglycemia, brain edema) was recorded.

Hypoglycemia was defined as serum glucose <60 mg/dl, hypokalemia as <3.5 mEq/L, hypophosphatemia as <4.6 mg/dl, hyponatremia as corrected serum sodium level <135 mEq/L. Corrected sodium (meq/L) was calculated as measured sodium+1.6x [serum glucose-100/100], effective osmolarity (mOsm/kg) was calculated as [2x plasma sodium]+ [serum glucose/18]. Outcomes were evaluated as intensive care duration in days, hospital duration in days and survival.

All patients were categorized as newly diagnosed Diabetes Mellitus (DM) and formerly diagnosed DM patients. Data collected from patients was compared between two groups. We took study permission by local ethic committee of Ankara City Hospital (E2-21-659).

Descriptive analysis of the results conducted by using the SPSS 17.0 software package for Windows (IBM Company, New York, NY). Categorical data expressed as proportions (%). Median and inter quartile range (25^{th}-75^{th} percentile) were used for quantitative data. Differences were evaluated by Chi-Squared test in cases of categorical variables; nonparametric test (Mann-Whitney U) for continuous variables. Data was considered statistically significant at $p < 0.05$.

RESULTS

During study period 115 patients were followed up in pediatric intensive care unit as DM. Eight patients were excluded because of diabetic ketosis. 11 patients had multiple admissions. First admissions of patients who had multiple admissions were collected. 107 patients were included into study. Demographic data was demonstrated in Table I. Most of the patients were male (51.4%). Adolescent age group were the largest group between our patients (57.0%). Most of the newly diagnosed patients were in 6-10 age groups (49.2%). Difference between age groups were statistically significant (p=0.001). Severity of DKA was not differ between age groups (p=0.637). There were not any differences between groups in pre-PICU interventions. If complaints before admission evaluated, nausea was statistically significant higher in formerly diagnosed DM patients (p=0.041). Malaise, polyuria, polydipsia, weight loss complaints were statistically significant higher in new diagnosed-Type-1 DM (p value respectively 0.001, 0.001, 0.001, 0.001). Time period between starting of symptoms till hospital admission was significantly longer in new diagnosed DM patients (p=0.001). Median time for disease duration in formerly diagnosed DM was 5 (2.0-7.25) years. Patients without family history of diabetes mellitus were suffered severe DKA more than patients with family history of diabetes mellitus (p=0.004).

Critical care follow-up and evaluation of complications were presented in Table II. Twelve patients GCS was below 15. Most of patients whose GCS <15 was between 6-10 years age (p=0.029). Below 5 year old age group distortion of conscious was seen at highest rate (30.0%). Impaired conscious did not differ in formerly or newly diagnosed DM patients (p=0.283). Medical treatments apart from regular insulin were oral antibiotic, proton pump inhibitors, hypertonic saline and sodium bicarbonate respectively. Invasive mechanical ventilation was applied to one patient for three days. Brain computerized tomography performed to two patients. Radiologic assessment of patients who had cranial screening did not show any sign

Table I: Demographic characteristics and pre-intensive care interventions of DKA patients.

Characteristics	DKA (Total) (n=107)	DKA (Formerly diagnosed) (n=42)	DKA (Newly diagnosed) (n=65)	p
Gender (Male), n (%)	55 (51.4)	22 (47.6)	33 (50.7)	0.871
Age (month), median (IQR)	126 (89-174)	161 (123-199)	109 (76-148)	0.352
Age groups, n (%)				0.001
0-5 years	10 (9.3)	2 (4.7)	8 (12.3)	
6-10 years	36 (33.6)	4 (9.5%)	32 (49.2)	
11-18 years	61 (57.0)	36 (85.7)	25 (38.4)	
Body weight (kg), median (IQR)	34 (22-50)	48 (31.5-57.0)	27 (20-41)	0.760
DM family history presence, n(%)	45 (42.1)	18 (42.9)	27 (41.5)	0.893
Pre-PICU interventions, n (%)				
Saline bolus	76 (71.0)	29 (69.0)	47 (72.3)	0.718
Hydration	39 (36.4)	17 (40.5)	22 (33.8)	0.489
Insulin treatment	30 (28.0)	15 (35.7)	15 (23.1)	0.157
Other treatments	12 (11.2)	2 (4.8)	10 (15.4)	0.091
Symptoms, n (%)				
Fever	11 (10.3)	6 (14.3)	5 (7.7)	0.275
Nausea	35 (32.7)	18 (42.9)	17 (26.2)	0.073
Vomiting	53 (49.5)	26 (61.9)	27 (41.5)	0.041
Diarrhea	5 (4.7)	4 (9.5)	1 (1.5)	0.057
Malaise	45 (42.1)	9 (21.4)	36 (55.6)	0.001
Tachypnea	17 (15.9)	7 (16.7)	10 (15.4)	0.860
Polyuria	46 (43.0)	2 (4.8)	44 (67.7)	0.001
Polydipsia	46 (43.0)	2 (4.8)	45 (69.2)	0.001
Polyphagia	4 (3.7)	0 (0)	4 (4.6)	0.103
Weight loses	36 (33.6)	1 (2.4)	35 (53.8)	0.001
Abdominal pain	22 (20.6)	10 (23.8)	12 (18.5)	0.506
Period before hospital admission (day), median (IQR)	3 (1-7)	1 (1-2)	7 (3-21.5)	0.001

DKA: *Diabetic Ketoacidosis,* ***DM:*** *Diabetes Mellitus,* ***IQR:*** *Interquartile Range,* ***PICU:*** *Pediatric Intensive Care Unit*

Table II: Evaluation of intensive care floow-up and complications of DKA patients.

	DKA (Total) (n=107)	DKA (Formerly diagnosed) (n=42)	DKA (Newly diagnosed) (n=65)	p
GCS at PICU admission, median (IQR)	15 (15-15)	15 (15-15)	15 (15-15)	0.233
DKA severity, n (%)				
Mild	45 (42.1)	19 (45.1)	26 (40.0)	0.780
Moderate	35 (32.7)	12 (28.6)	23 (35.4)	
Severe	27 (25.2)	11 (26.2)	16 (24.6)	
Venous blood gas parameters, median (IQR)				
pH	7.12 (7.05-7.22)	7.13 (7.06-7.21)	7.12 (7.03-7.22)	0.318
pCO2 (mmHg)	20.6 (15.9-24.7)	22.3 (18.6-26.1)	19.7 (15.6-23.5)	0.319
HCO3 (mmol/L)	6.8 (4.5-9.3)	7.9 (4.9-9.7)	6.4 (4.1-8.9)	0.668
BE (mmol/L)	-20.3 (-23.3- -16.5)	-19.1 (-22.6 --16.4)	-20.4 (-23.9- -16.4)	0.303
Lactate (mmol/L)	2.02 (1.52-2.91)	2.56 (1.67-3.66)	1.78 (1.48-2.51)	0.291
Biochemical parameters, median (IQR)				
Serum glucose (mg/dl)	437.0 (330.0-526.0)	459.5 (367.2-533.0)	500 (325.0-512.5)	0.564
Blood ketone level (mmol/L)	5.6 (4.6-6.1)	5.3 (4.1-6.0)	5.6 (4.9-6.1)	0.715
Sodium (mEq/L)	134.0 (131.0-137.0)	133.5 (130.0-137.2)	134.0 (131.0-137.0)	0.645
Potasium (mEq/L)	4.4 (4.0-5.1)	5.0 (4.4-5.4)	4.4 (3.8-4.4)	0.057
Phosphate (mEq/L)	4.1 (3.1-5.1)	4.9 (4.1-6.0)	3.5 (3.0-4.1)	0.042
Clor (mEq/L)	104 (100.0-108.0)	102.0 (97.5-106.2)	105.0 (101.5-109.0)	0.370
BUN (mg/dl)	28.0 (19.0-40.0)	39.5 (28.5-48.0)	21.0 (17.0-30.0)	0.106
Creatinine (mg/dl)	0.92 (0.76-1.11)	0.97 (0.85-1.18)	0.86 (0.71-1.04)	0.189
AST (U/L)	17 (12-25)	22 (12.7-28.2)	15.0 (11.0-21.0)	0.143
ALT (U/L)	18 (13-22)	20.0 (15.7-32.5)	16.0 (13.0-21.0)	0.605
Corrrected sodium (mmol/L), median (IQR)	142 (139.4-144.2)	141.9 (139.1-144.8)	142.0 (139.4-144.1)	0.506
Effective osmolarite (mOsm/kg), median (IQR)	291 (287.4-298.0)	291.1 (286.0-299.5)	291.0 (284.5-297.1)	0.390
Anion gap (mmol/L) median(IQR)	23 (20.5-27.0)	25.6 (20.5-29.0)	22.0 (20.4-24.3)	0.250
HbA1c (%), median (IQR)	11.9 (10.8-13.1)	11.3 (9.7-12.4)	12.1 (11.0-13.6)	0.487
DKA complications, n (%)				
Hiponatremi	6 (5.6)	3 (7.1)	3 (4.6)	0.579
Hipoglisemi	4 (3.7)	1 (2.4)	3 (4.6)	0.554
Hipokalemi	38 (35.5)	9 (21.4)	29 (44.6)	0.015
Hipofosfatemi	81 (75.7)	29 (69.0)	52 (80.0)	0.199
Brain edema	3 (2.8)	1 (2.4)	2 (3.1)	0.831
DKA resolution period (hour), median (IQR)	12 (8-18)	11.25 (7.0-15.0)	14 (10-19)	0.741

AST: *Aspartate amino transferase,* ***ALT:*** *Alanine amino transferase;* ***BE:*** *Base Excess,* ***BUN:*** *Blood Urea Nitrogen,* ***DKA:*** *Diabetic Ketoasidosis,* ***IQR:*** *Interquartile range,* ***GCS:*** *Glasgow Coma Scale,* ***PICU:*** *Pediatric Intensive Care Unit*

Table III: Outcomes of DKA patients.

	DKA (Total) (n=107)	DKA (Formerly diagnosed) (n=42)	DKA (Newly diagnosed) (n=65)	p
Intensive care period (day), median (IQR)	1 (1-2)	1 (1-1.25)	1 (1-2)	0.145
Hospitalization period (day), median (IQR)	10 (7-12)	8 (5-10)	10 (9-12)	0.007
Mortality, n (%)	0 (0)	0 (0)	0 (0)	

DKA: *Diabetic Ketoasidosis,* ***IQR:*** *Interquartile range*

of brain edema. Hypophosphatemia was the most common complication during treatment period. Hypokalemia was statistically higher in new diagnosed DM group during diabetic ketoacidosis treatment (p=0.015). Hypoglycemia was seen in 4 patients. Three patients with hypoglycemia were in severe DKA group (p=0.02). Brain edema was spotted in three patients. Hypertonic saline was applied to patients as brain edema treatment. Patients with brain edema cured without sequel.

Venous blood gas parameters, serum glucose and ketone levels of patients with low GCS and normal GCS presented in Table III. Patients with altered conscious had more severe acidosis, higher glucose levels but their ketone levels were lower.

Outcomes were presented in Table III. Although there was not any difference in intensive care days, total hospitalization days was statistically longer in newly diagnosed DM patients (p values

respectively 0.145, 0.007). Patients with low GCS had longer PICU hospitalization than patients with normal GCS (p=0.12). Hospitalization of these patients whose had low GCS a little bit longer than normal GCS patients but it was not statistically significant (p=0.051). All patients survived.

DISCUSSION

In our study, we spotted that new diagnosed DM was more commonly seen in school age children. Nausea was the most common symptom in formerly diagnosed T1DM patients, whereas malaise, poliuria, polydipsia and weight loss complaints were more common in new diagnosed DM patients. Time period between starting of symptoms till hospital admission time was longer in new diagnosed DM patients. Hypokalemia was higher in new diagnosed DM group during diabetic ketoacidosis treatment Total hospitalization days was longer in newly diagnosed DM patients group.

Incidence of diabetes mellitus is increasing in children and adolescents in the world and growing faster in particularly below 5 years age children (6). Annual increase of T1DM was 3% in children and 5% in adolescent age group (4). Children under 5 years old more often suffers from DKA (3). Apart from literature DKA was more common in adolescent age group in the previous study. Parental care difference may affect this result. Parents may be more careful about their children's behavior changes like polyuria, polydipsia etc. at small ages and early recognition of symptoms lead to reach early proper treatment An article about fifteen years experience of DKA patients also reported that DKA was more common in adolescent age group (7). In developed world most common admission in T1DM patients is hyperglycemia without acidosis. In developing and underdeveloped countries DKA is the most common type of admission of T1DM patients (8). The prevalence of DKA varies between countries (15-67%) (6). There are several risk factors related with DKA (9). Misdiagnosis at first visit, delay in treatment, previous infection history, younger age, low body mass index and low socioeconomic level were common risk factors (9). There should be more multi-center prospective studies to evaluate risk factors of DKA in Turkish children.

Polyuria, polydipsia and polyphagia which are starting symptoms of DM are ensued from hyperglycemia and glycosuria. If patients are not diagnosed at this stage, vomiting, abdominal pain, anorexia, dehydration, Kussmall breathing, loss of consciousness and finally coma will be seen in these patients (7). Most reported symptoms of the patient's with DKA were polyuria and polydipsia (10).

Most reported symptoms in newly diagnosed T1DM patients were polyuria, polydipsia and weight loss (7,10,11). Our study results also demonstrated same results with other studies in literature. Apart from literature, malaise and weight loss were common in our study group. Vomiting was also common in formerly diagnosed DKA patients like other studies (1,3).

A multicenter study from Europe was showed newly diagnosed DKA patients had symptoms at least two weeks (12). Articles from Turkey also reported that period before DKA diagnosis was usually two weeks (7,10,13). In our study, we reached our study populations admission time was same as other reports in literature. Formerly diagnosed DKA patients are more careful about DKA symptoms due to educations performed in their clinical care so their admission time was shorter than newly diagnosed T1DM patients.

Parent's unawareness of symptoms of DM may affect DKA incidence (14). Positive family history for T1DM is defined as a risk factor for DKA (15). We did not find any difference between formerly or newly diagnosed T1DM with positive family history of DM concurrently. But we found that severe DKA related with presence of DM family history. This result also suggests requirement of more public educations about awareness of DM. A public campaign about DM in Italy for health professionals and families lowered DM prevalence from 78 to 12.5% (6).

If we evaluate electrolyte disturbances of patients at admission and during treatment period, we found that hypophosphatemia was the most common electrolyte disturbance. This result did not show actual result because intravenous phosphate forms are mostly absent in our hospital so patients could not get IV phosphate support during treatment properly. Hypokalemia was the most common electrolyte disturbance in newly diagnosed DKA patients like other studies published from Turkey and other countries (1,4,7). Children with DKA usually suffers from hypokalemia because of transcellular potassium shift and increaring loss from the body because of vomitting and secondary hyperaldosteronism (5). A single center study from Turkey reported that hypokalemia was developed because of inadequate replacement (7). Hypophosphatemia could be seen in DKA patients result of osmotic diuresis and depletion of intracellular phosphate (5). Hypophospahatemia can cause several complications like rhabdomyolysis, respiratory failure, hemolysis, metabolic encephalopathy and myopathy (5). Pediatric DKA guideline did not recommend routine hypophosphatemia treatment but it recommends potassium replacement with potassium chloride and potassium phosphate together (5). Severe hypophosphatemia (serum phosphate levels <1 mg/dl) should be treated (5). Recent published single center study from Netherlands did not show any difference between hypophosphatemic and normophosphatemic adult DKA patients (16). There should be more studies done in pediatric DKA patients about electrolyte disturbances.

Brain edema was seen in DKA episodes in 1% of patients (7). Brain edema was the most serious complication of DKA (14). In our study group brain edema incidence (2.8%) was higher than literature data. This will be associated with our center was a

referral center in Ankara City and Central Anatolia region. More complicated cases referred to our facility. Despite that we did not see any mortality in our cohort.

There are several restrictions of our study. Our study was single-centered and retrospective. Parental education level and patients' socioeconomic conditions were not reported in patient files. Family history of diabetes did not classify as T1DM and T2DM result of invalid data. Severity of dehydration did not record at time of admission into patient files. The data of DM patients with old diagnosis whether DKA was present at the time of diagnosis could not be accessed because of missing registry. Treatments before PICU may not be recorded properly. Assessment of brain edema may be lacking and some patients with brain edema could not be detected. Nearly all DKA patients are hospitalized in PICU in our facility. But, there would be patients with DKA whom did not referred to PICU for follow-up and hospitalized to ward from emergency service. Our data will not show our countries proper DKA data. Multicenter prospective studies should be designed.

In conclusion, diabetic ketoacidosis is an important patient group in PICU. Most of the DKA patients were adolescent age group in formerly diagnosed T1DM patients. School age group was the most common age group in newly diagnosed T1DM. Malaise, polyuria, polydipsia, weight loss are most seen symptoms in newly diagnosed patients. Vomiting is the most common symptom in formerly diagnosed T1DM patients. Time period before PICU admission was longer in newly diagnosed T1DM. Hypophosphatemia is common in PICU admission. Hypokalemia was mostly seen in DKA in newly diagnosed T1DM patients. Diagnostic tools of brain edema should be more effectively used in PICU. There should be educations or commercials for school age group to provide public awareness for DM. Formerly diagnosed adolescent patients should have strict control for DKA and doctors should be more cautious about their parental education for DM.

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Developmental Risk Factors of Young Children with Inherited Metabolic Disorders During the COVID-19 Pandemic

Erken Çocukluk Döneminde Kalıtsal Metabolik Hastalığı Olan Çocukların COVİD-19 Pandemisinde Gelişimsel Risk Etmenleri

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) pandemic has led to emergence of new developmental risk factors. Developmental risk factors for young children with inherited metabolic disorders have not been studied based on a comprehensive framework. We aimed to determine the developmental risk factors of young children with inherited metabolic disorders during COVID-19 pandemic based on bioecological theory.

Material and Methods: In a cross-sectional design, children aged 0-42 months that who had appointments at Ankara University School of Medicine Department of Pediatrics (AUDP) Pediatric Metabolism Division with the diagnoses of inherited metabolic disorders were recruited between October 1st, 2020 to January 1st, 2021. Developmental risk factors were assessed with a semi-structured interview based on questions of the Expanded Guide for Monitoring Child Development revised for the pandemic at AUDP Developmental Pediatrics Division.

Results: The sample consisted of 95 children with inherited metabolic disorders (median age:25, IQR: 17-35 months, 57.9% boys). Most children (54 children, 56.8%) had amino-acid metabolism disorders. Child-related developmental risk factors included new behavioral problems in most of the sample (53 children, 55.8%) and increased screen time in 26 children (27.3%). As family-related developmental risk factors, 40 children (42.1%) were living with a family member diagnosed with major depression. In environment-related developmental risk factors; 41 families (43.2%) experienced a decrease in their household income and 21 (22.1%) loss of job during the pandemic, 17 (17.9%) delay in health care follow up visits, 8 of 28 (28.6%) discontinuity of intervention and rehabilitation services. Participation in life was severely limited in 42 (44.2%) children with inherited metabolic disorders.

Conclusion: Apart from life threatening medical problems, children and their families in Turkey and potentially in other low- and middle-income countries face multiple developmental risk factors. Preventable or reducible risk factors should be addressed to support these children's development in this pandemic and beyond.

Key Words: Child Development, COVID-19, Family, Inborn Errors of Metabolism, Risk Factors

ÖZ

Amaç: Koronavirus hastalığı 2019 (COVİD-19) pandemisi, yeni gelişimsel risk faktörlerinin ortaya çıkmasına neden olmuştur. Ancak kalıtsal metabolik hastalıkları olan küçük çocuklar için gelişimsel risk faktörleri, kapsamlı bir çerçeveye dayalı olarak çalışılmamıştır. Bu araştırmanın amacı COVİD-19 pandemisinde kalıtsal metabolik hastalığı olan küçük çocukların biyoekolojik kuram çerçevesinde gelişimsel risk etmenlerini belirlemektir.

Gereç ve Yöntemler: Kesitsel desendeki araştırmada, Ankara Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı (AUÇH) Çocuk Metabolizma Bilim Dalında kalıtsal metabolik hastalık tanısı ile randevusu olan 0-42 aylık

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ethics Committee of the Ankara University School of Medicine (Decision number: İ8-484-20, 10.09.2020).

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

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çocuklar, 1 Ekim 2020-1 Ocak 2021 tarihleri arasında çalışmaya alındı ve AUÇH Gelişimsel Pediatri Bilim Dalında Genişletilmiş Gelişimi İzlenme ve Destekleme Rehberi'nin sorularına dayalı olarak yarı yapılandırılmış bir görüşme ile gelişimsel risk etmenleri değerlendirildi.

Bulgular: Örneklem, kalıtsal metabolik bozukluğu olan 95 çocuktan oluşmaktadır (ortanca yaş: 25, ÇAA: 17-35 ay, %57.9 erkek). Çocukların çoğunda (54 çocuk, %56.8) aminoasit metabolizma bozukluğu tanısı bulunmaktaydı. Çocukla ilgili gelişimsel risk etmenleri alanında örneklemin çoğunda (53 çocuk, %55.8) yeni ortaya çıkan davranış sorunları ve 26 çocukta (%27.3) artmış ekran süresi saptandı. Aile ile ilgili gelişimsel risk etmenleri olarak, 40 çocuğun (%42.1) evinde majör depresyon tanısı almış bir birey bulunmaktaydı. Çevre ile ilgili gelişimsel risk etmenleri alanında 41 aile (%43.2) pandemide hane gelirinde azalma, 21 aile (%22.1) iş kaybı, 17 aile (%17.9) sağlık izlemlerinde gecikme, girişim ve rehabilitasyon hizmetleri alan 28 ailenin 8'i (%28.6) kesinti bildirdi, 42 (%44.2) çocuğun yaşama katılımı ciddi şekilde sınırlıydı.

Sonuç: Türkiye'de ve büyük olasılıkla diğer düşük ve orta gelirli ülkelerde kalıtsal metabolik hastalığı olan çocuklar yaşamı tehdit eden tıbbi sorunların yanı sıra birden fazla çevresel gelişimsel risk etmeni ile karşı karşıyadır. Bu çocukların pandemi ve diğer olası kriz dönemlerinde gelişimlerini desteklemek için önlenebilir risk etmenleri önlenmeli ve mümkün olduğunca risk etmenleri azaltılmalıdır.

Anahtar Sözcükler: Gelişim, COVİD-19, Aile, Kalıtsal Metabolik Hastalıklar, Risk Etmenleri

INTRODUCTION

During Coronavirus disease 2019 (COVID-19) pandemic, considerable strain on daily life of children with inherited metabolic disorders and their families has led to emergence of new developmental risk factors (1,2). Knowledge of the developmental risk factors of children with inherited metabolic disorders is crucial as the management of developmental difficulties in young children cannot be accomplished without information on risk factors.

Developmental risk factors are the factors that may affect the child, the child's proximal or distal environment and have a negative influence on child development. These factors may be biomedical, psychosocial or both together (3). Children with inherited metabolic disorders have well known and mostly severe biomedical risk factors that affect development in developmental domains including cognitive, language, motor and social-emotional development. These biomedical risk factors arise from complex and chronic health care problems that may include almost all organ systems such as cardiac, pulmonary, renal, hepatic, endocrine, central and peripheric nervous system and may cause failure to thrive, developmental difficulties and disabilities (4-7). Children with inherited metabolic disorders need close health care follow up by specialized teams, specific diet according to their disease, ongoing management of specific treatments and metabolic destabilizations that gained more importance in the COVID-19 pandemic (2,8).

In low and middle income counties (LMICs) many children younger than 5 years are exposed to complex interaction of biomedical and psychosocial multiple risk factors, which detrimentally affect their cognitive, motor, and social-emotional development (9). It was reported that children with inherited metabolic disorders may have important psychosocial risk factors such as poverty, unstimulating home environments, lack of social support, stigmatization, and limited participation in life that pose additional serious risks for their development. The pandemic brought new risk factors (10). Even in high income countries more than half of the families of children with inherited metabolic diseases reported the need for including food and financial assistance, and childcare support during COVID-19 pandemics as well as access to medical care (2,11).

According to Bronfenbrenner's bioecological theory development of a child happens through the complex and dynamic interactions among the child's health conditions, temperament, developmental strengths and difficulties; the relationships and interactions with and within the family including closest caregivers, siblings, as well as proximal caregiving environment and distal environment such as living and working conditions, health and social services, physical environment, education and intervention services (12). Therefore, the developmental risk factors that affect a child development may be related to the child, proximal caregiving environment (family) and distal environment. Although COVID-19 pandemic had an enormous effect on children with inherited metabolic disorders, developmental risk factors for youngest children with inherited metabolic disorders who have the most potential to reach their optimal development with interventions have not been studied based on a comprehensive framework.

In this study, we aimed to determine the developmental risk factors of young children with inherited metabolic disorders during COVID-19 pandemic based on bioecological theory.

METARIAL and METHODS

In a cross-sectional design, children aged 0-42 months that who had appointments at Ankara University School of Medicine Department of Pediatrics (AUDP), Pediatric Metabolism Division with the diagnoses of inherited metabolic disorders were recruited in three-months period between October 1st, 2020 and January 1st, 2021. Children were included if they were able to come to the hospital during the study period and their parents provided informed consent to participate in the study. The study was approved by the Ethics Committee of the Ankara University School of Medicine (Decision number: İ8-484-20, 10.09.2020).

The assessment of developmental risk factors of children with inherited metabolic disorders was conducted at AUDP,

Developmental Pediatrics Division. All children with inherited metabolic disorders have appointments in the Developmental Pediatrics outpatient clinic at the day of their appointments in Pediatric Metabolism outpatient clinic as per routine patient follow up procedures. In the Developmental Pediatrics outpatient clinic, after asking for informed consent for the study, a semi-structured interview lasting approximately 20 minutes was conducted with the parents who provided their consent using questions of the Expanded Guide for Monitoring Child Development (Expanded GMCD) (13). Sociodemographic data was also retrieved from the Expanded GMCD. Information related to the health conditions of the child such as the diagnoses, medications, and specific diet requirements and developmental conditions including delays, disabilities and related disability reports were determined from the hospital records.

The Expanded GMCD is a written questionnaire based on the World Health Organization International Classification of Functioning, Disability and Health (ICF) and Nurturing Care frameworks (13). The Expanded GMCD provides information on health conditions, developmental functioning, activities and participation, as well as the environmental factors including developmental risk factors. A previous study has shown that the open-ended questions of the Expanded GMCD were accepted and responded by the families of children with inherited metabolic disorders (14).

Developmental risk factors were conceptualized on the bioecological theory and included child, family and environment related factors. Child related developmental risk factors included having diet dependent metabolic disorders, need for hospitalization during the pandemic, COVID-19 infection in the child, any regression stated by the families in language, motor, cognitive or social-emotional domains due to pandemic related conditions (not due to metabolic decompansations, examples include seize of special education and/or rehabilitation services, difficulties in caregiving environment etc.), existence of sleep, eating/feeding and other behavioral problems (such as stubbornness, frequent meltdowns, excessive crying etc.) and increased screen time during the COVID-19 pandemic. Family related developmental risk factors included low maternal and paternal education defined as ≤5 years, change of primary caregiver in the pandemic, increased maternal fatigue, mother spending less daily time with her child than the pre-pandemic period, mother or father having treatment for major depression as well as diagnosis of depression in other household members, COVID-19 infection and COVID-19 related death in the household members. Environment related developmental risk factors included decrease in monthly household income compared to pre-pandemic period, loss of job in the household members, and discontinuation to health care follow up, intervention and rehabilitation services due to pandemic related conditions (such as quarantine periods or fear of infection). Therefore, we have added pandemic-related developmental risk factor questions to the "Developmental functioning", "Activities and participation in life" and "Environmental factors" sections of the Expanded GMCD for the purpose of this study. These were asked as structured questions and coded as "present" or "absent." During the assessment these questions were read to the parents and the answers were recorded by the developmental pediatrician. The presence of another child and/or family-environment related developmental risk factor in the interview was also recorded. Reported developmental risk factors were addressed when possible and developmental support was provided at the developmental pediatrics outpatient clinic.

Sociodemographic data included age, gender, number and age of siblings, maternal and paternal age and education, monthly household income, number of family members living together, the city that the family lives as well as whether the child lives in a nuclear or an extended family.

Data analyses

Descriptive statistics were used as frequencies for categorical data; means and standard deviations for normal continuous distributions; and medians and interquartile ranges (IQR) otherwise. The Shapiro-Wilk test was used to check whether there was a normal distribution of the numerical variables. Statistical analyses were done using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program.

RESULTS

A total of 98 young children younger than 42 months with inherited metabolic disorders who were seen at AUDP, Pediatric Metabolism Division in the study period were considered for eligibility for this study. Of these 3 did not provide consent for the study and the sample consisted of 95 children with inherited metabolic disorders.

Sociodemographic and health related characteristics of the sample

The sociodemographic characteristic of the sample are shown in Table I. The median age of the sample was 25, IQR: 17-35 months, 55 children were boys (57.9%). Median maternal and paternal ages were 30.0 (IQR: 25-35) and 33.0 (IQR: 29-38) years. Most of the children had at least one sibling and 47 (49.5%) children were born to parents with consanguinity. Most of the children were residing in Ankara, the capital of Turkey. Most mothers 89 were homemakers (93.7%) whereas 85 fathers (89.5%) were working on a job.

The diagnoses of the children were as following: 54 children (56.8%) had amino acid metabolism disorders (29 had biotinidase deficiency, 10 hyperphenylalaninemia, 9 organic acidemia, 4 phenylketonuria, 1 tyrosinemia, 1 cystinuria), 15(16.7%) mitochondrial disorders, 7(7.4%) lysosomal and

Table I: Sociodemographic characteristics and diagnoses (n=95).

Characteristics of children	n (%)
Boys	55 (57.9)
Girls	40 (42.1)
Age (months)	
0-12	15 (15.8)
13-24	30 (31.6)
25-42	50 (52.6)
Maternal education	
Never went to school	4 (4.2)
Primary school	18 (18.9)
Secondary school	29 (30.5)
High school graduate	26 (27.4)
University education or higher	18 (18.9)
Paternal education	
Never went to school	1 (1.1)
Primary school	19 (20.0)
Secondary school	18 (18.9)
High school graduate	34 (54.7)
University education or higher	23 (24.2)
Number of siblings	
Only child	35 (36.8)
One sibling	30 (31.6)
≥2 siblings	30 (31.6)
Nuclear family	75 (78.9)
Residing in Ankara	58 (61.1)

peroxisomal disorders, 4(4.2%) carbohydrate metabolism disorders, 3 (3.2%) congenital glycosylation disorders, 1 (1.1%) fatty acid oxidation disorder, 1 (1.1%) urea cycle disorder, and 10 (10.5%) other metabolic disorders. Most of the children (67.4%) had developmental delay in at least one domain of development, 33 (34.7%) had disability benefits report and 7 (7.4%) used orthoses.

Developmental risk factors in the COVID-19 pandemic

The developmental risk factors conceptulized on bioecological theory as child-related and family/environment-related developmental risk factors are summarized in Table 2. All of the sample had at least one child related developmental risk factor due to their metabolic disease, most (69 children, 72.6%) had two, 46 (48.4%) children had ≥3 child -related developmental risk factors. Most of the sample 52 (54.7%) had ≥3 family and/or environment related developmental risk factors; 84 children, (88.4%) had at least one, 77 (81.1%) had two family and/or environment related developmental risk factors. When child and family and/or environment related developmental risk factors are considered 31 (32.6%) children had ≥6 developmental risk factors.

Child-related developmental risk factors. When the families were asked about the traejctory of their child's development including in language, motor, cognitive or social-emotional development domains; 7 families (7.4%) reported that their child regressed in developmental functioning in at least one

Table II. Developmental risk factors of the sample.

Child related developmental risk factors	n (%)
Biomedical risk factors	
Having a diet dependent metabolic disease	23 (24.2)
Hospitalization during the pandemic	17 (17.9)
COVID-19 infection in the child	0 (0.0)
Existence of behavioral problems during the pandemic	
Sleep difficulties	20 (21.1)
Difficult behavior such as meltdowns, excessive crying etc.	19 (20.0)
Eating and/or feeding difficulties	14 (14.7)
Increased screen time	26 (27.3)
Regression in development in at least one developmental domain	6 (6.3)
Family related developmental risk factors	
Maternal education ≤ 5 years	22 (23.2)
Paternal education ≤ 5 years	20 (21.1)
Increase in maternal fatigue	34 (35.8)
COVID-19 infection in the family members	23 (25.0)
Diagnosis of depression in the family	
Maternal depression	15 (15.8)
Paternal depression	7 (7.4)
Depression in other household members	18 (18.9)
Change of primary caregiver during the pandemic	14 (14.7)
Mother spending less daily time with her child than usual	5 (5.3)
Death due to COVID-19 in the family members	0 (0.0)
Environment related developmental risk factors	
Decrease in monthly household income	41 (43.2)
Loss of job in the household members	21 (22.1)
Delay in their health care follow up visits	17 (17.9)
Discontinuity of intervention and rehabilitation services (n=28)	8 (28.6)
Getting out from home for leisure activities/ visiting relatives etc. ≤once a week	56 (58.9)

domain since the beginnig of the pandemic. The reasons provided by the parents included discontnuity to rehabilitation services in 3 families, family members' COVID-19 infection in 2, and depression in caregivers in 2 families. Most of the families (55.8%) reported a behavioral problem in their child that existed during the pandemic including eating/feeding, sleep or other daily behaviors. Almost one third of the children (32.6%) had experienced eating/feeding difficulty in the pandemic including 14 (14.7%) undereating and 17 (17.9%) overeating when compared to pre-pandemic period. Sleep schedule and duration has not changed significantly for most of the children (68.4%) according to families, while in 20 (21.1%) children the family reported exitence of sleep problems.

Family related developmental risk factors. Almost one fifth of the sample maternal (23.2%) and paternal (21.1%) education was ≤ 5 years. Seventy (73.7%) families stated that the time that the mother spent with her child to support development (like playing, reading, talking during daily activities) did not change and 20 (21.1%) spent more time than usual. Fourty children

(42.1%) were living with a family member diagnosed with major depression.

Environment related developmental risk factors. Most families' income (53.5%) was less than minimum wage and almost one fifth (22.1%) of the families experienced a loss of job during the pandemic. Loss of job involved fathers in 17 families, other household members such as uncle or grandfather in 2 families and one family experienced loss of job in both the mother and the father. In the participation in life domain, when the families were asked about the frequency of getting out from their home with their child for leisure activities, going to parks or visiting friends/relatives etc.; 42 (44.2%) children did not have a regular outside activity per week, 14 children (14.7%) were getting out home for one of these activities once a week, 17 children (17.9%) 2-3 times a week and 22 children (23.2%) ≥4 times a week.

DISCUSSIONS

This study demonstrated the developmental risk factors of young children with inherited metabolic disorders during COVID-19 pandemic from a middle-income country, Turkey. Many developmental risk factors arised during the COVID-19 pandemic. All young children had at least one, one third of the sample had six or more developmental risk factors based on bioecological theory. These findings draw attention to addressing the preventable risk factors that the children with inherited metabolic disorders carry during crises periods like a pandemic and imply for clinicians and policy makers in the COVID-19 pandemic and beyond.

There have been studies including the developmental risk factors of children with inherited metabolic disorders while our study is the first study investigating the developmental risk factors based on bioecological framework for youngest children with inherited metabolic disorders. Almost one third of the sample had a cumulation of six or more child and family/ environment related risk factors. Historically, the cumulation of biomedical and psychosocial risk factors has been referred as "double jeopardy" to describe the detrimental effect of poverty on child development (15).

In our study as child related developmental risk factors; all children had metabolic disorders and most had known developmental delays. More than half of the families reported behavioral problems and one fourth increased screen time parallel to studies showing increased behavioral difficulties in young children with specific health care needs during the COVID-19 pandemic (16). Additional to these risk factors, most common family and/or environment related risk factors were low maternal and paternal education, depression in family members, financial difficulties, limited participation in life. Oge Enver et al. reported difficulties for children with inherited metabolic disorders (mean age was 7, higher than our study) from Turkey in the COVID-19 pandemic. The results included financial difficulties in most of the sample as an environmental developmental risk factor which was also evident in our study (17). A recent qualitative study from Canada highlighted the experiences of families of children with inherited metabolic disorders and it was reported that participation in social life was one of the themes that arised in the interviews (18). Another important environmental risk factor was discontinuity to health care and intervention and/or rehabilitation services due to quarantines and fear of COVID infection which was evident in many countries around the world (2,11). Evidence shows that timely interventions addressing developmental risk factors such as poverty, maternal depression, low maternal education, restricted learning opportunities and inequities can improve early childhood development especially in low and middle countries (19,20). At AUDP the clinicians from Pediatric Metabolism Division reached the children and their families via telehealth during the pandemic, provided support in information, answered the questions of the family. System related difficulties were suspended with efforts of the clinicians. Additionally, AUDP Developmental Pediatrics Division provided early intervention with Guide for Monitoring Child Development (GMCD) early intervention package with telehealth (21-23). These may be protective for these vulnerable children and their families during crises. There is need for research on child and family related protective factors and resilience for young children with inherited metabolic disorders during crises.

Our study has some limitations. The cross-sectional design precludes drawing casual associations. We have provided the number of risk factors but we don't know the effect size of risk factors and the relationship between different risk factors (such as financial difficulties may cause depression). Our small sample size is relatively large while the sample was heterogenic in terms of diagnosis and included both severe (such as urea cycle disorders) and less severe metabolic diseases (such as hyperphenylalaninemia). The major strength of this study is the conceptual framework based on the bioecological theory.

The implications of our study are important for the care of children with metabolic disorders in this pandemic and other crises periods. Our results indicate that apart from life threatening medical problems, children and their families in Turkey and potentially in other low- and middle-income countries face multiple child, family and environment related developmental risk factors that puts further burden in their developmental trajectory. Preventable or reducible risk factors such as inappropriate caregiving environment, depression, financial difficulties, continuum of care in health and intervention services should be addressed by multisectoral coverage.

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Evaluation of Self-Efficacy and Health-Related Quality of Life in Pediatric-Onset Multiple Sclerosis Patients

Çocukluk Çağı Başlangıçlı Multipl Skleroz Hastalarında Öz Yeterlilik ve Sağlıkla İlişkili Yaşam Kalitesinin Değerlendirilmesi

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ABSTRACT

Objective: To assess the self-efficacy level and health-related quality of life in pediatric-onset multiple sclerosis (POMS) patients.

Material and Methods: A cross-sectional study was conducted between January-April 2022 at Hacettepe University Department of Pediatric Neurology using The Pediatric Rating of Chronic Illness Self-Efficacy (PRCISE) Scale and Pediatric Quality of Life Inventory (PedsQL).

Results: Twenty-nine POMS patients with a median age of 16.4 years (F/M: 20/9) were included in the study. The mean PRCISE Scale score was 101.8±22.4 and the mean PedsQL score was 66.5±16.2. Both scores were lower than previously reported in the literature.

Conclusion: Lower self-efficacy and HRQoL levels might be attributed to fatigue which is common in POMS. The impact of the COVID-19 pandemic on mental health and quality of life should be addressed in patients with POMS.

Key Words: Childhood, Health-related quality of life, Multiple sclerosis, Self-efficacy

ÖZ

Amaç: Bu çalışma ile çocukluk çağı başlangıçlı multipl skleroz (çMS) hastalarının öz yeterlilik ve sağlıkla ilişkili yaşam kalitesi düzeylerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2022 – Nisan 2022 tarihleri arasında kesitsel olarak gerçekleştirilen bu çalışmada çMS tanılı hastalalar Pediatrik Kronik Hastalık İçin Öz Yeterlilik Ölçeği (PKHÖYÖ) ve Çocuk Çağı Yaşam Kalitesi Ölçekleri (ÇÇYKÖ) ile değerlendirilmiştir.

Bulgular: Ortalama yaşları 16.4 yıl olan 29 çMS hastası (K/E:20/9) çalışmaya katılmıştır. PKHÖYÖ ortalaması 101.8±22.4 puan elde edilmiş olup, ÇÇYKÖ skorlamasında ortalama 66.5±16.2 puan elde edilmiştir. Her iki değerin literatürde daha önceki yapılmış olan çalışmalardan düşük olduğu görülmüştür.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Ethical approval was obtained from Hacettepe University Clinical Research Ethics Committee (2022/01-07).

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

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Sonuç: Pediatrik Kronik Hastalık İçin Öz Yeterlilik Ölçeği ve ÇÇYKÖ ortalama skorlarının düşük olması çMS hastalarında yaygın görülen kronik yorgunlukla ilişkili olabilir. Ayrıca COVID-19 pandemisinin çMS hastalarında mental sağlık ve yaşam kalitesi üzerindeki etkisi de bu sonuçlar yorunmlanırken göz önünde bulundurulmalıdır.

Anahtar Sözcükler: Çocukluk Çağı, Sağlıkla İlişkili Yaşam Kalitesi, Multipl Sklerosis, Öz Yeterlilik

INTRODUCTION

Pediatric-onset multiple sclerosis (POMS) defines multiple sclerosis manifesting before age 18 years. Approximately 90% of POMS cases present during adolescence, an age group where autonomy, individuation, self-efficacy, and self-reliance are in development (1, 2). Self-efficacy refers to an individual's confidence in their own ability for a specific behaviour or achievement. In terms of health conditions, self-efficacy comprises the belief in one's ability to manage the requirements of a disease adequately (3). The perception of self-efficacy is an important predictor of health-related behaviour and adherence to treatment in chronic diseases (4).

The multi-dimensional impact of a health condition and its treatments on the individual's physical, mental, emotional, and social well-being is defined as health-related quality of life (HRQOL) (5). Adolescents' and young adults' mental and emotional health and quality of life affect their education and career choices, their parents, and their use of the health care system. Therefore, the management of their disease often extends beyond the physical effects of medical treatment. The aim of this study was to evaluate self-efficacy and HRQOL in patients with POMS.

MATERIALS and METHODS

We conducted a cross-sectional study between January and April 2022 with patients who had been diagnosed with POMS in Hacettepe University Faculty of Medicine, Department of Pediatric Neurology. Patients with POMS lasting more than three months and were able to read and complete the Turkish version of The Pediatric Rating of Chronic Illness Self-Efficacy Scale (PRCISE) and Pediatric Quality of Life Inventory (PedsQL) were included in the study. After informed consent from patients or parents to participate in the study, patients were asked to fill out the PRCISE and PedsQL during their routine clinical visit. Demographic and clinical data included age, gender, duration of disease, treatments, and last available expanded disability status scale (EDSS) scores were recorded from hospital registry. Ethical approval was obtained from Hacettepe University Clinical Research Ethics Committee (2022/01-07).

Statistical analyses:

Statistical analyses were performed using a package program called SPSS (IBM SPSS Statistics 24). The data of the patients were classified by various parameters. Frequency tables and descriptive statistics were used to interpret the findings.

Outcome measures:

Self-efficacy levels were measured with the PRCISE. The scale was developed by Emerson et al (6). It comprises 15 items and 6 sub-dimensions: exercise (1 item), obtain help from family, friends and doctors (4 items), illness management (3 items), chores, hobbies and recreation (3 items), symptoms (3 items) and mood (1 item). All items are answered on a Likert scale from 0 to 10 ranging from 0 for "not at all sure" to 10 for "very sure". A total PRCISE score ranges from 0 to 150, the maximum total score of 150 indicating the highest self-efficacy level. The Turkish version of the PRCISE Scale was adapted from the original scale by Gürcan et al (7) with acceptable validity and reliability for Turkish children.

Health Related Quality of Life (HRQoL) was measured using the Turkish version of PedsQL. Version 4.0 for 13 -18 years old. The PedsQL was developed to evaluate child perceptions of HRQOL in children with various health problems. This 23-item scale based on child/adolescent self-report consists of four domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). PedsQL assesses the frequency of problems that occurred in the last one month. All items are answered on a Likert scale from 0 to 5 ranging from 0 for "never a problem" to 5 for "almost always a problem". All the items are then reverse scored and transformed into a 0-to-100-point scale (0=100; 1=75; 2=50; 3=25; 4=0), where a higher total score of PedsQL 4.0 indicates a better HRQoL. The validity and reliability of the Turkish version of PedsQL 4.0 Version for 13-18 Years Old were proven by Memik et al (8).

RESULTS

Total 29 POMS patients, median age 16.4 years (range: 13.4-17.7), female/male 20/9, were enrolled in the study. All patients had been on a disease modifying therapy for more than 3 months. All had an

Table I: Demographic and clinical characteristics of POMS patients.

F/M n (%)	20/9 (69/31)
Age (years) median (25-75%)	16.4 (13.4-17.7)
Disease duration	26 months (5-64 months)
Treatments (n)	
Interferons	11
Teriflunomide	9
Dimethyl fumarate	7
Ocrelizumab	1
Fingolimod	1

POMS: *Pediatric Onset Multiple Sclerosis,* ***F:*** *Female,* ***M:*** *Male*

Expanded Disability Status Scale (EDSS) score of 0 indicating no neurological disability, and none had a comorbid disease (Table I).

The mean PRCISE Scale score was 101.8±22.4 (median 103, 101.62 for girls and 102.12 for boys). The mean PedsQL score was 66.5±16.2 (median 66, 66.7 for girls and 66.2 for boys).

DISCUSSIONS

Self-efficacy measurement is a standardized and practical way to evaluate a patient's self-management ability and identify patients at risk for medical nonadherence. It has been recommended as a part of chronic care and management (9). In our study we found the mean PRCISE score of 101.8±22.4 out of 150. In a previous validation and reliability study of PRCISE Scale on Turkish adolescents with different chronic illnesses, the mean PRCISE score was determined as 106±17.9 and no significant relation was found between self-efficacy level and age, sex and disease duration (7). The mean PRCISE score of the subgroup including patients with neurological disease was 104.9±22. In the original study of PRCISE scale conducted by Emerson et al. (6) the mean PRCISE score was 114±31.7 in 7- 20-year-old patients with various chronic diseases, and the subgroup comprising patients with neurological diseases had a mean PRCISE score of 113.5±32.7. The self-efficacy level of our patients was lower than those reported.

Self-efficacy is affected by type of illness, multimorbidity and functional disability (10). In our study, none of the patients had a chronic comorbid condition and neurological disability. Nevertheless, the lower self-efficacy level in our patients may be attributed to several reasons. One is fatigue, the feeling of exhaustion and tiredness known as one of the most common and disabling symptoms MS and affecting 9-76% of children and adolescents with POMS (11). In a recent study of adult MS patients from Turkey, the frequency of fatigue was reported as 68.2% (12). However, no available data was found regarding the prevalence of fatigue in Turkish POMS patients, and fatigue was not questioned in our study either. MS-related fatigue may impact physical functioning even in the absence of obvious neurological disability. An inverse association exists between fatigue and self-efficacy (13).

Both self-efficacy and fatigue have been found to be the major determinants of quality of life in adult patients with MS, along with neurological disability (14). The HRQoL evaluated in our study showed the mean score of 66.5±16.2. In the validation and reliability study of Turkish PedsQL for adolescents aged 13 to 18 years, the mean PedsQL score of patients with chronic diseases was 74.82 and a recent systematic review and meta-analysis in POMS patients using PedsQL, reported mean HRQoL scores as 67.3-82.4 (15). The mean PedsQL score of our POMS patients was in the lower range of those reported in this meta-analysis. One possible reason of this result is the COVID-19 pandemic. Social distancing, self-isolation, and various restrictions that people faced in all around the world during the last 2.5 years affected mental health of people, particularly those in younger age (16). Recent studies have shown that both self-efficacy and quality of life declined significantly in individuals due to COVID-19 pandemic (17, 18). Moreover, our study was conducted in a time frame where the highest COVID-19 cases were reported in Turkey (19). Therefore, the probable adverse impact of the pandemic on our results cannot be ignored.

The small number of patients, the inability to apply the scales according to the treatment subgroups, and the absence of a control group are the limitations of our study. Besides that, we did not evaluate our patients for psychiatric and behavioral problems, including depression or adjustment disorders, which may affect our results. Further studies with larger cohorts are required to address these limitations. The fact that PRECISE and PedsQL can be applied in chronic diseases such as POMS with a low incidence and prevalence is one of the strengths of our study.

We found both the self-efficacy and HRQoL levels were lower in POMS patients. These two variables interact in their effect on the patients' and parents' life. Developing strategies to support the self-management and strengthen the self-efficacy in POMS patients may help these adolescents to cope with MS and bring a higher quality of life.

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Evaluation of Pediatric Residents' Knowledge Levels on Inhaler Techniques Used in Asthma Treatment and the Effect of Education on the Level of Knowledge

Pediatri Asistanlarının Astım Tedavisinde Kullanılan İnhaler Tedavi Teknikleri Konusunda Bilgi Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objective: The use of inhaler drugs results in clinical success only when they are applied using the right technique. Faulty inhaler application techniques reduce therapeutic efficacy, impair treatment compliance, and lead to inadequate control of the disease. This study aimed to evaluate the knowledge levels of pediatric residents who play an important role in the follow-up of patients with pediatric asthma in both inpatient and outpatient services in a tertiary children's hospital and to determine the effect of short-term training on the level of knowledge.

Material and Methods: All participants were asked to demonstrate the use of inhaler devices using demo devices. This assessment was designated as the "Pre-test." The participants were then given face-to-face inhaler device training in groups of up to 15 people, which included all application steps. At the end of the training, the steps of inhaler device use were reassessed.

Results: Pre-training evaluation of inhaler technique on Metered Dose Inhaler and Dry Powder Inhaler devices showed that none of the 148 participants successfully completed the predetermined mandatory steps of the inhaler technique. After the training, it was observed that all participants were able to fully apply the steps of the previously determined checklist.

Conclusion: Medical school curricula and specialty education should include the application training of inhaler devices, which are extremely important for asthma treatment. Regular repetition of in-service training involving inhaler technique and application among health professionals can correct application errors and increase awareness regarding the importance of the right inhaler technique in the treatment of asthma.

Key Words: Asthma, Children, Inhaler, Treatment techniques

ÖZ

Amaç: İnhaler ilaçların tedavi başarısı ancak doğru bir teknikle uygulanırsa mümkün olmaktadır. Hatalı inhaler teknik; terapötik etkinliği azaltır, tedavi uyumunu bozar ve hastalığın yetersiz kontrolüne yol açar. Çalışmamızda; üçüncü

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basamak çocuk hastanesinde hem yataklı servis hem de poliklinik hizmetlerinde astımlı çocuk hasta takibinde önemli rol üstlenen pediatri asistan hekimlerinin uygun inhaler teknik konusundaki bilgi düzeylerini değerlendirmek ve kısa süreli bir eğitimin bilgi düzeyine katkısını belirlemek amaçlanmıştır.

Gereç ve Yöntemler: Tüm katılımcılardan demo cihazlar ve manken kullanarak, inhaler cihaz kullanımını göstermeleri istendi. Bu değerlendirme 'Ön-Test' olarak adlandırıldı. Daha sonra katılımcılara maksimum 15 kişiden oluşan gruplar halinde, tüm uygulama basamaklarını içeren yüz yüze inhaler cihaz kullanım eğitimi verildi. Eğitim sonunda inhaler cihaz kullanımına ait basamaklar tekrar değerlendirildi.

Bulgular: Ölçülü Doz İnhaler ve Kuru Toz İnhaler cihazlara ait inhaler teknik ile ilgili eğitim öncesi değerlendirme sonucunda 148 katılımcıdan hiçbirinin önceden belirlenmiş zorunlu basamakları eksiksiz tamamlayamadığı görüldü. Eğitim sonrasında tüm katılımcıların önceden belirlenen kontrol listesinin adımlarını tam olarak uygulayabildikleri gözlemlendi.

Sonuç: Tıp fakültesi müfredatı ve uzmanlık eğitim sürecine astım tedavisi için son derece önemli olan inhaler cihazların uygulama eğitiminin dahil edilmesi gerektiğine dikkat çekmek istiyoruz. Sağlık profesyonelleri arasında, inhaler teknik uygulamalarını içeren hizmet içi eğitimlerin düzenli aralıklarla tekrarlanması uygulamadaki hataları gidermekle birlikte astım tedavisinde doğru inhaler tekniğin önemi konusundaki farkındalığı da arttıracaktır.

Anahtar Sözcükler: Astım, Çocuk, İnhaler, Tedavi Teknikleri

INTRODUCTION

Asthma is the most common chronic disease among children, and its incidence is gradually increasing. Inhaler therapies have been used for several years and are the most effective asthma treatment. The most important advantages of inhaler treatment include the fact that the application is non-invasive, contains lower doses than oral and parenteral treatments, has fewer systemic side effects, provides local and fast efficacy, and is portable in such a way that the patient can carry the inhaler with him or her at any time (1).

The use of inhaler drugs results in clinical success only when they are applied using the right technique. Faulty inhaler application techniques reduce therapeutic efficacy, impair treatment compliance, and lead to inadequate control of the disease (2-4).

A technique considered ideal for one device can be completely faulty when using another device. For this reason, patients and their parents should be provided with detailed training on the recommended inhaler device, usage technique, and application steps. Further, the inhaler technique employed by patients should be assessed at each doctor visit to prevent possible errors (5,6).

Presently, a metered-dose inhaler (MDI) and dry powder inhaler (DPI) devices, which have completely different working principles, are frequently used in the treatment of childhood asthma. Each inhaler device has its unique usage technique, advantages, and disadvantages. This should be taken into account when choosing the appropriate device for the patient (7-9). The fact that health professionals who provide education to patients and their families teach inhaler devices and application steps clearly and accurately plays a key role in the treatment of asthma.

This study aimed to evaluate the knowledge levels of pediatric residents who play an important role in the follow-up of patients with pediatric asthma in both inpatient and outpatient services in a tertiary children's hospital and to determine the effect of short-term training on the level of knowledge.

MATERIALS and METHODS

The study was conducted between September and December 2021 at Ankara City Hospital Pediatric Allergy and Immunology Clinic. Ethics committee approval was obtained from the Ankara City Hospital Clinical Research Committee (decision number E2-21-846). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Work experience in pediatric health and diseases, pediatric allergy and immunology clinics, and pediatric emergency departments were recorded in addition to demographic characteristics, such as age and gender. Further, a general evaluation form was distributed to all participants. This form comprised whether the participants had previously been trained in inhaler treatments, whether they provided inhaler training to any patient, and information on inhaler device preferences by age group.

A checklist was prepared to assess the use of MDI and DPI (turbuhaler and diskus) devices, which are often used in the treatment of childhood asthma. It comprised the mandatory steps mentioned in the literature and was modified in accordance with our clinical experience (9-12).

All participants were asked to demonstrate the use of inhaler devices using demo devices. Meanwhile, the steps were scored as true or false by the pediatric allergy and immunology specialist. This assessment was designated as the "Pre-test." The participants were then given face-to-face inhaler device training in groups of up to 15 people, which included all application steps. The training was provided by the same specialist and lasted for approximately 30 min. At the end of the training, the steps of inhaler device use were reassessed. These data were recorded as the "Post-test." The steps involved in the evaluation of the inhaler technique are shown in Table I.

RESULTS

A total of 148 resident doctors working in pediatric clinics were included in the present study. The mean age of the participants was 28.0 ± 2.1 years (Inter-quartile range [IQR]; 26–29 years), and 58.8% were female. The participants' average work experience in the pediatric health and diseases clinic was 1.7 ± 0.9 (min-max; 0.2-5 years) years. Fifty-seven (38.5%) participants were actively working in the outpatient clinic during their residency. Twenty-nine (19.6%) participants were observers at the pediatric allergy and immunology outpatient clinic for at least one month. All participants stated that they worked in the inpatient ward and were actively involved in the follow-up of the patients hospitalized due to asthma. It was found that 26 (17.6%) participants had previously received training on inhaler drugs and application techniques at least once. Further, 60.1% reported that they provided inhaler training for the first time to a patient who had not received any treatment before. When participants were asked about the principles of the devices that they were well aware of, 62.2% responded as MDI, 16.9% as DPI, and 20.9% responded as both. Only 15.5% of the participants stated that they had adequate knowledge about inhaler drugs and application techniques. The characteristics of the participants are summarized in Table II.

Participants were also asked about the inhaler devices that they would choose as their first choice according to age groups in children with asthma. For the 0–5 years age group, 64.2% of the participants stated that their first choice would be nebulizer devices. For the 5–12 years age group, spacer with face mask and spacer with mouthpiece MDI devices were preferred similarly. For children over the age of 12 years, more than half of the participants stated that they would prefer DPI. Inhaler devices preferred by pediatric residents according to age groups are summarized in Table III.

For MDI devices, the steps that were frequently forgotten in the pre-test were "the inhaler device is shaken for 5 sec before application," "the mask part of the spacer is placed on the face to fully cover the nose and mouth," and "inhaler device is reshaken before the second dose is applied".

Among DPI (turbuhaler and diskus) devices, most erroneous applications were observed in turbuhaler devices. When application steps were evaluated, the steps that were incorrectly applied by the participants included "keep turbuhaler upright," "exhale before application," and "wait for 1 min before the second inhalation". For diskus, the incorrectly applied steps were "hold diskus in a horizontal position," "exhale before application," and "hold your breath for 5–10 sec after application."

After the training, it was observed that all participants were able to fully apply the steps of the previously determined checklist. The correct response rates of participants to the required steps in pre-test and post-test applications are shown in Figure 1 (A, B, C).

Table I: Check-list containing all application steps of proper inhalation technique

Metered dose inhaler with spacer	Dry Powder inhaler (Turbuhaler)	Dry Powder inhaler (Diskus)
Step 1. Remove the protective cap and shake the inhaler for 5 s	**Step 1.** Remove the turbuhaler cap and hold it upright	**Step 1.** Open the diskus with one hand and push the notch forward with the thumb of the other hand.
Step 2. Hold the inhaler in the upright position, put it into the hole of the spacer. Place your fingers to support the inhaler and spacer.	**Step 2.** urn the base part first to the right and then to the left to hear the 'click' sound	**Step 2.** Pull the latch to hear the 'click' sound
Step 3. Place the mouthpiece between your teeth and lips or cover the nose and mouth with the mask of spacer	**Step 3.** Exhale to residual volume (away from inhaler)	**Step 3.** Hold diskus in horizontal position
Step 4. Press down the inhaler once and breathe in deeply and slowly 5-6 times from the spacer (approximately 10 seconds)	**Step 4.** Place mouthpiece between teeth and lips	**Step 4.** Exhale to residual volume (away from inhaler)
Step 5. Shake the inhaler again before the second dose	**Step 5.** Take a forcefully and deeply breath	**Step 5.** Place mouthpiece between teeth and lips
Step 6. Close cap after use	**Step 6.** Remove the device from the mouth before breathing out and hold your breath for 10 s	**Step 6.** Take a forcefully and deeply breath
	Step 7. Wait one minute before second inhalation	**Step 7.** Remove the device from the mouth before breathing out and hold your breath for 10 s
	Step 8. Turn the base again and prepare for the second inhalation	**Step 8.** Wait one minute before second inhalation
	Step 9. Close cap after use	**Step 9.** Pull the latch again for the second dose
		Step 10. Close cap after use

Table II: Characteristics of the participants.

Characteristics of the participants	n (%)
Age (year)	28.0 ± 2.1 (IQR;26-29)
Gender Male	87 (58.8)
Resident duration (years) Mean	1.7 ± 0.9
0-12 month	23 (15.5)
12-24 month	41 (27.7)
24-36 month	51 (34.5)
36-48 month	33 (22.3)
Rotated departments	
Child health and diseases out-patient clinic	57 (38.5)
Pediatric Allergy and Immunology out-patient clinic	29 (19.6)
Pediatric emergency outpatient clinic	94 (63.5)
Have you received any training on inhaler devices and administration techniques? Yes	
From whom did you receive the training?	26 (17.6)
Pediatric Allergy and Immunology specialist	10 (38.4)
Child health and diseases specialist	6 (23.0)
Senior doctors	10 (38.4)
Have you ever started inhaler treatment for the first time to a patient who has not received any treatment before? Yes	89 (60.1)
How many patients/parents have you trained inhalers so far?	
<10	82 (55.4)
10-50	46 (31.1)
> 50	20 (13.5)
Which of the inhaler devices do you think you know the principles of use correctly?	
Metered dose inhaler	92 (62.2)
Dry powder inhaler	25 (16.9)
Both of them	31 (20.9)
Do you consider your level of knowledge about inhaler drugs and administration techniques sufficient? Yes	23 (15.5)

Table III: Inhaler device preferences of participants according to age groups in patients.

Which would be your first choice?	MDI (Spacer with face mask)	MDI (Spacer with mouthpiece)	DPI	Nebulizers
0-5 years	44 (29.7)	8 (5.4)	1 (0.7)	95 (64.2)
6-12 years	50 (33.8)	58 (39.2)	12 (8.1)	28 (18.9)
> 13 years	9 (6.1)	38 (25.7)	86 (58.1)	15 (10.1)

MDI: *Metered dose inhaler,* ***DPI:*** *Dry powder inhaler*

DISCUSSION

The study aimed to evaluate the level of knowledge regarding inhaler technique among pediatric residents, who are frequently involved in the treatment of childhood asthma. Pre-training evaluation of inhaler technique on MDI and DPI devices showed that none of the 148 participants successfully completed the predetermined mandatory steps of the inhaler technique. It was shown that the inhaler technique could be improved post-training.

There are many studies in the literature evaluating inhaler technique and skills in patients with pediatric asthma and their parents. Although there are differences in the age group, asthma control levels, treatment compliance of patients, and definition of correct inhaler technique among these studies, it can be concluded that there are flaws in the correct application of inhaler devices in the pediatric patient group in general (8,13-16). However, studies that evaluate the level of knowledge of health professionals, especially pediatricians, who provide training to patients, are limited (17). Resnick et al. (18) evaluated the MDI application technique by pediatricians and reported that only 1/4th of the pediatricians were able to complete the steps without errors. Owayed et al. (16) reported that only 15.5% of pediatricians were able to apply MDI devices without any errors. Another study involving nurses and doctors responsible for pediatric patient follow-up found that only <50% of the participants could perform the MDI application steps without any errors. In this study, inhaler technique scores of nurses were higher than that of doctors and no difference was found between residents and senior doctors, which are notable results (19). In the present study, inhaler technique scores of the

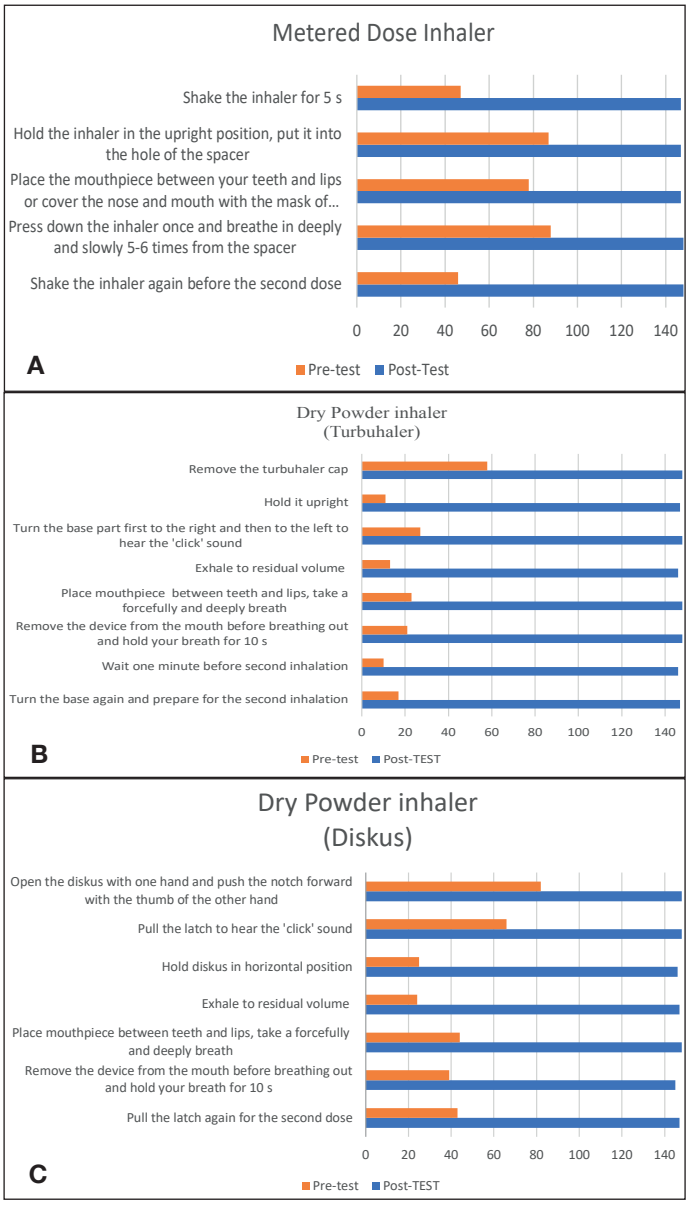

Figure 1: A) Metered Dose Inhale, **B)** Dry Powder Inhaler (Turbuhaler), **C)** Dry Powder inhaler-Diskus

participants were lower than those reported in previous studies, which may be due to the fact that the study sample comprised residents of different seniority, lack of experience due to the short periods of active work in outpatient clinics, and the fact that the technique was evaluated via face-to-face supervision instead of multiple-choice questions.

In the present study, the most frequently made mistakes during inhaler treatment were consistent with the mistakes identified in previous studies involving patients with asthma and their caregivers (8,9,20,21). This suggests that educators and doctors also need training, and a few steps should be further emphasized during training. Various training methods related to inhaler techniques have been examined in several different clinical settings. Some studies have reported that group training is the most effective training method among these methods, whereas other studies argue that better results can be achieved with one-to-one training (22,23). The use of visual materials, models, and standard checklists during training can act as reminders for both patients and medical personnel, and the use of these aids has been found to be more effective than oral or written information alone (22).

In the present study, evaluations after group training using demo inhaler devices and models showed that inhaler technique skills can be improved even with short training programs. Kellman et al. applied a short training program to emergency room doctors and nurses and reported that the training increased the success scores from 34% (before the training) to 91% (24). Plaza et al. (25) evaluated the level of knowledge of doctors regarding inhaler technique and determined that the participants mostly obtained their current knowledge via scientific meetings, articles on the subject, personal experiences, and emphasized that the subject was not given the necessary importance in medical school curricula, which should be the primary place of obtaining such knowledge. Timothy et al. (23) outlined their recommendations for improving the skills of health professionals in inhalation therapies as follows: raising awareness, providing training, assessing the impact of training, repeating training, and promoting patient education with reimbursement.

In the present study, pediatric residents were also asked about inhaler device preferences according to pediatric age groups, and it was determined that there were incorrect applications in this regard. It is noteworthy that nebulizer devices are recommended more frequently than MDI devices by health professionals, especially in the 0–5 years age group. Due to the limited side effects, no external power supply, shorter application time, portability, lower cost, and similar efficacy, the use of Spacer and MDI devices is the first choice of recommendation in the current guidelines (26). Nebulizer devices are offered as an alternative method for a small group of patients who cannot use inhaler devices effectively (27).

Although it was determined that training increased success in inhaler application skills in the present study, it was not possible to evaluate how long the effect of a single training lasted due to the fact that the post-test was applied immediately after the training. This can be seen as a limitation of the study. However, the fact that 17.6% of the participants reported that they had previously been trained in inhaler application techniques but continued to make errors during application highlights the issue of regular repetition of the same training. In a systematic review of studies evaluating inhaler technique in children with asthma, it was recommended to treat each outpatient visit as an opportunity and to check the inhaler technique applied by the patients, to identify the wrong steps, and to repeat the training (28). From this point of view, regular repetition of training can also be recommended for health professionals.

The strengths of the present study include a very high number of health professionals evaluated in a single center and the use of pre-test and post-test evaluations before and after face-to-face inhaler technique training. In contrast to the literature, the inhaler technique was also evaluated on DPI devices, the use of which has increased recently in line with the recommendation of the current guidelines. Studies evaluating inhaler techniques on DPI devices in the pediatric population are quite limited in the literature. A systematic review of studies evaluating inhaler techniques among health professionals found that the application errors in DPI devices were more frequent compared with MDI devices (29). Similarly, it was found in the present study that more errors were reported during the application steps of both turbuhaler and diskus devices compared with MDI devices. This may be related to the fact that DPI devices are prescribed less frequently than MDI devices in the pediatric age group and that different forms of DPI devices (turbuhaler/diskus) require different technical knowledge.

In countries such as Turkey, where the number of pediatric allergy and immunology specialists is limited, the treatment follow-up of pediatric patients diagnosed with asthma is mostly conducted by pediatricians. For this reason, medical school curricula and specialty education should include the application training of inhaler devices, which are extremely important for asthma treatment. Regular repetition of in-service training involving inhaler technique and application among health professionals can correct application errors and increase awareness regarding the importance of the right inhaler technique in the treatment of asthma.

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Determining Screen Time of Children Between 3-9 Years During COVID-19 Pandemic And Investigation of Factors Related To Screen Time

COVİD-19 Salgını Sürecinde 3-9 Yaş Arasındaki Çocukların Ekran Maruziyet Süresinin Belirlenmesi ve Ekran Maruziyetine Etki Eden Etmenlerin İncelenmesi

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ABSTRACT

Objective: The first COVID-19 case in Turkey was detected on March 11, 2020, and measures were taken to prevent the epidemic's progression. As the schools were closed and curfew was imposed on children with periodically updated bans, children had to spend more time at home during the day. In the study, we aimed to determine how the COVID-19 pandemic has influenced the screen time of children aged 3-9 in Turkey and examine the factors affecting screen time.

Material and Methods: This descriptive cross-sectional study was conducted between May 3, 2020, and May 30, 2020. Throughout Turkey, mothers or fathers with at least one child between the ages of 3 and 9 were invited to the online survey via social media, telephone message groups, or e-mail. The parents who voluntarily answered the online questionnaire constituted the study participants.

Results: A total of 9483 parents with children between the ages of 3 and 9 participated in the study. It was determined that 82.9% of the children participating in the study had increased screen time compared to the pre-pandemic period. The mean increase in screen time was 151±96 minutes/day. The increase was more than one hour per day in 74.9% of the participants (n=5122). The average daily screen time of the children participating in the study on the dates specified during the pandemic period was 193±124, the average time spent for online education was 67±62 minutes/day, and for leisure activities with the screen was 133±121 minutes/day. Screen time was significantly higher in children whose parent did not have a plan for child's screen use (OR: 3.085, 95% CI, 2.723 to 3.494, p<.001) or children who did not use the screen under parental control (OR: 1.533, 95% CI, 1.352 to 1.73, p<.001).

Conclusion: During the pandemic, daily screen time increased in a significant number of children, and the time they spent in front of the screen was relatively high. The purpose and duration of screen use varied between preschoolers and school children. Parental attitudes and behaviors were related to children's screen time during the pandemic period.

Key Words: COVID-19, Child, Screen time, Pandemic

ÖZ

Amaç: Türkiye'de ilk COVİD-19 vakası 11 Mart 2020'de tespit edilmiş ve salgının ilerleyişini önlemek için hızlıca tedbirler alınmaya başlanmıştır. COVİD-19 pandemi süresi boyunca çocuklara getirilen sokağa çıkma yasağı, okulların kapatılması ve salgının seyrine göre periyodik olarak yasakların güncelleştirilmesi ile çocuklar gün içerisinde zorunlu olarak evlerde

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

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Ethical approval was obtained from the Clinical Studies Ethics Committee of Akdeniz University Faculty of Medicine (Decision No: KAEK-353).

Contribution of the Authors / Yazarların katkısı*: *TURE S: 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. ***VEKLIPASAOGLU 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 logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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daha fazla zaman geçirmek zorunda kalmıştır. Bu çalışmada COVİD-19 pandemi sürecinin Türkiye'deki 3-9 yaş arasındaki çocukların ekran süresini nasıl etkilenmiş olduğunu belirlemek ve ekran süresine etki eden etmenlerin neler olduğunu incelemek amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışma tanımlayıcı-kesitsel tipte bir çalışma olup 3 Mayıs 2020-30 Mayıs 2020 tarihleri arasında yapılmıştır. Türkiye genelinde çevrim içi anket formunun ulaştırılabildiği, 3-9 yaş arasında çocuğu olup anketi dolduran ebeveynler araştırmaya dahil edilmiştir.

Bulgular: Çalışmaya 3-9 yaş aralığında çocuğu olan 9483 ebeveyn katıldı. Çalışmaya katılan çocukların %82.9'unun pandemi öncesi dönem ile kıyaslandığında ekran süresinin artmış olduğu saptandı. Ekran süresindeki ortalama artış 150.84±95.842 dakika/gündü. Katılımcıların %74.9'unda (n=5122) artışın günde bir saatten fazla olduğu gözlendi. Pandemi döneminde belirtilen tarihlerde çalışmaya katılan çocukların günlük ortalama ekran süresi 193.2±123.8, ortalama çevrim içi eğitim süresi 66.8±62.2, çevrim içi eğitimden farklı bir nedenle ekran süresi 133±121.2 dakikaydı. Ebeveynin ekran süresi planının olmaması, ekranı ebeveyn kontrolünde izlememek, ebeveynin çocukla temel aktivitesinin ekran aracılı olması, çocuğun ekran kullanımındaki temel amacının oyun/eğlence olması artan ekran süresi ile ilişkili bulundu.

Sonuç: Pandemi döneminde çocukların önemli bir kısmının günlük ekran süresi artmıştır ve ekran karşısında geçirdikleri süre oldukça fazladır. Yaş gruplarına göre çocukların ekran kullanım amacı ve bu amaca yönelik olan ekran süreleri de değişiklik göstermektedir. Ebeveynlerin tutum ve davranışlarının pandemi döneminde çocukların ekran süresi ile ilişkili olduğu gözlenmiştir.

Anahtar Sözcükler: COVİD-19, Çocuk, Ekran süresi, Pandemi

INTRODUCTION

The first Covid-19 case in Turkey was detected on March 11, 2020, and measures were taken to prevent the epidemic's progression. While schools and preschools were closed as of March 12, 2020, a curfew was imposed on people under the age of 20 on April 3, 2020. With the curfew imposed on children, the closure of schools, and the periodic updating of the bans according to the course of the epidemic, children had to spend more time at home during the day.

For a healthy lifestyle, institutions such as the World Health Organization (WHO) and the American Academy of Pediatrics (AAP) recommend one hour of physical activity a day and as little screen time as possible for children and adolescents (1,2). At the same time, while one hour of daily screen exposure is accepted as 'excessive screen exposure' in children between the ages of 2-5, there are also studies that accept the 'excessive screen exposure' limit as 2 hours in children and young people (3).

Most studies examining the physical and psychological effects of screen time on children were conducted before the pandemic. These studies have shown the adverse effects of prolonged screen time on children (1-3). Being obliged to stay at home added to the long screen time may negatively reflect children's health. Therefore many institutions, including WHO and AAP, prepared recommendations for families and healthcare professionals to diminish the risks of new lifestyles imposed on children because of the pandemic (1,2,4-6).

The detrimental effects of prolonged screen time, such as cardiovascular diseases and obesity, on physical health are related to staying immobile and increasing high-calorie food intake in front of the screen, rather than the content watched on the screen (7). On the other hand, the psychological and developmental effects of the screen are mostly related to the screen content, and the characteristics of this influence may vary according to age (2,3,7-9). AAP recommending strict limits on children's screen time warns that attention should be paid to the screen's content, the purpose of use, and the length of time spent in front of the screen in pandemic period (4,5). Using screens to video chat and connect with important people in their lives, such as family, relatives, and friends, is essential for children's well-being (6). Particular attention should be paid to the time spent in front of the screen in preschool children who need to receive appropriate stimuli for neuromotor development (8). In general, screen time should not replace physical activity, adequate sleep, and nutrition in all age groups (4,5).

It may be beneficial to convey the principles of children's appropriate screen use to parents and to conduct counseling and awareness training on this subject (9-13). Counseling on this subject can be given by health, education, and social service providers. The responsibility of minimizing the negative impact of the COVID-19 epidemic on children and their families needs to be shared by all institutions (9).

So far, few studies have been conducted on the impact of the COVID-19 pandemic on children's screen time (4,14-16). Identifying the risk factors affecting screen time during the pandemic can offer an opinion for developing intervention programs to reduce screen time and prevent physical, psychological, and adverse social effects of screen exposure under extraordinary circumstances such as a pandemic. The study aimed to determine the effect of the pandemic period on the screen time of children aged 3-9 in Turkey and the factors associated with it.

MATERIAL and METHODS

This descriptive cross-sectional study was conducted between May 3, 2020, and May 30, 2020. Permission for the study was obtained from the Ministry of Health of the Republic of Turkey. Ethical approval was obtained from the Clinical Studies Ethics

Committee of Akdeniz University Faculty of Medicine (Decision No: KAEK-353).

Parents with children between the ages of 3 and 9 who filled out the online questionnaire across Turkey were included in the study.

The total number of children aged 3-9 in Turkey, which constitutes the universe of the study, is around 7 million (18), and the sample size calculated with a confidence interval of 99.9% and a margin of error of ±2 was 6759.

An online questionnaire was prepared to determine the time spent by children in front of the screen for a day when there was a curfew and schools were closed. The change in the duration of screen use was compared to the pre-pandemic period. Throughout Turkey, mothers or fathers with at least one child between the ages of 3 and 9 were invited to the survey via social media, telephone message groups, or e-mail. The parents who voluntarily answered the online questionnaire constituted the study participants.

Information regarding sociodemographic characteristics, average daily screen time of children and parents, parents' attitudes towards their children's screen time, the change in children's screen time during the pandemic period were sought. The total daily screen time of the children (the time to look at the screen with such as tv, tablet, computer, phone) and the screen time for online education were asked separately. Thus, the screen time for education and non-educational reasons were determined in addition to the total screen time. While determining the parents' screen time, work time, socialization/entertainment, and communication with family/friends were asked separately. The total screen time was obtained by adding these intervals.

Statistical analysis

The data obtained in the study were entered into the SPSS 22 (Statistical Package for the Social Sciences) statistical package program and evaluated with descriptive and comparative statistical analyzes. Descriptive statistics are presented with frequency, percentage, mean, standard deviation, median, minimum, maximum, 25%-75% percentile (Q1-Q3), or IQR values. Categorical data were evaluated using the chi-square test. Binary Logistic Regression Analysis was conducted to determine the independent risk factors that affect the frequency of increased screen time during the pandemic period. As a statistical significance level, p values <0.05 were considered significant.

RESULTS

The study included 10.525 parents who filled out the online questionnaire. When those who answered the question "Specify the age of your child" in the online questionnaire form outside the age range of 3-9 were excluded from the study, the study continued with the data of the remaining 9483 questionnaires (weighted mean [SD] age, 6,94 [1.58] years). 3488 (36.8%) were six years old or younger. Most mothers (68.2%) and fathers (65.7%) had high school or lower education. Most of the children (82.7%) lived with their nuclear families. Nearly one-fifth of working mothers (20.2%) and one-third (32.1%) of working fathers stopped working due to the pandemic. The sociodemographic characteristics of the children are summarized in Table I.

During the pandemic, the average daily screen time of the children was 193±124 minutes (min-max; 0-840) (min: minimum; max; maximum). Average daily screen use for online education was 67±62 minutes (min-max; 0-540) and for leisure activities was 133±121 (min-max; 0-840) minutes. The average daily screen time of the parents was 269±190 minutes (min-max;0-1200). Of the participants, 82.9% (n=7598) indicated that their children's screen time increased during the pandemic compared to the pre-pandemic period. The average increase in screen time was 151±96 (min-max; 10-840, median;120, IQR;120) minutes, and this increase was more than one hour per day in 74.9% (n=5122) of the children (Table II). Only 25 (0.3%) of the children participating in the study had no screen exposure.

Screen use for 1-2 hours/day was more common in the 3-6 age group, and screen use over two hours was more common in the 7-9 age group during the pandemic. When the screen times are examined according to the purpose of use, for a reason other than online education, the frequency of screen use was higher in the 3-6 age group. The frequency of screen use for education was higher in the 7-9 age group. The screen time frequencies of children 1-2 hours/day and more than two hours per day during the pandemic are summarized in according to the types of screen time Table III.

In the group whose screen time increased compared to the pre-pandemic period, the factors that could affect this were evaluated with binary logistic regression analysis. In the model evaluated, the mother's working status, the mother being the child's primary caretaker during the day, and the total screen time of the parents were not found to be related to increased screen time. Screen time was significantly higher in children whose parent did not have a plan for child's screen use (OR: 3.085, 95% CI, 2.723 to 3.494, p<.001) or children who did not use the screen under parental control (OR: 1.533, 95% CI, 1.352 to 1.73, p<.001). Other factors are listed in Table IV.

When the participation of children in online education was examined, it was observed that 288 (4.8%) of 5995 children in the 7-9 age group never followed online education, 1228 (20.5%) followed it sporadically, and 4479 (74.7%) regularly. In the group of children who cannot follow the online training regularly, having an extended family, more than two siblings,

Table I: Characteristics of the participants.

Characteristics (number of participants answering the relevant question)	n (%)
Child's Age (n=9483)	
3-4-5-6	3488 (36.8)
7-8-9	5995 (63.2)
Mother's education level (n=9409)	
High school or less	6413 (68.2)
University	2996 (31.8)
Father's education level (n=9409)	
High school or less	6183 (65.7)
University	3226 (34.3)
Family Type (n=9483)	
Nuclear family	7845 (82.7)
Extended family	1638 (17.3)
Number of siblings (n=9429)	
No siblings	1694 (18.0)
Has one sibling	4705 (49.9)
Has two or more siblings	3030 (32.1)
Change in mother's working status during the pandemic (n=9051)	
Was unemployed before the pandemic and is still not working	4179 (46.2)
Continues to work	2339 (25.8)
On temporary layoff	1827 (20.2)
Reduced working hours	706 (7.8)
Change in father's working status during the pandemic process (n=8823)	
Continues to work	5087 (57.7)
On temporary layoff	2835 (32.1)
Reduced working hours	901 (10.2)

Table II: Features of screen use during the pandemic period.

	n (%)
Screen time change compared to the pre-pandemic period (n=9163)	
Screen time increased	7598 (82.9)
Screen time not increased	1565 (17.1)
Total screen time per day (min/day)	
Mean±SD	193±123
Median (range)	180 (0-840)
Interquartile range	120
Screen time used for online education (min/day)	
Mean±SD	67±62
Median (range)	60 (0-540)
Interquartile range	60
Duration of screen use for a reason other than online education (min/day)	
Mean±SD	133±121
Median (range)	120 (0-840)
Interquartile range	120
The daily increase in screen time compared to the pre-pandemic period (min/day)	
Mean±SD	151±95
Median (range)	120 (1840)
Interquartile range	120
Parents' total daily screen time (min/day)	
Mean±SD	269±190
Median (range)	220 (0-1200)
İnterquartile range	205

Table III. The frequency and cause of screen use 1-2 hours/day and more than two hours per day in children during the pandemic period according to age groups.

	All age groups (n=9299)	3-6 age group (n=3425)	7-9 age group (n=5874)	Odds Ratio (95% CI) (Reference group= 3-6 age group)	p
Total screen time					
1-2 hours/day	2242 (24.1)	914 (26.7)	1328 (22.6)	0.920 (0.885-0.956)	<.001
>2 hours/day	5497 (59.1)	1876 (54.8)	3621 (61.6)	1.125 (1.085-1.167)	<.001
Screen time used for education					
1-2 hours/day	1632 (17.5)	362 (10.6)	1270 (21.5)	1.290 (1.250-1.332)	<.001
>2 hours/day	878 (9.4)	234 (6.9)	644 (10.9)	1.590 (1.377-1.835)	<.001
Screen time is used for a reason other than education.					
1-2 hours/day	2145 (23.5)	821 (24.5)	1324 (22.9)	0.967 (0.931-1.004)	0.07
>2 hours/day	3482 (38.1)	1349 (40.3)	2133 (36.8)	0.915 (0.867-965)	0.01

Chi-Square Tests

a parent with a lower education level, and the father's job being adversely affected by the pandemic were more common (p<.001).

Among the parents, 85.9% indicated that they have problems spending time with their children without a screen device. The most frequently expressed problem by the mothers was lack of time while it had a hectic work for the fathers. There was a statistically significant difference between the answers of the mothers and fathers in almost all titles. Parental views on other causes are summarized in Table V.

To the question of what activity they do with their children during the day, the parents indicated a screen-mediated activity such as tv/video/digital game with a rate of 14.2% (n=1317). Of the parents, 40% (n=3714) stated that they did lessons and educational activities together, while 45.73% (n=4240) stated that they played games.

Table IV: Binary logistic regression analysis of the factors that may influence the increase in screen time.

Independent variables/ Categories	Number of participants answering the question about screen time in this group	Increased screen time during the pandemic n (%)	Adjusted odds ratio (95% CI)	p
Age group				
3-4-5-6 years	3372	2754 (81.7)	1	<.001
7-8-9 years	5791	4844 (83.6)	1.304 (1.147-1.483)	
Mother's education level				
High school or less	6152	4955 (80.5)	1	<.001
University	2941	2586 (87.9)	1.434 (1.191-1.727)	
Father's education level				
High school or less	5933	4788 (80.7)	1	<.001
University	3160	2753 (87.1)	1.401 (1.183-1.659)	
Mother's working status				
Working	3434	2965 (86.3)	1.089 (0.931-1.273)	0.28
Not working	5648	4567 (80.9)	1	
Family type				
Nuclear family	7606	6370 (83.7)	1.193 (1.023-1.392)	0.02
Extended family	1557	1228 (78.9)	1	
Who is primarily involved in the care of the child?				
Mother	8121	6696 (82.5)	1.120 (0.890-1.410)	0.33
Other people	1042	902 (86.6)	1	
Child's private screen tool possession				
Yes	4387	3743 (85.3)	1.194 (1.057-1.348)	0.01
No	4776	3855 (80.7)	1	
The main activity of the parent with the child				
Game/activity/lesson	7684	6282 (81.8)	1	0.01
TV/movie/video/digital game	1278	1152 (90.1)	1.384 (1.142-1.677)	
Parental plan for the child's screen use				
There is a limitation	2946	1695 (67.9)	1	<.001
No limitation	6640	5895 (88.8)	3.085 (2.723-3.494)	
Parental supervision over the screen content				
Present	4101	3152 (76.9)	1	<.001
Not present	5062	4446 (87.8)	1.533 (1.352-1.737)	
The main purpose of the child's screen use				
Education	2326	1767 (76)	1.305 (1.143-1.490)	<.001
Gaming/entertainment/watching videos	6837	5831 (85.3)	1	

Nagelkerke R Square: 0.133.

Table V: Reasons why parents could not do an activity with their child without using a screen device.

	Parents' answer (n=9409) n(%)	Mothers' answer (n=7752) n(%)	Fathers' answer (n=1657) n(%)	p
I do not have time because of other duties such as cleaning/cooking/ housewor	3760 (39.6)	3528 (45.5)	232 (14)	<.001
My child has no desire to play with me	2589 (7.5)	2198 (28.4)	391 (23.6)	<.001
I do not have time because I also have to take care of my other child(ren)	2135 (22.7)	1836 (23.7)	299 (18)	<.001
My work is hectic.	1709 (18.2)	1094 (14.1)	615 (37.1)	<.001
I also like to spend time with the screen	545 (5.8)	290 (3.7)	255 (15.4)	<.001
I do not have the patience to play games	412 (4.4)	319 (4.1)	93 (5.6)	0.01
It is normal for my child to spend time with the screen	154 (1.6)	106 (1.4)	48 (2.9)	<.001
If I do not use a screen device, my child prefers to play with siblings/ friends rather than with me	102 (10.84)	88 (1.1)	14 (0.8)	>0.05

DISCUSSION

This study determined that the screen time of 82.9% of children aged 3-9 years increased during a certain period of the pandemic compared to the pre-pandemic period. The mean increase in screen time was 151±96 minutes/day. The absence of a parental screen time plan, not watching the screen under parental control, the parent's main activity with the child being

screen-mediated, and the child's primary purpose of screen use being game/entertainment were associated with screen time increase.

Before the pandemic period, it was reported that 12.1% of children aged 6 to 9 years were in front of the screen for more then two hours a day (14). The average screen time for children aged between 2 and 6 years was 86 minutes per day (15). In the present study covering the pandemic period, the frequency of screen time over 2 hours was 59.1%, while the average daily screen time of children aged 3-6 was around 180 minutes.

The fact that the study data were collected when the curfew was imposed on children and the schools were closed can be considered a reasonable date to evaluate the effect of the pandemic on the screen time of the 3-9 age group. In a study conducted by Oflu et al. (16) using face-to-face questionnaire filling technique with 253 children of similar age and date range in Turkey who were admitted to the hospital, it was observed that the frequency of screen use longer than one hour a day for purposes other than online education was 88.9%. In our study, the frequency of screen use longer than one hour for a reason other than online education was 61.5%, while the frequency of screen use longer than one hour a day for any reason was 83.2%. The lower frequency in the study of Oflu et al. (16) may be due to methodological differences between the two studies. The main advantage of our study is that it is not performed on children admitted to the hospital but in a broader participant population by accessing them using online methods.

In a study conducted in Germany, screen time for entertainment and recreational screen time was found to be 194.5±141.3 minutes/day in 1711 participants aged 4-17 years (18). In the present study, we found a non-educational screen time of 133 min/day, which was less than the entertainment/recreational screen time determined in Germany. This difference may be due to the inclusion of older children in the study in Germany.

In Shanghai, the screen time of 2426 children aged 6-17 years during the pandemic was examined using the same method as our study. During the pandemic period, the total screen time was approximately 334 min/day, the non-educational screen time was 64 min/day, and the daily screen time of 30.9% of the participants exceeded two hours (19). In our study, the total screen time of the participants was 193 min/day, nearly half of the time observed in Shanghai, while the non-educational screen time was 133 min/day, which was nearly twice that in Shanghai. The difference between the Shanghai study and ours may be due to age range, cultural differences, and the variety of off-screen activities (19). In addition, as the online education time increases, children's free time and the time they spend in front of the screen may decrease. In support of this view, our study determined that the 3-6 age group, outside the target group of compulsory education, used screens for more extended periods for non-educational reasons than the 7-9 age group.

In this study, the total daily screen time of the 3-6 age group, who did not have to use the screen for compulsory education, was similar to the 7-9 age group who had to use a screen for education. There is no study in the literature that we can access, including the 3-6 age group during the pandemic period and comparing the total screen time with other age groups. It is thought that it is crucial to conduct more comprehensive and structured studies in younger age groups where appropriate stimuli are essential for neuromotor development, and more strict screen time limitations should be used (8,9).

One of the critical reasons for the increase in screen time during the pandemic is online education. It is expected and necessary for children to increase their screen time to use their right to education during the pandemic. Some opinions using screens to video chat, connect with influential people in their lives (such as family, relatives, friends), and continued education supports children's well-being (6). One of the points to be considered in screen time is the purpose of using it. Appropriate screen time for games/entertainment according to the child's age group during the COVID-19 pandemic is essential for physical and psychosocial health (20).

Identifying the risk factors affecting screen time during the pandemic may help reduce screen time for COVID-19 and possible future pandemics. It can also offer essential ideas for developing intervention programs to prevent physical, psychological, and social adverse effects of screen exposure.

In this study, when the factors affecting the duration of screen used for purposes other than online education during the pandemic period were evaluated by regression analysis; It has been determined that lack of parental screen time plan, not using the screen under parental supervision, the parent's primary activity with the child being screen-mediated, and the child's primary purpose of screen use for game/entertainment were significantly associated with increased screen time.

According to the study of Eyimaya et al. (21), covering the 6-13 age group in Turkey, the absence of a parental screen time plan is a significant risk factor for increased screen time of children. Studies conducted before the pandemic revealed that determining the house rules and having a parental plan for screen time reduce children's screen use (10-13).

The COVID-19 pandemic presents new and unique challenges for parents. For many parents, it is difficult to fulfill both their daily duties and responsibilities for supervision of their children throughout the day and to spend quality time with them. In this study, 85.9% of parents stated that they had problems spending time with their children without a screen device. When it was questioned why parents could not spend time with their children without using the screen during the pandemic period, the parents' answers on this issue differed. Parents must develop balanced and practical approaches to screen use to support children's physical and psychological health during the epidemic. The literature on how and how much time

parents spend with their children during the day showed that there was not enough study on this subject. In a study from the pre-pandemic period, it was found that parents spend less time as their children get older (22). Considering factors such as the pandemic period, the advancement of technology, and easy access to many types of screens, it would be helpful to conduct up-to-date and comprehensive studies on the quantity and quality of the time parents spend with their children today.

One of the crucial findings of this study was that 25.3% of the children aged 7-9 years never participated in online education or participated sporadically. It was determined that low education level of parents, having two or more siblings, a father losing his job due to the pandemic or having to work with short-time working allowance, and having a large family were risk factors for not being able to follow online education in the 7-9 age group. UNICEF's report also drew attention to the inequality in children's access to education (23). There were different results between countries depending on the socioeconomic level of the families. It has been stated that children do not have access to online education, which is more common in developing countries. Even worse, up to 43% of children cannot continue their education (23).

It is essential to protect every child's right to education during the pandemic period and provide an urgent solution by determining the obstacles in front of children's access to education through more comprehensive studies (4,13).

Strengths and weaknesses of the study

The fact that the study was conducted with an on-line questionnaire and parents were reached by using on-line links may have reduced the capacity of the sample group to represent the general population. At the same time, since parents' information about children's screen time is based on estimates and average times, the information given may also be affected by parents' characteristics and perceptions.

Forgetting to include a gender question in the questionnaire and the impossibility of accessing this retrospective information may have caused the inability to detect gender-based differences.

While considering a specific age group in the study provides an opportunity for a better evaluation of this age group, it should be kept in mind that the results should not be generalized to the whole child age group.

The strength of the current study is that it is a study with large sample size, including children aged 3-9 in Turkey, living in rural and urban areas.

CONCLUSION

During the pandemic period, children's total daily screen time has increased. According to age groups, the purpose of children's screen use and the screen time for this purpose vary. Parents should be adequately informed about the negative consequences of children's unlimited and excessive screen exposure in this process. The necessary support should be provided for children to plan their screen time.

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Therapeutic Plasma Exchange Application in the Treatment of Sepsis in A Pediatric Burn Center

Çocuk Yanık Merkezinde Sepsis Tedavisinde Terapötik Plazma Değişimi Uygulaması

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ABSTRACT

Objective: In our study, we aimed to analyze the use of Therapeutic plasma exchange (TPE) in the manage-ment of septic and Thrombocytopenia-associated multiple-organ failure (TAMOF) in the burn in-tensive care unit of a children's hospital retrospectively.

Material and Methods: Demographic, clinical, and laboratory data of the pediatric burn patients who were applied TPE between 1 January 2016 and 1 January 2021 were obtained from the hospital information system and medical records and analyzed. The patients were divided into two groups those who died du-ring follow-up and those who recovered.

Results: TPE was performed on 14 burned children (Boy: Girl 5:9). The median age of the patients was 6,6 years (range 1-18 years). The mean TBSA of the patients was 47.76% (20-75). The most common cause of burns was flame burn. The mean hospital stay of the patients was 18.4±12.6 (7-94) days.

4 patients in group 1 recovered and 10 patients in group 2 died during follow-up. There was no statistical difference between the groups in terms of age, gender, and TBSA (p=0.590, 0.890, 0.990). We determined that patients in group 2 were statistically higher in terms of MODS (p=0.030), Pelod score (p=0.001), and expected death rate according to Pelod score (p=0.003). It was observed that the application of TPE in the first 24 hours after the occurrence of TAMOF significantly reduced mortality (p=0.010).

Conclusion: TPE should be used as an additional treatment method to conventional therapy in critically ill pati-ents in pediatric burn intensive care units. TPE application in the first 24 hours after the occurrence of TAMOF reduces mortality.

Key Words: Child, Intensive care, TAMOF, Plasma exchange

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ÖZ

Amaç: Çalışmamızda, bir çocuk hastanesinde yanık yoğun bakım ünitesinde septik ve Trombositopeni ile ilişkili çoklu organ yetmezliği (TAMOF) tedavisinde Terapötik plazma değişimi (TPE) kullanımını geriye dönük olarak incelemeyi amaçladık.

Gereç ve Yöntemler: 1 Ocak 2016-1 Ocak 2021 tarihleri arasında TPE uygulanan yanık çocuk hastalarının demografik, klinik ve laboratuvar verileri hastane bilgi sistemi ve tıbbi kayıtlarından elde edilerek incelendi. Hastalar takipte ölenler ve iyileşenler olarak iki gruba ayrıldı.

Bulgular: 14 yanık çocuk hastaya (Erkek:Kadın5:9) TPE yapıldı. Hastaların ortalama yaşı 6.6 yıl (1-18 yıl)'di. Hastaların ortalama TBSA'sı %47.76 (20-75)'di. En sık yanık nedeni alev yanığıydı. Hasta-ların ortalama hastanede kalış süreleri 18.4±12.6 (7-94) gündü.

Grup 1'de iyileşen 4 hasta ve grup 2'de takip sırasında ölen 10 hasta vardı. Gruplar arasında yaş, cinsiyet ve TBSA açısından istatistiksel fark yoktu (p=0.590, 0.890, 0.990). Grup 2'deki hastaların MODS (p=0.030), Pelod skoru (p=0.001) ve Pelod skoruna göre beklenen ölüm oranı (p=0.003) açısından istatistiksel olarak daha yüksek olduğunu belirledik. TAMOF oluştuktan sonraki ilk 24 saat içinde TPE uygulamasının mortaliteyi anlamlı derecede azalttığı gözlendi (p=0.010).

Sonuç: Çocuk yanık yoğun bakım ünitelerindeki kritik hastalarda TPE konvansiyonel tedaviye ek bir teda-vi yöntemi olarak kullanılabilir. TAMOF oluştuktan sonraki ilk 24 saat içinde TPE uygulaması mortaliteyi azaltmaktadır.

Anahtar Sözcükler: Çocuk, Yoğun bakım,TAMOF, Plazma değişimi

INTRODUCTION

Burn is a serious trauma with high morbidity and mortality. Deterioration of skin integrity as a result of burns may lead to the entry of microorganisms into the body and thus the development of invasive infections (1). In addition, necrotic tissues formed after burns form a suitable medium for the growth of microorganisms. The risk of infection is increased in burn patients due to many factors such as heat damage, applied invasive procedures, presence of a catheter, colonization of the burn wound, translocation of the gastrointestinal microbiota, and long hospital stay (2,3).

Infections in burn patients can lead to sepsis and multiorgan failure. The traditional treatment of sepsis consists of supportive treatments such as control of the source of infection, intravenous antibiotic therapy, fluid replacement, use of inotropic drugs, and mechanical ventilation (4). Despite improvements in the follow-up and treatment of patients with sepsis and multi-organ failure, mortality and morbidity rates are still high (5,6). The benefit of therapeutic plasma exchange (TPE), especially in cases of thrombocytopenia-related organ failure (TAMOF), has been demonstrated by increasing evidence in recent years (5,6).

TPE is the process of separating the patient's plasma from whole blood with the help of a medical device and replacing it with albumin and/or fresh frozen plasma from healthy donors (7, 8). TPE removes thrombogenic and antifibrinolytic molecules and replaces missing anticoagulants and profibrinolytic molecules, providing normal hemostasis, and removing cytokines and mediators that may cause organ failure (9).

Studies show that TPE treatment in patients with sepsis and TAMOF causes a decrease in mortality rates compared to those who do not (10,11). In the literature, studies on the application of TPE in pediatric burns are limited. In our study, we aimed to share the results of TPE applied to pediatric burn patients with sepsis and TAMOF in our pediatric burn center and our experience.

MATERIAL and METHODS

Between January 2016 and January 2021, pediatric patients who underwent TPE due to burn-related sepsis and TAMOF in our pediatric burn center were included in the study. The patients were divided into two groups those who died during follow-up and those who recovered. who recovered. Groups were analyzed and compared retrospectively in terms of demographic data, total burn surface area(TBSA), burn factor, length of hospital stay, Multiple organ dysfunction score (MODS), Pediatric Logistic Organ Dysfunction (PELOD) score, expected mortality rates according to PELOD score, starting day of TPE application after TAMOF, number of TPE session, complications and mortality. Both electronic and physical files of the patients were scanned retrospectively. Approval was obtained from Ankara City Hospital, No. 2 Clinical Research Ethics Committee (No: E2-21-437, Date: 13/10/2021).

TPE was performed with the Fresenius Cup COM.TEC® device. The volume of plasma to be used; was calculated with the blood volume (patient weight x70) x (1-hematocrit) formula. 1-1.5 times the calculated plasma volume was used as replacement fluid. Transactions; It was done with fresh frozen plasma and/or albumin. Acid citrate dextrose (1:10-1:20 dilution) was used for the anticoagulation of the system. Prophylactic calcium gluconate infusion (1 mg/kg) was administered through a separate intravenous line during the procedure. All processes were performed using the cell separator centrifugation method. TPE session for each patient was determined by observing the course of the disease and clinical improvement. The patients were followed up by monitoring their vital signs throughout the TPE procedure. Consent was obtained from the parents of the patients included in the study.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 21 (SPSS Inc. Chicago, IL, USA). For the patients with numerical variables, age, length of stay, and localization, whether they were normally distributed or not was investigated with normality tests. The

differences between the groups were investigated using the Student-T test for normally distributed numerical variables and the Mann-Whitney U test for those not normally distributed. $p< 0.05$ was considered significant for all variables.

RESULTS

14 pediatric burn patients followed in the pediatric burn intensive care unit due to sepsis and TAMOF were included in the study. The mean age of the patients was 6.6 (1-18) years, five of them were (35.7%) girls and nine were (64.3%) boys. The mean TBSA of the patients was 47.76% (20-75). The most common cause of burns was flame burn (n=8), and the other factors were hot milk, scalding, and electrical burns, respectively. Pseudomonas aeurogenisa (n=9, 64.28%) was the most common cause of sepsis in blood and wound cultures. Other microorganisms were Acinetobacter baumannii (n=4) and klebsiella pneumonia (n=2). Five (35.7%) patients were referred to our center due to burn-related sepsis from the other centers. The mean length of hospital stay of the patients was 18.4±12.6 (7-94) days. The mean expected mortality rate according to the PELOD score of the patients was 90.64±5.6. Four patients who underwent TPE recovered (28.5%). The mean expected mortality rate of these four patients according to the PELOD score was 83.30 (±8.04).

The patients were divided into two groups group 1 who recovered (n=4) and group 2 who died during the follow-up (n=10). The data of the patients, Multiple organ dysfunction score (MODS), PELOD (pediatric logistic organ dysfunction) score, expected mortality rates according to the PELOD score, the start day of TPE application after TAMOF occurs, and the number of TPE sessions according to the groups are shown in Table I. No complication was observed during TPE application in both groups.

When the patients were examined in terms of TPE application time, we observed that one of the three patients who underwent TPE with conventional treatments in the first 24 hours after the TAMOF occurrence, died (33.3%). After 24 hours, nine of 11 patients who underwent TPE died (81.8%). It was observed that the application of TPE in the first 24 hours after the TAMOF occurrence significantly reduced mortality (p=0.010). All ex-patients were referred to our center due to sepsis on the multiple days of hospitalization from another center.

DISCUSSION

In sepsis, exogenous microbial agents cause the release of cytokines, chemokines, and other pro-inflammatory mediators from polymorphonuclear leukocytes and macrophages. In this process, depending on the released cytokines and mediators, an inflammatory response occurs that damages the host itself, and despite appropriate antimicrobial therapy and hemodynamic support, multiple organ failure and death may occur (12). Many studies demonstrate that TPE serves a beneficial role in the challenging burn resuscitation so TPE should be used as a useful tool in the management of severe burn septic shock (13-15).

TPE is an uncommonly used modality that has been used for rescue therapy. It is a form of extracorporeal blood purification, or component separation (apheresis), designed to remove large-molecular-weight solutes such as inflammatory mediators from the circulating blood volume (16). TPE has been used successfully to treat a wide variety of disease processes over the past 40 years, including many autoimmune disorders and inflammatory-mediated conditions (17-20). This success in treating autoimmune has led to the investigation of potential benefits of the use of TPE in many conditions commonly encountered in burn centers. The most recent American Society of Apheresis guidelines gives a level C evidence recommendation for use of TPE in sepsis-induced multiple organ failure, indicating that TPE may be used on an individual basis and acknowledging the need for the generation of more evidence (9).

Table I: The data according to the groups.

	Grup 1 (Full recovery cases)	Grup 2 (Ex cases)	p
n	4	10	
Sex (f:m)	01:03	04:06	0.590
Mean of the age	6.00 (±5.59)	6.45 (±5.37)	0.890
Mean of TBSA	47.75 (±11.44)	47.80 (±20.48)	0.990
Mean of the MODS (Multiple Organ Dysfunction Score)	9.75 (±1.70)	13.40 (±2.71)	0.030
Mean of the PELOD score	31.75 (±2.87)	44.70 (±4.16)	0.001
Mean of the expected mortality rate due to PELOD score	83.30 (±8.04)	93.58 (±2.90)	0.003
Mean of TPE session per case	3.5 (±1.73)	2.14 (±0.87)	0.060
Mean TPE starting day after onset of sepsis	5.25 (±8.34)	8.45 (±7.74)	0.240
Mean of the length of hospital stay	27.45 (±8.34)	15.45 (±8.34)	0.040

In the literature, there are few studies on the efficacy of TPE in sepsis in children (21). It has been reported that the levels of dead leukocytes in the blood taken from patients with sepsis are significantly higher and that high levels of dead leukocytes in the blood are positively correlated with the severity of organ dysfunction (22). It has been reported that TPE provides a significant decrease in the concentration of dead leukocytes in the blood and that organ failure can be protected by this mechanism (22). In a study, it was shown that TPE performed in pediatric patients with culture-positive sepsis and thrombocytopenia-related multi-organ failure reduced the organ damage score and improved 28-day survival rates (23). In another study, it was shown that TPE significantly reduced the mortality rate in pediatric patients with sepsis with multi-organ failure and thrombocytopenia compared to those who did not (24). The risk of sepsis and TAMOF and mortality increase in burn patients with a larger TBSA area (25,26). In a review of the literature, the mean TBSA of patients who developed sepsis due to burns and who was applied TPE in the treatment was 46.33 (37-52.2) (16). In our study, the mean TBSA of patients who was applied TPE was 47.76% (20-75). There was no significant difference between the groups in terms of mortality and the TBSA relationship (p=0.99).

In the literature, infections and related complications have been reported as the most common cause of mortality in pediatric burns (27,28). Pseudomonas aeuroginosa, Acinetobacter baumannii, Staphylococcus species, and Candida species are prominent as microorganisms causing mortality (28). In our study, the microorganisms in blood and wound cultures were pseudomonas aeurogenisa, Acinetobacter baumannii, and Klebsiella pneumonia, consistent with the literature.

MODS and PELOD score are calculated with the clinical and laboratory parameters of patients with sepsis and TAMOF, and the expected mortality rate for the patient is calculated (29). In our study, it was found that the mean MODS, PELOD score and the expected mortality rate according to the PELOD score were statistically higher in group 2.

There is still no consensus on the timing of TPE and studies are limited. Kawai et al. (30) also showed that in children with TAMOF, those who underwent TPE in the early period had a greater improvement in organ dysfunction and the need for inotropic agents decreased earlier than in those who underwent late TPE. In a study about the experience of TPE application in children with neutropenic sepsis, it was reported that the clinical course of patients with bacterial sepsis progressed faster and was mortal than in other patients, and TPE application was recommended in children with bacterial sepsis in the earlier period (31). In our study, we determined that the application of TPE in the first 24 hours after the TAMOF occurrence significantly reduced mortality (p=0.010).

Complications such as urticarial reactions, citrate-related hypocalcemia, catheter-related thrombosis, bleeding, infection, and transfusion-related lung injury may occur (32). Any complication was observed during TPE application in both groups.

CONCLUSION

In conclusion; TPE, which is an adjunct to the conventional treatment of pediatric burn patients who develop sepsis and TAMOF and do not respond to conventional treatment, is an important supportive treatment. Considering the hemodynamics and laboratory parameters of pediatric patients, it can be safely applied in intensive-care conditions. TPE applied in the first 24 hours after the TAMOF occurrence reduces mortality. Therefore, we think that TPE should be applied earlier. Prospective, randomized-controlled large series studies should be done.

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The Long Term Follow Up of Helmet Therapy Following Endoscopic Suturectomy For Infants with Sagittal Craniosynostosis

Sagital Kraniosinostoz Tanılı Bebeklerde Endoskopik Süturektomi Sonrası Kask Tedavisinin Uzun Süreli Takibi

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ABSTRACT

Objective: Infants with sagittal craniosynostosis are treated with endoscopic suturectomy and remodeling helmets. The long term effects and the effects that occur after the completion of remodeling helmet treatment have not been investigated. The purpose of this study is to investigate the long term effects of remodeling helmet and effects that occur after the completion of remodeling helmet treatment.

Material and Methods: 14 infants were included in the study. The children were assessed post-op, after the completion of remodeling helmet and at 6 months' follow-up using a 3D laser acquisition system. The anterior-posterior(AP), medio-lateral(ML) cranial measurements, cranial circumference(CC), diagonal measurements, cephalic ratio(CR) and cranial vault asymmetry index(CVAI) were assessed.

Results: The infants used the remodeling helmet for 35±3.4 weeks. When the post-op and completion results are examined, it can be seen that during remodeling helmet usage duration, AP, ML, CC measurements, the CR and CVAI have statistically improved, resulting in normalization of cranial shape ($p<0.05$). When the follow up results are examined, it can be seen that there was no deterioration in the symmetry of the cranial shape and the AP, ML, CC measurements and the CR and CVAI were preserved ($p>0.05$) whilst the infants' craniums continued to grow at a normal rate.

Conclusion: The present study shows that when remodeling helmet therapy is completed, cranial development continues at normal rates. There is no deterioration in cranial symmetry in the long term, and the effectiveness of the treatment continues after the remodeling helmet therapy is completed.

Key Words: Child development, Craniosynostoses, Endoscopy, Infant, Orthotic Devices

ÖZ

Amaç: Sagital kraniosinostozlu bebekler endoskopik süturektomi ve kranial kasklar ile tedavi edilir. Kullanılan bu kaskların uzun vadeli etkileri ve kask tedavisinin tamamlanmasından sonra ortaya çıkan etkiler henüz araştırılmamıştır. Bu çalışmanın amacı, kranial kaskın uzun vadeli etkilerini ve kask tedavisinin tamamlanmasından sonra ortaya çıkan etkileri araştırmaktır.

Gereç ve Yöntemler: Çalışmaya 14 bebek dahil edildi. Bebekler ameliyat sonrası, kaskın yeniden şekillendirilmesinin tamamlanmasından sonra ve 6 aylık takipte bir 3D lazer sistemi kullanılarak değerlendirildi. Anterior-posterior(AP), medio-lateral (ML) kranial ölçümler, kranial çevre(KÇ), diyagonal ölçümler, sefalik oran(SO) ve kranial kubbe asimetri indeksi(KKAI) değerlendirildi.

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

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Bulgular: Bebekler 35±3.4 hafta boyunca yeniden şekillendirme kaskı kullandılar. Ameliyat sonrası ve tamamlama sonuçları incelendiğinde, kranial kask kullanımı sırasında, AP, ML, KÇ ölçümlerinin, SO ve KKAI'nin istatistiksel olarak iyileştiği ve bunun sonucunda kafa şeklinin normalleştiği görülmektedir ($p<0.05$). Takip sonuçları incelendiğinde kranial şekil simetrisinde bozulma olmadığı ve bebeklerin kraniumlarında simetrinin büyüme devam ederken AP, ML, KÇ ölçümleri ile SO ve KKAI'nin korunduğu ($p>0.05$) görülmektedir.

Sonuç: Bu çalışma, kranial kask tedavisi tamamlandığında, kranial gelişimin normal oranlarda devam ettiğini göstermektedir. Uzun vadede kranial simetride herhangi bir bozulma olmadığı ve kranial kask tedavisi tamamlandıktan sonra tedavinin etkinliğinin devam ettiğini ortaya koymaktadır.

Anahtar Sözcükler: Bebek, Çocuk gelişimi, Endoskopi, Kraniosinostoz, Ortez Cihazları

INTRODUCTION

The neurocranium which surrounds and protects the brain forms the cranial vault of the skull. The cranial vault consists mainly of flat bones; the frontal and parietal bones; the squamous parts of the temporal bone; and interparietal part of the occipital bone. The development of these bones begins at early embryogenesis and continues until adulthood where the neurocranium eventually increases about 50% in size (1). Most of the growth of the skull occurs at sutures which are found between the cranial bones and it occurs perpendicular to the direction of the suture (2).

Craniosynostosis is defined as a congenital deformity that causes premature fusion of one or multiple cranial sutures (3). The premature and pathological closure of sutures prevents further bone formation at this site and an abnormal compensatory growth occurs in unaffected sutures. This compensatory growth results in abnormalities in the cranial and facial structures (4). Craniosynostosis occurs in approximately 1 in 2000 live births and is classified according to the fused suture (5). The prevalence of coronal synostosis (unicoronal or bicoronal) is 20–25% and metopic synostosis is 5–15%. The rarest form is lambdoid at 0–5% The most commonly encountered type is sagittal craniosynostosis which comprises 40–55% of craniosynostoses (6). Sagittal craniosynostosis, also called scaphocephaly, occurs due to the premature fusion of the sagittal suture and results in increased growth of the anteroposterior (AP) direction of the skull (7).

Until the mid-1900's simple suturectomies and cranial vault remodeling were widely used for the surgical treatment of craniosynostosis however, due to prolonged operative time, need for blood transfusion, significant scalp mobilization, and need for subsequent reconstructive procedures, nowadays, a novel procedure; endoscopic suturectomy is used (8). Endoscopic suturectomy adopts 3 basic principles. Firstly, endoscopic suturectomy is recommended early in life. Secondly, when endoscopic suturectomy is performed at the correct time, the growing brain causes expansion of the skull into a normal shape. Third, to prevent the tendency of the cranial vault to revert to a defective shape, an adjunct vault remodeling helmet which was introduced by Persing et al. (9) in 1986 is used (10). To fabricate a customized cranial orthosis (a remodeling helmet) the infants' skull is precisely measured after endoscopic suturectomy (11). Remodeling helmets promote the correction of head shape by alleviating the pressure on the flattened area of the cranium and allowing cranial expansion in the desired directions. This remodeling helmet which is worn 23 hours a day, is well tolerated, leads to significant correction of craniofacial abnormalities, is safe, effective, and associated with excellent results in the short term (12-14). However, the long term effects of remodeling helmet and the effects that occur after the completion of remodeling helmet treatment have not yet been investigated. Therefore, the aim of this study is to investigate the long term effects of remodeling helmet and effects that occur after the completion of remodeling helmet treatment.

MATERIALS and METHODS

Participants included in this study were infants with a diagnosis of sagittal craniosynostosis who were younger than 6 months of age and had been treated with endoscopic suturectomy. Infants who had syndromic craniosynostosis and those who had an accompanying disease were excluded from this study. Also if the obligatory remodeling helmet usage time was not adhered to, patients were excluded from the study. All parents provided their written informed consent. The study was approved by the Gazi University ethics review board, numbered 01.02.2021-E18936, and the authors complied with the ethical designs of the 1975 Declaration of Helsinki.

The patients were placed on the surgical table in the prone position using soft gel support. Two incision lines of 4 cm, which perpendicularly cut the sagittal suture, were determined 2-3 cm behind the anterior fontanel and 2 cm in front of the lambda. The periosteum between the incision lines was dissected. A 0 degree 4 mm thick endoscopic camera was used (Karl Storz Germany). The bone strip was removed using a Kerrison rounger, bone scissors and ultrasonic bone cutters. Barrel osteotomies were performed behind the coronal suture and in front of the lambdoid suture, parallel to the sutures. Following the bone strip excision, irrigation with Ringer's lactated solution and bleeding control was achieved in all patients. The skin was closed subcuticularly.

Following surgery, all patients were fitted with a custom made remodeling helmet within 1 week following the procedure. All patients were instructed to use the remodeling helmets 23 hours a day in order to achieve the desired head shape.

Remodeling helmets are made from thermoplastic material and this allows the ability for adjustments to be made. As the infants' skulls grew, the helmets were re-adjusted to enable a perfect fit. According to the literature, the usual duration of remodeling helmet usage is 1-1.5 years or until normocephaly is reached (13).

Prior to endoscopic suturectomy, following endoscopic suturectomy, and every 2 weeks until completion, the infants' heads were measured using the STARscanner imaging system. Also, this device was used to manufacture the remodeling helmet. The STARscanner imaging system has previously been used in infants with craniosynostosis to fabricate the remodeling helmet and follow-up cranial development (15). This device uses multiple surface lasers to generate a three dimensional (3-D) reconstruction of the patients' head. The infant is placed in supine position and the images are acquired with four safe, low-energy lasers in approximately 2 seconds. The sellion, left tragus, and right tragus are marked on the 3D image and from these measurements, an axial reference plane and 10 parallel levels are generated. Level 3 has previously been determined as the most useful plane for analysis (15).

Using the STARscanner software, measurements such as; oblique diagonal measurement, cranial length and breadth can be generated. Also specific measurements such as the cephalic ratio (CR) and the cranial vault asymmetry index (CVAI) can be measured. The CR is determined by dividing the cranial length by the cranial breadth. The CVAI is determined by taking the difference between the two oblique diagonal measurements and dividing by the larger of the two oblique–diagonal measurements. A CVAI of 0 represents ideal symmetry (15).

The infants were assessed periodically and three of these assessments were used in our analysis. The first assessment was performed within 1 week after endoscopic suturectomy. Using measurements obtained in this assessment, the infants were fitted with remodeling helmet and were assessed every two weeks. The second assessment included in the analysis was performed when the peak CR was achieved for 3 consecutive measurements and indicates the completion of the remodeling helmet treatment. The third assessment included in analysis was the 6 months' follow-up after the completion of remodeling helmet.

Statistical analyses

Statistical analyses of the study were carried out with "Statistical Package for Social Sciences" (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA) software. The normal distribution of the data was analyzed with visual (histogram and probability graphs) and analytical (Shapiro-Wilk test) methods. The Wilcoxon test was used to compare the change between post-op values and after the treatment values and also to investigate the change between after the treatment values and 6 months' follow-up after the completion of remodeling helmet. The level of significance was set at $p<0.05$.

RESULTS

14 infants, (6 female and 8 male) with sagittal craniosynostosis were included in the study. The average remodeling helmet usage in our study was 35±3.4 weeks. When the analysis results of the post-op and end-of-treatment measurements are examined, it can be seen that during remodeling helmet usage duration, the CR has statistically improved (Table I, $p=0.028$), indicating that the cranial shape has changed from a scaphocephaly to a normocephalic shape. The analysis of the circumference, ML, AP and diagonal measurements show that the infants' heads have grown larger in a symmetric ratio and that the asymmetry in the cranial vault (CVAI) has statistically decreased (TableI - II, $p<0.050$).

When the analysis results of the end-of-treatment and 6 months' follow-up measurements are examined, it can be

Table I: Comparison of Post-Op and End of Treatment Measurements.

	Post-Op Median IQR	End of the Treatment Median IQR	p*
Cranial breadth (M–L) (mm)	115.6 (107.3/119.1)	128.9 (122.3/133.9)	0.028
Cranial length (A–P) (mm)	151.9 (145.8/159.4)	159.9 (156.7/167.8)	0.018
Cephalic ratio (CR) (M–L/A–P)	0.74 (0.72/0.77)	0.78 (0.76/0.81)	0.028
Circumference (mm)	429.1 (415/446.3)	471.2 (449/487.2)	0.018
Oblique–diagonal 1, at 30.0 degrees (mm)	145.9 (138.7/153.8)	158.3 (152.5/165.7)	0.018
Oblique–diagonal 2, at 30.0 degrees (mm)	144.4 (138.4/149.3)	159.1 (152.2/165.8)	0.028
Oblique diagonal difference (mm)	2.7 (1.6/4.6)	0.3 (0.1/1.7)	0.063
Cranial vault asymmetry index (CVAI)	1.71 (1.07/3.19)	0.2 (0.1/1.07)	0.043

***p < 0.05 within the groups after helmet treatment (Wilcoxon Signed Ranks Test), **post-op:** postoperative, **IQR:** Interquartile Range, **mm:** millimeters, **M-L:** medial to lateral, **A-P:** anterior to posterior, **Circumference (mm):** Linear distance around the skull at the specified level, **Cranial breadth (M–L) (mm):** Maximum medial to lateral distance at the specified level, **Cranial length (A–P) (mm):** Maximum anterior to posterior distance at the specified level, **Cephalic ratio (M–L/A–P):** Ratio of maximum cranial breadth to maximum cranial length, **Oblique–diagonal 1, at 30.0 degrees (mm):** Maximum anterior to posterior diameter at 30 degrees from the sagittal plane (left), **Oblique–diagonal 2, at 30.0 degrees (mm):** Maximum anterior to posterior diameter at 30 degrees from the sagittal plane (right), **Oblique diagonal difference (mm):** Difference of the left and right oblique diagonal diameters, **Cranial vault asymmetry index (CVAI):** Difference between the two oblique diagonal diameters divided by the larger of the two oblique-diagonal diameters.*

Table II: Comparison of End of Treatment and 6 Months Follow-up Measurements.

	End of the Treatment Median IQR	6 Months Later Median IQR	p*
Cranial breadth (M–L) (mm)	128.9 (122.3/133.9)	130.1 (125.8/136.1)	0.018
Cranial length (A–P) (mm)	159.9 (156.7/167.8)	167.9 (164.8/175.5)	0.018
Cephalic ratio (CR) (M–L/A–P)	0.78 (0.76/0.81)	0.78 (0.75/0.79)	0.176
Circumference (mm)	471.2 (449/487.2)	485.8 (472.3/493.6)	0.018
Oblique–diagonal 1, at 30.0 degrees (mm)	158.3 (152.5/165.7)	161.8 (158.4/167.3)	0.018
Oblique–diagonal 2, at 30.0 degrees (mm)	159.1 (152.2/165.8)	163.8 (160.8/166.7)	0.018
Oblique diagonal difference (mm)	0.3 (0.1/1.7)	1.22 (0.61/2.73)	0.128
Cranial vault asymmetry index (CVAI)	0.2 (0.1/1.07)	0.75 (0.36/1.56)	0.128

***p < 0.05 within the groups after helmet treatment (Wilcoxon Signed Ranks Test), **post-op:** postoperative, **IQR:** Interquartile Range, **mm:** millimeters, **M-L, medial to lateral:** A-P, anterior to posterior, **Circumference (mm):** Linear distance around the skull at the specified level, **Cranial breadth (M–L) (mm):** Maximum medial to lateral distance at the specified level, **Cranial length (A–P) (mm):** Maximum anterior to posterior distance at the specified level, **Cephalic ratio (M–L/A–P):** Ratio of maximum cranial breadth to maximum cranial length, **Oblique–diagonal 1, at 30.0 degrees (mm):** Maximum anterior to posterior diameter at 30 degrees from the sagittal plane (left), **Oblique–diagonal 2, at 30.0 degrees (mm):** Maximum anterior to posterior diameter at 30 degrees from the sagittal plane (right), **Oblique diagonal difference (mm):** Difference of the left and right oblique diagonal diameters, **Cranial vault asymmetry index (CVAI):** Difference between the two oblique diagonal diameters divided by the larger of the two oblique-diagonal diameters.*

seen that 6 months after completion of remodeling helmet treatment, the improvements obtained in CR were preserved and no statistically significant change has occurred in the CR (Table II, p=0.176). This Indicates that the cranial shape did not deteriorate after discontinuing the remodeling helmet. Furthermore, the analysis of the circumference, ML, AP and diagonal measurements show that 6 months after discontinuing the remodeling helmet, the infants' heads continued growing larger in a symmetric ratio and normocephaly was preserved (Table II, p<0.050). The correction obtained in the CVAI was also statistically maintained (Table II, p>0.050.

DISCUSSIONS

As it can be seen from the results of the present study, endoscopic suturectomy and remodeling helmet used in conjunction lead to positive results in the early term correction of cranial measurements in infants with sagittal craniosynostosis. Additionally, the present study shows that when treatment is concluded and remodeling helmet therapy is completed, cranial development continues at normal rates. Furthermore, there was no deterioration in cranial symmetry in the long term, and the effectiveness of the treatment continued after the remodeling helmet therapy was completed.

In their study, Iyer et al. (11) investigated optimal duration of postoperative remodeling helmet use following endoscopic suturectomy for sagittal craniosynostosis. They concluded that continuing helmeting after peak CR was reached did not improve final outcomes. Additionally, patients who discontinued using remodeling helmet after reaching their peak CR were found to have significantly worse anthropometrics at last follow-up (11). These results imply that helmet removal when maximum CR is achieved may be appropriate for craniosynostosis patients, while helmeting beyond the peak does not change final outcome. In our study, we also concluded remodeling helmet when peak CR was reached and it can be seen that continuing remodeling helmet therapy until peak CR leads to positive results in the correction of head shape both in the short and long term in infants with sagittal craniosynostosis.

The study conducted by Pickersgill et al. (16), showed that there was a regression of CR following endoscopic suturectomy and remodeling helmet in craniosynostosis. In the mentioned study, remodeling helmet usage was around 28 weeks; however, the average remodeling helmet usage in our study was 35±3.4 weeks. Cranial growth rate is extremely rapid during the first few years of life but slows down as the child grows older. We believe the difference may have occurred due to the difference in remodeling helmet duration. The children in our study used the helmet until peak CR was achieved. Therefore, using the helmet for a longer period of time may have had a beneficial effect on the preservation of the achieved correction (14).

In the study performed by Berry-Candelario et al. (17), children who were treated with endoscopic suturectomy were followed until 6 years of age, however the cranial measurements were not taken, children were only monitored for complications. In a different study, Jimenez et al. investigated the management of craniosynostosis using endoscopic suturectomy and remodeling helmet for up to 50 months and concluded that treatment of craniosynostosis with endoscopic suturectomy was safe and efficacious. Even though the study states that subjectively normocephaly was reached, only information regarding the surgical procedures were provided and the long-term effects of remodeling helmet on cranial measurements were not assessed (18).

Riordan et. al conducted a retrospective cohort study where they examined the outcomes of endoscopic suturectomy in infants with craniosynostosis (19). Prior to and following endoscopic suturectomy and remodeling helmet, the children's head circumference was measured in centimeters and compared

to the World Health Organization's recommendation guideline, additionally the CR was calculated (20). Median follow-up was 5.9 years. When the results of the mentioned study were examined, it can be seen that there was a normalization in CR and head circumference in 95.4% of children. The patients showed normalization of head circumference postoperatively by 12 months of age relative to WHO normal head growth data and thereafter. These findings are similar to our study. However, our study presents further data on cranial measurements indicating that endoscopic suturectomy is effective in the correction of cranial shape. Furthermore, the effects after the completion of remodeling helmet are more detailed in our study.

Fearon et al. conducted two studies where surgical outcomes and long-term growth of infants with craniosynostosis was evaluated. The first study, published in 2006 and the second study published in 2009, both demonstrated abnormal skull growth in children in the long term following the surgical correction of scaphocephaly (21, 22). It was stated that subsequent calvarial growth was abnormal, with a tendency toward recapitulation of the primary deformity. These studies differ from ours and we believe the differences may have occurred due to surgical differences. The surgical procedure used in the mentioned studies was cranial vault remodeling. In our study, endoscopic suturectomy was used and since the procedure was minimally invasive may have affected the healing and shaping of the skull. Additionally, in the two studies by Fearon et al, remodeling helmet was not used following cranial vault remodeling. Nowadays, studies state that the success of endoscopic suturectomy depends greatly on the remodeling helmet. The helmet has the ability to modify the calvarial growth pattern, and hence, the direction of growth in three dimensions. Without this guidance, cranial expansion occurs equally in all directions and the obtained correction after suturectomy remains incomplete (13). Therefore, when these results are compared, endoscopic suturectomy used together with remodeling helmet leads to promising results in the long term and also when the helmet therapy is completed.

The study by Persad et al. (23) investigated long-term 3 Dimensional CT follow-up after endoscopic sagittal craniosynostosis. The infants were fitted with helmets following endoscopic suturectomy, they were followed monthly until they were 8 months old and then yearly until they were 5 years old. The results indicate that the pre-post CR improved significantly with endoscopic suturectomy and remodeling helmet and the correction established in CR was maintained at the 5 year follow-up (23). Even though the infants were followed-up for a longer term in the present study, our findings correlate with this study. This can indicate that endoscopic suturectomy and remodeling helmet lead to correction in head shape and a preservation of correction in the long term. Our study differs from this study with the assessment method used and duration of follow-up. The STARscanner which was used in our study is harmless when compared to CT and this is an advantage. However, the infants were followed-up for a shorter duration in our study and this is our limitation.

Our study has some limitations. Firstly our sample size was limited. Even though the effects of endoscopic suturectomy and remodeling helmet after the completion of the remodeling helmet treatment were investigated in this study, a study which investigates the effects in an even longer period would lead to great importance in understanding the long term effects that occur after the completion of remodeling helmet. There was no control group because all infants were treated with the same protocol which has been proven to be efficient, safe and bears great results.

CONCLUSION

In conclusion, the results of this study support the consensus of the literature that endoscopic suturectomy and helmet therapy improve cranial shape. Additionally, it shows that after the completion of remodeling helmet, cranial growth continues and the correction effect is maintained. The cranial development of subjects with sagittal craniosynostosis who used cranial orthosis after endoscopic suturectomy continued at normal rates, the infants did not have any deterioration in their cranial symmetry in the long term, and the effectiveness of the treatment continued after the completion of remodeling helmet treatment.

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Limb Girdle Muscular Dystrophy Type 2a: Case Report

Limb Girdle Muskuler Distrofi Tip 2a: Vaka Sunumu

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ABSTRACT

Limb Girdle Muscular Disease (LGMD) comprise a group of inherited muscular dystrophy with chronic progressive weakness of hip and shoulder girdles. The inheritance pattern is either autosomal dominant (LGMD1) or autosomal recessive (LGMD2). LGMD 2A is known as calpainopathy in which there was a defect of gene encoding the protein named as calpain. There are three calpainopathy phenotypes according to distribution of muscle weakness and age at onset. In this report, we presented an asymptomatic child with persistant hyper CKemia diagnosed with muscle biopsy and genetic testing. Genetical examination results of the patient showed homozygote mutation of *CAPN3* gene(c.2092C>A) and parents revealed that they were heterozygous unaffected carriers.

Key Words: Biopsy, Calpainopathy, Muscle, Muscular dystrophy, Limb girdle muscular distrophy

ÖZ

Limb Girdle Muskular distrofi (LGMD) kalça ve omuz ekleminde progresif kronik güçsüzlük ile seyreden kalıtımsal bir grup kas distrofisidir. Kalıtım paterni otozomal dominant (LGMD1) ve otozomal resesif (LGMD2) olarak ikiye ayrılır. LGMD tip 2A kalpain proteinini kodlayan gen defektine neden olan kalpainopati olarak bilinmektedir. Kas güçsüzlüğü ve başlangıç yaşına göre 3 çeşit kalpainopati tipi vardır. Bu yazıda asemptomatik persistan kreatin kinaz yüksekliği olan, kas biyopsisi ve genetik analiz ile LGMD tip 2A tanısı alan çocuk hasta sunulmaktadır. Genetik analiz sonucunda *CAPN3* geninde (c.2092C>A) homozigot mutasyonu mevcut olup ebeveynlerin genetik analizinde heterozigot taşıyıcı olarak saptanmıştır.

Anahtar Kelimeler: Biyopsi, Kalpainopati, Kas, Muskular distrofi, Limb girdle muskular distrofi

INTRODUCTION

Muscular dystrophies (MD) are a heterogenous group of disease as a result of defects in genes for normal function of skeletal muscle. Clinical manifestations of MD can range from asymptomatic cases with increase of creatinine kinase (CK) to severe debilitation and death early in life. Autosomal recessive forms of MD produce symptoms early in life and are severe whereas autosomal dominant forms have slower and less debilitating courses (1). Limb-girdle muscular disease (LGMD) comprise a group of inherited muscular dystrophy with chronic progressive weakness of hip and shoulder girdles. The inheritance pattern is either autosomal dominant (LGMD1) or autosomal recessive (LGMD2). There are 30 subtypes of LGMD and the number of disease was given according to the chronology of identification of their genetic loci. The recessive forms also can be divided at molecular level as sarcoglycanopathies and non-sarcoglycanopathies based on the affected mutation in a gene encoding sarcoglycan component of the dystrophin associated complex or not. LGMD 2A is in the group of non-sarcoglycanopathy and known as calpainopathy (2). There is the defect of gene encoding the protein named as calpain and has autosomal recessive inheritance pattern in LGMD 2A.

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Most common mutation is seen on *CAPN3* gene (15q15.1 loci) which encodes calcium sensing proteaz calpain 3 having role in muscle remodelling. Nowadays there are more than 450 pathogenic varient of *CAPN3* protein. There are three calpainopathy phenotypes according to distribution of muscle weakness and age at onset. The most common phenotype is pelvifemoral phenotype in which pelvic involvement occurs firstly. The onset age of this phenotype can be as early as before 12 years old or as late as 30 years old. The second phenotype is scapulohumeral phenotype that is milder form which is infrequent at early ages and shoulder involvement is seen firstly. Third phenotype is hyperCKemia which occurs in chidren and young ages without any symptom (3).

Here we report a case with third phenotype of LGMD and genetically diagnosed as type LGMD 2A to emphasize asymptomatic presentation of LGMD.

CASE REPORT

Twelve years-old female was admitted to pediatric clinic for primary care. She had no complaint of any muscle weakness. She had no sign and symptom of any infection and she had no medication. Her medical history was unremarkable and she had history of long time cycling. There was consanguinity among parents. Her cousin has walking disability with unknown diagnosis. Pedigree chart of family was at Figure 1. On physical examination weight and height percentiles were within 10-25 percentiles and system examination was normal. Muscle strength was 5/5, deep tendon reflexes were normal and she had normal gait examination. Hip and shoulder joint examinations were normal with normal muscle apperance. She was found to have alanine transferase (ALT) of 108 U/L (normal:0-34U/L) and aspartate transferase (AST) of 148 U/L (normal:15-60U/L). Bilirubin, alkalen phosphatase, PT/PTT and albumin levels were all normal. Hepatitis A, B and C screenings were unremarkable. Creatine kinase level was 7186 U/L(normal:<145U/L). We excluded extrahepatic casuses of elevated transaminases (1). She had normal thyroid function, renal function, celiac disease tests and fasting blood glucose. She had no hemolytic disease, adrenal insuffciency and rhabdomyolysis. As she had persistent CK increase, muscle biopsy was done. At muscle biopsy, variation in diameter of muscle fibers, some muscle fibers with internal nucleus, some degenerated muscle fibers and increase of lipid content in some muscle fibers were detected. There were rarely eosinophiles in interstitium but no increase of connective tissue (Figure 2: A-C). Immunohistochemical examination showed merosin, dystrophin, α, β, γ, δ and sarcoglycan antibodies positive. Although dystrophic or inflammatory changes not seen, eosinophilic infiltration can be seen in calpainopathy, genetic study of *CAPN3* gene was done. Genetic study results showed homozygote mutation of *CAPN3* gene (NM_000070.2, c.2092C>A, p. Arg698Ser). Subsequent testing of the patient's parents revealed that they were heterozygous unaffected carriers. Written informed consent form was obtained from the parents of patient.

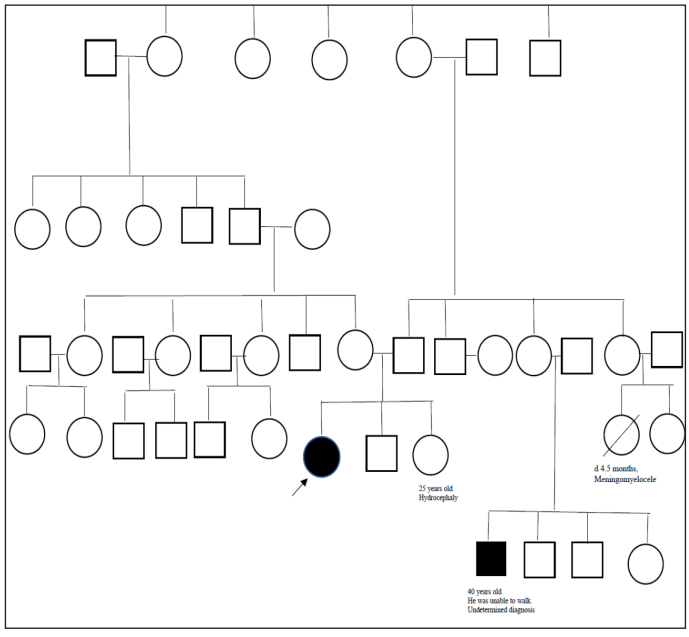

Figure 1: Pedigree chart of family.

DISCUSSION

We presented the asymptomatic child with LGMD type 2A confirmed by genetic study to emphasize asymptomatic presentation of muscle diseases. She was diagnosed when she was admitted to hospital for primary care. After detection of elevated transaminase levels and persistent high CK levels, we performed muscle biopsy and genetic study. Although there is no standard of care, medical therapy for LGMDs and no specific biomarkers for diagnosis other than genetic study, early diagnosis of patients may increase their life quality with supportive therapies. Extensive efforts to develop gene therapies for muscular dystrophies, including LGMD type 2A also increase the importance of early diagnosis.

Our case had no symptom and normal physical examination, patients with LGMD type 2A have heterogenous clinical presentations. Clinically the symptoms of patients with LGMD type 2A are difficulty to run and walk, toe walking, hyperlordosis, proximal muscle weakness (pelvic extensor ve adductor muscles are normal), wing scapula. Muscle atrophy is prominent. Joint contracture, shortness of aschille tendon, scoliosis at presentation can be seen at early period. The onset age can change between 2-40 years old, but the mean onset age of disease is 8-15 years old. Mostly mild and moderate clinic is seen at the beginning. The patient has inability to walk and adherence to wheelchair after 11-28 years of disease. Serum CK levels can increase 5-80 of normal level or can be

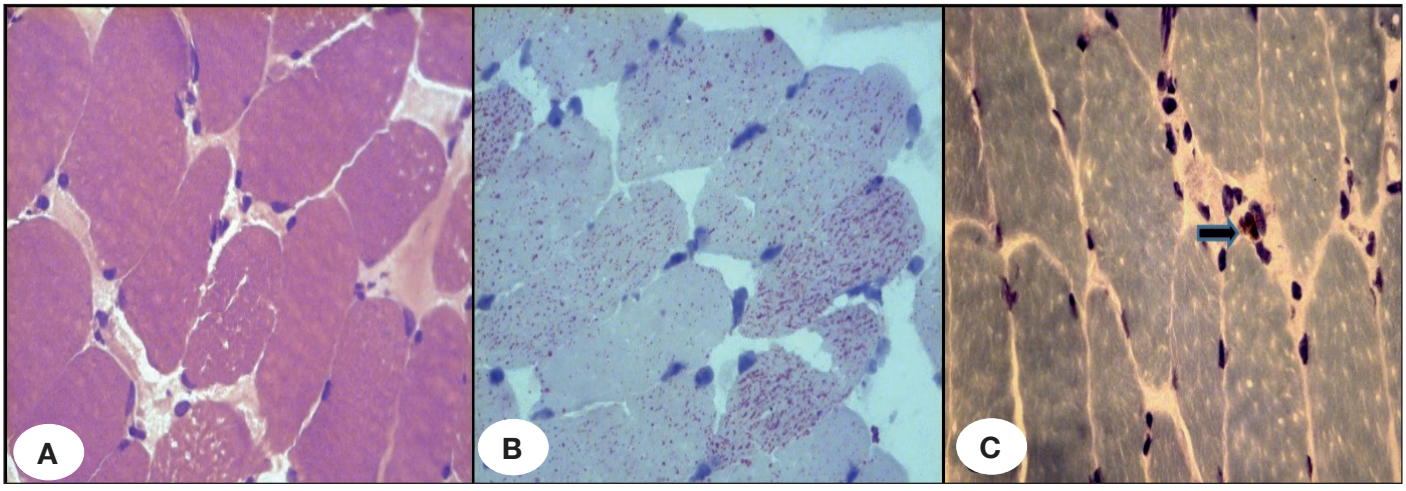

Figure 2: (A) At muscle biopsy, H&E staining, variation in diameters of muscle fibers and some degenarated muscle fibers, **(B)** ORO staining, increase of lipid content in some muscle fibers, **(C)** toluidin staining, eosinophil signed with arrow.

at normal range (4). Muscle biopsy of LGMD type 2A shows mostly a dystrophic pattern like increased fiber size variability, increased fibrosis, regenerating fibers, degenerating and necrotic fibers. Sometimes nonspecific myopathic features like increased central nuclei, fiber splitting, lobulated fibers (misaligned myofibrils that form a lobulated pattern), and type 1 fiber predominance can be seen (5). At diagnoses of MD, biochemical tests help to show deficiency or absence of specific proteins at biopsy material (6). Muscle biopsy should be used when molecular genetic analysis is not conclusive or for diagnostic confirmation. Calpain-3 immunoblot testing is useful in the diagnosis of calpainopathy. Molecular genetic testing of identification of biallelic pathogenic variants in CAPN3 gene or a dominantly acting heterogenic pathological variant for *CAPN3* 21-bp deletion is the gold standard for diagnoses of calpainopathy (3). In our patient we firstly performed muscle biopsy to understand muscle pathology and after result of muscle biopsy genetic testing confirmed diagnosis of LGMD type 2A. In a report of *CAPN3* mutation in Turkey, a total of 15 different *CAPN3* gene mutations were detected, 6 of which were novel (p.K211N, p.D230G, p.Y322H, p.R698S, p.Q738X, c.2257delGinsAA. In this report all LGMD2A-ascertained patients, the onset of symptoms was between 2.5 and 19 years of age. In general, the disease course was mild. Involvement of muscles predominated in the limb girdle and trunk muscles and was usually symmetrical. There was atrophy of the proximal muscles to varying degrees. CK levels were invariably highly elevated and usually measured in several thousands (2000–8000 U/l). None of the presented patients lost ambulation during the time of study. Cardiac functions of all patients were normal. Also, respiratory functions did not show any abnormalities (7).

In an asymptomatic case series with high CK levels (CK>500 IU/L), authors analysed muscle biopsy specimens of 104 patients. In the study, 13 were children (ages 4 to 15 years), 20 were young adults (ages 16 to 30 years), and 71 were adults (ages 31 to 79 years). Fifty patients were completely asymptomatic and 54 patients had myalgia, cramps, or fatigue. CK levels were 500 to 1000 UI/L in 50 patients (mean age 43 years), 1000 to 2000 UI/L in 30 patients (mean age 41 years), >2000 in 24 patients (mean age 30 years). They achieved a definite or probable diagnosis in 55% of cases and concluded that the probability of making a diagnosis was higher in children and when CK level was greater than 2000 UI/L. The most frequently identified diseases were glycogen storage diseases, muscular dystrophies, and inflammatory myopathies. There was 20 patients with diagnosis of muscular dystrohy and one patient was diagnosed as calpainopathy (8). The study also demonstrated that patients with MD may present with asymptomatic or mild clinic as our case.

There are no established drug therapy for LGMDs, but different therapeutic approaches, including gene therapy, cell therapy and pharmacological trials are currently under investigation in animal models and experimental studies (9, 10). After diagnosis of LGMD 2A, control of weight, avoidence of obesity, physiotherapy and support of mobility with stretch exercises, avoidance of joint contracture should be planned. Surgical interventions of orthopedic complications like foot deformity and scoliosis can be required. Follow up for cardiomyopathy should be done although it is uncommon. Baseline cardiac evaluation with echocardiography and respiratory function testing are advised. We can increase life quality of these group of patients with support of social and emotional aspects (6, 9). As we aimed to emphasize asymptomatic presentation of LGMD2A at pediatric age, our report did not mention about prognosis of our case.

As a conclusion, muscle disorders can present with asymptomatic clinic during childhood period. There is no specific biomarker for LGMDs but muscle biopsy helps

diagnosis and molecular genetic analysis makes the exact diagnosis of LGMDs. Early diagnosis is important to increase their life quality with supportive therapies and for future genetic therapies for MD including LGMD type 2A.

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A Confusing Final Diagnosis in the Differential Diagnosis of SARS-Cov-2 Associated Multisystem Inflammatory Syndrome in Children: *Salmonellosis*

Çocuklarda SARS-Cov-2 ile İlişkili Multisistem İnflamatuar Sendrom Ayırıcı Tanısında Kafa Karıştıran Bir Son Tanı: *Salmonelloz*

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ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a severe clinical condition associated with the SARS-CoV-2 infection characterized by an increased inflammatory response. MIS-C shares common features with other pediatric inflammatory and infectious conditions including bacterial infections. *Salmonella* infections should be kept in mind as a causative agent of bacterial gastroenteritis in the differential diagnosis of patients with suspected MIS-C to avoid misdiagnosis. In this report, a case series of pediatric patients with a final diagnosis of *salmonellosis* were presented, although a primarily diagnosis of MIS-C at admission was considered due to symptoms and findings together with strong laboratory or epidemiological evidence for SARS-CoV-2 infection.

Key Words: Children, Misdiagnosis, Multisystem Inflammatory Syndrome, SARS-CoV-2, *Salmonellosis*

ÖZ

Çocuklarda Multisistem İnflamatuar Sendrom (MIS-C), artmış inflamatuar yanıtla karakterize, SARS-CoV-2 enfeksiyonu ile ilişkili ciddi bir klinik durumdur. MIS-C, bakteriyel enfeksiyonlar dahil olmak üzere diğer pediatrik inflamatuar ve enfeksiyöz durumlarla ortak özellikler taşır. Yanlış tanıdan kaçınmak için MIS-C şüphesi olan hastalarda ayırıcı tanıda bakteriyel gastroenterit etkeni olarak *Salmonella* enfeksiyonları akılda tutulmalıdır. Bu raporda, SARS-CoV-2 enfeksiyonu için güçlü laboratuvar veya epidemiyolojik kanıtlarla birlikte semptomları ve bulguları nedeniyle başvuru sırasında öncelikle MIS-C tanısı düşünülmesine rağmen, kesin *salmonelloz* teşhisi konan pediatrik hastalardan oluşan bir vaka serisi sunulmuştur.

Anahtar Kelimeler: Çocuklar, Yanlış Teşhis, Multisistem İnflamatuar Sendrom, SARS-CoV-2, *Salmonelloz*

INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly reported phenomenon as a complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). This Syndrome is a more severe clinical condition than the infection itself, named as “coronavirus disease 2019 (COVID-19)”, and characterized by an increased inflammatory response (1, 2). The pathogenesis of MIS-C is unclear, but has features overlapping with a possible autoimmune etiology and suggestive of vasculitis (1). The patients typically presents 4–6 weeks after infection with fever, multi-organ dysfunction and strongly elevated markers of inflammation, and have molecular or serological laboratory evidence of SARS-CoV-2 infection, or have a strong evidence of contact with an infected person (3). Varied clinical signs and symptoms at initial evaluation were described in MIS-C patients. Most of them have fever and gastrointestinal symptoms alone or accompanied by changes, suggestive of Kawasaki-like disease (4). The situation that makes the disease so important is cardiac dysfunction that occurs in almost half of the patients and results with shock or death (5). However, knowledge about the clinical spectrum of MIS-C remains limited, and the lack of a diagnostic test or universally

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accepted definition makes the differential diagnosis difficult and causes it to be confused with many clinical situations (4, 5). Identification of MIS-C is important because timely initiation of treatment may help to correct the hyperinflammatory state, prevent end-organ damage and death (2). As MIS-C shares common features with other pediatric inflammatory and infectious conditions including bacterial infections and sepsis, the importance of differential diagnosis increases even more (1, 4). In addition, most of the MIS-C patients have gastrointestinal symptoms such as diarrhea together with fever, and of course infectious gastroenteritis with the same symptoms are frequently encountered in pediatric practice (6).

In this report, a case series of pediatric patients was presented diagnosed with *salmonellosis*, although a primarily diagnosis of MIS-C at admission was considered due to symptoms and findings together with strong laboratory or epidemiological evidence for SARS-CoV-2 infection.

CASES REPORT

Five children (three females, two males) aged 2.5-11.5 years who were admitted to a tertiary care hospital in the last three months of 2020 were presented in this report. All of the patients had a pre-diagnosis of MIS-C and a final diagnosis of confirmed salmonellosis. The suspicion of MIS-C was based on the case definitions established by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (7,8). For all patients, symptoms and physical examination findings on admission, comorbidities, laboratory tests including blood cell counts, C-reactive protein (CRP), procalcitonin, interleukin-6, liver function tests, serum creatinine level, coagulation tests, D-dimer, ferritin, blood culture, microscopic examination and culture of stool, viral testing including reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharyngeal sample, antibody testing detected IgM/IgG antibodies against SARS-CoV-2, imaging records, supportive treatments, treatments for MIS-C, antibiotherapies, and clinical outcome records were summarized separately in Table I-III.

Serovar determination was not performed on isolates obtained from any patient, since sub-species determination for *Salmonella* strains could not be performed in our center. Therefore, it could not be understood whether the patients had typhoid fever or invasive disease with non-typhoidal *Salmonella* species. Patient 4 and 5 were bacteremic supported by blood cultures. While all *Salmonella* strains were susceptible to ceftriaxone, ciprofloxacin and trimethoprim-sulfamethoxazole, ampicillin resistance was variable. However, clinical or laboratory response to the treatment were not obtained in patients 4 and 5, and antibiotherapy was switched to other agents although resistance to ceftriaxone was not detected. Fever resolved in these patients after 24 hours of the treatment change. Their clinical conditions improved, and no additional treatment was applied for MIS-C.

Patient 4 was a previously healthy child with no cardiac problem. Cardiac findings detected in echocardiography returned to normal on follow-up, but 1st degree Atrioventricular (AV) block was detected before discharge in serial electrocardiograms (ECG) (shown in Table I). Arrhythmia improved without specific treatment, and 24-hour ECG monitoring was reported as normal during hospitalization. At the beginning of the process,

Table I: Demographic characteristics, symptoms / findings on admission, symptom duration, and molecular / serological laboratory or epidemiological evidence of SARS-CoV-2 infection, for all patients.

Patients	Gender	Age (year)	Comorbidity	Presenting symptoms	Symptom duration (day)	Physical examination findings	RT-PCR for COVID-19	Antibodies against SARS-CoV-2	Contact with a person infected with COVID-19
1	Female	11.5	Canavan disease	Fever, diarrhea, vomiting, and abdominal pain	1	Toxicity, respiratory distress, and abdominal tenderness	positive	non-reactive	+ (mother)
2	Female	2.5	-	Fever, vomiting, diarrhea, and abdominal pain	3	Dehydration, toxicity, and abdominal tenderness	negative	reactive	-
3	Male	7.5	-	Fever, vomiting, diarrhea, and weakness	7	Dehydration and abdominal tenderness	negative	non-reactive	+ (father)
4	Female	4	-	Fever, abdominal pain, and diarrhea	1	Dehydration and toxicity	negative	non-reactive	+ (father)
5	Male	2.5	Hypogammaglobulinemia	Fever, vomiting, diarrhea, and headache	2	Dehydration, toxicity, and abdominal tenderness	negative	non-reactive	+ (grandmother)

Table II: Laboratory tests and culture results of the patients.

Laboratory tests	Patients				
	1	2	3	4	5
WBC (x10^9/L)	12.94	4.92	12.96	3.71	2.99
Neu (x10^9/L)	10.61	4.46	8.31	2.37	1.95
Lym (x10^9/L)	0.6	1.19	2.6	1.02	0.63
Hg (g/dL)	13.5	11.5	12.6	11.5	11
Plt (x10^9/L)	248	265	392	217	214
CRP (g/dL)	26	71	58	180	210
Procalcitonin (µg/L)	0.3	0.22	0.16	11.5	226.8
IL-6 (pg/mL)	4.14	3.14	28.5	77.7	232
ESR (mm/h)	9	15	83	32	86
Liver function tests	Elevated	Elevated	Elevated	Elevated	Elevated
Kidney function tests	Normal	Affected	Normal	Normal	Affected
Cardiac enzymes	Normal	Normal	Normal	Elevated	Elevated
Coagulation tests	Normal	Normal	Normal	Prolonged	Prolonged
D-dimer (mg/L)	1.1	1.8	0.9	19.2	3
Ferritin (µg/L)	25	29	226	511	239
Microscopic examination of stool	Rare leukocytes and 8-10 erythrocyte/hpf	Abundant leukocytes/hpf	2-3 leukocytes and 5-6 erythrocytes/hpf	Abundant leukocytes and 8-10 erythrocytes /hpf	Abundant leukocytes/hpf
Stool culture	*Salmonella enterica ssp enterica*	*Salmonella enterica ssp enterica*	*Salmonella enterica ssp enterica*	*Salmonella enterica ssp enterica*	*Salmonella enterica ssp enterica*
Blood culture	Negative	Negative	Negative	*Salmonella enterica ssp enterica*	*Salmonella enterica ssp enterica*

CRP: *C-reaktive protein (N: 0-5 g/dL), D-dimer (N: 0-0.55 mg/L),* ***ESR:*** *Erythrocyte sedimentation rate (N: 0-20 mm/h), Ferritin (N: 7-140 µg/L),* ***Hg:*** *Hemoglobin (N: 11.2-14.6 g/dL), IL-6: Interleukin 6 (N: 0-3.4 pg/mL),* ***Lym:*** *Lymphocyte (N: 1.5-6 x109/L),* ***Neu:*** *N0eutrophil (N: 1.5-8 x109/L), Procalcitonin (N: <0.16 µg/L),* ***WBC:*** *White blood cell (N: 4.8-12 x109/L).*

a clear distinction could not be made for the patient's severe cardiac findings as to whether it was due to MIS-C or salmonellosis. However, the fact that the findings returned to normal in a short time with antibiotherapy was considered as salmonellosis-related cardiac involvement, and MIS-C diagnosis was excluded. Abdominal findings of patient 4 and 5 returned normal before discharge. While the source of transmission for *Salmonella enterica ssp enterica* was consumption of raw chicken and raw quail eggs in patient 4 and 5, a clear source for bacterial contamination was not found in other patients. There were no symptoms suggestive of salmonellosis in any of the patients' family members.

DISCUSSION

Salmonellosis is a disease of global public health importance, and is directly related to water treatment, sewage disposal, animal exposures, and food-handling practices (9). *Salmonella* infections most often cause self-limiting gastroenteritis, but can also cause invasive infections with severe organ involvement that can result in morbidity or mortality (9, 10). Sepsis or sepsis-like conditions associated with invasive disease may not be attributed to *Salmonella* in the early period and may be confused with other conditions (10). Especially, enteric fever can mimic other infections of the reticuloendothelial system, or non-infectious illnesses such as collagen vascular diseases including juvenile rheumatoid arthritis and Kawasaki disease, and lymphomas (11). Similarly, Kawasaki syndrome and other vasculitis can be misdiagnosed as many infectious diseases (12). On this background of differential diagnosis challenge, MIS-C has emerged as an important cause of morbidity and mortality with the COVID-19 pandemic, and entered the world of pediatricians as a factor that causes serious confusion in diagnosis and treatment of many diseases.

MIS-C is a post-infectious event that occurs in individuals aged 0-21 years and causes symptoms a few weeks after infection with COVID-19 (1,2). Fever is a constant sign for MIS-C; cutaneous manifestations, abdominal symptoms and cardiovascular collapse are also common findings in most patients (13). Gastrointestinal manifestations including abdominal pain, diarrhea and vomiting are observed in 92% of patients; may be severe enough to require surgery, and also

Table III: Imaging records, supportive treatments, antibiotherapies and clinical outcomes, of the patients.

Patients	Chest X-ray	Abdominal ultrasonography	Echocardiography	Supportive treatments	Antibiotherapy/ duration	Clinical outcome
1	Normal	Normal	Normal	Oxygen and HFNC (High flow nasal cannula) for respiratory distress, intravenous (iv) hydration	Ceftriaxone / 10 days	Cured
2	Undrawn	Normal	Normal	IV hydration	Ceftriaxone / 10 days	Cured
3	Normal	Normal	Normal	IV hydration	Ceftriaxone / 10 days	Cured
4	Normal	Diffuse wall thickening (6 mm) in ileal loops, mesenteric contamination, and intraabdominal fluid (34 mm)	Dilatation in the left ventricle, mild mitral insufficiency, pericardial effusion in the posterior wall (2-3 mm), and bilateral pleural effusion (3 mm)	IV hydration Intravenous immunoglobulin (2 gr/kg) Acetyl salicylic acid (started at anti-inflammatory dose and decreased to antiaggregant dose)	Ceftriaxone / 4 days and Ciprofloxacin / 10 days	Intermittent outpatient controls are ongoing due to cardiac involvement
5	Undrawn	Oval-shaped hypoechoic lymph node with a size of 10x19 mm in the right lower quadrant, diffuse thickening of the intestinal walls (4 mm) and a small amount of fluid between the bowel loops	Secundum atrial septal defekt	IV hydration Intravenous immunoglobulin (2 gr/kg)	Ceftriaxone / 3 days and Trimethoprim-sulfamethoxazole / 7 days	Cured

may be the only additional system findings accompanying fever (13, 14). Cardiac findings are detected in almost 80% of the patients, and half of the patients may progress to a severe shock-like condition requiring intensive care follow-up (4, 13). Due to increased cytokine responses and high inflammatory markers together with other system involvements, and high risk of morbidity and mortality, immediate intervention is essential without delay (5). The necessity of immediate intervention in this disease has revealed a new pediatric emergency, and prompted clinicians to rapidly initiate MIS-C treatment to prevent secondary complications in patients who have direct or indirect contact with COVID-19 and present with non-specific signs and symptoms suggestive of the syndrome. However, with this rapid intervention, possible infectious and non-infectious causes included in the differential diagnosis of MIS-C may be overlooked or delayed in diagnosis. There will even be cases that receive unnecessary treatment since there is no specific marker to make definitive diagnosis of MIS-C. For this reason, a careful analysis and careful examination of differential diagnosis is very important both during the patient's admission and during the follow-up. All of the patients in this case series presented with fever and significant gastrointestinal symptoms. In all of them, the significant elevations in inflammatory markers and strong evidence for infection or indirect contact with COVID-19 forced us to consider the diagnosis of MIS-C firstly. Some of the patients were even applied MIS-C initial treatments due to the deterioration of the general condition and toxic appearance on admission. Finally, stool and blood cultures obtained for possible infectious causes led us to a definitive diagnosis. To our knowledge, there is only one case report and one case series in the literature, that were considered a pre-diagnosis of MIS-C and were diagnosed with salmonellosis on follow-up (15, 16). There are also rare case reports of pediatric patients presented with findings indicative of MIS-C and were diagnosed with different infectious disease except for salmonellosis (17, 18).

Salmonella serotypes are designated based on the immunoreactivity of two cell surface structures, the O and H antigens, and serovars are identified beyond differentiating *Salmonella* isolates by subspecies level (18, 19). Clinically important *Salmonella* consist principally of a single species, *Salmonella enterica*, and *S. enterica* is further subdivided into six subspecies that are designated by taxonomic names: *enterica, salamae, arizonae, diarizonae, houtenae* and *indica* (17). The S. enterica subspecies covering more than 2500 serovars commonly encountered in clinical practice are grouped as typhoidal and non-typhoidal (11). Infection caused by *Salmonella* bacteria in the non-typhoidal group predominantly cause local intestinal inflammation, while those in the typhoidal group lead to systemic disease named as enteric (typhoid) fever (11, 13).

These differences in the manifestations of infection by the 2 groups of pathogens brings about changes in the approach to infection and treatment plan (9-11). Among *Salmonella* infections, early diagnosis and treatment of typhoid fever with appropriate antimicrobials are essential (11). In *Salmonella* gastroenteritis other than typhoid fever, antimicrobial treatment do not have a clear indication (20). Because antibiotics do not shorten the course of illness and may prolong shedding of the organism in the stool (20, 21). There are also exceptions to the generalization that *Salmonella* gastroenteritis should not be treated; and also non-typhoidal *Salmonella* strains could cause disease mimicking enteric fever (11, 21). After all that mentioned, subtyping and serovar determination of *Salmonella* spp obtained in any culture is important. Unfortunately, serovar determination was not performed on isolates obtained from our patients, and we could not understand whether the patients had typhoid fever or invasive disease with non-typhoidal *salmonella species*. However, the use of raw animal products in patients 4 and 5 made us think that non-typhoidal serovars may be causative agents. The severity of clinical conditions and significantly elevations in inflammatory markers of the patients suggested invasive disease associated with *Salmonella spp* and antibiotherapy treatments were arranged accordingly. *Salmonella enterica ssp enterica* was observed in cultures of all patients, but since serotyping could not be performed, the antimicrobial treatments initiated were completed to the appropriate time for enteric fever or invasive non-typhoidal salmonellosis.

Varying degrees of AV blocks can occur for many reasons including infections and infection-associated myocarditis (22, 23). COVID-19-related cases and MIS-C patients with myocarditis have also been described (24, 25). Peri-myo-endocarditis and arrhythmias are well known complications of *Salmonella* infections and have also been reported in children (26). Abnormal echocardiographic findings detected in patient 4 were interpreted as heart failure due to myopericarditis and secondary pleural effusion. Cardiac complications in this patient may have occurred due to both MIS-C and salmonellosis. However, the cardiac involvement was interpreted as releated to the infection more than MIS-C, since the findings did not gradually get worse and resolved spontaneously without additional treatment for MIS-C.

MIS-C overlaps with many other infectious and inflammatory diseases or syndromes that pediatricians often encounter in daily practice. Maintaining a proper clinical suspicion for other possibilities in the differential diagnosis is important in children presenting with clinical signs / symptoms suggestive of MIS-C and laboratory findings consistent with this syndrome. Appropriate index of suspicion is essential to not to miss the diagnosis of other possible infectious or non-infectious diseases and avoid over-treatment due to the possibility of MIS-C. This case series demonstrated the necessity of a careful treatment plan and a thorough review of other possible diagnoses in each step in children admitted with features suggestive of MIS-C along with severe elevations in inflammatory markers and strong evidences for COVID-19. *Salmonella* infections should be kept in mind as a causative agent of bacterial gastroenteritis in the differential diagnosis of patients with suspected MIS-C who present with increased cytokine levels accompanying fever and gastrointestinal system findings.

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Çocukluk Çağı Akciğer Hastalıklarında Sağlıklı Beslenmenin Önemi

The Importance of Healthy Nutrition in Childhood Lung Diseases

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ÖZ

Sağlıklı beslenme akciğerlerin gelişiminde önemli bir role sahiptir. Birçok sistem üzerine olumsuz etkiye neden olan malnütrisyonun özellikle solunum sistemi gelişimi ve akciğer hastalıkları üzerindeki etkileri, ileri yaşlarda solunum fonksiyonlarında kalıcı bozulmaya yol açabilmektedir. Malnütrisyonun çocukluk çağında önlenmesi, erken tanınması ve gerekli müdahalelerde bulunulması morbidite ve mortaliteyi azaltmaya katkıda bulunacaktır. Bu derlemede; sağlıklı beslenmenin akciğer gelişimine etkisi, çocuklarda görülen malnütrisyonun akciğer hastalıklarının sıklığına ve bu hastalıkların klinik gidişine etkilerinin tartışılması, çocukluk çağı akciğer hastalıklarında beslenme önerilerinin ve malnütrisyonu önlemeye yönelik çözüm önerilerinin incelenmesi, dünyada bu konuda alınan önlemlerin gözden geçirilmesi amaçlanmıştır. Bebeklik ve çocukluk dönemindeki malnütrisyonun akciğer sağlığı ve solunum fonksiyonlarına etkileri net bilinmemekle birlikte, yapılan çalışmalar erken çocukluk dönemindeki malnütrisyonun solunum fonksiyonlarını olumsuz yönde etkilediğini göstermiştir. Malnütrisyon, hücresel immünite ve kazanılmış immüniteye etkilerinin yanında akciğer gelişimine olan etkileri ile de solunum yolu enfeksiyonları sıklığını ve riskini artırmaktadır. Bunların yanı sıra bu etkiler kronik akciğer hastalıkları gelişme riskini de artırmaktadır. Çocukluk çağında solunum yolu hastalıklarına bağlı ölümlerin büyük bölümü önlenebilir ölümlerdir. Ancak bu konuda etkili önlemlerin alınması ve uygun yaklaşımların yapılması önemlidir. Anne sütü alımının desteklenmesi, annenin gebelikte yeterli beslenmesi, mikrobesin ögelerinin alımının desteklenmesi, kronik solunum yolu hastalıklarında erken dönemde beslenme durumunun kontrol edilmesi ve önlemlerin alınması hastaların ileri yaştaki prognozunu olumlu etkileyecektir. Sonuç olarak; çocukların rutin izlemlerinde büyümenin, yeterli kilo alımı ve boy uzamasının olup olmadığının değerlendirilmesi önlenebilir sorunlarda erken müdahaleler açısından önemli bir yere sahiptir.

Anahtar Sözcükler: Çocukluk çağı akciğer hastalıkları, Malnütrisyon, Nutrisyon, Solunum fonksiyonları

ABSTRACT

Nutrition has an important role in the development of the lungs. Malnutrition, which causes adverse effects on many systems, especially its effects on respiratory system development and lung diseases can lead to permanent impairment in respiratory functions in older ages. Prevention of malnutrition in childhood, early recognition and necessary interventions will contribute to reducing morbidity and mortality. In this review article, it is aimed to discuss the effects of nutrition on lung development, the effects of malnutrition on the frequency of lung diseases in children and the clinical course of these diseases, to evaluate nutritional suggestions and solutions to prevent malnutrition in childhood lung diseases, and to review the measures taken in this regard in the world. Although the effects of malnutrition in infancy and childhood on lung health and pulmonary functions are not known clearly, recent reports have shown that malnutrition in early childhood adversely affects the pulmonary functions. Besides, malnutrition has effects on both cellular and acquired immunity and on the frequency and risk of respiratory tract infections. Furthermore, all these influences increase the risk of developing chronic lung diseases. Majority of deaths due to respiratory diseases in childhood are preventable, however, it is important to take precautions and appropriate attitude in this regard. Supporting breastfeeding, adequate nutrition of the mother during pregnancy, supporting the intake of micronutrients, controlling the nutritional status in

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the early period in chronic respiratory diseases and taking precautions will positively affect the prognosis of patients in older ages. In conclusion, evaluation of the growth, adequate weight gain and height in the routine follow-up of children have an important role in terms of early interventions in preventable conditions.

Key Words: Childhood lung diseases, Malnutrition, Nutrition, Pulmonary functions

GİRİŞ:

Sağlıklı beslenme akciğerlerin gelişiminde önemli bir role sahiptir. Malnütrisyonun, birçok sistem üzerine olumsuz etkisi bilinmekle birlikte özellikle solunum sistemi gelişimi ve akciğer hastalıkları üzerindeki etkileri, ileri yaşlarda solunum fonksiyonlarında kalıcı bozulmaya yol açabilmektedir (1).

Malnütrisyon, düşük ve orta gelirli ülkelerde yaşayan çocuklarda mortalitenin önemli nedeni olmaya devam etmektedir (2,3). Bu durumun en önemli nedenlerinden biri malnütrisyonun enfeksiyonlara yatkınlık yapması ile birlikte, enfeksiyon hastalıklarının da malnütrisyona yol açmasıdır. Malnütrisyonun çocukluk çağında önlenmesi, erken tanınması ve gerekli müdahalelerde bulunulması morbidite ve mortaliteyi azaltmaya katkıda bulunacaktır (2-5).

Bu makalede; sağlıklı beslenmenin akciğer gelişimine etkisi, çocuklarda görülen malnütrisyonun akciğer hastalıklarının sıklığına ve bu hastalıkların klinik gidişine etkilerinin tartışılması, çocukluk çağı akciğer hastalıklarında beslenme önerilerinin ve malnütrisyonu önlemeye yönelik çözüm önerilerinin incelenmesi, dünyada bu konuda alınan önlemlerin gözden geçirilmesi amaçlanmıştır.

1. Sağlıklı Beslenme ve Akciğer Gelişimine Etkisi

Akciğerlerin gelişim süreci, biyokimyasal, mekanik ve anatomik farklı evrelerden oluşmakta olup postkonsepsiyonel 3. haftadan başlayarak tüm gebelik ve doğum sonrası dönemde de devam etmektedir ve bu gelişimin 22 yaşına kadar sürdüğü bilinmektedir. Gebelik dönemi, doğum süreci ve doğumdan hemen sonra gelişen akciğer hasarı tüm yaşam boyunca akciğer sağlığı ve solunum fonksiyonlarını etkilemektedir. Bebeklik ve çocukluk dönemindeki malnütrisyonun ise akciğer sağlığı ve solunum fonksiyonlarına etkileri net bilinmemekle birlikte, bu dönemde yaşanan problemlerin de akciğer boyutlarını etkilediği gösterilmiştir (1,6).

- ***Fetal Dönemde Beslenme ve Akciğer Gelişimi***

Fetal yaşamda özellikle akciğerlerin sakkuler ve alveolar gelişim evrelerinde genetik ve epigenetik faktörler alveollerin gelişimini olumsuz etkilemektedir, intrauterin büyüme geriliğinin de iletici hava yollarının gelişimine olumsuz etkisi bilinmektedir (6). Bu konuda yapılan 5000 çocuğun incelendiği bir kohort çalışması intrauterin büyüme geriliğinin hava yolu direncini artırıp solunum fonksiyonlarını etkileyerek vizing ve astım gelişme riskine neden olduğunu göstermiştir (7). Düşük doğum ağırlığı ile doğan bireylerin erişkin yaşta da maksimum solunum fonksiyonlarına ulaşamadıkları ve bu bebeklerde erişkin yaşta kronik obstruktif akciğer hastalığı gelişme riskinin arttığı da bilinmektedir (8).

- ***Postnatal Dönemde Beslenme ve Akciğer Gelişimi***

Doğumdan sonra hava yollarının boyutunda artış, alveollerin de hem sayısı hem de boyutlarında artış olmaktadır. Erken doğan bebeklerde, akciğer gelişiminde özellikle alveolar ve sakkuler evrede (Gebeliğin 24-40. haftası) beslenme önemli role sahiptir, bu nedenle de doğumdan sonra beslenme özellikle prematüre bebeklerde bu süreç postnatal dönemde de devam ettiğinden önemlidir. Bu bebeklerde yaşamın erken dönemde postnatal beslenmenin yeterli olmaması hiperoksinin alveoller üzerindeki olumsuz etkisini artırmaktadır; bu durumun da bronkopulmoner displazi patogenezinde etkili olacağı düşünülmektedir (1,6).

Anne sütü ile beslenmenin ilk iki yaşta viral enfeksiyonların neden olduğu vizinge karşı koruyucu olduğu bilinmektedir (9). Bu etkinin anne sütünün bağışıklık sistemini güçlendirici etkisine bağlı çocukluk çağı viral enfeksiyonlarının sıklığını azaltmasıyla ilişkili olduğu düşünülmektedir. Bu konuda yapılmış bir sistematik derlemede; özellikle 4 ayın üzerinde anne sütü ile beslenen bebeklerin formula besin alan bebeklerle karşılaştırıldığında solunum fonksiyonlarının daha iyi olduğu görülmüştür (10). Bu bilgiler anne sütünün akciğer maturasyonunda görevli TGF beta gibi sitokinler ve büyüme faktörlerini aktive ederek akciğerlerin gelişimini olumlu etkilediğini ve ileri yaştaki solunum fonksiyonlarını olumlu etkileyeceğini düşündürmektedir (6).

- ***Bebeklik ve Çocukluk Döneminde Beslenme ve Akciğer Gelişimi***

Bebeklik ve çocukluk döneminde beslenmenin akciğer gelişimine etkileri ile ilgili yeterli sayıda çalışma bulunmamaktadır. Alveoler gelişimin iki yaşına kadar devam ettiği bilindiğinden bebeklerdeki malnütrisyonun daha geç çocukluk dönemindeki malnütrisyonla karşılaştırıldığında akciğer sağlığını ve akciğer gelişimini olumsuz yönde etkilediği tahmin edilmektedir. Bu konudaki kohort çalışmaları da bu görüşü desteklemektedir. Özellikle erken çocukluk dönemindeki malnütrisyonun solunum fonksiyonlarını olumsuz yönde etkilediği gösterilmiştir (6,11).

2. Malnütrisyonun Tanımı ve Çocuklarda Malnütrisyonun Etkileri

Dünya Sağlığı Örgütü (DSÖ) malnütrisyonu; kişinin enerji ve / veya besin alımındaki eksiklikler, aşırılıklar veya dengesizlikler olarak ifade eder. Buna göre malnütrisyon üç alt başlığa ayrılabilir (12):

a. **Yetersiz beslenme:** Zayıflık (boya göre düşük ağırlık), bodurluk (yaşa göre düşük boy) ve düşük kilololuk (yaşa göre düşük ağırlık).

b. **Mikro besinlerle (Vitamin, mineraller) ilgili yetersiz beslenme:** Mikro besin eksikliklerini veya mikro besin fazlalığını içerir.

c. Fazla kiloluluk: Obezite ve diyetle ilgili bulaşıcı olmayan hastalıklara bağlı durumlar (kalp hastalığı, diyabet gibi).

Dünya Sağlığı Örgütü 2020 yılı verilerine göre 5 yaş altı çocuklarda 47 milyon çocukta zayıflık, 144 milyon çocukta bodurluk ve 38.3 milyon çocukta fazla kiloluluk durumunun önemli bir sağlık problemi olduğu görülmektedir. Beş yaş altı çocuk ölümlerinin %45'inin yetersiz beslenme ile ilişkili olduğu bildirilmiştir. Bu durum düşük ve orta gelirli ülkelerde önemli bir sağlık sorunu olmaktadır. Malnütrisyonun ekonomik, sosyal ve tıbbi etkileri dünyada da önemli bir problem olmaya devam etmektedir. Özellikle kadınlar, bebekler, çocuklar ve adolesanlar malnütrisyon açısından risk altındadırlar. Bu nedenle de özellikle konsepsiyon sonrası 1000 günü içeren yaşamın erken dönemlerinde beslenmenin düzenlenmesi ve gereken önlemlerin alınması uzun dönem etkileri nedeniyle önemlidir (12).

Yoksulluk, yetersiz beslenme ve buna bağlı riskleri artırmaktadır. Yoksul insanların malnütrisyondan etkilenme olasılığı daha yüksektir. Ayrıca, yetersiz beslenme sağlık hizmetleri maliyetlerini artırmakta, üretkenliği düşürmekte ve ekonomik büyümeyi yavaşlatmaktadır, bu durum da yoksulluk ve hastalık döngüsünü devam ettirmektedir (12).

Yetersiz beslenen çocuklarda enfeksiyöz hastalık sıklığının artmasına ek olarak, daha şiddetli hastalık riski mevcuttur ve bu durum enfeksiyon durumunda akut dönemde ve kronik süreçte mortalite ve morbiditenin önemli nedenidir (2).

Malnütrisyon, hücresel immünite ve kazanılmış immüniteye etkilerinin yanında akciğer gelişimine olan etkileri ile de solunum yolu enfeksiyonları sıklığını ve riskini artırmakla birlikte kronik akciğer hastalıkları gelişme riskini de artırmaktadır. Şekil 1'de malnütrisyonun akciğer gelişimi ve akciğer hastalıkları üzerine etkileri özetlenmiştir (13).

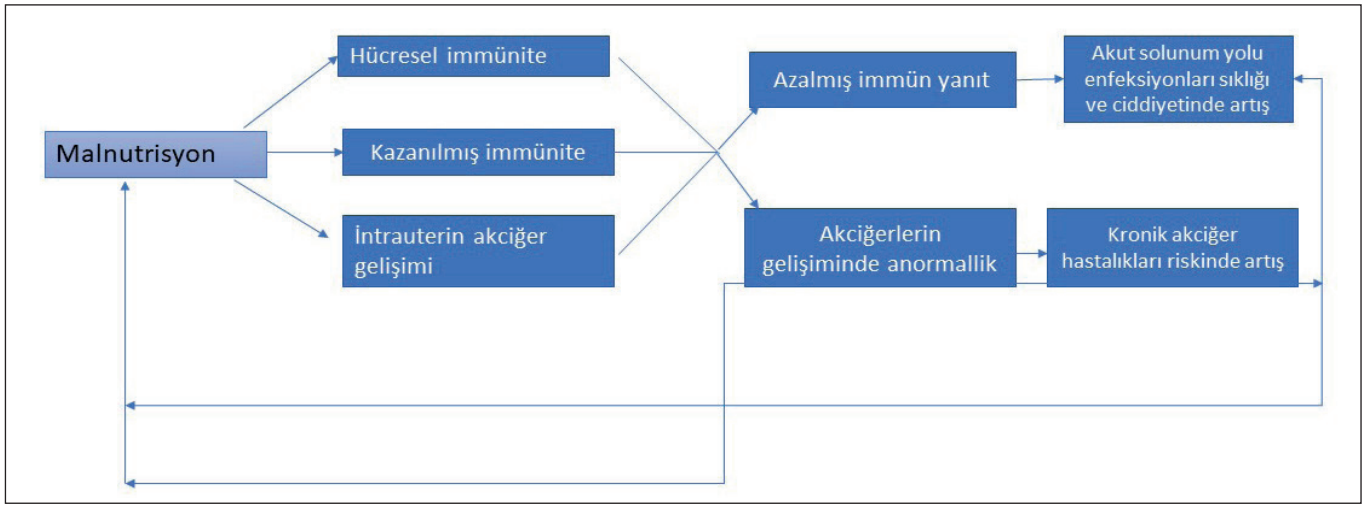
3. Akciğer Hastalıkları ve Malnütrisyon İlişkisi

Solunum sistemi hastalıkları, mortalite ve morbiditenin önemli nedeni olan hastalıklardır. Bebekler ve çocukların akciğer hastalıklarına daha hassas olduğu; özellikle düşük ve orta gelirli ülkelerde akciğer enfeksiyonlarının önemli bir mortalite nedeni olduğu bilinmektedir (14). Beş yaş altı çocuk ölümlerine bakıldığında yıllık 6.6 milyon çocuk ölümünün olduğu ve her yıl 1.3 milyon çocuğun pnömoni nedeniyle kaybedildiği görülmektedir; pnömoniler bu ölümlerin önemli nedenini oluşturmaktadır (15). Buna ek olarak malnütrisyon veya HIV enfeksiyonu da çocuklarda ölüm sayısında artışın önemli nedenlerindendir. Malnütrisyon sadece pnömoni riskinde artış ile ilişkili değil, aynı zamanda hastalığın ciddi seyrinde ve buna bağlı ölümlerle de yakından ilişkilidir (14). Malawi'de yapılan ve 16475 çocukluk pnömoni olgusunun değerlendirildiği bir çalışmada ağır malnütrisyonun hipoksemi ile benzer şekilde mortalite riskini artırdığı gösterilmiştir (16). Kenya'da yapılan 4187 çocuğun alındığı başka bir çalışmada da hastanede yatırılan ağır pnömoni hastalarının %25'inin malnütrisyonunun olduğu ve bu durumun pnömoni ağırlığı ile birlikte hastanedeki mortaliteyi artırdığı gösterilmiştir (17).

Tüberküloz, HIV prevalansı ve malnütrisyon sıklığı fazla olan ülkelerde mortalite ve morbiditenin önemli nedenlerinden biridir. Çocuklarda mikrobiyolojik tanı koymadaki zorluklar nedeniyle çocukluk çağı tüberküloz yükünün doğru bir şekilde ölçülmesi zor olsa da, insidansı yüksek ülkelerde çocukların ülkenin toplam tüberküloz yükünün %15 ila %20'sini oluşturduğu tahmin edilmektedir (14). Malnütrisyonu olan çocuklarda artmış tüberküloz riskinin nedeni, malnütrisyonun sekonder immün yetmezliğe neden olarak konağın enfeksiyonlara yatkınlığını artırmasıdır. Malnütrisyon hücre içi enfeksiyonlara ve ölüme neden olan önemli bir risk faktörü olduğundan beslenme durumunun bozulması, latent enfeksiyonun reaktivasyonuna da neden olabilir. Tüberküloz tedavisi sırasında beslenme durumu iyi olan çocukların tedavi yanıtlarının daha iyi olduğu gösterilmiştir (18). Bazı düşük ve orta gelirli ülkelerde malnütrisyon ile akciğer hastalıkları yükü arası ilişki Tablo I'de sunulmuştur (19-22). Bu çalışmalar da ağır malnütrisyonu olan çocuklarda pnömoni,

Tablo I: Düşük ve Orta Gelirli Ülkelerde Malnütrisyonu Olan Çocuklarda Akciğer Hastalıkları Yükü.

Referans	Yıl	Ülke	Çalışma tipi	Çalışma grubu	Bulgular
Munthali ve ark.[19]	2015	Zambia	Gözlemsel	5 yaş altı ağır malnütrisyonu olan 9450 çocuk	En sık morbiditeler: %25.3 pnömoni, %5.3 septisemi, %6.8 tüberküloz
Agarwal ve ark. [20]	2015	Hindistan	Gözlemsel	5 yaş altı 458 çocuk	Malnütrisyon son üç aydaki akut solunum yolu enfeksiyonu sıklığını artırıyor (OR=1.58).
Chisti ve ark.[21]	2013	Güney Afrika, Etopya, Gambia, Tayland	Gözlemsel çalışmaların derlemesi	5 yaş altı ağır malnütrisyonu olan 747 çocuk	%12 aktif tüberküloz
Bhat ve ark. [22]	2013	Hindistan	Gözlemsel	Akut alt solunum yolu enfeksiyonu olan 5 yaş altı 107 çocuk	Malnütrisyon, akut alt solunum yolu enfeksiyonu gelişme riskini artırıyor (OR=1.75 %95 GA=1.84-3.67).



Şekil 1: Malnütrisyon, akciğer gelişimi ve akciğer hastalıkları ilişkisi.

tüberküloz riskini ve hastalığa bağlı artmış mortalite oranını göstermektedir.

Son yıllarda çocukluk çağı obezitesinin prevalansında artışla birlikte, bu artışın akciğer sağlığına etkileri de önemli bir sorun haline gelmeye başlamıştır (23). Uzun dönemli çalışmalar, obezitenin çocukluk çağı astımı gelişme riskini artırdığını göstermiştir (24). Obezitenin solunum fonksiyonlarına olan etkisi bronş hiperreaktivitesi ve obezitenin etkisi ile gelişen sistemik inflamasyonla açıklanabilir (25). Obezitesi olan çocuklarda adipoz dokuda biriken makrofajların ürettiği inflamatuar sitokinler ve adipokinlerin etkisi ile akciğer ve immün sistem doğrudan etkilenmektedir, bu durum sistemik inflamasyon patogenezinde önemlidir. Diğer bir neden de özellikle karın ve göğüs kafesindeki yağ kitlesinde artış, akciğerlerin ve göğüs kafesinin genişlemesini engelleyen bir sorun olduğundan solunum fonksiyonlarında düşmeye yol açmaktadır (26).

Obezitenin astım ile nedensel ilişkisi konusunda farklı çalışmalar bulunmaktadır (26,27). Erken okul çağı döneminde aşırı kilolu veya obezitesi olan çocuklarda ergenlik döneminde astım riskinin arttığı gösterilmiştir. Bu çocukların astıma bağlı solunum fonksiyonlarında düşme ile ilişkili olarak günlük fiziksel aktivitelerinin kısıtlanması da obeziteye neden olan önemli bir durumdur (28). 2016 ve 2020 yıllarında yayınlanan iki farklı sistematik derlemede obezitesi olan çocuklar ve ergenlerin akciğer volümleri ve kapasitesinde düşme olduğu bildirilmiştir (26,27).

Çocukluk çağı obezitesinin neden olduğu durumlardan biri de obstruktif uyku apnesidir ve bu durumun farkındalığının az olması tanıda gecikmelere neden olmaktadır (23). Çocukluk çağı obezitesinin obstruktif uyku apnesi gelişiminde bağımsız bir risk faktörü olduğu gösterilmiştir (29). Astımla benzer şekilde bu çocuklarda da görülen azalmış egzersiz kapasitesi obezitenin artışına neden olmaktadır (24,29).

- ***Mikrobesinler ve Akciğer Hastalıkları ile İlişkisi***

Mikrobesinler, akciğerlerin doğumdan önce gelişiminde önemli bir rol oynar ve akciğer gelişiminin kritik aşamalarındaki eksiklikleri, erken doğan bebeklerde solunum morbiditesi ve sonraki yaşamda vizing insidansının artışı üzerinde etkiye sahip olabilir (30). Mikrobesinlerle ilişkili malnütrisyon enfeksiyonlara yatkınlığı ve ağır hastalık geçirme riskini artırmakta; iyileşmeyi geciktirmektedir. Annedeki eksiklikler, bebeklerde olumsuz etkilere neden olmaktadır. Vitamin A, C, D, çinko, demir ve folik asit önemli mikrobesinler olup çocuklarda enfeksiyon hastalıklarının önlenmesinde ve tedavisinde kullanılan önemli mikro besinlerdir (2). Vitamin A, akciğer gelişiminde rol oynamaktadır ve enfeksiyonlara karşı immünolojik yanıtta etkilidir; eksikliği çocuklarda mortalite ve morbidite ile ilişkili bulunmuştur. Vitamin D'nin de immunomodulatuar etkileri ile enfeksiyonlara karşı koruyucu olduğu düşünülmektedir. Yine yeterli C vitamini ve çinko alımının immünolojik fonksiyonları artırarak pnömoni gibi enfeksiyonlara bağlı morbiditeyi azalttığı gösterilmiştir (2,6).

4. Çocukluk Çağı Akciğer Hastalıklarında Sağlıklı Beslenmeye Yönelik Öneriler

Çocukluk çağında solunum yolu hastalıklarına bağlı ölümlerin büyük bölümü önlenebilir ölümlerdir. Ancak bu konuda etkili önlemlerin alınması ve uygun yaklaşımların yapılması önemlidir. Bu önlemlere uyulmasıyla pnömoniye bağlı ölümlerin %65'inin 2025 yılına kadar önlenebileceği düşünülmektedir. Bu durumun da sağlık hizmetlerine ulaşımın artırılması, beslenmenin iyileştirilmesi, anne sütü alımının desteklenmesi, yaşam koşullarının düzeltilmesi, ev içi ve ev dışı hava kirleticilerinin azaltılması ile mümkün olacağı düşünülmektedir (12).

- ***Çocuklarda Akut Solunum Yolu Hastalıklarında Beslenme Önerileri***

a. Anne sütü ile beslenme:

Anne sütü ile beslenme, düşük ve orta gelirli ülkelerdeki çocuklarda enfeksiyon sıklığını azaltmakta ve yaşam süresini uzatmaktadır. Bu kadar güçlü kanıtlara rağmen dünyada her beş çocuktan sadece ikisi ilk altı ayda anne sütü almaktadır. Anne sütünün yetersiz alımına bağlı gelişen akciğer enfeksiyonlarını

azaltmak için, anne sütünü desteklemeye yönelik eğitimlerin verilmesi önemlidir (2). Filipinler'de yapılan bir çalışma, anne sütü ile beslenme eğitim programı sonrası 2-7 ay arası bebeklerin kontrollere göre daha sağlıklı olduklarını göstermiştir (31). Anne sütünün buna ek olarak aşıya karşı gelişen antikor yanıtını artırdığına dair de kanıtlar bulunmaktadır (2).

b. Annenin gebelikte yeterli beslenmesi:

Annenin gebelikte yeterli beslenememesi yenidoğanın büyüme ve gelişimi üzerinde olumsuz etkilere yol açabilir (2). Bu nedenle de gebeliği süresince annenin beslenmesi desteklenmeli ve mikrobesin eksiklikleri önlenmelidir. Bangladeş'te yapılan randomize kontrollü bir çalışmada annenin gebelikte çinko alımının bebeğin büyümesini etkilediği ve enfeksiyon hastalıklarına bağlı morbiditeyi azalttığı gösterilmiştir (32).

c. Mikrobesin ögelerinin desteklenmesi:

Vitamin A desteğinin, solunum sistemi enfeksiyonlarına etkisini araştıran farklı çalışmalar bulunmaktadır. Dünya Sağlık Örgütü'nün vitamin A ve pnömoni çalışma grubu, gelişmekte olan ülkelerde vitamin A desteğinin pnömoni insidansını (RR=0.95 %95 Güven Aralığı=0.89-1.01) etkilemediğini göstermiştir. Vitamin A desteği 6 ay-5 yaş arası çocuklarda kızamığa bağlı mortaliteyi azaltmaktadır (2,6). 96203 anne ve 6 ay altı 59042 bebeğin alındığı 13 randomize kontrollü çalışmayı içeren bir araştırmada anneye veya bebeğe vitamin A desteği verilmesinin bebeklerdeki mortalite ve morbiditeye etkisi gösterilememiştir (33).

Vitamin C ile ilgili çalışmalara bakıldığında profilaktik veya tedavi edici dozda C vitamini verilmesinin pnömoni insidansını azalttığı gösterilmiştir. Ancak bu konu ile ilgili yeterli sayıda randomize kontrollü çalışma olmamasına rağmen, maliyeti ve riskleri düşük olması da göz önüne alındığında pnömoni tedavisinde vitamin C desteği uygulanabilir (2).

Vitamin D desteğinin çocuklarda pnömoni insidansı ve ciddiyetine olan etkisi tam olarak bilinmemektedir. 11 plasebo kontrollü çalışmayı içeren 5660 hastanın incelendiği bir meta analizde vitamin D desteği verilmesinin solunum yolu enfeksiyonlarına karşı koruyucu olduğu (OR=0.64 %95 Güven aralığı=0.49-0.84) gösterilmiştir (34). Vitamin D eksikliğinin çocuklarda tüberküloz enfeksiyonu ve tüberküloz hastalığı ile de ilişkili olduğu bildirilmiştir (2).

Çinko desteği verilmesinin, çeşitli çalışmalarda pnömoniye bağlı daha düşük morbidite ve mortalite riskleriyle ilişkili olduğu gösterilmiştir. Çocuklarda 2 ay-5 yaş arasında çinko desteği verilmesinin pnömoni insidansını %13 azalttığı bildirilmiştir. Bu nedenle de günlük veya haftalık çinko desteği verilmesinin morbiditeye olan etkisi ile pnömonide gereksiz antibiyotik kullanımını da azaltarak faydalı olabileceği düşünülmektedir (2,3).

- ***Çocuklarda Kronik Solunum Yolu Hastalıklarında Beslenmenin Önemi***

Malnütrisyon ve tekrarlayan akut solunum yolu enfeksiyonları kronik akciğer hastalıklarının gelişimine neden olmakta ve hastalığa bağlı ciddi sonuçlara yol açmaktadır. Bu nedenle de beslenme kronik akciğer hastalıklarında hastalığın klinik gidişine etkilerinden dolayı önemli yer tutmaktadır (2). Çocukluk çağı astımı ile ilgili yapılan prospektif bir çalışmada, yenidoğan dönemindeki akciğer gelişiminin ve solunum fonksiyonlarının astım riski ile ilişkili olduğu gösterilmiştir (35).

Kistik fibrozis, interstisiyel akciğer hastalıkları, bronşektazi, primer siliyer diskinezi gibi kronik akciğer hastalıklarında çocukluk çağında beslenmenin iyileştirilmesinin daha iyi solunum fonksiyonları ile ilişkili olduğu gösterilmiştir. Bu nedenle de erken dönemde beslenme durumunun kontrol edilmesi ve önlemlerin alınması hastaların ileri yaştaki prognozunu olumlu etkilemektedir (2). Anne sütü ile beslenen çocukların mama ile beslenen çocuklara göre vizing insidansının daha düşük olduğu görülmüştür. Diyetteki vitamin D, poliansature yağ asitleri, antioksidanlar ile astım insidansı arasındaki ilişki bilinmektedir. Ancak bu besin ögelerinin desteklenmesinin astım klinik gidişi ile ilişkisini kanıtlayan yeterli sayıda çalışma bulunmamaktadır. Bunun yanında annenin gebelikte beslenme durumu çocukluk çağı astımı ile ilişkili bulunmuştur, gebelikte vitamin D alınması ve poliansature yağ asitleri alımının astıma bağlı hastalık yükünü azalttığı düşünülmektedir. Gelişmekte olan ülkelerde kronik akciğer hastalıklarına yönelik beslenme önerileri ile ilgili yeterli çalışma bulunmamaktadır (2).

5. Çocuklarda Malnütrisyonu Önlemeye Yönelik Yapılması Gerekenler

Çocukların büyüme ve gelişmesinin hızlı olduğu yaşamın ilk iki yılında beslenmelerine gereken önem verilmelidir. Bu nedenle de anne sütüne mümkün olan en kısa sürede başlanması ve ilk 6 ay sadece anne sütü ile beslenmeleri bebeklerin büyümesi ve gelişmesi için önemli bir yere sahiptir. Anne sütü ilk iki yıl devam edilmelidir. Altıncı aydan itibaren, bebeklerin besin ihtiyaçları arttığından anne sütüne ek olarak tamamlayıcı besinlere geçilmesi önerilir. Tamamlayıcı beslenme, çocuklarda artan ihtiyaçla birlikte gelişebilecek yetersiz beslenmeyi önlemek amacıyla altıncı ayda başlanmalıdır. Aynı zamanda bebeklerin beslenmesi yeterli miktarda mikrobesin ögelerini de içermelidir (36).

Mikrobesin eksiklikleri vitamin ve minerallerin yetersiz alımına bağlı geliştiğinden özellikle gebelikte ve erken çocukluk döneminde yeterli miktarlarda alınması desteklenmelidir. Örneğin boy kısalığı ve bilişsel fonksiyonlarda azalmaya neden olan iyot eksikliği önlenebilir bir nedendir. Benzer şekilde vitamin A eksikliği beş yaş altı çocuklarda görülen önemli bir halk sağlığı problemi olup, vitamin A desteği uygulaması kızamık ve ishal gibi hastalıklarda mortalite riskini azaltmaktadır (36).

Annenin gebelikte yeterli beslenmesi, iyi bakım alması ve sağlıklı bir ortamda yaşaması, bebeğin sağlıklı olması için ön koşullardan biridir. Bu koşulların uygun olması bebekte düşük doğum ağırlığına neden olabilecek durumların önlenmesi ve tedavi edilmesi için gereklidir. Yenidoğan bebeğin doğum ağırlığı, anne-bebek sağlığı ve beslenme durumlarının önemli göstergelerinden

biridir. Düşük doğum ağırlıklı bebeklerin yaşamın ilk 28 gününde ölüm riski yüksektir. Ek olarak bu bebeklerin yetişkin dönemde obezite, diyabet gibi kronik hastalık risklerinin daha fazla olduğu bilinmektedir.

Çocukların rutin izlemlerinde büyümenin, yeterli kilo alımı ve boy uzamasının olup olmadığının değerlendirilmesi önlenebilir sorunlarda erken müdahaleler açısından önemli bir yere sahiptir (28).

6. Beslenme Üzerine Dünya Sağlık Örgütü ve Birleşmiş Milletlerin Hedefleri

Birleşmiş Milletler (BM) genel kurulu 1 Nisan 2016' da, 2016–2025 yılları arasındaki süreyi beslenme üzerine 10 yıllık eylem planı yılı ilan etti. Bu plana göre on yıllık süre tüm malnütrisyon tiplerini ele almak için iyi bir fırsat olarak düşünülmektedir. DSÖ ve Birleşmiş Milletler Gıda ve Tarım Örgütü (FAO) liderliğindeki BM beslenme üzerine 10 yıllık eylem planı, 6 temel alanda politika eylemi çağrısı yapmaktadır (12):

a. Sağlıklı beslenme için sürdürülebilir, dayanıklı gıda sistemleri oluşturmak;

b. Herkese sosyal koruma ve beslenme ile ilgili eğitim vermek;

c. Sağlık sistemlerini beslenme ihtiyaçlarına uygun hale getirmek ve temel beslenme müdahalelerinin evrensel olmasını sağlamak;

d. Ticaret ve yatırım politikalarının beslenmeyi iyileştirmesini sağlamak;

e. Her yaşta beslenme için güvenli ve destekleyici ortamlar oluşturmak;

f. Beslenme yönetimini ve hesap verilebilirliği her yerde güçlendirmek ve teşvik etmektir

Sonuç olarak; çocukluk çağı solunum yolu hastalıklarında malnütrisyon önemli bir neden olarak karşımıza çıkmaktadır. Çocukların izlemlerinde büyümenin, yeterli kilo alımı ve boy uzamasının olup olmadığının değerlendirilmesi önlenebilir sorunlarda erken müdahaleler açısından önemli bir yere sahiptir. Beslenme ile ilgili erken müdahalelerin solunum yolu hastalıklarını önlemede ve iyileştirmede etkili olduğu kanıtlanmakla birlikte bu konuda yeni araştırmalara ihtiyaç bulunmaktadır.

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