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On yıldır sürdürdüğüm Güncel Pediatri baş editörlük görevimden ayrılıyorum. Dergimizin taze ve genç bir enerji ile daha iyi bir düzeye ilerleyeceğine inanıyorum.

Beraber çalıştığımız Editörler Kurulu'muza, okurlarımıza ve yazarlarımıza teşekkür ediyorum. Yayın sürecini yöneten Galenos Yayınevi'ne ve teknik destekleri için LookUs firmasına çok teşekkürler. Yoğun programlarından zaman ayırıp makale değerlendirmelerine katkı sunan değerli hakemlerimize saygılarımı sunuyorum.

Yeni dönemde baş editörlüğü üstlenen Uludağ Üniversitesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı Başkanı Prof. Dr. Özlem Bostan'a ve göreve devam eden editör arkadaşlarıma başarılar diliyorum. Dergimizin ulusal ve uluslararası indekslerdeki prestijinin artarak devam edeceğine inanıyorum.

Prof. Dr. Ömer Tarım

ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Prematüre Bebeklerde Nekrotizan Enterokolit Riskinin Değerlendirilmesinde GutCheck-NEC ve e-NEC Skorlama Sistemlerinin Kullanımı

Utility of GutCheck-NEC and e-NEC Scoring Systems in Assessing the Risk of Necrotizing Enterocolitis in Preterm Infants

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Öz

Giriş: Nekrotizan enterokolit (NEK) prematüre yenidoğanlarda ciddi morbidite ve mortaliteye yol açabilen başlıca gastrointestinal acil durumlardan biridir. Bu çalışmada, gestasyonel yaşı (GY) ≤32 hafta olan prematüre bebeklerde NEK gelişimini öngörmede GutCheck-NEC (GCN) ve e-NEC skorlama sistemlerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Ocak 2020 – Aralık 2021 tarihleri arasında Gazi Üniversitesi Tıp Fakültesi Yenidoğan Yoğun Bakım Ünitesi'nde yürütülen bu prospektif gözlemsel çalışmaya GY ≤32 hafta olan 60 prematüre bebek dahil edildi. Tüm olgular 3., 7., 14., 21. ve 28. günlerde GCN ve e-NEC skorlarıyla değerlendirildi. NEK gelişimi ile bu skorlar ve olası risk faktörleri karşılaştırıldı.

Bulgular: On dört (%23,3) bebekte Bell evresi ≥2 NEK gelişti. GCN skoru 72. saat, 14. gün ve 21. günde NEK gelişenlerde anlamlı derecede daha yüksekti (p değeri: 72. saatte: 0,014; 14. günde: 0,032; 21. günde 0,047). Çalışmamızda GCN skorlamasına ait düşük ve orta risk grupları "az riskli", yüksek ve çok yüksek risk grupları "çok riskli" olarak birleştirildi. Yaşamın 72. saatinde az riskli ve çok riskli grup arasında NEK gelişimi açısından anlamlı fark saptandı (p=0,046). e-NEC skoru ise NEK gelişen ve gelişmeyen grupları ayırt etmede anlamlı fark göstermedi. Anne sütü ile beslenme NEK açısından koruyucu bulundu (p=0,026).

Sonuç: GCN skoru, prematürelerde NEK gelişimini öngörmede klinik pratikte kullanılabilir bir araç olabilir. e-NEC skoru ise hemşirelik izlemlerinde farkındalığı artırmak amacıyla değerlendirilebilir

Anahtar kelimeler
Anahtar Kelimeler: Nekrotizan enterokolit, prematüre bebek, risk değerlendirmesi, prognoz

Keywords
Enterocolitis, necrotizing, infant, premature, risk assessment, prognosis

Abstract

Introduction: Necrotizing enterocolitis (NEC) is one of the leading gastrointestinal emergencies causing significant morbidity and mortality in premature neonates. This study aimed to evaluate the effectiveness of the GutCheck-NEC (GCN) and e-NEC scoring systems in predicting necrotizing enterocolitis (NEC) in premature infants with a gestational age (GA) ≤32 weeks.

Materials and Methods: This prospective observational study was conducted between January 2020 and December 2021 in the Neonatal Intensive Care Unit of Gazi University Faculty of Medicine. A total of 60 premature infants with GA ≤32 weeks were included. All cases were assessed using the GCN and e-NEC scores on days 3, 7, 14, 21, and 28 of life. NEC development was compared with these scores and other potential risk factors.

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Results: NEC of Bell stage ≥2 developed in 14 (23.3%) infants. GCN scores were significantly higher in infants who developed NEC on the 72nd hour, 14th day, and 21st day (p-values: 72nd hour: 0.014; 14th day: 0.032; 21st day: 0.047). In our study, the low and moderate risk groups according to the GCN score were combined as the "low-risk" group, and the high and very high-risk groups were classified as "high-risk." A significant difference in NEC development was found between the low-risk and high-risk groups on the 72nd hour of life (p=0.046). The e-NEC score did not show a significant difference in distinguishing between infants with and without NEC. Breastfeeding was found to be protective against NEC (p=0.026).
Conclusion: The GCN score may be a useful tool in predicting NEC in premature infants in clinical practice. The e-NEC score, on the other hand, may be used to raise awareness in nursing follow-ups.

Giriş

Nekrotizan enterokolit (NEK), prematüre yenidoğanlarda ciddi morbidite ve mortaliteye yol açabilen başlıca gastrointestinal acil durumlardan biridir. Bağırsak duvarında inflamasyon, bakteriyel invazyon, gaz oluşumu ve koagülasyon nekrozu ile karakterizedir (1). Genellikle terminal ileum, çekum ve sağ kolon tutulur. Hastalığın evrelemesi ilk olarak Bell tarafından tanımlanmış, daha sonra Walsh ve Kliegman tarafından modifiye edilerek IA'dan IIIB'ye kadar altı basamaklı bir sınıflandırmaya dönüştürülmüştür (2,3). NEK'in etiyopatogenezi multifaktöriyeldir. Prematüre bağırsakta immatürite, inflamatuvar yanıtın aşırı aktivasyonu, intestinal mikrobiyota dengesizliği ve iskemik hasar gibi mekanizmalar öne çıkmaktadır. Anne sütüyle beslenme koruyucu etki sağlarken, formül mama hiperozmolaritesi ve koruyucu faktör eksikliği nedeniyle riski artırır. Bakteriyel aşırı çoğalma ve zayıf mukozal bariyer, inflamasyonun artmasına ve nekroza zemin hazırlar. Ayrıca hipoksi–reperfüzyon hasarı da süreci ağırlaştırmaktadır (4-9).

En sık gestasyonel yaşı (GY) <32 hafta ve doğum ağırlığı <1500 g olan prematürelerde görülür. Türkiye'de 2016–2017 yılları arasında yapılan çok merkezli bir çalışmada çok düşük doğum ağırlıklı bebeklerde NEK insidansı %9,1 olarak bildirilmiştir (10). Dünya genelinde ise bu oran %7 civarındadır. Mortalite %35–50'ye kadar çıkabilmektedir. Özgül semptomlarının olmaması tanıyı geciktirebilir; bu da perforasyon, sepsis ve ölüm gibi ağır sonuçlara yol açabilir (11,12). Bu nedenle risk altındaki bebeklerin erken dönemde tanımlanmasına yardımcı olacak öngörü araçlarına ihtiyaç duyulmaktadır. Literatürde yer alan, bu amaca yönelik geliştirilen GutCheck-NEC (GCN) (Tablo 1) ve e-NEC (Tablo 2) gibi skorlama sistemleri mevcuttur (13,14).

GCN skoru, teorik ve ampirik risk faktörlerinin e-Delphi yöntemiyle içerik geçerliliği sağlanarak oluşturulmuş, <1500 g prematüre bebekler için 8–58 puan aralığında risk skoru üreten bir sistemdir. GY, ırk, doğum yeri, yenidoğan yoğun bakım ünitesi (YDYBÜ)'nin NEK hızı, beslenme şekli, probiyotik kullanımı, enfeksiyon, eritrosit süspansiyonu (ES) transfüzyonu, inotrop kullanımı ve metabolik asidoz gibi parametreleri içerir. Skor ≥36 olan bebekler "çok yüksek riskli" olarak değerlendirilir e-NEC ise beslenme intoleransı ve NEK riskini değerlendiren çok parametreli bir sistemdir. Skorlamada GY, doğum ağırlığı, beslenme tipi, postnatal ve maternal perinatal risk faktörleri yer alır. Toplam skor ≥9 olduğunda bebek NEK açısından yüksek riskli kabul edilir. Sistem, hemşirelik pratiğinde erken farkındalık sağlamayı amaçlamaktadır (13-15).

Gereç ve Yöntem

Bu prospektif gözlemsel çalışma, Ocak 2020 ile Aralık 2021 tarihleri arasında Gazi Üniversitesi Tıp Fakültesi YDYBÜ'de yürütüldü. Çalışmaya, GY≤32 hafta olan prematüre bebekler aile onamı alındıktan sonra dahil edildi. Olguların klinik ve demografik özellikleri ile birlikte NEK gelişimiyle ilişkili olabilecek antenatal ve postnatal değişkenler sistematik olarak incelendi.

Toplanan veriler arasında doğum ağırlığı, doğum şekli, cinsiyet, GY'a göre ağırlık sınıflaması, erken membran rüptürü, koryoamniyonit, antenatal steroid kullanımı, doğumda resüsitasyon ihtiyacı, APGAR skorları, erken ve geç dönem antibiyotik tedavisi, umblikal arter/ven kateterizasyonu ve süresi, patent duktus arteriozus (PDA) varlığı ve İbuprofen tedavisi, ES transfüzyonu, hipotansiyon, inotrop ve steroid kullanımı, solunum desteği tipi, sepsis varlığı ve beslenme şekli yer aldı. NEK tanısı konulan olgularda hastalığın evresi ve tedavi yaklaşımı kaydedildi.

Tüm hastalar için yaşamın belirli günlerinde (3., 7., 14., 21. ve 28. günler) GCN ve e-NEC skorlama sistemleri uygulandı. GCN skorlama sistemine göre alınan puanlar, <20 ise düşük risk, ≥20-32 arası orta risk, ≥33-36 arası yüksek risk ve >36 puan ise çok yüksek risk olarak sınıflandırılmaktadır. Bu çalışmada, veriler hem bu dört risk kategorisiyle ayrı ayrı değerlendirildi, hem de düşük ve orta risk grupları "az riskli", yüksek ve çok yüksek risk grupları ise "çok riskli" olarak birleştirilerek ikili gruplama şeklinde de analiz edildi.

Çalışmamızda kullanılan diğer skorlama sistemi olan e-NEC'e göre, alınan puan ≤5 ise düşük risk, ≥6- 7 orta risk, ≥8 ise yüksek risk olarak sınıflandırılmaktadır. Bu çalışmada, veriler hem bu üçlü risk kategorisine göre analiz edildi, hem de düşük risk grubu "az riskli", orta ve yüksek risk grupları ise "çok riskli" olarak birleştirilerek ikili gruplama şeklinde de değerlendirildi.

Tablo 1. GutCheck NEC Skorlama Sistemi (<1500 gram)

			Puan	
Gestasyonel Yaş 1. Trimester US'ye göre ancak takipsiz gebelikse Ballard ya da Dubowitz skorlamalarına göre	<28 hafta 9 puan	28-31 6/7 8 puan	≥32 0 puan	
Irk Hispanik (İspanyol köken) ya da siyahi ise 2 puan alır, her iki kökenden ise sadece 2 puan alır, diğerleri 0 puan alır	Siyahi 2 puan	Hispanik 2 puan	Diğer Irklar 0 puan	
Başka Yerde Doğum Bebek doğum sonrası herhangi bir zamanda hastanenize başka bir merkezden geldiyse 3 puan alır	Evet 3 puan		Hayır 0 puan	
YDYBÜ NEK Hızı (maksimum 23 puan) 1500 gram altında doğan bebekler için yıllık olarak hesaplanan bir değerdir. Eğer %2 nin altı ise 0 puan alır ünitenin nek hızı bilinmmiyorsa 16 puan verin	%2-4,99 9 puan	%5-7,99 16 puan	%8-11,99 19 puan	>%12 23 puan
Yalnızca Anne Sütü ile Beslenme (maksimum 0 puan) Yaşamın 7. ve 14. Gününde anne sütü ile beslenme olarak tanımlanır. Volüm tanımlanmamıştır. Eğer hem 7. hem de 14. günde bir miktar anne sütü verildiyse total skordan 3 çıkarılır. Yaşamın 14. gününden önce buradan puan çıkarılamaz	Evet -3 puan		Hayır 0 puan	
Probiyotik (maksimum 0 puan) Herhangi bir probiyotik herhangi bir dozda ya da volümde verildiyse 5 puan çıkar	Evet -5 puan		Hayır 0 puan	
Yaşamın 3. gününden sonra kültür pozitif olarak kanıtlanmış enfeksiyon sayısı (maksimum 6 puan)	Bir 4 puan	İki 6 puan	Hiç 0 puan	
ES Transfüzyonu (maksimum 8 puan) Beslenme durumu ve verilen volümden bağımsız olarak ES aldıysa evet, almadıysa hayır	Evet 8 puan		Hayır 0 puan	
İnotropik İlaç Verilen Hipotansiyon Dopamin, dobutamin, milrinon dozdan ve süreden bağımsız olarak verildiyse evet deyin, bir kere evet ise öyle kalacaktır.	Evet 4 puan		Hayır 0 puan	
Metabolik Asidoz (maksimum 3 puan) Doğum sonrası ilk 12 saatten sonra asidozu olduysa evet deyin. Düşük pH, HCO3 <17, normal ya da normale yakın CO2 (pH <7,30) ya da laktat >6,1 mmol/L. Platelet düşüklüğü ve nonspesifik abdominal değişiklikleri olan infantta sonraki dönemde de metabolik asidoz NEC şiddeti ile ilişkili	Evet 3 puan		Hayır 0 puan	
Yaşamın ilk 72 saatinde skorlama yapılır. Sonra 12-24 saatte bir tekrarlanır. Eğer yeni risk faktörleri eklenirse 7, 14, 21 ve 28. günlerde tekrar puanla.				
Düşük Risk: <20 puan Orta Risk: 20-32 puan Yüksek Risk: 33-36 puan Çok Yüksek Risk: >36 puan				
Toplam skor 8-58 arasında değişir				

Tablo 2. e-NEC Skorlama Sistemi	
eNEC Puan	**Değişken Kategoriler ve Risk Faktörleri**
Doğumda Gestasyonel Yaş	(Biri seçilecek)
1	32-36,6/7 hafta(preterm)
2	28-31,6/7 hafta (çok preterm)
3	<28 hafta (ileri derece preterm)
Doğum Ağırlığı	(Biri seçilecek)
0	≥2500 g
1	1500-2499 g (düşük doğum ağırlığı)
2	1000-1499 g (çok düşük doğum ağırlığı)
3	<1000 g (aşırı düşük doğum ağırlığı)
Beslenme	(Uygulananların hepsi seçilecek)
0	Annenin kendi sütü
1	Dönörden anne sütü
1	İnek+İnsan Sütü Takviyesi
3	İnek sütü bazlı formula
Bebekle İlişkili Postnatal Faktörler	(Uygulananların Hepsi Seçilecek)
1	ES transfüzyonu
1	Konjeniatal Kalp Hastalığı ya da PDA
2	Polisitemi (Htc>60)
2	Respiratuar Distres (>24 saat solunum desteği)
3	Doğumda Hipoksi/Asfiksi
3	Sepsis
3	≥5 gün antibiyotik kullanımı
3	IUGR ya da SGA olmak
Anne ile İlgili Perinatal Faktörler	
1	Hamilelikte sigara kullanımı
2	Abrupsiyo Plasenta
2	Klinik Korioamniyonit
2	Gebelikte Madde Kullanımı
2	Erken Membran Rüptürü
2	Uzamış Membran Rüptürü (≥18 saat)
3	Antenatal steroid verilmemiş ya da eksik verilmiş)
3	Bebeğin intrauterin end diastolik akım yokluğu ya da ters akım
Toplam skora göre risk	Skor 1-5: Düşük Risk, Skor 6-8: Orta Risk, Skor ≥8: Yüksek Risk

İstatistiksel Analiz

Verilerin analizi SPSS Statistics v25.0 (IBM Corp., Armonk, NY) programı ile yapıldı normal dağılımı değerlendirmek için Kolmogorov–Smirnov testi kullanıldı. Kategorik değişkenler sayı ve yüzde, sürekli değişkenler ortalama ± standart sapma veya medyan (min–maks) olarak verildi. Gruplar arası karşılaştırmalarda Mann–Whitney U testi ve Ki-kare/Fisher's exact test uygulandı. NEK gelişimini öngören bağımsız risk faktörlerini belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı. $p<0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bu çalışma için, Gazi Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından 22.02.2021 tarihli ve 196 sayılı karar ile onay alındı. Çalışma için herhangi bir dış fon kullanılmadı ve araştırma sürecinde ek maliyet oluşmadı.

Bulgular

Çalışmaya GY ≤32 hafta olan toplam 60 prematüre bebek dahil edildi. Olguların %53,3'ü kız (n=32), %46,7'si erkek(n=28) olup tüm hastalar taburculuk veya eksitus gerçekleşene kadar izlendi. Bebeklerin %18,3'ü 28 haftanın altında, %81,7'si 28–32 hafta aralığında saptandı. Doğum ağırlığı <1500 gram olan bebek oranı %75; sezaryen doğum oranı %98,3 olarak belirlendi (Tablo 3).

Toplamda 14 (%23,3) hastada Bell evresi ≥2 olan NEK gelişti ve bu hastaların %57,1'i evre 2A, %28,6'sı evre 2B ve %14,3'ü evre 3B sınıfındaydı. NEK gelişme zamanı 15,7±9 gün ve DY 31,8±2,4 hafta olarak saptandı. NEK gelişen ve gelişmeyen hastaların demografik ve antenatal özellikleri arasında anlamlı fark saptanmadı (Tablo 4)

NEK gelişen hastalarda invaziv mekanik ventilasyon (İMV) kullanımı (%71,4), NEK gelişmeyenlere (%37) göre anlamlı derecede daha yüksekti (p=0,023). Ayrıca anne sütü ile beslenen hastaların NEK geliştirme riski anlamlı şekilde daha düşüktü (p=0,045); çok değişkenli analizde de bu koruyucu etki istatistiksel olarak anlamlıydı (p=0,026). Dopamin kullanımı, ES transfüzyonu ve PDA varlığı NEK gelişenlerde daha sık gözlendi ancak istatistiksel olarak anlamlı fark saptanmadı.

GCN skoru medyan değerleri 72. Saat, 14. Gün ve 21. Günde NEK gelişenlerde anlamlı derecede daha yüksekti (p değeri: 72. saatte: 0,014; 14. günde: 0,032; 21. günde 0,047). Ancak 7. ve 28. gün skorlarında fark istatistiksel anlamlılığa ulaşmadı (Şekil 1, Tablo 5).

GCN skorlamasına ait düşük ve orta risk grupları "az riskli", yüksek ve çok yüksek risk grupları "çok riskli" olarak birleştirildi 72. saatte "çok riskli" grubunda yer almak,

tek değişkenli analizde NEK gelişimi ile anlamlı bulundu (p = 0,046). Bu sınıflama, NEK gelişimini öngörmede %50 duyarlılık, %78,3 özgüllük, %41,2 pozitif prediktif değer ve %83,7 negatif prediktif değer sağladı. Pozitif olasılık oranı 2,3; negatif olasılık oranı ise 0,6 olarak saptandı (Şekil 2 ve Tablo 6,7).

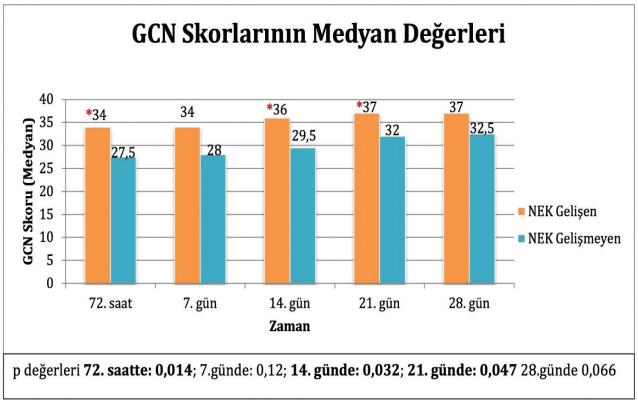
Tablo 3. Demografik Özellikler

Demografik Özellikler		NEK Gelişenler (n=14)	NEK Gelişmeyenler (n=46)	Tüm Hastalar (n=60)	p
Cinsiyet					0,74[a]
	Kız	8 (%57,1)	24 (%52,2)	32 (%53,3)	
	Erkek	6 (%42,9)	22 (%47,8)	28 (%46,7)	
GY					0,71[c]
	<28 hafta	3 (%21,4)	8 (%17,4)	11 (%18,3)	
	28-32 hafta	11 (%78,6)	38 (%82,6)	49 (%81,7)	
Doğum Ağırlığı					0,16[c]
	<1500 gram	13 (%92,9)	32 (%69,6)	45 (%75)	
	≥1500 gram	1 (%7,1)	14 (%30,4)	15 (%25)	
Doğum Şekli					>0,99[c]
	CS	14 (%100)	45 (%97,8)	59 (%98,3)	
	NSVY	0 (%0)	1 (%2,2)	1 (%1,7)	
Doğum Yeri					>0,99[c]
	GÜTF	14 (%100)	45 (%97,8)	59 (%98,3)	
	GÜTF Dışı	0 (%0)	1 (%2,2)	1 (%1,7)	

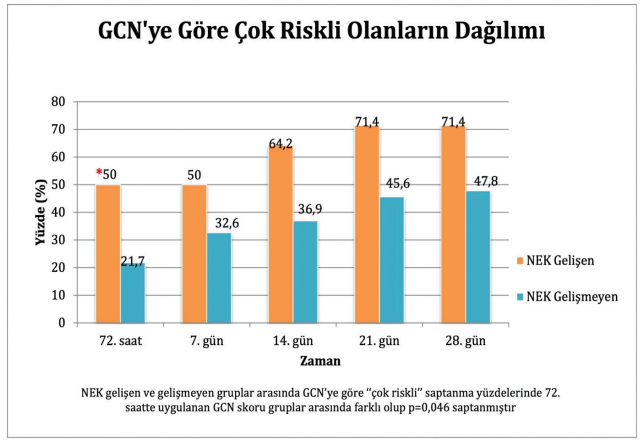
[a]Chi-square
[c]Fisher's Exact Test

Tablo 4. NEK Gelişme Zamanı

Yaş	Ortalama ± Standart Sapma	Ortanca (Min–Maks)
NEK geliştiğinde takvim yaşı (gün)	15,7 ± 9	13,5 (5 – 37)
NEK geliştiğinde düzeltilmiş yaş (hafta)	31,8 ± 2,4	31,5 (28 – 35)



Şekil 1. GCN Skorlarının Medyan Değerleri



Şekil 2. GCN'ye göre Çok Riskli Olanların Dağılımı

Tablo 5. GCN Skoru İstatistikleri				
GCN Skorları ve Risk Grupları	**Tüm Hastalar (n=60)**	**NEK Gelişen (n=14)**	**Diğer (n=46)**	**p**
GCN skor 72. saat				0,014[b]
ortalama±SS	28,7±6,3	32,4±5,4	27,5±6,2	
ortanca (min-max)	28 (16-41)	34 (24-40)	27,5 (16-41)	
GCN skor 72. saat*				0,17[a]
Düşük	4 (6,7)	0 (0)	4 (8,7)	
Orta	39 (65)	7 (50)	32 (69,6)	
Yüksek	9 (15)	4 (28,6)	5 (10,9)	
Çok yüksek	8 (13,3)	3 (21,4)	5 (10,9)	
GCN skor 72 saat*				0,087[c]
Düşük + Orta	43 (71,7)	7 (50)	36 (78,3)	
Yüksek + Çok yüksek	17 (28,3)	7 (50)	10 (21,7)	
GCN skor 7. gün				0,12[b]
ortalama±SS	30,5±7,7	33,4±6,7	29,6±7,8	
ortanca (min-max)	28 (16-45)	34 (24-45)	28 (16-44)	
GCN skor 7. gün*				0,52[a]
Düşük	4 (6,7)	0 (0)	4 (8,7)	
Orta	34 (56,7)	7 (50)	27 (58,7)	
Yüksek	6 (10)	2 (14,3)	4 (8,7)	
Çok yüksek	16 (26,7)	5 (35,7)	11 (23,9)	
GCN skor 7. gün*				0,24[a]
Düşük + Orta	38 (63,3)	7 (50)	31 (67,4)	
Yüksek + Çok yüksek	22 (36,7)	7 (50)	15 (32,6)	
GCN skor 14. gün				0,032[b]
ortalama±SS	31,3±7,9	35,4±7,2	30,1±7,8	
ortanca (min-max)	31,5 (13-46)	36 (21-45)	29,5 (13-46)	
GCN skor 14. gün*				0,28[a]
Düşük	3 (5)	0 (0)	3 (6,5)	
Orta	31 (51,7)	5 (35,7)	26 (56,5)	
Yüksek	10 (16,7)	3 (21,4)	7 (15,2)	
Çok yüksek	16 (26,7)	6 (42,9)	10 (21,7)	
GCN skor 14. gün*				0,071[a]
Düşük + Orta	34 (56,7)	5 (35,7)	29 (63)	
Yüksek + Çok yüksek	26 (43,3)	9 (64,3)	17 (37)	
GCN skor 21. gün				0,047[b]
ortalama±SS	32,6±7,9	36,3±7,3	31,4±7,7	
ortanca (min-max)	33,5 (13-46)	37 (21-45)	32 (13-46)	
GCN skor 21 gün*				0,29[a]
Düşük	3 (5)	0 (0)	3 (6,5)	
Orta	26 (43,3)	4 (28,6)	22 (47,8)	
Yüksek	12 (20)	3 (21,4)	9 (19,6)	
Çok yüksek	19 (31,7)	7 (50)	12 (26,1)	
GCN skor 21. gün*				0,091[a]
Düşük + Orta	29 (48,3)	4 (28,6)	25 (54,3)	
Yüksek + Çok yüksek	31 (51,7)	10 (71,4)	21 (45,7)	

Tablo 5. Devam				
GCN Skorları ve Risk Grupları	**Tüm Hastalar (n=60)**	**NEK Gelişen (n=14)**	**Diğer (n=46)**	**p**
GCN skor 28. gün				0,066[b]
ortalama±SS	32,8±8,1	36,3±7,3	31,7±8,1	
ortanca (min-max)	34 (13-46)	37 (21-45)	32,5 (13-46)	
GCN skor 28. gün*				0,38[a]
Düşük	4 (6,7)	0 (0)	4 (8,7)	
Orta	24 (40)	4 (28,6)	20 (43,5)	
Yüksek	11 (18,3)	3 (21,4)	8 (17,4)	
Çok yüksek	21 (35)	7 (50)	14 (30,4)	
GCN skor 28. gün*				0,12[a]
Düşük + Orta	28 (46,7)	4 (28,6)	24 (52,2)	
Yüksek + Çok yüksek	32 (53,3)	10 (71,4)	22 (47,8)	

*n (parantez içinde % belirtilmiştir)
[a]Chi-square NEK gelişen ve gelişmeyen hastalar
[b]Mann-Whitney U NEK gelişen ve gelişmeyen hastalar
[c]Fisher's Exact Test NEK gelişen ve gelişmeyen hastalar

Tablo 6. GCN'de Çok Riskli Saptanma Tek Değişkenli ve Çok Değişkenli Analiz				
NEK Gelişimi Risk Faktörleri	**Tek Değişkenli Analiz**		**Çok Değişkenli Analiz**	
	OR (%95 GA)	**p değeri**	**OR (%95 GA)**	**p**
GCN 72 saat (Y+ÇY→D+O)	3,60 (1,02-12,70)	0,046	1,20 (0,29-13,91)	0,49

OD: Odds ratio, GA: Güven aralığı
Y: yüksek risk, ÇY: çok yüksek risk, D: Düşük risk, O: Orta risk

Tablo 7. GCN 72. Saatteki Testin Geçerlilik ve Güvenilirliği						
Risk Kategorisi	**Sensitivite (%)**	**Spesifite (%)**	**Pozitif Prediktif Değer (%)**	**Negatif Prediktif Değer (%)**	**Pozitif Olabilirlik Oranı**	**Negatif Olabilirlik Oranı**
GCN 72 saatte çok riskli (yüksek+ çok yüksek risk) kategori	50	78,3	41,2	83,7	2,3	0,6

Hastalar e-NEC skoru açısından değerlendirildiğinde, NEK gelişen tüm hastalar (%100) ve gelişmeyenlerin büyük çoğunluğu (%97,8) yüksek risk grubunda yer aldı ve iki grup arasında aldıkları puan ve bulundukları kategori açısından istatistiksel anlamlılık saptanmadı.

Tartışma

Bu çalışmanın en temel bulgusu, bir klinik risk skorlaması olan GCN, yaşamın ilk 72. saati gibi çok erken bir dönemde NEK gelişenlerde anlamlı olarak daha yüksek bulunmasıdır. Bu sonuç, GCN skorunun NEK riski altındaki hassas prematüre bebek popülasyonunda potansiyel bir erken uyarı sistemi olarak kullanılabileceğini göstermektedir. Böyle bir erken tespit, klinisyenlere beslenme stratejilerini düzenleme, daha yakın izlem yapma ve koruyucu önlemleri zamanında devreye sokma gibi proaktif adımlar atma imkânı tanıyabilir.

Bulgularımız, Gephart ve ark. (14) GCN skorunu geliştirdiği ve NEK öngörüsündeki etkinliğini gösteren öncü çalışmalarını destekler niteliktedir (13-16). Benzer şekilde, Behera ve Menan (17) yakın zamanda Kuzey Hindistan'da yaptığı prospektif bir çalışma da GCN skorunun 86. saatte %88,9'luk bir hassasiyetle NEK'i öngördüğünü ve skorun farklı coğrafi popülasyonlarda da değerli bir araç olduğunu teyit etmiştir. Bizim araştırmamız ise, skorun etkinliğini yaşamın ilk üç günü gibi kritik ve spesifik bir zaman diliminde ortaya koyarak bu çalışmalara ek bir kanıt sunmaktadır. Ayrıca, çalışmamızda GCN skorunun "az riskli" ve "çok riskli" şeklinde basitleştirilmiş bir sınıflandırmayla etkinliğin olduğu gösterilmiştir. Bu bulgu, yoğun bakım ünitelerindeki pratik ve hızlı kullanım potansiyelini artırmaktadır.

e-NEC skoru ise çalışmamızda farklı risk grupları arasında ayrım sağlayamadı. GY ≤32 hafta olan hastaların neredeyse tamamı yüksek riskli grupta yer aldı, NEK gelişen ve gelişmeyen gruplar arasında anlamlı fark görülmedi. Bu nedenle, e-NEC skoru NEK gelişimini öngörme açısından yeterli ayırıcı güce sahip görünmemektedir. Ancak klinik hemşirelik pratiğinde farkındalığı artırma yönüyle faydalı olabilir.

Ayrıca bulgularımız literatürle benzer şekilde İMV kullanımı, dopamin uygulaması, düşük doğum ağırlığı, anne sütü ile beslenmeme gibi faktörlerin NEK gelişimiyle ilişkili olabileceğini göstermektedir (18).

Çalışmanın Kısıtlılıkları

Çalışmamızın başlıca kısıtlılıklarından biri, GCN skorunun özgün olarak <1500 gram doğum ağırlığına sahip bebekler için geliştirilmiş olmasına rağmen, örneklemimize ≥1500 gram olan olguların da dahil edilmesidir. Ancak NEK yalnızca <1500 gram bebeklerle sınırlı olmayıp daha yüksek doğum ağırlıklı prematürelerde de gelişebildiğinden, bu hastaların dışlanmaması klinik açıdan uygun bulunmuştur. Bununla birlikte, çalışmanın tek merkezli ve sınırlı örneklemle yürütülmüş olması, bazı ilişkilerin istatistiksel anlamlılığa ulaşamamasına neden olmuş olabilir

Sonuç

GCN skoru, prematüre bebeklerde özellikle yaşamın ilk günlerinde NEK gelişimini öngörmede kullanılabilecek pratik ve anlamlı bir araçtır. e-NEC skoru ise NEK gelişimi açısından yeterli ayrım sağlayamamakla birlikte, hemşirelik izlemlerinde riskli bebeklere dikkat çekmek amacıyla kullanılabilir. Prematürelerde NEK gelişimini önlemede, invaziv girişimlerin azaltılması, anne sütüyle beslenmenin desteklenmesi ve yüksek riskli bebeklerin yakın izlenmesi kritik öneme sahiptir. Geniş örneklemli, çok merkezli ileri çalışmalara ihtiyaç vardır.

Etik

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Dipnot

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Effectiveness of Antiseizure Medications and the Clinical Utility of the Spike-Wave Index in Children Diagnosed with SeLECTS With and/or Without ADHD

DEHB Eşlik Eden ve Etmeyen SeLECTS Tanılı Çocuklarda Antiepileptik İlaçların Etkinliği ve Spike-Wave İndeksinin Klinik Faydası

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Abstract

Introduction: This study aims to investigate the clinical and electroencephalographic characteristics of children diagnosed with SeLECTS (Self-limited epilepsy with centrotemporal spikes), comparing the effectiveness of antiseizure medications (ASMs) based on the presence or absence of Attention Deficit Hyperactivity Disorder (ADHD), and evaluating the prognostic value of the spike-wave index (SWI).

Materials and Methods: A retrospective review was conducted on 914 children diagnosed with SeLECTS between 2005–2023. A total of 542 patients who met the inclusion criteria were followed for a minimum of three years with at least three EEG recordings. SWI values were analyzed according to the type of ASM valproic acid (VPA), carbamazepine (CBZ), and levetiracetam (LEV), ADHD status, and age. The predictive power of SWI for EEG improvement and seizure control was assessed using ROC curve analysis.

Results: The mean age was 8.18±3.35 years; the male-to-female ratio was 1.47:1. Onset before age five was associated with more frequent seizures (p=0.003). VPA was more effective for EEG improvement, while LEV provided better seizure control. SWI was significantly higher in children with ADHD. SWI values decreased over time. ADHD prevalence was 19.9%.

Conclusion: SWI is a valuable tool for assessing treatment response. Epilepsy burden is higher in patients with ADHD. VPA is superior in EEG normalization, whereas LEV offers more effective seizure control.

Keywords
SeLECTS, attention deficit hyperactivity disorder, antiseizure medications, spike-wave ındex, EEG, childhood epilepsy

Öz

Giriş: Bu çalışma, SeLECTS (Self-limited epilepsy with centrotemporal spikes) tanısı almış çocukların klinik ve EEG özelliklerini incelemeyi, dikkat eksikliği hiperaktivite bozukluğu (DEHB) eşlik edip etmediğine göre antiepileptik ilaçların (AEİ) etkinliğini karşılaştırmayı ve spike-wave indeksinin (SWI) prognostik değerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: 2005-2023 yılları arasında SeLECTS tanısı almış 914 çocuk retrospektif olarak değerlendirildi. Dahil edilme kriterlerini karşılayan 542 çocuk çalışmaya alındı. Hastalar en az üç yıl boyunca, üç EEG kaydı ile takip edildi. SWI değerleri, AEİ türü valproik asit (VPA), karbamezapin (CBZ, levetirasetam (LEV), DEHB varlığı ve yaşa göre analiz edildi. SWI'nin EEG iyileşmesi ve nöbet kontrolü üzerindeki öngörü gücü ROC eğrisi ile değerlendirildi.

Anahtar kelimeler
SeLECTS, dikkat eksikliği ve hiperaktivite bozukluğu, antinöbet ilaçları, diken-dalga indeksi, EEG, çocukluk çağı epilepsisi

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Bulgular: Ortalama yaş 8.18±3.35 yıl; erkek/kız oranı 1.47:1 idi. Beş yaş altı başlangıç, daha sık nöbet ile ilişkiliydi (p=0.003). VPA EEG iyileşmesinde; LEV ise nöbet kontrolünde daha etkiliydi. DEHB'li çocuklarda SWI daha yüksekti. Zamanla SWI değerlerinde azalma izlendi. DEHB sıklığı %19.9'du.
Sonuç: SWI, tedavi yanıtını değerlendirmede faydalı bir araçtır. DEHB eşlik eden hastalarda epilepsi yükü daha fazladır. VPA EEG normalleşmesinde, LEV nöbet kontrolünde daha başarılıdır.

Introduction

Attention deficit and hyperactivity disorder (ADHD) is reported as the most common disorder accompanying epilepsy in preschool and school-age children (1-6). It has been reported that the risk of developing ADHD in children with epilepsy is 2.5-5.5 times higher than in healthy children (7). Literature also indicates that epilepsy symptoms are more serious and seizures start at an earlier age in patients with epilepsy who develop ADHD (4,5). The prevalence of ADHD in Self-limited epilepsy with centrotemporal spikes (SeLECTS) is higher than in other epilepsies. Of note, the prevalence of ADHD in such patients was reported as 64.9% in one study and 24.6% in another study, while it was much higher than 3.7%-5.6% in an epidemiological survey (5,6).

In recent years, the clinical significance of SWI in children diagnosed with SeLECTS has been increasingly studied (8). Yılmaz et al. (9) demonstrated its prognostic value based on a ten years follow-up, while our study showed that SWI was significantly higher in patients with comorbid ADHD. The relationship between epilepsy and ADHD comorbidity and neuroimaging findings was examined by Rubinstein et al. (10) who proposed standard neurophysiological mechanisms. Furthermore, the ADHD prevalence of 19.9% identified in our cohort is consistent with the findings of Yuen et al. who systematically reviewed ADHD prevalence in children with epilepsy (11).

Regarding the choice of antiseizure medications, Wirrell et al. (12) emphasized in their systematic review that LEV is particularly effective for seizure control, whereas VPA is more advantageous for EEG normalization. These findings are consistent with the results of our study.

In this study, we aimed to assess the effectiveness of ASM based on EEG parameters (SWI% and SW resolution velocity) and the outcome predictors in a large cohort and prevalence of monotherapy using drug follow-ADHD in SeLECTS

Materials and Methods

Study Settings and Design

We collected clinical and electrographical data regarding the children diagnosed with SeLETCS having at least three EEG recordings during at least three-years follow-up from pediatric neurology center from 2005 to January 2023 in our region.

Total 914 patients demographic and clinical characteristics including age, gender, fever history, seizure type and frequency, family history, and diagnosis and treatment were retrieved from the clinical records of the patients. The patients and their parents completed the general information forms and informed consent forms under the guidance of clinicians.

Inclusion criteria were as follows patients who had their first seizure at the age of 3-15 years, had normal findings on neurological examination and magnetic resonance imaging (MRI), had both initial and follow-up EEGs, and had been followed up for at least three years. Exclusion criteria included seizure Electrical Status Epilepticus during Sleep (ESES) initial EEG (n:74) or presence of Landau-Kleffner syndrome (LKS, n:12), abnormal MRI findings (n:58), abnormal neurodevelopmental status (n:35), and pre-emptive unfollowed EEG examination (n:35) and polytherapy SeLETCS (n:158). Based on these exclusion criteria, 542 patients were recruited into the study.

Diagnosis of SeLECTS and ADHD

We used the following criteria when diagnosing SeLECTS. The clinical and accurate history was to establish the diagnosis: (1) characteristic symptoms (2) presence of motor seizures, (3) normal neurological examination and brain MRI, (4) normal laboratory examination and metabolic screening, and (5) an age of onset between 3-15 years. The EEG criteria used to support the diagnosis of SeLECTS were patients diagnosed according to the International League Aganist Epilepsy (1989) SeLETCS epilepsy diagnostic criteria; It was taken as the dipole indicating a positivity in the general centropemporal region of the waves and within the boundaries of the borders and in the crest or frontal region.

Edition (DSM-IV) criteria based on the clinical interview and diagnostic tests at the Child Adolescent Mental Health and Diseases outpatient clinic, he was diagnosed with ADHD according to DSM-IV-TR criteria. The patients' file records were examined retrospectively. Age, gender, age of first and last seizure, age at diagnosis of ADHD, time of antiseizure

medications (ASMs) initiation, seizure characteristics, AED and other treatments used, electroencephalography (EEG) and brain magnetic resonance imaging (MRI) findings, the relationship between ADHD treatment and seizures, and the time between the onset of ADHD and epilepsy were recorded. In addition, in patients with epileptic activity at the first EEG findings and who underwent periodic EEG monitoring at intervals of 1-6 months, EEG recovery times were determined based on the time when the first normal EEG examination was detected.

542 patients who were followed up with the diagnosis of SeLECTS with/without ADHD, receiving monotheraphy; those who used single medication due to ADHD (n: 108) and those who were followed without medication (n: 434) patients were divided into three groups according to their ages: (i) <5 years, (ii) 5-10 years, and (iii) >10 years. The study group were also categorized seizure burden with seizure frequency (I) >2 seizures and (II) >5 seizures. Seizure outcome was evaluated based on the reduction in seizure frequency over 6-month periods: (1) 50% reduction and (2) seizure-free (complete response).

ASM Drug Initiation Protocol

The following ASMs were reported as initial monotherapy in the patient evaluation chart: CBZ 10-30 mg/kg/day, VPA 10-30 mg/kg/day, and LEV 20-60 mg/kg/day. An ASMs (monotherapy) was administered if the frequency of seizures persisted despite the administration of the full dose of the initial drug.

EEG Recordings

Departmental EEG recording protocols were evaluated each center. Then the following international basic recording parameters were reported. An international 10-20 electrode placement system was used (Nihon Kohden, Tokyo, Japan). Electroencephalograms were recorded by placing scalp electrodes with silver-silver chloride discs according to the international 10-20 system, and recordings were made while awake, drowsy, and asleep (at least 40 minutes with eyes closed, intermittent photic stimulation, and hyperventilation). Response to ASM was evaluated based on the differences among the initial (baseline), second (first year), and third (second year) EEG recordings. EEG records were evaluated by experts with at least ten years experience. The recordings of the spikes occurring during sleep were evaluated as follows: a. Spike-wave-index (SWI) quantified the frequency of spikes in NREM sleep EEG monitoring. SWI was calculated as follows: the number of seconds in which one or more surges were present in the first 30 minutes of non-rapid movements of the first sleep cycle divided by 3600 and then multiplied by 100. Results were expressed as a percentage; b. In the storage of serial EEG according to age; c. Duration and threshold value of response in EEG,; d. EEG recordings in antiepileptic response.

Statistical Analysis

Data analysis was performed using SPSS 23.0 for Windows (Armonk, NY: IBM Corp.). Continuous variables were expressed as mean, standard deviation (SD), comprehensive content, minimum, and maximum and categorical variables were expressed as frequencies (n) and percentages (%). Normal distribution of data was analyzed using one-sample Kolmogorov-Smirnov test, which found that the data was nonnormally distributed. Independent groups were compared using Mann Whitney U test and Kruskal Wallis test with Bonferroni correction. They are dependently estimated data. The metric measurements were tested with the metric values. Preferred assistance program of their first age with the height of Spi in their karaaWs in their observations in their taranaW Spi, and analysis of seizures in the target in seizure prediction with the Receiver Operating Characteristics (ROC) curve and the target. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the cutoff values were calculated. A p value of <0.05 was considered significant.

This study was approved by the Clinical Research Ethics Committee of Karadeniz Technichal Universty under the decision numbered 2023/512, and was conducted as a single-center, retrospective study.

Results

Demographcis

Table 1 presents demographic and clinical characteristics of children (N=542) with childhood epilepsy, centrotemporal spikes (SeLECTS). Mean age was 8.18±3.35 (range, 3-15) years and the male-to-female ratio was 1.47:1. No significant difference was found between the genders with regard to seizure onset age (male 7.80±3.35 years, female 8.08±3.07 years; p=0.502). Family history was positive in 17.1% of the patients.

Table 1. The comparison of demographic and EEG characteristics (N=513) with using monotherapy in SeLECTS's patients with /without ADHD

Monotherapy	**ADHD -**	**ADHD +**	**P**
Demographic and EEG	**434 (78.5%)**	**108 (%19.9)**	
Age (years)	9.3±2.3	8.8±5.3	**0.003**
Female/Male	167/238	39/69	
Age at onset of seizures (months)	10.2±3.8	8.1±4.3	**0.004**
Family history of epilepsy	65 **(14.4%)**	17 **(15.7%)**	0.320
Age at onset of seizures (years) <5 5-10 >10	 34 (6.0 %) 316 (75.5%) 85 (18.5%)	 4 (3.8 %) 75 (69.4%) 29 (26.8%)	 **0.007** 0.060 **0.014**
Seizure semiology Sleep / wakeful	269 (66.4%)/136 (33.6%)	85 (66.6%)/23 (33.4)	**0.0040**
İnitiation time of ASM types (months, mean ± SD)	70.6±0.9	45.1±12.9	0.005
EEG discharges on initial record Unilateral Bilateral	 135 (33.3%) 270 (66.7%)	 32 (29.7%) 76 (70.3%)	 **0.023** **0.005**
EEG improvement with SWI % ≥50% <50%	 37.2 72.8	 69.3 20.7	 **0.008** 0.060

SWI: Spike-wave index

ASM selection

Most commonly preferred initial ASM was CBZ (n=266; 49.1%), followed by VPA (n=119; 21.9%) and LEV (n=157; 29.0%). In hospitalized patients receiving CBZ, VPA, and LEV as the initial drug, respectively.

Monotherapy

Monotherapy was administered in 64.6% of children aged below 5 years, in 75.9% of children aged 5-10 years, and in 85.6% of children aged over 10 years. Seizure control was achieved with monotherapy in 80.2% of patients aged 5-10 years. Table 1 presents the clinical and electroencephalographic characteristics of the groups receiving monotherapy.

Seizure Semiology and Seizure Burden

Most of the patients (n=473; 78.3%) had their first seizure during sleep. Additionally, 19.3% of the patients who had seizures more than twice a year during their follow-up, who were initiated on drug therapy, those who received monotherapy (p=0.000). Patients that had their first seizure before 5 years of age had more repetitive number of seizures in sleep than the other patients (p=0.000). An analysis of the drugs used and the frequency of seizures indicated that 75.7% of those who had seizures 2-5 times a year were in the LEV group, while the frequency of seizures was higher in the CBZ group compared to other groups (p<0.001). Table 2 presents the comparison of monotherapy groups with respect to ASM response and EEG.

EEG Improvement

In the LEV group, 86.9% of the patients achieved seizure control with ASMs. Additionally, LEV was superior to CBZ about its effectiveness in controlling seizures and reducing the burden of interictal discharges, while VPA achieved the highest EEG response (60.8%). On the other hand, the presence of bilateral EEG findings was the most important risk factor for VPA therapy and patients that received VPA therapy had frequent bilateral discharges and their SWI values were ≥50%. Mean SWI value before the initiation of monotherapy was 31.7±29.7, 33.9±28.8, and 23.5±19.6 in the VPA, CBZ, and LEV groups, respectively, and the mean SWI value at the end of the second year in subsequent EEG recordings showed a significant decrease in the LEV group (17.9±14.0) compared

to the others (p=0.000). SWI increased with decreasing age (p=0.000). The effect of baseline SWI value on seizure recurrence varied with age, whereby baseline SWI value was higher in patients with a lower age at onset (Table 3). On the other hand, baseline SWI value decreased in subsequent EEG recordings and was lower in higher ages, children receiving monotherapy are shown in Figure 1.

The Predictive Value of SWI for ADHD

In our study, ADHD was observed in 19.9% (n=108) of the patients followed up with the diagnosis of SeLECTs. Of note, ADHD was present in 16.8% of girls vs 21.9% of boys (p=0.120). There was no relationship between the coexistence of AHDH and family history, epilepsy history, and number of siblings. On the other hand, ADHD was detected in 19.2% of the patients diagnosed before the age of five years, in 72.5% of patients diagnosed between 5-10 years of age, and in 8.3% of children diagnosed after the age of 10 years. On the other hand, ADHD was detected in 37.0% (n=40) of patients using VPA, in 41.6 % (n=45) of patients using CBZ, and in 21.2 % (n=23) of patients using LEV (p=0.410, p=0.001, and p=0.041, respectively). Additionally, patients with ADHD had a higher

Table 2. The comparison of selected drugs with respect to seizure outcome and EEG parameters in SeLECTS patient with/without ADHD

	VPA (n=111)		**CBZ (n=269)**		**LEV (n=133)**		**P**
			ADHD (-/+)				
Seizure frequency (N)							
<5 per year	60/35		136/65		91/39		
>5 per year	10/6		43/25		2/1		
Seizure outcome							
Seizure-free achivement time (months)	32.7±19.0	36.9±28.0	26.9±14.8	29.8±21.0	22.4±15.2	16.9±8.0	p^1:0.208, p^2:**0.023**, p^3:**0.013**
Overall seizure outcome	86 (88.6%)		208 (86.6%)		108 (**95.5%**)		
EEG Improvement							
EEG remission time (months)	23.9±11.9	26.9±9.2	18.9±17.6	16.7±10.5	17.4±15.3	18.9±12.9	p1:0.025, p^2:0.126, p^3:0.212
Spike-free EEG response (at 2years of ASM)	19 (**19.5%**)		25 (10.4%)		18 (15.9%)		p^1:<**0.001**, p^2:0.07 p^3:<**0.001**
Overall EEG remission rate	59 (**60.8%**)		143(34.2%)		63 (55.7%)		

(*) Spike-wave clearence in the two-year follow-up EEG, VPA: Valproic acid, CBZ: Carbamazepine, LEV: Levetiracetam

Table 3. Spike wave index (SWI) evolution in serial EEG; SeLECTS patient with/without ADHD

Monotherapy	**ADHD - (n=434)**				**ADHD + (n=108)**				
Age groups (n)	**Baseline SWI**	**First-year SWI**	**Second-year SWI**	**p**	**Age groups (n)**	**Baseline SWI**	**First-year SWI**	**Second-year SWI**	**p**
<5 years (n=108)	31.3±13.8	31.8±15.8	26.0±16.5	0.000	**<5 years (n=27)**	34.16±10.5	41.7±33.0	35.5±15.0	0.005
5-10 years (n=254)	29.0± 17.3	27.5± 16.5	20.0± 15.8	0.000	**5-10 years (n=63)**	37.6±18.6	38.1±34.6	34.2±12.2	0.002
>10 years (n=72)	28.4±14.4	26.4±10.0	26.6±14.6	0.000	**>10 years (n=18)**	20.9±19.4	30.2±20.4	35.0±16.3	NS
P	0.042	0.024	0.032		**P**	0.012	0.019	0.550	

SWI: Spike-wave index, NS: non-significant. (Ÿ) p<0.05

seizure frequency (p = 0.06) and a more extended seizure-free period (p=0.005), but when compared in terms of seizure reduction and EEG regression time, especially <5 years old patients, the VPA-using group showed faster seizure freedom and long-term EEG improvement (p=0.005). In subsequent EEG recordings of patients with ADHD, SWI was higher in the first-year (34.8±15.2) and third-year (21.25±12.25) recordings compared to patients without ADHD (p=0.0035). In children aged below five years, SWI was higher in patients with ADHD than in patients without (p=0.0038). Figure 1 illustrates the importance of the diagnostic value of SWI in subsequent EEG recordings in patients with ADHD. SWIs of patients with ADHD decreased significantly regardless of age, and the absence of ADHD findings in patients with decreased SWI values on subsequent EEG recordings was diagnostic (Figure 1).

Discussion

SeLECTS is a benign inherited epileptic syndrome characterized by age-dependent seizure semiology and EEG characteristics (1). This study evaluated the clinical features of patients with SeLECTS as well as their frequency of seizures, semiology, treatment decisions, EEG characteristics, and ASM selection trend in a large patient group. The results indicated that patients who had their first seizure before 5 years of age had more number of seizures than the other age groups. Among the ASMs, VPA group had the shortest time to the achievement of 50% reduction in seizures with monotherapy. Additionally we also investigated the predictive value of interictal paroxysmal discharges (spike-wave index -SWI) for seizure outcome, and differentiating antiseizure medications. SWIs of patients with ADHD decreased significantly regardless of age, and the absence of ADHD findings in patients with decreased SWI values on subsequent EEG recordings was diagnostic.

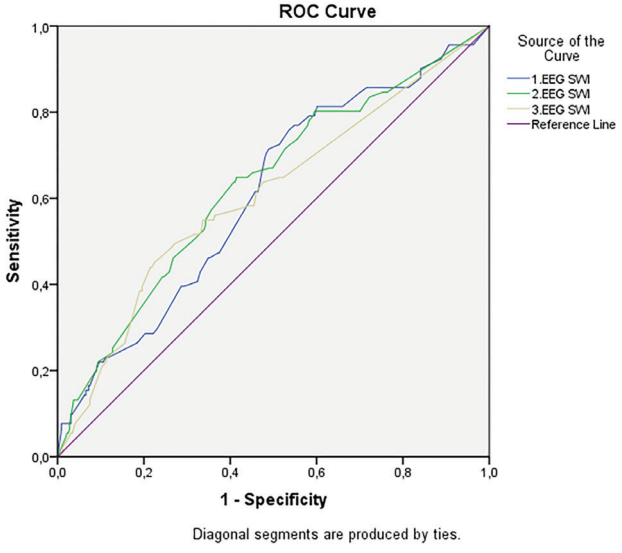

Figure 1. SWI evolution in serial EEG recording of children receiving monotherapy therapy in ADHD patients.
(1.EEG SWI: AUC: 0.607 [CI: 0.552-0.672], Cutoff value:33.5 Sensitivity: 59.8 Specificity: 59.2 PPD: 26.7 NPD: 85.6; 2.EEG SWI: AUC: 0.630 [CI: 0.564-0.696], Cutoff value:10.0 Sensitivity: 61.5 Specificity: 54.1 PPD: 26.9 NPD: 83.6; 3.EEG SWI: AUC: 0.607 [CI: 0.538-0.675], Cutoff value: 3.5 Sensitivity: 69.2 Specificity: 40.2 PPD: 22.4 NPD: 83.9)

To our knowledge, there are only a handful of studies demonstrating the onset and recurrence of seizures and the follow-up and course of rolandic discharges in SeLECTS with respect to seizure outcome and cognitive outcome (9-13). The age at the onset of seizures is significant for the development of brain plasticity, with the ages of 5-6 years constituting the most critical period (14-16). Arhan et al. (13) found that high-amplitude paroxysmal EEG discharges were most commonly seen in the age group of 6-8 years and there was a significant relationship between these discharges and seizure recurrence. In our study, patients that had their first seizure before 5 years had more seizures than the other patients (22.1%). Moreover, it was also noted that SWI decreased with increasing age. Taken together, the findings of our study indicated that seizure recurrence and the high frequency of paroxysmal discharges are dependent on patient age in children with SeLECTS. On the other hand, the presence of bilateral EEG findings was the most important risk factor for ADHD in monotherapy, and patients that received therapy had frequent bilateral discharges, use who have seizure but maximum drug doses and their SWI values were ≥50%. EEG regression time, especially <5 years old patients, the VPA-using group showed faster seizure freedom and long-term EEG improvement (p=0.005). In subsequent EEG recordings of patients with ADHD, SWI was higher in the first-year (34.8±15.2) and third-year (21.25±12.25) recordings compared to patients without ADHD (p=0.0035). In children aged below five years, SWI was higher in patients with ADHD than in patients without (p=0.0038).

Several studies have examined the differences among the drugs used in SeLECTS with regard to their effects on seizures and EEG (17-25). One of these studies evaluated the effects of LEV on EEG in SeLECTS and showed that it reduced epileptiform discharges (21,22). Literature indicates that children with similar bilateral findings on EEG respond well to VPA, CBZ, and OXC, while children with unilateral EEG findings respond better to CBZ or OXC (23). It has also been shown that low-dosage VPA and LEV monotherapies

are equally effective in controlling seizures and that VPA is more effective than LEV in improving electrophysiological abnormalities in children (20). CBZ is the initial drug of choice in children diagnosed with SeLECTS, while VPA is the first choice of monotherapy in pediatric patients with high SWI values (8). In our study, the selection of a patient population with a lower seizure frequency and a lower SWI value might have led to faster remission in the LEV group. In SeLECTS patients diagnosed with ADHD, bilateral SWIs of patients in EEG discharge and being younger than 5 years of age are important in choosing VPA receiving monotherapy.

SWI, a quantitative scoring system of the EEG calculated during NREM sleep. SWI is frequently used in the evaluation of electroencephalogram in CSWS patients (25-29). SWI can be highly useful in the follow-up period, particularly in patients with neuronal network problems, intense discharges, and high percentile rates. Accordingly, the present study aimed to investigate the utability of SWI in showing the intensity and load on EEG in SeLECTS patients (8). Among the studies investigating the suppression of interictal EEG abnormalities with drugs in patients with recurrent seizures, there have been very few studies examining the differences among the drugs with respect to the changes in the localizations of EEG patterns in subsequent EEG recordings (29). A study by Tekgul et al. (8) found no significant difference among the drugs with regard to EEG features (sharp waves and ripples [SWRs], localization, and topography) both before ASM treatment and just before ASM discontinuation. However, the rate of spike was more pronounced in the second year of treatment in children receiving monotherapy and in the third year of treatment in children receiving dual therapy. Kanemura et al. (20) evaluated EEG data based on spike activity in minutes, number of spikes, and localization and reported that the EEG response in patients that received LEV was faster than those who received CBZ/VPA. Our study had a remarkably larger patient population than those of other studies and, to our knowledge, it is the first study in the literature to analyze SeLECTS patients with SWI. Although SWI measured before the initiation of monotherapy was higher in the VPA group, it showed a significant decrease in the LEV group in subsequent EEG recordings compared to other groups. Moreover, LEV had the lowest SWI value (≤5.5) for the prediction of initial drug to be used in patients followed up for RE, which could be a reason as to why the LEV group had better seizure control and EEG response compared to other groups.

The present study also aimed to find clues about the relationship between ADHD and SeLECTS in children coexisting with these diseases. The prevalence of ADHD in SeLECTS is reported with higher rates when compared to other epilepsies. Of note, a previous study reported the prevalence of ADHD in SeLECTS patients as 64.9% (19). In our study, ADHD was present in 19.9% of the patients that were followed up with the diagnosis of SeLECTS. ADHD symptoms are reported to worsen as the age of seizure onset decreases (29). In addition, in epileptic patients, the presence of epileptic discharge or electrographical seizures on EEG in the periods when no or minimal seizures are seen may impair the attention and cognitive functions of the patients (26,29). Our study also examined the seizure status and the abnormalities in subsequent EEG recordings in patients with both ADHD and SeLECTS. In line with the literature both the seizure frequency and SWI were higher in children with ADHD in our patients. A previous study compared patients with temporal lobe epilepsy, a form of focal epilepsy, and patients with idiopathic generalized epilepsy with respect to seizure types and reported that attention control was more impaired in patients with temporal lobe epilepsy (29). In our study, patients with ADHD had more frequent seizures and had a more extended seizure-free time, while there was no significant difference between these two groups with regard to seizure reduction and EEG remission. It has also been shown that the presence of <50% EEG discharges in the NREM phase at the time of diagnosis, male gender, and coexistence of bilateral discharges. The fact that VPA is a frequently used ASM in ADHD with SeLECTS might be associated with the high prevalence of SeLECTS in our patients; however, the age at the first seizure was lower in the VPA group. Even so, no significant difference was found between VPA and other ASMs with regard to seizure control, EEG recovery time, ADHD onset age, and the coexistence of SeLECTS and ADHD. Age at the diagnosis of ADHD differs significantly among patients coexisting with ADHD and SeLECTS (18). In our study, it was observed that epilepsy and the requirement of ASMs were concentrated in two periods: early childhood and school-age. Additionally, keeping in mind the coexistence of these two diseases will contribute to the early diagnosis and treatment of patients. Although it is well known that ADHD can also be seen in preschool children, this disease is difficult to diagnose in this age group since it can be confused with normal age-related behaviors (23). Accordingly, clinicians need to be aware of the coexistence of these two diseases, particularly in younger age groups. Additionally, we suggest that the measurement of SWI on EEG may be important for clinical follow-up for the prediction and follow-up of these two diseases (30). In our study, SWI was higher in children aged below 5 years with ADHD than in those without. In

addition, SWIs were significantly higher in patients with ADHD compared to those without. On the other hand, SWIs of patients with ADHD decreased significantly regardless of age, and the absence of ADHD findings in patients with decreased SWI values on subsequent EEG recordings was diagnostic. Accordingly, it is necessary to determine the specific features of the treatment and prognosis as well as the clinical and EEG parameters in children coexisting with SeLECTS and ADHD. SWIs of patients with ADHD decreased significantly regardless of age, and the absence of ADHD findings in patients with decreased SWI values on subsequent EEG recordings was diagnostic.

In recent years, the clinical importance of the Spike-Wave Index (SWI) in children diagnosed with SeLECTS has been increasingly investigated. Yilmaz et al. (9), through a ten years follow-up study, demonstrated the prognostic value of SWI, while our study showed that SWI levels were particularly higher in patients with comorbid ADHD (8,30). The association between epilepsy and ADHD in terms of neuroimaging was evaluated by Rubinstein et al. (10), who suggested standard neurophysiological mechanisms. Furthermore, Yuen et al. (11) systematically reviewed the prevalence of ADHD in children with epilepsy, supporting the 19.9% prevalence found in our study. Regarding the choice of antiseizure medications, a systematic review by Wirrell et al. (12) emphasized that LEV is more effective in seizure control, while VPA is superior in EEG normalization. These findings are consistent with the results of our current study.

Study Limitations

Our study has some limitations of the retrospective studies; first: the selection characteristics of ASM in children with SeLECTS was not based on a standardized protocol. There was no clear single protocol for dosage adjustment or standardization of starting dose. Second; A full spectrum of well-defined SeLECTS patients who stayed on ASM therapy only monotherapy were included into the study group. Data on seizure outcome and drug-related side effects were obtained from the retrospective records of the patients. This situation prevented us from obtaining an opinion about the patients whose drug tolerance development may occur during ASM therapy and treatment withdrawal rate due to adverse events. This study also compares certain demographic, seizure semiology, seizure burden, and EEG characteristics (baseline SWIs and follow-up SWIs on ASMs) in children with /without ADHD in a large SeLECTS cohort.

Conclusion

This study provides following conclusions. Among the most commonly used ASMs CBZ, LEV, and VPA are recommended as first-line agents in the treatment of focal seizures in children, as per NICE guidelines (1). SeLECTS is a characteristics ADHD was seen in 19.9% of the patients followed up with a diagnosis of SeLECTS. As the number of antiseizure drugs used in the therapy increased, the scores associated with attention deficit increased. SWI might be used for prediction of ASM selection and certain cognitive co-mobidities like ADHD. Patients with ADHD had more frequent seizures and had a more extended seizure-free time. SWI was higher in children aged below 5 years with ADHD than in those without. In addition, SWIs were significantly higher in patients with ADHD compared to those without. On the other hand, SWIs of patients with ADHD decreased significantly regardless of age, and the absence of ADHD findings in patients with decreased SWI values on subsequent EEG recordings was diagnostic.

Ethics

Ethical Approval: This study was approved by the Clinical Research Ethics Committee of Karadeniz Technichal Universty under the decision numbered 2023/512, date: 15.04.2021 and was conducted as a single-center, retrospective study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Retrospective Evaluation of Patients Presenting with Puberty Precocious Complaints with Clinical and Laboratory Findings

Puberte Prekoks Şikayetleri ile Başvuran Hastaların Klinik ve Laboratuvar Bulguları ile Retrospektif Olarak Değerlendirilmesi

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Abstract

Introduction: In this study, clinical characteristics and laboratory results of girls presenting with precocious puberty complaints were compared according to age groups. The effects of GnRHa (gonadotropin-releasing hormone analog) treatment were evaluated by assessing the anthropometric data and predicted adult height (PAH) of the treated and untreated cases.

Materials and Methods: A total of 75 girls were included in the study. Cases were divided into four groups; cases between the ages of 5-8 years who started treatment constituted Group 1 and those who did not start treatment constituted Group 2; cases between the ages of 8-10 years who started treatment constituted Group 3 and those who did not start treatment constituted Group 4. The anthropometric data, pubertal stages, bone age (BA), the change in the ratio of BA to chronological age (CA) (BA/CA), and the changes in PAH during follow-up were analyzed.

Results: Target Height (TH) - PAH changes were compared in the treated and untreated groups. C Height, height-SDS, BMI, BMI-SDS, PAH, TH, TH-PAH values, and pubertal developmental stages at presentation were similar between Group 1 and Group 2, and between Group 3 and Group 4. At the initial presentation, the BA and BA/CA values of Group 1 and Group 2 were similar, whereas the BA value in Group 3 was significantly more advanced than in Group 4. BA/CA values at presentation were similar between groups 3 and 4. During follow-up, height, height-SDS, BMI, BMI-SDS, BA, and BA/CA changes were similar, and TH - PAH values were similar in the treated and untreated groups.

Conclusion: According to age groups, ΔBA/ΔCA, TH – PAH, ΔBMI-SDS values were similar between treated and untreated subjects, and GnRHa treatment had no significant effect on height and weight during follow-up in our case group.

Keywords
Precoccious puberty, GnRHa therapy, predicted adult height

Anahtar kelimeler
Puberte prekoks, GnRHa tedavisi, öngörülen son boy

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Öz

Giriş: Bu çalışmada puberte prekoks şikayetleri ile başvuran kız çocuklarının klinik özellikleri ve laboratuvar sonuçları yaş gruplarına göre karşılaştırıldı. GnRHa (gonadotropin salgılatıcı hormon analoğu) tedavisinin etkileri, tedavi edilen ve edilmeyen olguların antropometrik verileri ve öngörülen son boyları (ÖSB) hesaplanarak değerlendirildi.

Gereç ve Yöntem: Çalışmaya toplam 75 kız çocuğu dahil edildi. Olgular dört gruba ayrıldı; 5-8 yaş arasında tedavi başlananlar Grup 1'i, başlanmayanlar Grup 2'yi; 8-10 yaş arasında tedavi başlananlar Grup 3'ü, başlanmayanlar Grup 4'ü oluşturdu. Antropometrik veriler, puberte evreleri, kemik yaşı (KY), KY'nın takvim yaşına (TY)

oranındaki değişim (KY/TY) ve takip sırasında ÖSB'deki değişiklikler analiz edildi. Hedef Boy (HB) - ÖSB değişiklikleri tedavi edilen ve edilmeyen gruplarda karşılaştırıldı.
Bulgular: Başvuru sırasındaki boy, boy-SDS, VKI, VKI-SDS, ÖSB, HB, HB - ÖSB değerleri ve pubertal gelişim evreleri Grup 1 ve Grup 2 ile Grup 3 ve Grup 4 arasında benzerdi. İlk başvuru sırasında Grup 1 ve Grup 2'nin KY ve KY/TY değerleri benzerken, Grup 3'ün KY değeri Grup 4'e göre anlamlı derecede daha ileriydi. Başvuru sırasındaki KY/TY değerleri Grup 3 ve 4 arasında benzerdi. Takip sırasında boy, boy-SDS, VKI, VKI-SDS, KY ve KY/TY değişiklikleri benzerdi ve HB - ÖSB değerleri tedavi edilen ve edilmeyen gruplarda benzerdi.
Sonuç: Yaş gruplarına göre, ΔKY/ΔTY, HB - ÖSB, ΔVKI-SDS değerleri tedavi edilen ve edilmeyen olgular arasında benzerdi ve GnRHa tedavisinin olgu grubumuzda takip sırasında boy ve kilo üzerinde anlamlı bir etkisi yoktu.

Introduction

The onset of breast development in girls before the age of 8 years is called precocious puberty (PP) (1). However, the age of onset and progression of puberty are heterogeneous (2-4). In an early completed pubertal development, a temporary tall stature first occurs due to the peak growth rate experienced in the early stages of puberty. However, due to the premature closure of the epiphyseal plates, the target height (TH) cannot be reached, and the final height (FH) becomes short. Therefore, early onset of puberty is associated with short stature (5,6). This situation leads to the concern that the final adult height will be short, which has been increasing worldwide, especially in the last 20 years. This results in an increase in unnecessary outpatient clinic visits (7).

In the treatment of PP, GnRHa (gonadotropin-releasing hormone agonists) are used that suppress the hypothalamic-pituitary-gonadal axis (HHG). This treatment is aimed to stop the progression of puberty and bone age (BA) so that the child can reach the target height (TH) (8). However, recently, it has also become widespread that GnRHa treatment does not increase final height (FH) as much as thought (9). It is not clear whether pubertal development, especially starting early and continuing within the normal range, causes short stature (2,3). Those with slowly progressing puberty or those close to the age of normal pubertal development can reach their predicted adult height (PAH) even without any treatment (9,10). It is reported that those who benefit most from treatment are children whose pubertal development begins at an early age, especially before the age of 6, and has a rapid course (1,9). For girls with later-onset central precocious puberty (CPP) and/or slowly progressing puberty without a growth spurt, it is recommended that pubertal progression be followed up at three to six-month intervals (3).

The need for a critical weight for growth spurt and menarche in adolescent girls was stated by Frish and Revelle about 55 years ago (11,12). In a study, a significant increase in BMI was reported in the transition from stage 1 to stage 2 of puberty (13) and early menarche was associated with high body mass index (BMI) (14). In addition, there are also papers indicating that GnRHa treatment increases obesity in patients (15).

In this study, we aimed to investigate the effect of treatment on height, weight, BMI, BA and PAH by grouping the patients according to their age and whether they received treatment or not. In addition, we aimed to investigate the prevalence of overweight/obesity in PP patients by determining the overweight/obesity ratio of the patients at the beginning of treatment.

Materials and Methods

Cases who presented to the pediatric endocrinology outpatient clinic of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital l between January 2015 and January 2017 with findings of breast development, pubic hair growth, axillary hair growth and menarche were assessed. The records of 75 girls who were followed up for at least 1 year were evaluated retrospectively. The patients were divided into groups according to their age and puberty-arresting treatment initiation status. Accordingly, Group 1 consisted of 28 patients aged 5-8 years who were started on medication; Group 2 consisted of 23 patients aged 5-8 years who were not started on medication; Group 3 consisted of 5 patients aged 8-10 years who were started on medication; and Group 4 consisted of 19 patients aged 8-10 years who were not started on medication.

At 3-month intervals, height and BMI were calculated at each visit and compared with the standard curves established for Turkish children, and height-SDS and BMI-SDS were calculated according to chronological ages (CA) (16). Subjects with a BMI-SDS value above 2 SDS were considered obese and subjects with a BMI-SDS value between 1.5 SDS and 2 SDS were considered overweight. Pubertal status was determined according to Tanner staging based on breast development and pubic hair growth (17). LH, FSH, and estradiol measurements were performed. Basal LH level ≥ 0.3 mIU/L was considered as activation of the HHG axis. In

GnRH stimulation test performed in patients with basal LH level <0.3 mIU/mL, LH ≥ 5mIU/mL or LH/FSH ratio >0.66 was considered as activation of the HHG axis. Pelvic USG was performed at initial presentation and at 6-month intervals. On pelvic USG, ovarian volumes >1-3 mL, uterine size >3.4-4 cm and volume >2-3mL and endometrial thickness >2-3 mL were considered as findings supporting precocious puberty.

Left wrist radiography was performed in all patients at admission and then once a year during follow-up and BA was determined according to the Greulich-Pyle atlas. According to BA, PAHs were calculated using the Bayley-Pinneau method. Bone maturation was calculated using the ΔBA/ΔCA ratio, taking into account the annual change in the treated and untreated groups. The heights of the parents were measured in the outpatient clinic and the target heights (TH) and TH-SDS of the patients were calculated. TH for girls was calculated with the formula (mother's height + father's height − 13) ÷ 2. THs were compared with PAHs according to years. The effect of treatment on height was evaluated by comparing the TH - PAH difference between the treated and untreated groups. Brain and pituitary MRI was performed to detect possible intracranial pathology in patients with pubertal symptoms that began before the age of six, and who had rapidly progressing pubertal symptoms.

Ethics committee approval was obtained from University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 17.07.2017 with protocol number 17.07.2017-2017/07/23.

Statistical Analysis

Data were analyzed with SPSS for Windows version 23.0. Descriptive statistics of continuous variables were expressed as mean and standard deviation; categorical variables were expressed as numbers and percentages. For categorical variables, the significance of the difference between the groups was evaluated by Chi-Square test. The significance of the difference between the continuous variables of the paired groups was evaluated by Mann Whitney-U test. A value of $P < 0.05$ was considered statistically significant.

Results

Of 75 patients, 36 (48%) were diagnosed with ICPP and 24 (66%) of these patients had rapidly progressive puberty. At the time of initial presentation, the mean age of Group 1 was 7 ± 0.8 years, and the mean age of Group 2 was 6.8 ± 0.8 years, and there was no significant difference between them (p: 0.407). The complaints of the patients in Group 1 started 5±4 months before the first visit, and those of the patients in Group 2 started 6±8 months before, and they were statistically similar (p:0.825). Of all patients, 10% were obese and 11% were overweight. Overweight or obese patients constituted 35.7% (10) of the patients in Group 1, 30.4% (7) of the patients in Group 2 and 21% (4) of the patients in Group 4. There were no overweight or obese patients in Group 3. Overweight/obese ratio was higher in Group 1 and Group 2. Brain and pituitary MRI was performed in 26% (20) of the patients and no pathology was found.

Table 1 shows the anthropometric data, pubertal stages, laboratory findings and BAs of all groups at the time of initial presentation. At baseline, there was no statistically significant difference between Groups 1 and 2 in terms of height, height-SDS, BMI, BMI-SDS values (124.5cm and 123cm, p_1: 0. 264; 0.7 and 0.6, p_2: 0.339; 17.7kg/m^2 and 17.8kg/m^2, p_3: 0.828; 0.9 and 1, p_4: 0.762). Breast development and pubarche stages were similar in Group 1 and Group 2 (p_1: 0.339, p_2: 0.510). There was no statistically significant difference between the FSH, LH and estradiol values of Group 1 and Group 2 at baseline (p_1: 0.092, p_2: 0.155, p_3: 0.154). The median values of BA and BA/CA at baseline were 7.8 years and 1.07 in Group 1 and 7.5 years and 1.01 in Group 2, respectively, and there was no statistically significant difference between them (p_1: 0.124; p_2: 0.059).

The mean age at initial presentation was 8.7 ± 0.3 years in Group 3 and 8.4 ± 0.3 years in Group 4 and there was no significant difference between them (p: 0.343). The complaints of the patients in Group 3 started 8 ± 4 months before the first visit, and those of the patients in Group 4 started 7 ± 4 months before, and they were statistically similar (p:0.743). At baseline, there was no significant difference between Groups 3 and 4 in terms of height, height-SDS, BMI, BMI-SDS values (130cm and 129.5cm, p_1: 0.498; 0.5 and -0.1, p_2: 0.320; 18.6 kg/m2 and 17.2 kg/m2, p_3: 0.374; 0.9 and 0.5, p_4: 0.414). Breast development stages were similar in Group 3 and Group 4 (p: 0.077), whereas the pubarche stage was more advanced in Group 4 (p: 0.038). There was no significant difference between groups 3 and 4 in terms of FSH, LH and estradiol median values at baseline (p_1: 0.402, p_2: 0.198, p_3: 0.099). The median value of BA at presentation was 9 years in Group 3 and 8 years in Group 4 and was significantly higher in Group 3 (p:0.043). The BA/CA median value was 0.98 in Group 3 and 0.97 in Group 4 and statistically similar (p:0.238) (Table 1, Figure 1).

Group 1 was followed-up for a mean of 2.4 ± 0.8 years and Group 2 for a mean of 1.9 ± 0.8 years and there was no difference between them in terms of follow-up time (p:0.063). The median height, height-SDS, BMI and BMI-SDS changes

in Group 1 and Group 2 were statistically similar during the follow-up period (12.2 cm and 9.5 cm, p_1: 0.140; 0.1 and 0.2, p_2: 0.501; 2.2 kg/m2 and 1.68 kg/m2, p_3: 0.399; 0.16 and 0.13, p_4: 0.520) (Table 2). There was no significant difference between groups 1 and 2 in pubertal stages at presentation, in the first year and in the second year (p_1:0.526; p_2:0.307, p_3:0.513). The median value of BA change was 2 years in Group 1 and 1.3 years in Group 2 and was statistically similar (p:0.231). At the first year of follow-up, the median value of ΔBA/ΔCA was 1.09 in Group 1 and 0.66 in Group 2 and there was no statistically significant difference between them (p:0.297). At the second year of follow-up, the median value of ΔBA/CA was 0.9 in Group 1 and 0.92 in Group 2, with no statistically significant difference (p:0.580) (Table 2).

The mean follow-up times of groups 3 and 4 were 1.6 ± 0.4 years and 1.5 ± 0.4 years, respectively, and statistically similar (p:0.894). The median height, height-SDS, BMI and BMI-SDS changes of Group 3 and Group 4 were statistically similar during the follow-up period (9cm and 9.5cm, p_1: 0.972; 0.03 and 0.2, p_2: 0.082; 2.9kg/m^2 and 1.3kg/m^2, p_3:

Table 1. Anthropometric data, pubertal stages, laboratory values and bone ages at baseline in all groups

	Group 1 median (min – max)	**Group 2 median (min – max)**	**p**	**Group 3 median (min – max)**	**Group 4 median (min – max)**	**P**
Age, year	7.1 (5 – 7.9)	7 (5.1 – 7.9)	0.718	8.7 (8.3 – 9.1)	8.4 (8 – 8.9)	0.068
Height, cm	124,5 (109.5 – 144.5)	123 (108.5 – 130.6)	0.264	130 (128 – 141)	129.5 (118 – 142)	0.498
Height-SDS	0,7 (-2.2 – 27)	0,6 (-2.2 – 2.5)	0.339	0.5 (-0.5 – 2.1)	-0.1 (-1.9 – 1.8)	0.320
BMI, kg/m^2	17,7 (13.8 – 23.7)	17,8 (13.2 – 23)	0.828	18.6 (15.9 – 19.9)	17.2 (13.8 – 24.5)	0.374
BMI-SDS	0,9 (-1.1 – 2.5)	1 (-1.7 – 2.5)	0.762	0.9 (-0.2 – 1.3)	0.5 (-1.5 – 2.3)	0.414
Thelarche n, (%) 1 2 3 4 5	 3 (11%) 14 (50%) 10 (36%) 1 (3%) -	 6 (26%) 12 (52%) 5 (22%) - -	0.339	 - 1 (20%) 4 (80%) - -	 6 (32%) 8 (42%) 5 (26%) - -	0.077
Pubarche n, (%) 1 2 3 4 5	 17 (61%) 11 (39%) - - -	 16 (70%) 7 (30%) - - -	0.510	 2 (40%) 1 (20%) 2 (40%) - -	 12 (63%) 7 (37%) - - -	0.038
FSH, mIU/L	3.47 (0.8 – 11.2)	1.89 (0.7 – 11.1)	0.092	3,95 (1,9 – 6,1)	2.,5 (0.6 – 6.4)	0.402
LH, mIU/L	0.38 (0.1 – 4.2)	0.25 (0 – 1.6)	0.155	2.08 (0.1 – 2.1)	0.45 (0.05 – 1.8)	0.198
Estradiol, pg/mL <20 ≥20	 15 (75%) 5 (25%)	 14 (93%) 1 (7%)	0.154	 3 (60%) 2 (40%)	 12 (9%) 1 (8%)	0.099
BA	7.8 (6 – 10.5)	7.5 (6 – 8.5)	0.124	9 (8 – 11)	8 (7.5 – 10.5)	0.043
BA/CA	1.07 (0.9 – 1.4)	1.01 (0.9 – 1.3)	0.059	0.98 (0.9 – 1.3)	0.97 (0.9 – 1.2)	0.238

*BA: Bone age, BMI: Body mass index, CA: Chronological age, SDS: Standard deviation score

0.200; 0.34 and 0.17, p_4: 0.522) (Table 2). There was no statistically significant difference between groups 3 and 4 in pubertal stages at presentation, year 1 and year 2 (p_1:0.438; p_2:0.046, p_3:0.299). The median value of BA change was 2 years in Group 3 and 2.4 years in Group 4 and was statistically similar (p:0.593). At the first year of follow-up, the median value of ΔBA/ΔCA was 0.37 in Group 1 and 1.56 in Group 2 and there was no significant difference between them (p:0.270). At the second year of follow-up, the median value of ΔBA/ΔCA was 1.21 in Group 3 and 0.93 in Group 4 and there was no statistically significant difference between them (p:0.724) (Table 2).

There was no statistically significant difference between the median values of PAH and TH-PAH between Group 1 and Group 2 at the first visit (163.7 and 161.2cm, p_1:0.953; 2.6 and 5.4cm p_2:0.529). In the first year of follow-up, PAH median values were similar in Group 1 and Group 2 with 163.7cm and 166.8cm, respectively, whereas TH - PAH median values were 4.3 cm in Group 1 and 8 cm in Group 2, and significantly higher in Group 2 (p: 0.009). At the second year of follow-up, the median PAH and TH-PAH values of Group 1 were 163.2 cm and 5cm, respectively, while the median PAH and TH-PAH values of Group 2 were 164.2cm and 3.5cm, respectively, with no significant difference (p_1: 0.563; p_2: 0.786) (Table 3).

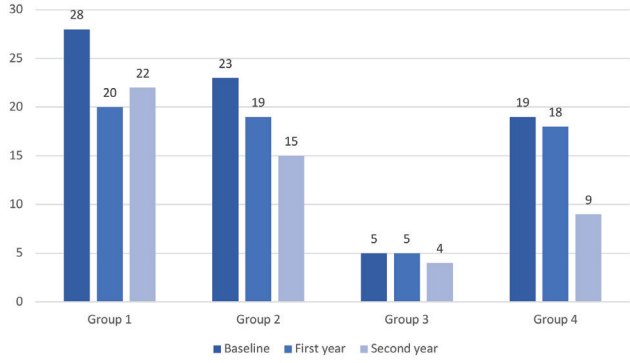

Figure 1. Number of cases in all groups by years

Group 3 had a median TH of 163.8 cm and a TH-SDS of 0.09, while Group 4 had a median TH of 160.3 cm and -0.47, with no significant difference between them (p_1:0.222, p_2:0.222). There was not significant difference between PAH and TH – PAH median values at the first visit between Group 3 and Group 4 (164.7 and 162.45cm, p_1:0.881; -0.9 and -0.95cm p_2:0.595). At the first year of follow-up, the median values of PAH and TH - PAH in Group 3 and Group 4 were 164.7cm and 162.4 cm; -2.3cm and 1cm, respectively, with no significant difference (p_1: 0.903; p_2: 0.734). In the second year of follow-up, the median PAH and TH-PAH values of Group 3 were 166.1cm and -0.7cm, respectively, while the median PAH and TH-PAH values of Group 4 were 160.7 cm and 1.6 cm, respectively, and no significant difference was found between them (p_1: 0.248; p_2: 0.513) (Table 3).

BMI-SDS values at admission were similar between Group 1 and Group 2 and between Group 3 and Group 4, and ΔBMI-SDS was similar during follow-up. The change in ΔBMI-SDS was similar in treated and untreated groups and no significant effect of treatment on BMI was found.

Table 2. Anthropometric change in all groups by years

	Group 1 median (min – max)	Group 2 median (min – max)	p	Group 3 median (min – max)	Group 4 median (min – max)	p
ΔHeight, cm	12.2 (6 – 21)	9.5 (4.5 – 21)	0.140	9 (6 – 14.3)	9.5 (5 – 17.7)	0.972
ΔHeight-SDS	0.1 (-2.3 – 1.5)	0.2 (-1.3 – 0.79)	0.501	0.03 (-1.2 – 0.4)	0.2 (-0.4 – 1.5)	0.082
ΔBMI, kg/m^2	2.2 (-4.3 – 5.6)	1.68 (-0.8 – 10.4)	0.399	2.9 (1.3 – 3.3)	1.3 (-1.3 – 4.7)	0.200
ΔBMI-SDS	0.16 (-2.7 – 1.5)	0.13 (-0.7 – 0.7)	0.520	0.34 (-0.05 – 0.6)	0.17 (-0.8 – 0.9)	0.522
ΔBA	2 (0.2 – 3.7)	1.3 (0.3 – 2)	0.231	2 (0.3 – 4)	2.4 (1.7 – 4.2)	0.593
ΔBA/CA (1st year)	1.09 (0 – 7.3)	0.66 (0 – 1.96)	0.297	0.37 (0 – 2.8)	1.56 (0.67 – 3.5)	0.270
ΔBA/CA (2nd year)	0.9 (0 – 1.7)	0.92 (0.6 – 1.1)	0.580	1.21 (0.1 – 2)	0.93 (0.2 – 1.7)	0.724

*BA: Bone age, BMI: Body mass index, CA: Chronological age, SDS: Standard deviation score

Table 3. PAH and TH - PAH values in all groups by years

	Group 1 median (min – max)	Group 2 median (min – max)	p	Group 3 median (min – max)	Group 4 median (min – max)	p
Baseline						
TH, cm	159.8 (151 – 168.5)	159 (147.5 – 168.5)	0.255	163,8 (157 – 169.5)	160.3 (154.5 – 167)	0.222
TH-SDS	-0.52 (-1.9 – 0.8)	-0.64 (-2.4 – 0.8)	0.265	0.09 (-1 – 0.97)	-0.47 (-1.3 – 0.66)	0.222
PAH, cm	163.7 (145.3 – 178.5)	161.2 (150.6 – 183.3)	0.953	164.7 (145 – 170.5)	162.45 (149.4 – 178.6)	0.881
TH – PAH, cm	2.6 (-12.5 – 13.8)	5.4 (-12.8 – 18.8)	0.529	-0.9 (-15 – 2.3)	-0.95 (-8.1 – 11.6)	0.595
First year						
PAH, cm	163.7 (151.9 – 177.5)	166.8 (155.3 – 174.4)	0.311	161.5 (151.8 – 166.5)	159.8 (148.2 – 169.2)	0.903
TH – PAH, cm	4.3 (-3.6 – 16.2)	8.05 (-1.8 – 15.1)	0.009	-2,3 (-8.2 – 4.5)	1 (-11.9 – 5.2)	0.734
Second year						
PAH, cm	163.2 (150.9 – 182.8)	164.2 (153.4 – 171)	0.563	166.1 (153.4 – 169.8)	160.7 (156.2 – 162.1)	0.248
TH – PAH, cm	5 (-5 – 22.8)	3.5 (-4.3 – 12.2)	0.786	-0,7 (-4.1 – 12.8)	1.6 (0.2 – 4.7)	0.513

*PAH: Predicted adult height, SDS: Standard deviation score, TH: Target height

Discussion

In this study, no statistically significant difference was found in the PAHs and TH-PAH changes of the treated and untreated groups during the follow-up period in all groups. BMI-SDS changes were also similar in the treated and untreated groups. Different results have been reported in various studies regarding the effect of treatment on height in children with CPP. Some studies have reported that treatment in cases of CPP improves PAH and final adult height, while other studies have reported that untreated girls can also reach their TH (9,18). It is thought that obtaining different results in different studies may be due to differences in the distribution of age groups, small number of cases and individual differences in the progression of puberty (19).

In a study conducted by Kauli et al. (20), 28 untreated children who started to show signs of puberty before the age of 8 and were diagnosed with CPP, were observed. Of these children 14 had slowly progressive puberty and 14 had rapidly progressive puberty. While the TH of children with slowly progressive puberty were 159.5 ± 6.6 cm, their FH reached 160.2 ± 7.1 cm. However, the subjects with rapidly progressing puberty could not catch up with their TH and their TH were 159.2 ± 5.9 cm while their FH reached 150.8 ± 4.3 cm. In another study in which cases were divided according to age groups, patients <6 years of age who received or did not receive treatment and patients >6 years of age who received or did not receive treatment were compared. When these cases were evaluated according to TH, it was observed that height gain in treated cases were 2.7 cm in the group aged <6 years and no height gain was observed with the treatment in the group aged >6 years (21).

Glab et al. (22) followed 40 girls with CPP at a mean age of 6.0 ± 1.9 years and started GnRHa therapy at a mean age of 7.5 ± 2.2 years. Among these patients, those who started treatment before the age of 7 years were found to benefit more from treatment in terms of final height. In a metanalysis, final height and PAH were assessed in 332 girls aged 7-10 years with and without treatment from six different studies. It was observed that there was no significant difference in final height between those who received treatment and those who did not (mean difference = 0.50 cm, 95% confidence interval = −0.72 to 1.73 cm, I^2 = 0%). In the PAH-based analysis, children were divided

into three groups: <155cm and <TH; <TH but >155cm and equal to TH. No difference was found between the groups in terms of final height averages (23). In another study in which one hundred and fifteen female patients with CPP were evaluated, the subjects were divided into three groups according to their age at the time of diagnosis (<6 years, 6-8 years, 8-9 years) and the effect of GnRHa treatment on FH was examined. They found TH 159.3 ± 5.0 cm, PAH 162 ± 7.3 cm and FH 162.8 ± 5 cm in the group below 6 years of age; TH 157.8 ± 5.2 cm, PAH 161.4 ± 6.5 cm and FH 157.9 ± 5.1 cm in the group between 6-8 years of age; TH 156.9 ± 4.7 cm, PAH 158.4 ± 5.8 cm and FH 153.9 ± 4.6 cm in the group between 8-9 years of age. As a result of this study, the positive effect of GnRHa treatment on FH was observed only in the <6y group and FH was found to be significantly higher than TH and PAH (24). In our study, PAH and TH - PAH values were similar in children aged 5-8 years and in children aged 8-10 years, who received and did not receive treatment during two year follow-up period.

Wang (25) explained that the prevalence of BMI, subcutaneous adipose tissue and obesity was higher in girls with early pubertal development than in girls with normal and late pubertal development. During lockdown at the time of the COVID pandemic, it has been observed that girls who were unable to move, confined to the house, and gained weight at this process, had earlier puberty and pubertal signs progressed much more rapidly (26). Our study shows similar findings with the literature and obesity rate was higher in Groups 1 and 2, which were younger age groups, compared to Groups 3 and 4.

There are different opinions about the effects of GnRHa treatment on BMI. Lee et al. (27) reported the changes in BMI-SDS of 38 girls with early puberty who received GnRHa treatment for 18 months. BMI-SDS increased from 0.58 ± 1.1 at baseline to 0.79 ± 0.84 after 12 months of treatment and to 0.96 ± 0.83 after 18 months of treatment. There was a significant increase in BMI-SDS with treatment. In a study by Wolters et al. (28), 92 children with CPP and early puberty receiving GnRHa treatment were assessed according to their weight status at baseline and change in weight with treatment. Surprisingly, BMI-SDS increased with treatment in normal-weight children (0.32 ± 0.66) but remained stable in overweight children (-0.02 ± 0.27). In addition, when BMI-SDS of 25 overweight children who were not treated with GnRHa was compared with 25 overweight children who received treatment, it was observed that BMI-SDS increased more in the untreated group at the end of the treatment period (+0.18 ± 0.22 in untreated group vs -0.02 ± 0.27 in treated group). None of the overweight children received any lifestyle modification intervention or any changes in their diet or exercise habits. As a result, GnRHa treatment was reported to have a positive effect on BMI-SDS in overweight children. Brito et al. (29) found that 42% of 45 female patients with PP who received GnRHa treatment were found to be overweight at the beginning of treatment, 47% at the end of treatment and 40% when they reached FH and it was reported that GnRHa treatment did not cause a significant increase in BMI. In our study, similar to the study of Brito et al. (29), BMI and BMI-SDS were similar between Groups 1 and 2 and between Groups 3 and 4 at baseline, and no significant difference was found between the groups with treatment.

Study Limitations

The limitations of the study were the retrospective design of the study, irregular follow-up of the patients and the small number of cases. It was planned to call back the cases to the hospital to evaluate their heights when they were thought to have reached the final height. However, since this period coincided with and after the COVID pandemic, a sufficient number of patients could not be reached and final heights could not be reported. Since the patients followed up had not yet reached FH, the effects of treatment were evaluated on the basis of PAH. PAH measurement is a BA-based measurement and the Greulich-Pyle atlas is used in BA assessment, and the fact that it is a subjective measurement method casts doubt on the reliability of the study on PAH.

Conclusion

In conclusion, since the changes in anthropometric values were similar in all groups in this study, it was concluded that treatment with GnRHa did not have a significant effect on anthropometric values in our limited patient group. Patients have been followed for a certain period of time and their development is not yet complete, so these results may be variable.

Ethics

Ethical Approval: Ethics committee approval was obtained from University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 17.07.2017 with protocol number 17.07.2017-2017/07/23.

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Footnotes

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluating the Quality of Responses by ChatGPT-3.5, Google Gemini, and Microsoft Copilot to Common Pediatric Questions: A Content-Based Assessment

ChatGPT-3.5, Google Gemini ve Microsoft Copilot'un Yaygın Pediatrik Sorulara Verdiği Yanıtların Kalitesinin Değerlendirilmesi: İçerik Tabanlı Bir Değerlendirme

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Abstract

Introduction: The objective of this study was to compile a list of the most frequently asked questions by parents during their first visits to the pediatrician and to evaluate the reliability and success of responses provided by artificial intelligence-supported chatbots against these questions.

Materials and Methods: The 20 most frequently asked questions by parents of infants during their pediatrician outpatient visits were posed to ChatGPT3.5, Google Gemini, and Microsoft Copilot applications. The responses provided by the applications were evaluated on a Likert scale from 1 (least adequate) to 5 (most adequate) by a pediatric gastroenterologist, pediatrician, and pediatric assistant, all of whom were physicians.

Results: Upon scoring the responses provided by artificial intelligence (AI) applications to the 20 questions posed, Google Gemini was found to have received the highest score (286) and was statistically significant ($p < 0.001$). No significant difference was observed when Copilot and ChatGPT were compared. Upon evaluation of responses generated by AI applications, pediatricians were found to have assigned the highest ratings.

Conclusion: The Gemini AI application demonstrated greater success than ChatGPT3.5 and Copilot in responding. While AI chatbots demonstrate the capability to deliver information, advice, and guidance regarding health and diseases, it is imperative that the responses generated by these systems undergo rigorous evaluation by healthcare professionals.

Öz

Giriş: Bu çalışmanın amacı, ebeveynlerin çocuk doktoruna yaptıkları ilk başvurular sırasında en sık sordukları soruların bir listesini derlemek ve yapay zekâ destekli sohbet robotları tarafından bu sorulara verilen yanıtların güvenilirliğini ve başarısını değerlendirmektir.

Gereç ve Yöntem: Bebeklerin poliklinik ziyaretleri sırasında ebeveynleri tarafından en sık sorulan 20 soru, ChatGPT3.5, Google Gemini ve Microsoft Copilot uygulamalarına yöneltilmiştir. Uygulamalar tarafından verilen yanıtlar; bir çocuk gastroenteroloğu, bir çocuk sağlığı ve hastalıkları uzmanı ve bir pediatri asistanı olmak üzere üç hekim tarafından 1 (en yetersiz) ile 5 (en yeterli) arasında derecelendirilen Likert ölçeği kullanılarak değerlendirilmiştir.

Keywords
Artificial intelligence, pediatrics, chatbot, parental counseling, content evaluation

Anahtar kelimeler
Yapay zeka, pediatri, chatbot, ebeveyn danışmanlığı, içerik değerlendirme

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Bulgular: Yapay zekâ (YZ) uygulamalarının yöneltilen 20 soruya verdikleri yanıtların puanlanması sonucunda, en yüksek puanı Google Gemini almış (286) ve bu sonuç istatistiksel olarak anlamlı bulunmuştur ($p < 0,001$). Copilot ve ChatGPT karşılaştırıldığında ise anlamlı bir fark saptanmamıştır. Yapay zekâ uygulamaları tarafından üretilen yanıtların değerlendirilmesi sonucunda, en yüksek puanlamayı çocuk sağlığı ve hastalıkları uzmanlarının yaptığı belirlenmiştir.
Sonuç: Gemini yapay zekâ uygulaması, ChatGPT3.5 ve Copilot'a kıyasla sorulara yanıt verme konusunda daha başarılı bulunmuştur. Yapay zekâ destekli sohbet robotları; sağlık ve hastalıklarla ilgili bilgi, öneri ve rehberlik sunma potansiyeline sahip olmakla birlikte, bu sistemler tarafından üretilen yanıtların sağlık profesyonelleri tarafından titiz bir değerlendirmeye tabi tutulması zorunludur.

Introduction

In recent years, the application of artificial intelligence (AI) has become increasingly prevalent in all areas of our daily lives. Despite the perception that AI will not replace human doctors in the health sector, it is anticipated that it will assist in diagnosing and treating patients through algorithms (1). Experimental studies on AI are being conducted in some hospitals worldwide. Artificial intelligence-supported chat robots (AISR), which can interact with users using natural language, have started to replace conventional search engines with the widespread use of smart devices (2). It is anticipated that AI will be extensively employed in the future to address individuals' health concerns (3). There is a growing trend towards the utilization of AI-powered online platforms that offer health-related advice. Nevertheless, concerns about the reliability of these platforms persist (4,5).

ChatGPT3.5 is an OpenAI-developed AISR with the most commonly known natural language processing and machine learning capabilities. According to analyst data, the application, which was released in November 2022, achieved a remarkable milestone of over 100 million users within a mere two months. This exponential growth trajectory established it as an unparalleled phenomenon in the realm of consumer applications (6). Despite generating highly detailed and persuasive responses to a wide range of health-related inquiries, from general patient questions to complex scientific queries posed by medical professionals, these systems frequently produce inaccurate and contradictory information (7). Google Gemini was developed by Alphabet and DeepMind, one of Google's parent companies, in the final months of 2023 and was made available to users in 2024. Microsoft Copilot is an AI-based chatbot developed by Microsoft. The present landscape is characterized by a multitude of AI models designed to execute a broad spectrum of tasks, encompassing image and sound processing, creative generation, computational operations, and statistical analysis. Our research focused on three specific AI chatbots due to their accessibility at no cost, prevalence in real-world applications, and the substantial backing provided by large corporations for their underlying infrastructure and ongoing development.

The lack of experience, limited knowledge, fear of making mistakes, and protective instinct are among the factors that contribute to stress and depression in first-time parents (8). Parental self-efficacy is the self-confidence that parents possess to have children and fulfill child-rearing tasks. A study found that parental self-efficacy was low in families with a nuclear family structure that did not receive support from family elders (9). It is not uncommon for parents to be unable to reach a pediatrician after the birth of their child and to search for information on the internet instead. Subsequent to the COVID-19 pandemic, the exponential growth in telehealth services has positioned AI-driven chatbots as indispensable tools for patient engagement and remote healthcare delivery (10). The growing reliance of parents on electronic resources to alleviate medical concerns and obtain expert opinions has yielded several potential advantages. One such advantage is the 24/7 accessibility of AISRs, providing a convenient resource for parents, particularly during off-hours (11-13). This technology can be particularly beneficial in reducing the burden on healthcare providers in developing countries where access to care is often limited, especially for rural populations and the uninsured by offering an alternative means of delivering healthcare services and contributing to the reduction of disparities in access and quality (14).

Previous research has not yielded any articles that assessed the sufficiency and trustworthiness of responses generated by AISRs to the frequently asked questions of parents regarding pediatric care. The role of AISRs in healthcare delivery is a subject of considerable debate. While proponents extol their potential to address individual health concerns and reduce the workload of healthcare professionals, critics caution against their limitations, such as the accuracy of AI-generated diagnoses, the unique nature of individual patient presentations, and the lack of human oversight. The ongoing debate underscores the need for further research to determine the most appropriate and reliable methods for integrating AISRs into clinical practice (6,15,16). Recent systematic reviews have highlighted the potential and limitations of AI chatbots in pediatric settings, particularly regarding the accuracy of medical information and parental satisfaction (4,17). These findings underscore

the need for real-world evaluations, as addressed in our study.

This study aims to evaluate the accuracy and reliability of AI-generated responses in addressing parents' questions with a focus on content. The evaluation will be conducted using ChatGPT-3.5, Google Gemini, and Microsoft Copilot.

Materials and Methods

The study was conducted at Suleyman Demirel University, Department of Pediatrics, in accordance with the Declaration of Helsinki. Given that the study did not entail the use of personal data, human participants, or medical records, it was concluded that review by an ethics committee was not required. The 20 most frequent questions were selected based on a combined approach: (1) a systematic review of online sources, (2) the authors' own clinical experience, and (3) a nationwide consultation via messaging apps with actively practicing pediatricians to validate the representativeness of these questions (Table 1).

Table 1. Most frequently asked questions to pediatricians

Can I give my baby a pacifier?
When can the baby be bathed after birth?
How can I tell if breast milk is enough for my baby?
Is it recommended to use a baby walker for babies?
What foods should not be given to the baby before the age of one year?
Does my baby have gas pains, and how can I help them?
How often should I change my baby's diaper, and how I do it?
How can I establish my baby's sleep patterns?
How can I strengthen my baby's immune system and protect them from diseases?
Should I worry if my baby hiccups or sneezes frequently?
Which products should I use for my baby's skincare, and which products should I avoid?
What activities can I do for my baby's emotional and mental development?
Can I let my baby watch television?
What should I pay attention to for my baby's ear care, and how should ear cleaning be done?
My baby has hair loss. Is it normal?
Does the temperature rise after vaccination in babies? What should I do if they have a fever?
When and how long should I allow my baby to be exposed to sunlight, and how should sun protection be provided?
Is my baby's breathing normal, and what should I pay attention to regarding breathing problems?
Is my baby's appetite normal, and is it getting enough food? How can I assess this?
Is my baby's sweating normal, and what should I do to prevent excessive sweating?

Questions were asked to AISRs in Turkish. A comprehensive literature review was conducted using the search term 'most common questions asked of pediatricians.' Additionally, pediatricians practicing in diverse regions of Turkey were contacted via messaging apps to gather firsthand information on the most frequently asked questions by new parents. The collected data, combined with our own clinical expertise, was analyzed to identify the top 20 most recurrent questions. These questions formed the foundation of our research. The questions were posed to ChatGPT3.5, Google Gemini, and Microsoft Copilot AI software in the same format in May 2024 in a new chat window to minimize the influence of previous posts, and the responses were recorded without data loss. The study was completed with the active versions of all three AI chatbot tools in May 2024. The questions were then scored by a pediatric gastroenterology specialist (PGS), a pediatrician (P), and a pediatric assistant (PA) using a 5-point Likert scale. Three clinicians, PGS, P, and PA, possessing 35, 15, and 3 years of clinical experience respectively, were tasked with independently assessing the accuracy and reliability of responses generated by the AISR. To ensure objectivity, each clinician evaluated the responses across five predefined categories without knowledge of the others' assessments. In accordance with the aforementioned criteria, the following responses were recorded: (1) AI provided an incorrect answer; (2) AI was unable to provide an adequate response and could not identify the correct source; (3) AI was unable to provide an adequate response but suggested the correct source; (4) AI provided an adequate response but not an optimal one; (5) AI provided an optimal response. According to this scaling, the lowest rating was given to (1), while the highest rating was given to (5). The scoring system yielded total scores ranging from 20 to 100. The absence of a validity and reliability assessment for this system was recognized as a limitation of the present study.

Statistical Analysis

IBM SPSS Statistics 27 (Corp. I. IBM SPSS Statistics for Windows. Version 270. Armonk: NY: IBM Corp; Released 2020). package program was used for statistical analysis. Since each of the three clinicians evaluated the same 20 questions across three different AI applications using a 5-point Likert scale, the data represent repeated measures with related (dependent) samples. Additionally, as the Likert scale provides ordinal data and the assumption of normality was not met, non-parametric methods were preferred. The Friedman test was used to compare the differences in

scores across the three AI systems, which is the appropriate non-parametric alternative to repeated-measures ANOVA. Pairwise comparisons were conducted using the Wilcoxon signed-rank test. Statistically, $p<0.05$ was considered statistically significant.

Results

A comparison of the scores obtained by the physicians of the AISR revealed that Gemini received the highest score, while ChatGPT3.5 and Copilot received the lowest score (Table 2).

In the evaluation, PGS ranked Gemini as the highest performing model and ChatGPT 3.5 as the lowest. Similarly, P ranked Gemini highest and ChatGPT lowest. PA's evaluation indicated Gemini as the top-performing model while Copilot was ranked the lowest. The results demonstrated that Gemini scored statistically significantly higher than the other AIs ($p<0.001$). No statistically significant difference was observed when Copilot and ChatGPT were compared.

Table 2. Comparison of the scores of AI applications

	ChatGPT3.5	Gemini	Copilot	p*
PGS median total	4 (1-5) 73	5 (4-5) 95	4 (2-5) 74	<0.001
P median total	4 (3-5) 75	5 (4-5) 96	4 (2-5) 79	<0.001
PA median total	4 (3-5) 76	5 (3-5) 95	3,5 (2-5) 71	<0.001
Total score	224	286	224	

Descriptive statistics are given as median (min.-max.) and total score.
*Friedman test, **Wilcoxon test
PGS: Pediatric gastroenterology specialist, P: Pediatrician, PA: Pediatric assistant

Upon evaluation of responses generated by AI applications, pediatrician were found to have assigned the highest ratings (Table 3).

A statistically significant difference was identified between the scores assigned by P and PA to Copilot ($p = 0.033$).

The items that all AIs most successfully answered were questions 12 and 14. These were: 'What kind of activities can I do for my baby's emotional and mental development?' and 'What should I pay attention to for my baby's ear care, and how should ear cleaning be done?'. The questions numbered 5 and 6, which inquired about the foods that should not be given to babies before the age of one year and about the causes and treatment of infant gas pains, respectively, were the least successfully answered. A detailed breakdown of the scores assigned by the evaluators is provided in Table 4.

The analysis revealed that the AI model exhibited significant inaccuracies when responding to questions concerning nutrition and colic. These errors may be attributed to the specific phrasing of the questions or to inherent limitations within the AI model, such as the generation of hallucinated content. While the overall evaluation suggests satisfactory performance in terms of accuracy and reliability, the identified shortcomings in the context of health-related inquiries warrant further investigation.

Discussion

Our study represents the inaugural investigation of the utilization of AISR in our country's pediatrics domain. The results of this study highlight the promising potential of AI technologies in the healthcare sector. However, given the nascent stage of these technologies, ongoing evaluation by domain experts is crucial to ensure their reliability and safety. Rather than focusing on technological differences between AI platforms, this study aimed to determine the reliability of

Table 3. Comparison of the scores given by the physicians to the applications

	PGS score median (min-max)	P score median (min-max)	PA score median (min-max)	p*	PGS-P**	PGS-PA**	P-PA**
ChatGPT-3.5	4 (1-5)	4 (3-5)	4 (3-5)	0.828	0.763	0.405	0.705
Gemini	5 (4-5)	5 (4-5)	5 (3-5)	0.819	0.564	1	0.564
Copilot	4 (2-5)	4 (2-5)	3,5 (2-5)	0.08	0.132	0.366	0.033
Total score	242	250	242				

Descriptive statistics are given as median (min.-max.) and total score.
*Friedman test, **Wilcoxon test
PGS: Pediatric gastroenterology specialist, P: Pediatrician, PA: Pediatric assistant

Table 4. Median scores (min-max) given to each AI model by question					
Question No	**Question Topic**	**ChatGPT3.5**	**Gemini**	**Copilot**	**Best Scoring Model**
Q1	Use of pacifiers	4 (4-4)	5 (5-5)	3 (2-3)	Gemini
Q2	Bathing after birth	3 (4-4)	4 (3-4)	5 (5-5)	Copilot
Q3	Breastfeeding adequacy	3 (3-4)	5 (5-5)	3 (3-4)	Gemini
Q4	Baby walker use	4 (3-4)	5 (5-5)	4 (3-4)	Gemini
Q5	Unsafe foods before 1 year	3 (1-4)	5 (4-5)	3 (2-3)	Gemini
Q6	Infantile colic / gas pain	4 (3-4)	4 (4-4)	2 (2-3)	ChatGPT and Gemini
Q7	Diaper change	4 (4-4)	5 (5-5)	3 (3-4)	Gemini
Q8	Sleep patterns	4 (4-4)	5 (5-5)	4 (3-5)	Gemini
Q9	Strengthening immunity	5 (4-5)	5 (4-5)	4 (3-4)	ChatGPT and Gemini
Q10	Hiccups and sneezing	3 (3-3)	5 (5-5)	3 (3-4)	Gemini
Q11	Skincare products	4 (4-4)	5 (5-5)	4 (4-4)	Gemini
Q12	Emotional and mental development	4 (4-5)	5 (5-5)	5 (5-5)	Gemini and Copilot
Q13	Screen time	4 (4-5)	5 (5-5)	5 (4-5)	Gemini and Copilot
Q14	Ear care	5 (4-5)	5 (5-5)	5 (4-5)	Equal
Q15	Hair loss	3 (3-4)	5 (5-5)	5 (4-5)	Gemini and Copilot
Q16	Post-vaccine fever	4 (3-4)	5 (5-5)	4 (4-5)	Gemini
Q17	Sun exposure and protection	4 (4-4)	5 (5-5)	4 (3-4)	Gemini
Q18	Breathing patterns	4 (3-4)	5 (4-5)	2 (2-3)	Gemini
Q19	Appetite and feeding assessment	3 (3-3)	5 (4-5)	4 (4-4)	Gemini
Q20	Sweating	4 (3-4)	4 (4-4)	3 (3-4)	ChatGPT and Gemini
Descriptive statistics are given as median (min-max). N/A: Not applicable					

chatbot responses from the perspective of pediatric care. The findings have direct implications for how parents interact with AI tools when pediatric consultation is not immediately accessible.

Conversational tools that establish dialogue with the user by mimicking human interaction through written, verbal, and visual communication are referred to as AISR. With the increasing use of technological devices (e.g., smartphones and computers) and access to the Internet, AISR is becoming accessible and interesting. They offer the potential to provide health-related information and autonomous services, which could be promising for technology-assisted interventions. Moreover, these chatbots have the potential to alleviate current healthcare resource burdens by automating functions that previously required face-to-face interaction (18). Gonsard et al. (19) aimed to assess the acceptability of AI-powered home monitoring systems among pediatric asthma patients. Their findings revealed a notable generational gap, with adolescents expressing a more positive attitude towards self-management using AI-driven tools than their parents. Nevertheless, at this juncture, healthcare professionals must validate the veracity of the information provided by AI. The application of AI to analyze vast datasets and medical records has yielded remarkable results in the diagnosis of complex and intricate diseases (20,21). Ying et al. (22) demonstrated that while ChatGPT performed reasonably well in providing responses to queries related to the diagnosis and screening of pediatric endocrine disorders, it exhibited limitations in its ability to account for nuances within disease subgroups. Furthermore, the study highlighted the inconsistency of

responses across different languages, suggesting a lower level of reliability.

In our study, the questions were posed in the same format to the AISRs, who responded with varying content and length. In similar studies conducted by Taşkın et al. (23) and Perez-pino et al. (24), it was observed that the AISRs provided different responses to the same questions. This discrepancy affects the dependability of the received output. The discrepancy may be attributed to the sources from which the AISR is derived. In our study, it was observed that the answers given by AI were long. In fact, if we had designed a study comparing the answers given by clinicians and the answers given by AI to the same questions, we could have obtained different results. As a matter of fact, in a study conducted on this subject, the answers given by clinicians were found to be shorter and more superficial than the answers given by AI (25). However, we do not know how AISRs will perform when responding to patient questions in a real clinical setting. We hope that research on this subject will encourage future studies for the routine use of AI in the healthcare.

Although studies examining the answers given by asking health-related questions to AI are increasing today, they are still few. In the ophthalmology clinic, the AISR, was employed for diagnostic and triage purposes. The ChatGPT4 achieved the highest accuracy rate (3). In our study, Gemini was the application that received the most successful responses to the questions. The pediatrician assigned the highest scores overall, which may reflect greater familiarity with AI interfaces or a more forgiving evaluation approach compared to the pediatric gastroenterologist or assistant. This evaluator effect underlines the subjectivity inherent in expert scoring, despite efforts to standardize the evaluation categories. The pediatric assistant tended to give more conservative scores compared to the specialist physicians. This may reflect a more cautious approach due to limited clinical authority or less familiarity with AI-generated content. Understanding such evaluator variability is crucial for interpreting subjective rating-based research. Future studies may benefit from including more raters and inter-rater reliability testing to strengthen the generalizability of findings. ChatGPT4 is a more recent and paid version than the previous version, ChatGPT3.5. We used the free version instead of ChatGPT4 because we prefer AI applications that are easily and freely accessible to the general public.

In our study, Google Gemini received significantly higher scores than ChatGPT3.5 and Copilot across all evaluators. This result may be attributable to Gemini's underlying model infrastructure, which was observed to provide more structured, concise, and medically relevant responses. Notably, Gemini performed especially well in questions related to infant care routines and developmental advice, such as emotional development and hygiene practices, whereas it underperformed—along with other models—in addressing nutrition-related concerns like gas pain or food restrictions. These findings suggest that current AI systems may be more reliable for behavioral and general care topics than for complex, medically nuanced issues requiring clinical judgement. This demonstrated that parents can obtain accurate responses to certain queries through AI applications without consulting a physician. However, AI applications that lack a robust infrastructure comprising health professionals may provide erroneous and inadequate responses, potentially posing significant legal and vital risks. In this context, Rokhshad et al. (26) asserted that chatbots are valuable tools for training and disseminating patient information. Still, they are not yet equipped to replace physicians in making diagnostic decisions.

AISRs can support the simple questions of patients with messages during the busy shifts of clinicians or allied health personnel. However, it should be reviewed and evaluated by the healthcare personnel that correct and consistent answers are given to the questions by AI. Thus, in countries with limited health personnel and clinicians, time savings and the ability to assign personnel to more critical units can be achieved. Especially out-of-hours patients who have problems in reaching the health centre and who cannot take time off from their workplace can get answers to their health-related questions quickly and unnecessary clinic visits and loss of labour force can be prevented. If more patients' questions are answered quickly, empathically and to a high standard, unnecessary clinic visits may decrease and resources may be freed up for those in need (27).

There is a pressing need for comprehensive studies on the use of AI, which has become a popular source of health information in recent years. Given that AI constantly evolves, further studies utilizing the latest AI versions may be advisable. It is important to recognize that the results of such studies may differ significantly over time. Future research could involve comparative analyses of responses provided by advanced AI applications and human healthcare professionals to fundamental health-related queries.

Study Limitations

The main limitation of our study was that it compared fixed answers to specific questions. Since the patient's previous health records were not analysed here, personalised disease

states may have been omitted because the patient-physician relationship and related conditions vary. As it is known, diseases can be personalised and may occur with different symptoms instead of the same symptoms in every situation and in every individual. In addition, the directions made by the AI's answers to the questions in the clinicians' opinions were not taken into account. The absence of a validity and reliability assessment for this system was recognized as a limitation of the present study. If the study had evaluated the answers given by clinicians and AI with unbiased physicians, different results may have emerged. Due to the evolving nature of AI platforms, the same question may yield different answers over time. This temporal variability limits reproducibility and generalizability. Although the evaluators of our study were blinded to each other, they were also co-authors of the study and this may have biased the study.

Conclusion

The potential exists for AI applications to alleviate the burden on healthcare systems in developing countries. In our study, Gemini, Copilot, and ChatGPT-3.5 demonstrated satisfactory performance in general and exhibited considerable potential for patient information and education. Nevertheless, it is necessary to conduct an evaluation and preliminary examination by experts in the before recommending the use of AI in healthcare. Although our study shows promising results, it needs to be studied for a long time due to its limitations and ethical issues related to AI-supported healthcare.

Ethics

Ethical Approval: The study was conducted at Süleyman Demirel University, Department of Pediatrics, in accordance with the Declaration of Helsinki. Given that the study did not entail the use of personal data, human participants, or medical records, it was concluded that review by an ethics committee was not required.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Can Asprosin be Used as a Diagnostic Biomarker for Non-Alcoholic Fatty Liver Disease in Obese Children?

Asprosin, Obez Çocuklarda Alkole Bağlı Olmayan Karaciğer Yağlanması için Tanısal Bir Biyobelirteç Olarak Kullanılabilir Mi?

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Abstract

Introduction: As obesity rates rise among children, non-alcholic fatty liver disease (NAFLD) is becoming more prevalent. Although liver biopsy is considered the gold standard for diagnosing NAFLD, it is an invasive procedure and not practical for screening. Asprosin, a recently unveiled adipokine, is released in response to fasting. In this study, we aimed to investigate the diagnostic value of asprosin for NAFLD in obese patients.

Materials and Methods: A total of 142 participants (71 obese, 71 control) aged between 6 and 18 years were included in the study. Obese patients were also divided to subgroup as NAFLD (+) and NAFLD (-) according to hepatobiliary ultrasonopgraphic features and compared with each other regarding their clinical and laboratory features, including asprosin level.

Results: When comparing obese and non-obese patients, asprosin levels were significantly higher in the obese group (P=0.034). NAFLD was diagnosed in 35 (49.2%) of the obese cases. While body mass index (BMI) were similar; waist circumference and insulin resistance were higher in patients with NAFLD. When comparing Asprosin, interleukine-6 (IL-6), and tumor necrosing factor alpha (TNF-α) levels, no statistically significant differences were observed between the NAFLD (+) and NAFLD (-) subgroups. The level of Asprosin showed a positive correlation with IL-6 and TNF-α levels, while no significant relationship was found between the asprosin and any clinical or laboratory parameters in obese patients with NAFLD.

Conclusion: Serum asprosin levels were elevated in obese children. However, there were no significant findings to support the use of asprosin levels as a non-traumatic diagnostic indicator for NAFLD diagnosis in the pediatric age.

Keywords
Asprosin, obesity, fatty liver, adipokine

Anahtar kelimeler
Asprosin, obezite, karaciğer yağlanması, adipokin

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Öz

Giriş: Çocuklar arasında obezite oranlarının artmasıyla birlikte, alkole bağlı olmayan karaciğer yağlanması hastalığı (NAFLD) daha yaygın hale gelmektedir. Karaciğer biyopsisi NAFLD tanısında altın standart olarak kabul edilse de, invaziv bir işlem olması nedeniyle tarama amaçlı kullanımı pratik değildir. Yakın zamanda keşfedilen bir adipokin olan asprosin, açlık durumunda salınmaktadır. Bu çalışmada, obez hastalarda NAFLD tanısında asprosinin tanısal değerini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya yaşları 6 ile 18 arasında değişen toplam 142 katılımcı (71 obez, 71 kontrol) dahil edildi. Obez hastalar, hepatobilier ultrasonografik bulgulara göre NAFLD (+) ve NAFLD (-) olarak iki alt gruba ayrıldı ve klinik ve laboratuvar bulguları (asprosin düzeyi dahil) açısından karşılaştırıldı.

Bulgular: Obez ve obez olmayan hastalar karşılaştırıldığında, obez grupta asprosin düzeyleri anlamlı derecede daha yüksekti (P=0.034). Obez olguların 35'ine (%49,2) NAFLD tanısı konuldu. Vücut kitle indeksi (VKİ) benzer olmasına rağmen, bel çevresi ve insülin direnci NAFLD olan hastalarda daha yüksekti. Asprosin, interlökin-6 (IL-6) ve tümör nekroz faktörü alfa (TNF-α) düzeyleri karşılaştırıldığında, NAFLD (+) ve NAFLD (-) alt grupları arasında istatistiksel olarak anlamlı bir fark bulunmadı. Asprosin düzeyi, IL-6 ve TNF-α düzeyleriyle pozitif korelasyon gösterdi; ancak NAFLD'li obez hastalarda asprosin ile herhangi bir klinik veya laboratuvar parametresi arasında anlamlı bir ilişki saptanmadı.
Sonuç: Serum asprosin düzeyleri obez çocuklarda artmış olarak bulundu. Ancak, asprosin düzeylerinin çocukluk çağında NAFLD tanısı için travmatik olmayan bir tanı aracı olarak kullanılmasını destekleyecek anlamlı bulgular elde edilemedi.

Introduction

Obesity is a chronic metabolic disease associated with numerous comorbidities, which has increased worldwide more than threefold in the last 20 years among childhood and adolescence. In many studies, obesity has been shown to cause serious complications such as hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and cancer later in life (1-3). As obesity rates rise among children, NAFLD is becoming more prevalent, potentially resulting in liver inflammation, fibrosis, and, in severe cases, cirrhosis. NAFLD is closely linked to metabolic syndrome traits and can be viewed as a hepatic indication of insulin resistance (4). Liver biopsy, the gold standard for assessing NAFLD, is the only reliable way to differentiate between non-alcoholic steatohepatitis and simple steatosis. Although liver biopsy is considered the gold standard for diagnosing NAFLD, it is an invasive procedure and not practical for screening a large number of high-risk patients or for monitoring individuals with NAFLD post-treatment. Considering the importance of NAFLD in clinical practice and the drawbacks associated with liver biopsy, there is an increasing demand for precise, non-invasive imaging methods for assessment (5). Several techniques, including ultrasonography (US), magnetic resonance imaging, computed tomography, and magnetic resonance spectroscopy, have been employed to evaluate individuals with NAFLD, primarily focusing on measuring the extent of hepatic steatosis.

White adipose tissue not only functions as a tissue that provides energy reserve but also acts as a dynamic organ responsible for the synthesis and secretion of many adipokines, growth factors, and inflammatory markers such as leptin, adiponectin, tumor necrosis factor-α (TNF-α), resistin, and interleukin-6 (IL-6) (6). A changed secretion profile of adipokines from adipose tissue depots often marks obesity and related comorbidities. Findings from studies on metabolic hormones indicate that obesity is associated with elevated levels of leptin, TNF-α, and IL-6, while ghrelin levels tend to decrease (7-9).

The count of recognized adipokines has rapidly surged over the last 20 years (10). Among these, asprosin, a recently unveiled adipokine, is released in response to fasting (11). Multiple studies in the adult population have indicated a notable increase in circulating asprosin levels among individuals with higher body weight, encompassing both overweight and obese individuals (12-14). A recent investigation by Ke et al. (15) demonstrated a significant elevation in serum asprosin levels in untreated adult patients with NAFLD. Research on asprosin within the pediatric age group, however, remains scarce.

In light of these findings, this study aims to comprehensively investigate the relationship between asprosin, IL-6, TNF-α, and biochemical and clinical parameters in subjects with and without obesity and obese subjects with and without NAFLD in pediatric and adolescent age groups.

Material and Methods

Study Design and Participants

This study was designed as a cross-sectional, single-center, case-control research. A total of 142 participants aged between 6 and 18 years were included in the study. Among these participants who were admitted to the pediatric endocrinology clinic of our hospital, 71 cases diagnosed with obesity were assigned to the obese group. The control group comprised 71 healthy non-obese volunteers of the same age and sex who visited the hospital where the study was conducted for routine health checkups, including services such as vaccination. Exclusion criteria for the obese group encompassed a prior diagnosis of any chronic disease affecting the endocrine system (e.g., Cushing's disease, hypothyroidism), syndromes associated with obesity (e.g., Prader-Willi, Bardet-Biedl syndromes), other systemic disorders, and a history of drug use.

The obese patients were compared with control subjects regarding their clinical and laboratory features. Obese patients were also divided into subgroups NAFLD (+) and

NAFLD (-) according to hepatobiliary ultrasonographic features and compared with each other. The correlations between clinical/biochemical parameters and Asprosin, TNF-α, and IL-6 were also investigated among obese patients with NAFLD.

Clinical Investigations and Anthropometric Data

Height measurements in both an upright standing position and during deep inspiration were obtained using a wall-mounted stadiometer. Body Mass Index (BMI) was calculated by dividing the weight by the square of height (kg/m2). Standard Deviation Scores (SDS) for height, weight, and BMI were determined based on reference values for Turkish children (16). Individuals with a BMI exceeding the 95th percentile for their age and sex, as per Turkish children's reference values, were classified as obese and included in the obese group. Participants with a BMI between the 3rd and 85th percentiles were categorized as a non-obese group, and overweight cases were not included in this group. Waist circumference was measured with a tape measure at the level of the umbilicus. Measurements were taken from children with their abdomen freely exposed while standing upright. Upper arm circumference was measured between the acromial process in the shoulder and the olecranon process at the elbow, with the elbow bent at a 90-degree angle. The measurements were recorded in centimeters (cm) and analyzed. Triceps skinfold (TSF) thickness measurement was conducted while the arm was freely hanging by the side of the body. A caliper was utilized to measure the midpoint of the anterior surface of the forearm. The Tanita BC-418 equipment from Tokyo, Japan, was employed for bioelectrical impedance analysis to assess the fat mass and percentage of body fat (PBF). Blood pressure measurements followed a validated protocol, with systolic blood pressure (SBP) and diastolic blood pressure (DBP) recorded twice on the right arm after a 10-minute rest in the supine position, using a calibrated sphygmomanometer and conducted by one of the investigators. The average of the two blood pressure readings was considered. Pubertal status was determined based on the Tanner classification and categorized as pubertal or prepubertal (17).

Laboratory Investigations and Sonographic Evaluations

Peripheral blood samples were collected in the morning (between 8:00 and 9:00 a.m.) following a 10-hour fasting period. Fasting glucose levels were determined using the hexokinase method while fasting insulin levels were measured using the radioimmunoassay technique. Insulin resistance (IR) was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula: fasting insulin (μU/mL) × fasting glucose (mg/L)/405. Subjects with HOMA-IR values above >4 in the pubertal stage and >2.5 in the prepubertal stage were considered IR (18). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using the spectrophotometric method. Triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) concentrations were determined enzymatically using DP Modular Systems (Roche Diagnostic Corp., Indianapolis, IN). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula when plasma TG was < 400mg/dL. The diagnosis of NAFLD was based on ultrasonographic evidence of hepatic steatosis, following the criteria outlined in the ESPGHAN Hepatology Committee's guidelines (19). The same qualified radiologist conducted all examinations.

The measurement methods and kit details for adipokines are as follows;

Asprosin: Serum samples were analyzed using the ELISA (Enzyme-Linked Immunosorbent Assay) method with a Sunred kit (SunRed Biotechnology, China) (Kit catalog no: 201-12-7193, reference no: DZE201127193, lot no: 202304). The intra-assay coefficient of variation (CV) was <% 10, and the inter-assay CV was <% 12. The kit sensitivity was 1.0 ng/mL, and measurement linearity ranged from 1 to 300 ng/mL. The kit was stored at 2-8°C until use.

IL-6: Serum samples were analyzed using the ELISA method with a Sunred kit (SunRed Biotechnology, China) (Kit catalog no: 201-12-0091, reference no: DZE201120091, lot no: 202304). Intra-assay CV was <% 10, and inter-assay CV was <% 12. The kit sensitivity was 2.11 ng/L, and measurement linearity ranged from 3 to 600 ng/L. The kit was stored at 2-8°C until use.

TNF-α: Serum samples were analyzed using the ELISA method with a Sunred kit (SunRed Biotechnology, China) (Kit catalog no: 201-12-0083, reference no: DZE201127193, lot no: 202304). Intra-assay CV was <% 10, and inter-assay CV was <% 12. The kit sensitivity was 2.827 ng/L, and measurement linearity ranged from 3 to 900 ng/L. The kit was stored at 2-8°C until use.

Statistical Analysis

We conducted the statistical analysis using The Statistical Package for the Social Sciences (SPSS for Windows, Version 23.0, Chicago, IL, USA). Continuous measurements were reported as either median [Interquartile range (IQR)] or

mean ± standard deviation (SD), while categorical data were presented as counts and percentages. We employed Pearson's chi-square and Fisher's exact tests to compare categorical variables. The Shapiro-Wilk test was used to assess normality, and distribution was also checked when comparing continuous measurements. Normally distributed parameters were compared using the t-Test, while non-normally distributed parameters were compared using the Mann-Whitney U test. The Pearson correlation test was utilized to explore relationships among normally distributed variables, and the Spearman correlation was employed for variables that did not adhere to a normal distribution. A p-value less than 0.05 was considered indicative of statistical significance.

Ethics

Approval was obtained from the Ethics Committee prior to the commencement of the study (protocol number: 70904504/103 dated March 09, 2022). Informed consent was acquired from the parents of all participants before their involvement. The study strictly adhered to the principles outlined in the Declaration of Helsinki and followed ethical guidelines.

Results

The clinical and laboratory characteristics of obese and non-obese subjects are summarized in Table 1.

The age, sex, and pubertal status were similar in the two groups. The BMI, BMI SDS, waist and upper arm circumferences, TSF thickness, total body fat mass, PBF, and

Table 1. The clinical and laboratory characteristics of obese and non-obese subjects

	Obese Subjects (n=71)	Non-obese Subjects (n=71)	P
Age (year)	11.9 ± 3.0	11.3±2.8	0.233
Male (%)	42.2	39.4	0.733
Pubertal (%)	77.4	76.0	1.000
BMI (kg/m^2)	31.8 (7.3)	17.6 (3.3)	<0.001
BMI SDS	2.7 (0.7)	-0.1 (1.3)	<0.001
Waist circumference (cm)	93.0 (18.8)	62.0 (8.8)	<0.001
Upper arm circumference (cm)	32.0 (6.8)	22.0 (3.8)	<0.001
TSF thickness (mm)	20.6 (9.1)	6.9 (6.5)	<0.001
Fat mass (kg)	28.5 (15.3)	7.2 (4.6)	<0.001
PBF (%)	37.0 (6.7)	20.3 (5.6)	<0.001
SBP (mmHg)	120 (10)	100 (20)	<0.001
DBP (mmHg)	80 (10)	70 (10)	<0.001
Glucose (mg/dL)	88.1± 6.7	85.0 ± 6.0	0.004
Insulin (uIU/mL)	20.3 (19.2)	7.0 (5.6)	<0.001
HOMA-IR	4.4 (4.6)	1.4 (1.3)	<0.001
ALT (U/L)	20 (16)	12 (3)	<0.001
AST (U/L)	19 (10)	22 (8)	0.359
Triglyceride (mg/dL)	90.0 (48)	63.5 (25)	<0.001
TC (mg/dL)	156.8 ± 27.0	156.1 ± 24.5	0.805
LDL-C (mg/dL)	95.0 ± 24.3	87.3 ± 18.9	0.033
HDL-C (mg/dL)	46.8 (14.1)	60.7 (21.3)	<0.001
Asprosin (ng/mL)	42.7 (31.1)	39.0 (23.3)	0.034
TNF-α (ng/L)	300.9 (195.9)	315.8 (127.8)	0.317
IL-6 (ng/L)	47.1 (39.0)	53.5 (25.1)	0.185

Data are given mean±SD, median (IQR) or n(%)

BMI: body mass index; BMI-SDS: standard deviation score of body mass index; TSF: triceps skinfold; PBF: percentage of body fat; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HOMA-IR: homeostasis model assessment of insulin resistance; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; TNF- α: tumor necrosis factor-α; IL-6: interleukine 6

SBP and DBP were significantly higher in the obese group (P<0.001). When laboratory parameters were examined, fasting glucose, HOMA-IR, ALT, triglyceride, and LDL-C levels were significantly higher in obese patients while HDL-C was lower (P<0.001) (Table 2).

When comparing obese and non-obese patients, IL-6 and TNF-alpha levels were similar, whereas Asprosin levels were significantly higher in the obese group (P=0.317; P=0.185; P=0.034; Figure 1).

Out of the 35 patients with NAFLD, 25 (71.4 %) had grade 1, 8 (22.8 %) had grade 2, and 2 (5.7 %) had grade 3 hepatosteatosis. Comparisons of the clinical and laboratory characteristics of obese subjects with and without NAFLD are demonstrated in Table 2. In patients with and without NAFLD, similar age, sex, and pubertal status were observed. While BMI and BMI SDS were similar, waist circumference was higher in patients with NAFLD (P=0.066; P=0.384; P=0.011). DBP and HOMA-IR were also higher in patients with NAFLD (P=0.029; P=0.032). Lipid profiles and liver enzymes were similar in both groups. No statistically significant differences were observed between the groups when comparing Asprosin, IL-6, and TNF-α levels.

Correlation analysis was performed, and the relationships between Asprosin, TNF-α, IL-6, and clinical and laboratory parameters in obese patients with NAFLD are presented in Table 3. The level of Asprosin showed a positive correlation with IL-6 and TNF-α levels, while no significant relationship was found between the adipokines and any clinical or laboratory parameters.

Table 2. Comparison of the clinical and laboratory characteristics of obese subjects with and without NAFLD

	NAFLD (+) Obese subjects (n=35)	NAFLD (-) Obese subjects (n=36)	P
Age (year)	12.4 ± 2.7	11.4 ± 3.3	0.170
Male (%)	48.5	36.1	0.411
Pubertal (%)	82.8	72.2	0.481
BMI (kg/m^2)	31.9 (7.5)	30.7 (6.7)	0.066
BMI SDS	2.9 (0.8)	2.6 (0.5)	0.384
Waist circumference (cm)	98 (16.5)	84.5 (21)	0.011
Upper arm circumference (cm)	33 (5.5)	31 (7.5)	0.050
TSF thickness (mm)	22.2 (8.9)	19.9 (8.6)	0.205
Fat mass (kg)	30.8 (13.9)	27.5 (17.2)	0.113
PBF (%)	37.0 (6.5)	36.6 (6.3)	0.904
SBP (mmHg)	120 (13.8)	120 (21.3)	0.306
DBP (mmHg)	80 (10)	75 (16.3)	0.029
Glucose (mg/dL)	88.8 ± 6.5	87.4 ± 6.9	0.361
Insulin (uIU/mL)	24.8 (18.4)	17.3 (20.8)	0.033
HOMA-IR	5.1 (3.7)	3.7 (4.3)	0.032
ALT (U/L)	20.5 (17.5)	16.0 (14.3)	0.461
AST (U/L)	18.5 (9.3)	19.5 (7.3)	0.782
Triglyceride (mg/dL)	89.0 (36.5)	91.5 (54.8)	0.932
TC (mg/dL)	155.4 ± 26.1	158.3 ± 28.1	0.657
LDL-C (mg/dL)	95.0 ± 22.3	94.9 ± 26.4	0.988
HDL-C (mg/dL)	43.9 (11.5)	50.1 (14.8)	0.112
Asprosin (ng/mL)	40.3 (17.6)	47.6 (51.1)	0.543
TNF-α (ng/L)	286.5 (90.9)	306.4 (261.9)	0.240
IL-6 (ng/L)	41.0 (23.8)	51.9 (56.3)	0.104

Data are given mean±SD, median (IQR) or n(%)

NAFLD: non-alcholic fatty liver disease; BMI: body mass index; BMI-SDS: standard deviation score of body mass index; TSF: triceps skinfold; PBF: percentage of body fat; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA-IR: homeostasis model assessment of insulin resistance; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; TNF-α: tumor necrosis factor-α; IL-6: interleukine 6

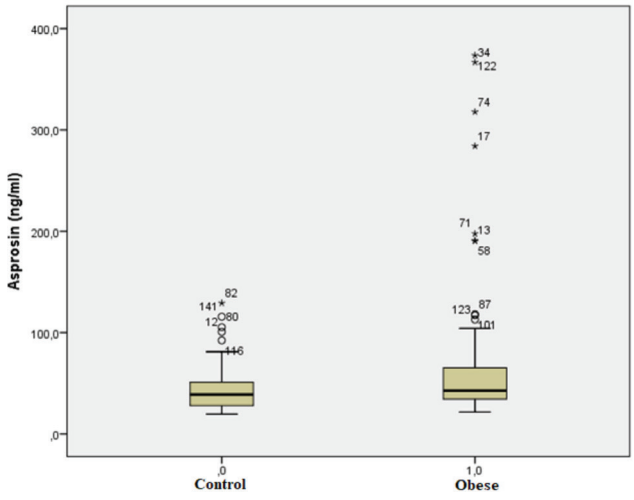

Figure 1. The distribution of asprosin levels in obese and non-obese subjects

Discussion

Obesity represents a significant global public health concern, leading to elevated rates of illness and death. It can stem from genetic, metabolic, or endocrine imbalances and, if left untreated, significantly reduces life expectancy while diminishing overall quality of life. (20) Researchers have conducted various studies to better understand the role of hormones and mediators released in the body in body weight and energy balance. Adipokines secreted from adipose tissue are also a significant focus of interest. Recent research has uncovered the intricate and paradoxical role of asprosin in obesity. Numerous studies have indicated elevated levels of asprosin in both humans and mice suffering from obesity. Pathologically high serum levels of asprosin have been observed in obese adults, children, and mice. In contrast, obese mice exhibited reduced body weight and food intake when treated with a specific asprosin antibody (13,21,22).

Additionally, a separate study highlighted the synthesis of asprosin in human salivary glands. A study conducted by Ugur et al. (14) found that as the BMI of subjects increased, the levels of LDL-C and asprosin in both saliva and blood also increased.

In our study, when we compared obese patients with healthy individuals of the same age group, matched for pubertal stage and gender ratio with the obese patients, we also found that the levels of asprosin were statistically significantly higher in the obese group. However, this difference was not markedly pronounced. While most studies investigating the relationship between asprosin and obesity are conducted in the adult age group, a study comparing obese

Table 3. The relationship between Asprosin, TNF-α, IL-6 and clinical and laboratory parameters in the obese patients with NAFLD

	Asprosin	TNF-α	IL-6
Age (year)	P:0.897 R:-0.023	P: 0.209 R:-0.218	P: 0.239 R:-0.204
BMI (kg/m^2)	P:0.520 R:-0.112	P: 0.312 R: -0.176	P: 0.570 R: -0.099
BMI SDS	P:0.754 R:0.055	P: 0.973 R: 0.06	P: 0.570 R: -0.099
Waist circumference (cm)	P: 0.427 R:-0.139	P: 0.318 R:-0.174	P: 0.541 R:-0.107
Upper arm circumference (cm)	P: 0.997 R:-0.001	P: 0.565 R:-0.101	P: 0.915 R:-0.019
TSF thickness (mm)	P: 0.332 R:0.174	P: 0.427 R: 0.143	P: 0.334 R: 0.174
Fat mass (kg)	P:0.428 R:-0.141	P:0.132 R:-0.264	P:0.336 R:-0.170
PBF (%)	P:0.099 R:-0.288	P:0.160 R:-0.247	P:0.396 R:-0.150
SBP (mmHg)	P: 0.702 R:-0.074	P: 0.505 R:-0.229	P: 0.598 R: -0.102
DBP (mmHg)	P: 0.071 R:0.340	P: 0.428 R: 0.153	P: 0.118 R: -0.177
HOMA-IR	P: 0.771 R:-0.051	P: 0.070 R:-0.203	P: 0.248 R:-0.200
ALT (U/L)	P:0.755 R:-0.055	P: 0.989 R: 0.003	P: 0.819 R: -0.040
AST (U/L)	P:0.933 R:0.015	P:0.295 R:0.182	P:0.576 R:0.098
Triglyceride (mg/dL)	P:0.831 R:0.037	P:0.476 R:-0.125	P:0.644 R:-0.081
TC (mg/dL)	P:0.543 R:-0.106	P:0.212 R:0.216	P:0.085 R:-0.295
LDL-C (mg/dL)	P:0.409 R:-0.144	P:0.183 R:-0.230	P:0.071 R:-0.309
HDL-C (mg/dL)	P:0.949 R:-0.011	P:0.127 R:-0.264	P:0.054 R:-0.328
Asprosin (ng/mL)	-	P<0.001 R:0.624	P<0.001 R:0.593
TNF-α (ng/L)	P<0.001 R:0.624	-	P<0.001 R:0.818
IL-6 (ng/L)	P<0.001 R:0.593	P<0.001 R:0.818	-

*Statistically significant correlation.

BMI: body mass index; BMI-SDS: standard deviation score of body mass index; TSF: triceps skinfold; PBF: percentage of body fat; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA-IR: homeostasis model assessment of insulin resistance; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; TNF- α: tumor necrosis factor-α; IL-6: interleukine 6

patients aged between 6-14 years with healthy individuals of normal body weight reported a negative correlation between asprosin levels and age- and gender-adjusted BMI. The findings of this study differ from the majority of studies in the literature, suggesting a complex relationship between asprosin and obesity (23). The degree of obesity may also be an essential factor affecting asprosin levels. In a study conducted by Romero et al. (11) in adult patients, the average BMI was >35 kg/m² (approximately equivalent to >+3 SD), and the patients' asprosin levels were significantly higher compared to the control group. Our study's median BMI SDS was 2.7, and the asprosin level was slightly higher than the control group. However, in the research conducted by Long et al. (23), the obese group exhibited relatively lower BMI standard deviations (2.09±0.47 in males and 2.22±1.08 in females) compared to previously mentioned studies. Surprisingly, their levels of asprosin were lower than those in the control group. Furthermore, the obese patients in this study had significantly lower insulin and HOMA-IR levels, indicating that they might be in a metabolically healthy 'honeymoon phase (24)'. This finding holds significance in light of the dose-dependent relationship between BMI and adverse health outcomes, particularly insulin resistance, which closely ties in with the role of asprosin (11, 24). Serum asprosin levels were found to be significantly different between groups in another study: 70.9 ± 17.4 ng/mL, 79.7 ± 29.5 ng/mL, and 106.2 ± 122.6 ng/mL in normal weight, overweight, and obese children, respectively, which is compatible with dose-dependent relationship between BMI and asprosin levels (25).

Non-alcoholic fatty liver disease is the most common chronic liver complication among adult and pediatric obese subjects (26). The relationship between asprosin and NAFLD in obese patients, as well as its role in the pathogenesis, remains under investigation. The role of asprosin in the pathogenesis of NAFLD has not yet been fully elucidated. Several hypotheses have been proposed in this regard. One of the proposed mechanisms is that excessive asprosin in obese patients increases hepatic glucose release, resulting in partial or systemic insulin resistance (11,27). Hyperinsulinemia and hyperglycemia induced by IR have been reported to create a lipid input-to-output imbalance, promoting hepatic steatosis (28). Another hypothesis suggests that the accumulation of fat in the liver is significantly influenced by de novo lipogenesis, a process involving the production and storage of elevated glucose in the form of triglycerides through glycolysis.

Additionally, a recent study highlighted the role of recombinant asprosin in promoting metabolic disorders, triggering inflammation through the TLR4/JNK pathway (29). Notably, Ke et al. (15) found significantly higher levels of serum asprosin in adult NAFLD patients, which was also corroborated in the pediatric age group (30). However, when we divided our obese patients into those with and without NAFLD, no difference in asprosin levels was observed. Obesity manifests in various forms, such as whole-body obesity and abdominal obesity. Abdominal obesity, in particular, is strongly linked to visceral obesity and NAFLD (31). In our research, we observed that obese children exhibited a broader waist circumference, indicating a predominance of abdominal obesity among our study participants.

Additionally, patients with NAFLD had wider waist circumferences compared to those without NAFLD. Compared to insulin resistance, which plays a crucial role in the pathogenesis of NAFLD, patients with NAFLD similarly exhibited higher fasting insulin levels and HOMA-IR index in cases with NAFLD. However, when we compared the levels of ALT, a well-known marker for NAFLD, between obese individuals with and without NAFLD, there was no statistically significant difference. Similarly, the levels of TNF-alpha and IL-6, markers of chronic inflammation, were not significantly increased in NAFLD patients. This may be explained by the higher number of cases in our patient population in the early stage of hepatosteatosis (grade 1, 71.8%). In the future, when a more chronic period develops and the degree of inflammation increases, asprosin levels may increase. Serum asprosin levels were positively correlated with TNF-alpha and IL-6. This finding suggests that asprosin may also play a role in chronic inflammation similar to proinflammatory cytokines. However, our study found no significant correlation between asprosin levels and the other parameters examined.

Study Limitations

There are certain limitations in our study. Being a case-control study precludes establishing a causal relationship between asprosin, obesity, and NAFLD. Secondly, we opted for liver ultrasonography as a diagnostic method for NAFLD, which, although non-invasive, has a slightly lower diagnostic accuracy than liver biopsy. Additionally, a post-hoc power analysis for the comparison of asprosin levels between obese subjects with and without NAFLD indicated a small effect size (Cohen's $d = 0.19$) and low statistical power (12.4% at $\alpha = 0.05$), suggesting that our study was underpowered to detect small differences between groups.

Conclusion

In conclusion, our results indicate that serum asprosin levels were elevated in obese children. However, when

comparing obese patients with and without NAFLD, similar levels of asprosin were observed. There were no significant findings to support the use of asprosin levels as a non-traumatic diagnostic indicator for NAFLD diagnosis in the pediatric and adolescent age group. Further studies are needed to explore the molecular mechanism of asprosin in childhood obesity and NAFLD.

Ethics

Ethical Approval: Approval was obtained from the Ethics Committee prior to the commencement of the study (protocol number: 70904504/103 dated March 09, 2022). Informed consent was acquired from the parents of all participants before their involvement. The study strictly adhered to the principles outlined in the Declaration of Helsinki and followed ethical guidelines.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

The Influence of Family Attitudes on the Development of Functional Constipation in Children

Aile Tutumlarının Çocuklarda Fonksiyonel Kabızlığın Gelişimi Üzerindeki Etkisi

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Abstract

Introduction: Functional constipation (FC) is a significant health issue among children and majority of treatment strategies are not evidence-based. In addition to medical treatments for FC, the psychological dimension that is believed to play a significant role.

Materials and Methods: This cross-sectional study was conducted on patients under 18 years of age who were diagnosed with chronic FC. The Parental Attitude Research Instrument (PARI) developed by Schaefer and Bell was applied to the parents of the patients.

Results: A total of 142 patients, 82 with FC and 60 control patients, were included. All three PARI sub-dimensions were significantly higher in the constipation group ($p<0.0001$). While overcontrol and strict discipline scores were also higher in the constipation group (<0.0001), they were not shown to be predictive factors. There was no correlation between the duration of constipation and PARI sub-dimension scores in the constipation group ($p>0.05$). When comparing PARI sub-dimensions according to fecal retention habit, encopresis, and eating disorder in patients with constipation, overcontrol sub-dimension score was found to be low in those with a fecal retention habit ($p=0.002$). In the multivariate regression analysis, only the democratic attitude and equality providing sub-dimension were found to be an independent risk factor.

Conclusion: This study suggests that improving parental attitudes may help prevent the development of FC habit in children. It is essential to address family attitudes in detail, particularly for children who do not respond well to medical treatment, and to conduct comprehensive studies on behavioral treatment and family therapy.

Keywords
Children, family attitudes, functional constipation, parental attitude research instrument

Anahtar kelimeler
Çocuklar, aile tutumları, fonksiyonel kabızlık, ebeveyn tutum araştırma aracı.

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Öz

Giriş: Fonksiyonel kabızlık (FK), çocuklarda önemli bir sağlık sorunudur ve tedavi stratejilerinin çoğu kanıta dayalı değildir. Tıbbi tedavilere ek olarak, FK'da psikolojik boyutun önemli rol oynadığına inanılır.

Gereç ve Yöntem: Bu kesitsel çalışma, kronik FK tanısı almış 18 yaş altı hastalar üzerinde yürütülmüştür. Schaefer ve Bell tarafından geliştirilen Ebeveyn Tutum Araştırma Aracı (PARI) hastaların ebeveynlerine uygulanmıştır.

Bulgular: 82'si FK'li ve 60'ı kontrol hastası olmak üzere toplam 142 hasta çalışmaya dahil edilmiştir. Üç PARI alt boyutu da kabızlık grubunda önemli ölçüde daha yüksekti ($p<0,0001$). Aşırı kontrol ve katı disiplin puanları da kabızlık grubunda daha yüksek olsa da (<0,0001), bunların prediktif faktörler olduğu gösterilememiştir. Kabızlık grubunda kabızlık süresi ile PARI alt boyut puanları arasında korelasyon

yoktur (p>0,05). Kabızlık olan hastalarda dışkı tutma alışkanlığı, dışkı kaçırma ve yeme bozukluğuna göre PARI alt boyutları karşılaştırıldığında dışkı tutma alışkanlığı olanlarda aşırı kontrol alt boyut puanı düşük bulundu (p=0,002). Çok değişkenli regresyon analizinde yalnızca demokratik tutum ve eşitlik sağlama alt boyutunun bağımsız risk faktörü olduğu bulundu.
Sonuç: Bu çalışma, ebeveyn tutumlarının iyileştirilmesinin çocuklarda FK alışkanlığının gelişmesini önlemeye yardımcı olabileceğini düşündürmektedir. Özellikle tıbbi tedaviye iyi yanıt vermeyen çocuklar için aile tutumlarının ayrıntılı olarak ele alınması ve davranışsal tedavi ve aile terapisi konusunda kapsamlı çalışmalar yapılması önemlidir.

Introduction

Functional constipation (FC) is a significant health issue among children that is widespread and has severe impacts on their lives and families. The prevalence rates of constipation in children vary based on geographical location, ranging from 1% to 30%, while fecal incontinence rates range from 1.6% to 4.4% (1). Bio-psychosocial risk factors such as psychological stress, poor dietary habits, obesity, and early caregiver changes are the most crucial predisposing factors for FC. While medications have proven useful in adults, the same cannot be said for children, and there is no consensus regarding their dosages and duration of use to relieve symptoms. Insufficient treatment can lead to FC persisting into adulthood (2,3).

Incontinence has a significant impact on quality of life and daily functionality, and it can be linked to behavioral issues in children. Treating underlying constipation and using a cognitive approach typically results in an improvement in incontinence (4). Majority of treatment strategies for childhood constipation are not evidence-based. Strategies such as eliminating stressor factors, toilet training, rational use of laxatives for defecation and maintenance, and regular follow-up are recommended (5). In addition to medical treatments for FC, the psychological dimension that is believed to play a significant role in constipation is often overlooked. Considering the possibility of constipation arising as a result of psychological anxiety, examining the temperament, attitudes, and psychological characteristics of the parents with whom the baby first establishes a relationship in the early stages can be guiding for treatment.

The aim of this study was to evaluate the effect of parental attitude and family structure on FC using the PARI scale in children who are resistant to medical treatment.

Materials and Methods

This cross-sectional study was conducted on patients under 18 years of age who were diagnosed with chronic functional constipation according to ROMA IV criteria and applied to the Pediatric Gastroenterology and Hepatology Clinic of Bursa City Hospital between February and August 2021. The presence of symptoms for at least one month and occurring at least once a week were accepted as criteria for chronic FC. The Parental Attitude Research Instrument (PARI) developed by Schaefer and Bell was applied to the parents of the patients (6). The PARI questionnaire was also administered to the parents of healthy children under 18 years old as a control group. Informed consent was obtained from the parents of all participants.

The Rome IV criteria were used to characterize constipation (7,8).

These are the criteria:

< 4 years old, with at least two of the following conditions met for at least one month:

- Less than two or two defecations per week
- History of excessive stool buildup
- Painful and hard defecations
- Large-diameter stools
- The presence of a large fecal mass in the rectum

>4 years old and after acquiring toilet skills, the following criteria can be used:

- History of fecal leakage at least once a week
- A history of large-scale defecation that may even block the toilet

Fecal incontinence, on the other hand, was defined as recurrent uncontrolled discharge of fecal material from the anus at least a few times a month for the last 3 months according to the ROMA IV criteria. We also asked patients about the presence of eating disorders and food intolerance to reflect secondary reflux caused by constipation and to determine other effects of parental attitude.

Assessment of Parental Attitude

The PARI scale is based on the principle that the child's personality development is directly influenced by the parents' child-rearing attitudes and family life. In this study, the shortened 60-clause form and three sub-dimensions (overcontrol, democratic attitude, recognition of equality, strict discipline) were used. The scale was applied to fathers as well, and only the factors of excessive protectiveness, democratic/equality, and strict discipline were used to identify attitudes. The dimensions of rejecting housekeeping

and marital conflict discrepancies were not included. The clauses in the scale dimensions are given mixed. The items do not have a question format and contain both positive and negative statements. It is a four-point Likert-type scale. One of the options "I find it very appropriate" 4 point, "I find it quite appropriate" 3 point, "I find it somewhat appropriate" 2 point, and "I do not find it appropriate at all" 1 point is marked for each expression. However, the answers given to clauses 29 and 44 are scored in reverse. "4" points are given for the "1" point answer, "3" points for the "2" point answer, "2" points for the "3" point answer, and "1" point for the "4" point answer. A separate score is obtained for each sub-test representing each dimension. The high total score for each sub-test indicates that the attitude reflected in that dimension is approved.

Overcontrol: Overcontrol, intrusiveness, asks the child to be dependent, active, and hardworking. It believes that the mother should be extremely self-sacrificing, and that the child should understand this. It measures the extent of the mother's forceful intervention in the child's life and the degree of the child's dependence on the parents. It explains 37% of the total variance. It contains 16 clauses. The lowest score is 16, the highest score is 64. High scores on this scale are considered negative.

Democratic Attitude and Providing Equality: It covers the extent to which parents provide equal rights to their children, encourage them to express their ideas openly, and establish a friendly and sharing relationship with them. The scale measures the degree of parental encouragement and sharing and accounts for 10% of the total variance. It consists of 9 items, with the lowest score of 9 and the highest score of 36. High scores are considered positive.

Strict Discipline: This sub-dimension mostly reflects a negative child-rearing attitude and encompasses issues such as suppressing sexual behavior and aggression, believing in strict discipline and punishment, and expecting absolute dominance and obedience from the child. The strict discipline dimension was formed by combining subscales that showed significant correlations with the other four factors, creating a distinct pattern. It includes 16 items, with the lowest possible score of 16 and the highest possible score of 64. High scores on this dimension are considered to be indicative of negative parenting attitudes.

Statistical Analysis

Categorical variables were expressed as percentages and compared between the two groups using the Chi-square test. The Shapiro-Wilk test was used to evaluate normal distribution conformity for continuous variables. As age and PARI sub-dimension scores did not follow a normal distribution, they were reported as median (min-max) and compared using the Mann Whitney U test. Univariate and multivariate logistic regression analyses were performed to identify risk factors for constipation. Variables with a p-value <0.05 in the univariate analysis were included in the multivariate analysis. Odds ratios were calculated with 95% confidence intervals. The constipation group was coded as 1 and the control group was coded as 0.

Results

A total of 142 patients, 82 with FC and 60 control patients, were included in the study. The constipation group had a median age of 4.8 (min 1.6- max 17.6) years, while the control group had a median age of 5 (min 4- max 17.2) years. There was no significant difference in the mean age between the two groups. Both groups had a higher proportion of females, but there was no significant difference in gender distribution between the two groups (p>0.05). In the constipation group, 46 (56%) patients were female, 36 (43.9%) patients were male and in the control group: therewere 36 (60%) healthy females, 24 (40%) healthy males (p=0.97). The median duration of constipation in the patients was 3 (min:1 - max: 7) months. Among the constipation group, 28 patients (36.4%) had a defecation frequency of once a week, 47 patients (61%) had a frequency of twice a week, and 2 patients (2.6%) had a frequency of less than once a week. Detailed defecation and nutritional characteristics of the patients are presented in Table 1. When comparing the PARI sub-dimension scores between the constipation and control groups, all three sub-dimensions were significantly higher in the constipation group (p<0.0001). Only the high score in democratic attitude and providing equality sub-dimension was identified as a positive predictor factor for constipation. While overcontrol and strict discipline scores were also higher in the constipation group compared to the control group (p<0.0001), they were not shown to be predictive factors for constipation (Table 2). There was no correlation between the duration of constipation and PARI sub-dimension scores in the constipation group (p>0.05). When comparing PARI sub-dimensions according to fecal retention habit, encopresis, and eating disorder in patients with constipation, overcontrol sub-dimension score was found to be low in those with a fecal retention habit (p=0.002). Logistic regression analysis was used to identify risk factors for constipation. In the univariate regression analysis, overcontrol and strict discipline sub-

dimension scores were identified as risk factors. However, in the multivariate regression analysis, only the democratic attitude and equality providing sub-dimension was found to be an independent risk factor (Table 3 and Table 4).

Table 1. Defecation and nutritional characteristics of patients with constipation

Characteristics	n (%)
Defecation quality Thick caliber Goat dung Fine caliber	 51 (66.2) 23 (29.9) 3 (3.9)
Presence of fecal retention habit	63 (81.8)
Presence of food allergy Egg Milk Other	11 (14.3) 7 (9.1) 2 (2.6) 2 (2.6)
Presence of encopresis	17 (22.1)
Eating disorder None Selective. Few Nausea. Dyspepsia	 40 (51.9) 29 (37.7) 8 (10.4)

Discussion

Chronic functional constipation is a significant health issue that results in abdominal pain, reflux, eating disorders, and encopresis. It leads to social isolation and anxiety disorder in children, thereby reducing their quality of life. Psychosocial effects also result in decreased school performance. Studies have reported that the quality of life of children with functional constipation and encopresis is worse than those with only functional constipation. Furthermore, older children with functional constipation have worse quality of life than younger age groups. Predisposing factors for childhood constipation include psychological stress related to home and school, siblings with health problems, parental separation, low sociocultural environment, poor childrearing style, low fiber diet, excessive consumption of junk food, food allergy, irregular eating habits with parents, obesity, physical or sexual-emotional abuse, and exposure to war (9,10). Stressors, including separation from a best friend, exam failure, severe illness of a family member, loss of parent's job, frequent punishment by parents, and living in a war-affected region, were identified in studies (11). Our

Table 2. Comparison of PARI sub-dimension scores according to the presence of constipation

PARI sub-dimensions	Those with constipation median (min, max)	Those with non-constipation median (min, max)	p
Overcontrol	45 (22-64)	36.5 (23-60)	<0.0001
Democratic Attitude and Providing Equality	30 (21-36)	27 (17-36)	<0.0001
Strict Discipline	37 (22-60)	32 (20-60)	0.002

Table 3. Comparison of PARI sub-dimensions according to fecal retention. encopresis and eating disorder

PARI sub-dimensions	Variables		p
	With fecal retention n:63 (%)	Without fecal retention n:14 (%)	
Overcontrol	41 (22-64)	53.5 (28-62)	0.03
Democratic attitude and Providing equality	30 (21-36)	30 (25-34)	0.87
Strict discipline	36 (22-60)	41.5 (29-57)	0.10
	With encopresis n=17 (%)	Those without encopresis n=60 (%)	
Overcontrol	43 (25-57)	46 (22-64)	0.26
Democratic attitude and Providing equality	30 (25-34)	30 (21-36)	0.70
Strict discipline	35 (28-49)	38 (22-60)	0.42
	Those with eating disorder n=37 (%)	Those without eating disorder n=40 (%)	
Overcontrol	46 (22-64)	44.5 (25-64)	0.86
Democratic attitude and Providing equality	30 (21-34)	30 (21-36)	0.34
Strict discipline	38 (22-60)	36.5 (22-58)	0.91

Table 4. Evaluation of risk factors for constipation with logistic regression analysis				
PARI sub-dimensions	Univariate logistic analysis		Multivariate logistic analysis	
	OR (%95 CI)	p	OR (%95 CI)	p
Age	0.942 (0.851-1.044)	0.25		
Female gender	0.989 (0.497-1.970)	0.97		
Overcontrol	1.063 (1.027-1.100)	<0.0001	1.024 (0.953-1.100)	0.51
Democratic attitude and providing equality	1.267 (1.136-1.413)	<0.0001	1.239 (1.104-1.390)	<0.0001
Strict discipline	1.070 (1.023-1.119)	0.003	1.032 (0.942-1.131)	0.49

study focused on investigating the effect of parents' attitudes towards events on their children's functional constipation, rather than the impact of individual stressor factors.

Every parent may display different attitudes towards their children, either knowingly or unknowingly. According to the literature, the mother's behavior and attitude directly influence the emotional state, temperament, and behavioral disorders of the child. Studies have shown that children whose parents are overprotective and preventive in the early years display negative emotions (12,13). In another study conducted with 101 children aged 2-6 years, it was seen that the rate of constipation was more common in children whose parent's attitude was more disciplined and stricter. In addition, FC is more common in children who are given toilet training rigidly or at an early age (14). In the study conducted by Akyıldız et al. with 47 children aged 2-13, it was found that 33% of the children were affected by maternal attitude (repressive toilet training, desire to give toilet training at an early age, broken family relationships) in constipation (15). Therefore, it is believed that the mother's attitude during the early period, when the body is used as a means of expression, may be related to the child's psychosomatic symptoms. In our study, we found that fecal retention behavior increased in children of over-controlled parents.

From a psychoanalytic perspective, fecal retention and encopresis in children are based on the inadequacy of the mother's inclusive functions in the early period and the child's intense fear of object loss. By controlling the muscles in the anus, the child creates a second skin for himself and holds the stool in. This is a defense mechanism against separation and loss fears, known as "holding the object in". Clinical studies emphasize the importance of archaic fears and early experiences in the development of intestinal distress. It is suggested that this situation is caused by the child's separation anxiety and the fear of not being able to exist in the early period. Each time the child has a bowel movement, it triggers these fears, and the fear of loss makes it difficult to separate from internal objects (such as feces) and to let go of the object. Therefore, it is stated that the child retains his stool when he thinks of the absence of his parents, and constipation appears as a symptom in order to avoid the anxiety of abandonment and loss (16). In our study, when we questioned the parents, we observed that constipation was triggered when the child started school and the mother started to work and changed caregivers.

In our study, we aimed to investigate the impact of parental attitudes on children with functional constipation who have been suffering for at least a month, encopresis and with or without fecal retention behavior. Our findings revealed that some children with constipation had over-controlled parents while others had parents who provided unlimited equal rights and allowed them to expand their boundaries. Although the tightly controlled and extreme discipline score was higher in those with constipation, no independent risk factors were found for constipation. Only democratic attitude and equal rights score were found to be high as independent risk factors for constipation. It was interpreted that children with strict control attitudes of parents in the constipation group tended to be more introverted and passive, while children with parents who had democratic attitudes and equal rights tended to direct their parents according to their wishes, had intense tantrums, difficulty complying with instructions, and were anxious. Similar to our study, Nishadi Ranasinghe et al found in the literature that these children exhibited some abnormal personality features and were more prone to anxiety problems (17). Therefore, we interpreted the behavior patterns of constipated children in this way, but we acknowledge that our study had limitations. Firstly, this is a single-center study, and there is a need for a multicenter study to validate similar findings across all constipated children. In that we did not evaluate these children with any specific scale in this respect. We believed that it is possible that these children developed voluntary sphincter control in order to manage their parents, react against strict discipline, or seek attention from their parents,

which may be a contributing factor in the development of chronic constipation.

It has been shown that older children with constipation exhibit more intense mood disorders such as hostility, aggression, negative self-efficacy, emotional unresponsiveness, and emotional instability (18,19). Our study emphasizes that mood disorders resulting from parental attitudes, rather than dietary factors, contribute to the persistence of functional constipation by facilitating reactive sphincter control and fecal retention behavior, leading to pelvic floor dyssynergia. Additionally, it has been found that health-related quality of life (HRQoL) is lower in children with mood disorders compared to controls (70.6 vs. 79.0, $p<0.05$).

Studies have shown that the competitive lifestyle of today's society leads parents to leave their children for long hours with grandparents, domestic servants, or in day care centers. The uncontrolled application of a democratic and equalitarian attitude results from a decreasing amount of time parents spend with children, the parents' sense of inadequacy and guilt, and the expansion of the children's restrictions (20). In our study, it was shown that the parents of children with fecal retention habits had a high excessive control attitude score ($p=0.03$). Although the strict discipline score was found to be significantly higher in patients without fecal retention habits, it may not be correct to interpret it in this direction due to the low number of patients in this group. In contrast to our study, in the study by Marieke et al., children of parents with high overprotection and self-pity attitudes were associated with increased fecal incontinence (20). We believe that this difference originates from social differences in child raising and individualization. In more patriarchal societies like ours, we attribute it to the delay in the child's identity development and individuation.

Study Limitations

One limitation of our study is that we did not apply a behavioral scale to the children and did not include all sub-dimensions of the PARI scale. However, studies that included certain sub-dimensions of the scale have been conducted (21). This is a single-center study, and we emphasize the need for a multicenter study to validate similar findings across all constipated children.

Functional constipation is a significant health concern in childhood, and the psychosocial influence of children is affected by the parents' approach, particularly the family's attitudes towards nutrition disorders. This study suggests that improving parental attitudes may help prevent the development of fecal retention habit in children. We found that an excess of democratic attitude increases the risk of chronic constipation in children. Furthermore, we observed that medical treatment alone is inadequate for children who continue their fecal retention habit and may lead to conflicts with the family. Therefore, it is essential to address family attitudes in detail, particularly for children who do not respond well to medical treatment, and to conduct comprehensive studies on behavioral treatment and family therapy.

Conclusion

Chronical functional constipation is an important problem that shopes and individual's family relation shapes and social life. The main components of treatment, cognitive therapy and family counseling. Family Dynamics and parent attitudes is raising children must be observed, examined and menaged. İn difficult and chronic cases, child psychiatry help should be sought.

Ethics

Ethical Approval: This study was performed in line with the principles of the Declaration of Helsinki. This study protocol was approved by the Bursa Institutional Ethics Committee with the decision number of 2021-3/9, date: 17.02.2021. An informed consent form was obtained from the participants before initiating the study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Pediatric Hypercalcemia: Insights into Clinical Features and Etiologies From a Tertiary Center

Pediatrik Hiperkalsemi: Üçüncü Basamak Bir Merkezden Klinik Özellikler ve Etyolojilere Dair Bulgular

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Abstract

Introduction: Hypercalcemia is rarer in children than in adults, but it is clinically significant.

Materials and Methods: This retrospective study evaluated 21 patients aged 0-18 years with hypercalcemia. Clinical characteristics, laboratory findings, and clinically indicated imaging and genetic analyses were reviewed. Patients were classified according to hypercalcemia severity and PTH status, and treatment outcomes were recorded.

Results: Of these, 33.3% were asymptomatic, and vomiting was the most common presenting complaint (19%). 66.7% of the patients had parathyroid hormone (PTH)-independent hypercalcemia, while 33.3% had PTH-dependent hypercalcemia. The etiologies included parathyroid adenoma in five patients, adrenal insufficiency in four patients, vitamin D intoxication in three patients, malignancy in three patients, osteomyelitis in one patient, pseudohypoaldosteronism in one patient, a CaSR variant in one patient, and hypophosphatasia in one patient. Four of the seven patients with PTH-dependent hypercalcemia underwent surgical treatment.

Conclusion: This study demonstrates that childhood hypercalcemia can result from a variety of factors. Measurement of serum calcium levels is essential in children with vague or nonspecific clinical symptoms. Diagnosis of malignancies may be delayed in the absence of additional findings. Early diagnosis and appropriate intervention can prevent significant complications.

Keywords
Etiology, hypercalcemia, malignancy, parathyroid hormone, pediatric

Öz

Giriş: Hiperkalsemi çocuklarda yetişkinlere kıyasla daha nadir görülmekle birlikte, klinik olarak önemli bir durumdur.

Gereç ve Yöntem: Bu retrospektif çalışmada hiperkalsemi saptanan 0–18 yaş arası 21 hasta değerlendirildi. Klinik özellikler, laboratuvar bulguları ile klinik gerekliliğe göre yapılan görüntüleme ve genetik analizler incelendi. Hastalar hiperkalsemi şiddeti ve PTH durumuna göre sınıflandırılarak tedavi sonuçları kaydedildi.

Bulgular: Hastaların %33,3'ü asemptomatikti ve en sık başvuru şikâyeti kusmaydı (%19). Hastaların %66,7'sinde paratiroid hormonuna (PTH) bağımsız hiperkalsemi saptanırken, %33,3'ünde PTH'ye bağlı hiperkalsemi mevcuttu. Saptanan etiyolojiler arasında beş hastada paratiroid adenom, dört hastada adrenal yetmezlik, üç hastada D vitamini intoksikasyonu, üç hastada malignite, birer hastada osteomiyelit, psödohipoaldosteronizm, CaSR varyantı ve hipofosfatazya yer almaktadır. PTH'ye bağlı hiperkalsemisi olan yedi hastadan dördü cerrahi tedavi almıştır.

Sonuç: Bu çalışma, çocukluk çağı hiperkalsemisinin çok çeşitli nedenlere bağlı olarak gelişebileceğini ortaya koymaktadır. Belirsiz veya spesifik olmayan klinik bulgularla başvuran çocuklarda serum kalsiyum düzeylerinin ölçülmesi büyük önem taşımaktadır. Ek bulguların yokluğunda malignite tanısı gecikebilir. Erken tanı ve uygun müdahale, ciddi komplikasyonların önlenmesine katkı sağlayabilir.

Anahtar kelimeler
Etiyoloji, hiperkalsemi, malignite, paratiroid hormon, pediatrik

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Introduction

Hypercalcemia is rarer in children than in adults, yet it is clinically significant (1). Ionized and total calcium levels vary according to age and gender (2). The etiology of hypercalcemia varies across different age groups. Congenital causes are more common in the neonatal period, while neoplasms are more frequently encountered in adolescents (1). A classification based on the presence or absence of hyperparathyroidism can facilitate the differential diagnosis. In the absence of hyperparathyroidism, potential causes of hypercalcemia include excessive intake or impaired breakdown of vitamin D, renal phosphate loss, dietary phosphorus deficiency, malignancies, immobilization, various syndromes, and rhabdomyolysis. When hyperparathyroidism is present, the causes of hypercalcemia may include neonatal acquired hyperparathyroidism, sporadic parathyroid gland tumors, multiple endocrine neoplasms (MEN), familial hypocalciuric hypercalcemia, and familial isolated hyperparathyroidism (3).

The calcium-sensing receptor (CaSR), which is expressed in the parathyroid glands and kidneys, plays a significant role in maintaining plasma calcium levels. Increased ionized calcium levels activate CaSR, leading to the inhibition of parathyroid hormone (PTH) secretion (4). PTH reduces renal phosphate reabsorption in the distal renal tubule while stimulating calcium reabsorption and promoting the conversion of 25-hydroxyvitamin D3 to calcitriol. Calcitriol, in turn, enhances calcium and phosphate absorption in the intestines, promotes bone mineralization, and increases renal calcium reabsorption (5).

Patients with hypercalcemia may present with a range of symptoms, including hypotonia, poor feeding, vomiting, constipation, abdominal pain, numbness, polyuria, dehydration, and seizures (6). Severe cases can lead to renal failure and pancreatitis (7). A detailed dietary history, medication review, family history, assessment for dysmorphic features, and evaluation of bone abnormalities are essential for differential diagnosis (8).

The severity of clinical symptoms is often correlated with plasma calcium concentrations and is classified as mild (<12 mg/dL), moderate (12-14 mg/dL), and severe (>14 mg/dL) (9). In cases of hypercalcemia, the diagnostic workup should include cessation of medications that may be contributing to hypercalcemia, a calcium-restricted diet, and ensuring adequate hydration (5). Treatment options for hypercalcemia include furosemide, calcitonin, prednisolone, bisphosphonates, and hemodialysis (10).

This study aims to raise awareness about pediatric hypercalcemia, a rare condition with diverse etiologies, which can lead to severe complications if not addressed promptly. Through the presentation of our patients with hypercalcemia, we aim to underscore the variety of underlying diagnoses in childhood.

Materials and Methods

Our study was retrospective in design, and the study protocol was approved by the University of Health Sciences Türkiye, Başaksehir Cam ve Sakura City Hospital Ethics Committee (approval code: KAEK 2023.06.276). Between 01.06.2021 and 01.03.2023, 21 patients aged 0-18 years who presented with at least two high calcium measurements were included in the study. Patient data, including age at presentation, symptoms, and physical examination findings, were recorded. Pre-treatment fasting morning samples were analyzed for serum calcium, phosphate, alkaline phosphatase, PTH, electrolytes, renal function tests, 25-hydroxyvitamin D (25-OHD), and urine calcium/creatinine ratio.

Thyroid-stimulating hormone (TSH), free thyroxine (fT4), neck ultrasonography, parathyroid gland scintigraphy with Tc-99m sestamibi, and genetic analysis were performed as necessary based on clinical indications.

Hypercalcemia was defined according to corrected total serum calcium levels. Total serum calcium levels between 11-12 mg/dL were classified as mild, levels greater than 12 mg/dL and up to 14 mg/dL were classified as moderate, and levels exceeding 14 mg/dL were classified as severe hypercalcemia (9).

Patients were categorized into two groups based on PTH levels. Despite elevated calcium levels, PTH levels that remain within the normal range or are increased indicate PTH elevation. Classification was performed based on this criterion. Group 1 included patients with unsuppressed PTH levels, known as the PTH-dependent group, while Group 2 comprised patients with suppressed PTH levels, referred to as the PTH-independent group. The level of suppression of PTH was determined based on our hospital's age-specific reference range.

The treatment modalities used for hypercalcemia in each patient, the time required for serum calcium levels to return to normal, and the long-term course of hypercalcemia were recorded for all patients.

Statistical Analysis

Statistical analysis was conducted using the SPSS statistical software (v.21.0). Categorical variables were expressed as frequencies and percentages, while continuous variables

were presented as median values and ranges. Due to the small sample size, non-parametric methods were used for comparisons. Probability tables (2x2) were analyzed using Fisher's exact test, while the chi-square test was used for higher-dimensional tables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 21 pediatric patients were included in the study, with 10 girls (47.6%) and 11 boys (52.4%). The mean age at presentation was 6.82±6.8 years (range: 0.01-17.1). The median body weight SDS was -0.35 (range: -3.80-1.24), the median height SDS was -0.91 range: -3.20-1.49), and the median BMI SDS was -0,09 (range: -3.48 - 3.50). A wide variation was observed in the anthropometric parameters. 33.3% of the patients were asymptomatic, and vomiting was the most common presenting complaint, occurring in 19% of the cases. The details of presenting complaints are listed in Table 1.

66.7% of the patients (n=14) had PTH-independent hypercalcemia, while 33.3% (n=7) had PTH-dependent hypercalcemia. The gender ratio was similar in both groups (p=0.534). The mean age at presentation in the PTH-dependent group was 14.8 years (min=8.2, max=17.1), while in the PTH-independent group, it was 0.34 years (min=0.01, max=14.2). The age at presentation was significantly higher in the PTH-dependent group (p=0.01). Calcium levels were not significantly different between the two groups.

When other laboratory findings were examined, the PTH-dependent group showed lower phosphorus, higher albumin, higher PTH, and a lower urine calcium/creatinine ratio (Table 2).

Neck ultrasonography was performed when the PTH level was not suppressed. Parathyroid adenomas were detected in four patients (19%) with PTH-dependent hypercalcemia. Adenoma localization was as follows: one patient had it in the upper right, two patients in the lower right, and one patient in the upper left. Patients with adenomas detected

Table 1. Chief complaints at presentation

Complaint	Frequency	Percent	Valid percent	Cumulative percent
None	7	33.3	33.3	33.3
Vomiting	4	19.0	19.0	81.0
Abdominal pain	2	9.5	9.5	90.5
Muscle pain	1	4.8	4.8	38.1
Short stature	1	4.8	4.8	42.9
Seizure	1	4.8	4.8	47.6
Itching	1	4.8	4.8	52.4
Joint pain	1	4.8	4.8	57.1
Decreased urination	1	4.8	4.8	61.9
Genital suspicion	1	4.8	4.8	95.2
Sweating	1	4.8	4.8	100.0
Total	21	100.0	100.0	

Chief complaints of 21 patients, ages range from 0-18 years, presented in this table with hypercalcemia between 2021-2023 years

Table 2. Laboratory findings in the patients

Variable	Calcium (mg/dL) PTH-I/PTH-D	Phosphorus (mg/dL) PTH-I/PTH-D	Albumin (mg/dL) PTH-I/PTH-D	Urine Ca/Cr PTH-I/PTH-D	PTH (pg/mL) PTH-I/PTH-D
N	14/7	14/7	13/7	9/7	14/7
Median	12.1/12.1	4.95/2.9	4/4.9	0.92/0.2	5.1/120
Minimum	10.2/10.78	3.00/1.6	3.2/4.6	0.05/0.01	1/78
Maximum	14.4/13.7	7.60/3.9	5.2/5.1	4.50/0.6	13/640
p	0.07	0.03	0.041	<0.01	<0.01

Laboratory findings of 21 patients are presented in this table.
PTH-I: Parathyroid hormone-independent, PTH-D: Parathyroid hormone-dependent

on ultrasound showed uptake activity suggestive of adenoma on parathyroid gland scintigraphy. In one patient with a normal ultrasound, scintigraphy suggested the presence of an adenoma. The size of the adenomas ranged from 3 to 25 mm.

When all investigations were completed and etiological classification was made, five patients (23.8%) were diagnosed with parathyroid adenoma, four patients (19%) had adrenal insufficiency, three patients (14.3%) had vitamin D intoxication, three patients (14.3%) had malignancy, one patient (4.8%) had osteomyelitis, one patient (4.8%) had pseudohypoaldosteronism, and one patient (4.8%) had hypophosphatasia. One patient (4.8%) was diagnosed with a CaSR. In two patients (9.5%), the etiology could not be determined, and spontaneous resolution was observed during follow-up. The mean age of patients with parathyroid adenoma was 14.36±3.21 years (range=8.2-17.1).

Among the patients with malignancy, two had acute lymphoblastic leukemia, and one had osteosarcoma. One patient was diagnosed with multiple endocrine neoplasia type 1.

Six patients did not require any treatment. Hydration was administered to 15 patients (71.4%), bisphosphonates to 7 patients (33.3%), furosemide to 10 patients (47.6%), and hydrocortisone to 4 patients (19%). Patients who received bisphosphonate therapy had calcium levels between 10.78 and 14.4 mg/dL. Four of these patients had parathyroid adenomas, and bisphosphonate therapy was used to normalize calcium levels before surgery. Other patients who received bisphosphonates were diagnosed with osteosarcoma, acute lymphoblastic leukemia, and pseudohypoaldosteronism. Pamidronate was administered at a dose of 0.5–1 mg/kg, with a maximum of two doses. This regimen was sufficient to normalize calcium levels within 48 hours.

Four of the seven patients with PTH-dependent hypercalcemia (those with adenomas) underwent surgical treatment. The patient with MEN1 syndrome was a 15-year-old female who presented with mild hypercalcemia and was found to have a parathyroid adenoma on both ultrasonography and scintigraphy. However, during follow-up, the adenoma showed regression, and surgical intervention was not required. The patient remained asymptomatic, and calcium levels remained stable without the need for medical treatment.

In addition, two cases with spontaneously resolved mild hypercalcemia were identified. The first was a 14.3-year-old male with PTH-dependent hypercalcemia and hypocalciuria; both neck ultrasonography and scintigraphy were unremarkable. The second was a 0.2-year-old female with PTH-independent mild hypercalcemia. Neither patient required treatment, and calcium levels normalized spontaneously during follow-up.

Genetic analysis was performed on four patients with parathyroid adenoma, and no variants were detected.

Renal ultrasonography was performed in all patients. Fourteen patients (66.7%) had normal findings, while nephrocalcinosis was detected in three patients (14.3%), renal stones in two patients (9.5%), and pelvicalyceal ectasia in two patients (9.5%). The diagnoses of patients who developed complications and their calcium levels are provided in Table 3. All patients are being followed with normal calcium levels.

Discussion

Hypercalcemia is rare in children and can manifest with either asymptomatic or nonspecific symptoms. When there are no complaints, hypercalcemia may not be detected until complications arise. In the study conducted by Çullas İlarslan et al. (11), 30% of the patients were asymptomatic, with gastrointestinal symptoms being the most common (nausea, vomiting, abdominal pain, constipation). Similarly, in our study, 33.3% of patients were asymptomatic, with vomiting being the most frequent symptom.

Table 3. Complications in patients

Diagnosis	Calcium (mg/dL)	Complication
Osteosarcoma	12.2	Nephrocalcinosis
Parathyroid adenoma	13.3	Renal stones
Excessive vitamin D intake	13.8	Nephrocalcinosis
Pseudoaldosteronism	13.0	Pelvicaliectasis
Adrenal insufficiency	11.1	Pelvicaliectasis
Hypophosphatasia	12.6	Nephrocalcinosis

In this table, calcium levels of cases with complications and the complications that developed are presented

The level of PTH in hypercalcemia cases provides a practical approach to diagnosis. Primary hyperparathyroidism accounts for 1% of hypercalcemia cases in children (12,13). In the study by Çullas İlarslan et al. (11), this rate was 35%, attributed to the study being conducted in a tertiary care center. In our study, the rate of PTH-dependent hypercalcemia was 33.3%. The lack of referral for mild hypercalcemia cases could be a contributing factor. The age at presentation was more advanced in the PTH-dependent group, consistent with findings in the literatüre (13).

In a review by Markowitz et al. (14), despite high calcium levels in hypercalcemia due to primary hyperparathyroidism, unrepressed or normal PTH levels were commonly observed. Several studies have reported that patients with primary hyperparathyroidism can have normal PTH levels at diagnosis (11,13). In our study, one patient in the PTH-dependent group had an average PTH level. All patients in the PTH-independent group had low PTH levels. Since normal PTH levels do not exclude primary hyperparathyroidism, investigations targeting the parathyroid gland should be pursued in the etiology workup.

Ultrasound and technetium thyroid scintigraphy are highly effective in identifying parathyroid gland pathology (4). In cases where scintigraphy and ultrasound fail to clarify the pathology, SPECT/CT can be used. Shafiei et al. (15) reported that the sensitivity of SPECT/CT in detecting parathyroid adenoma localization was 78%, with a specificity of 97%. Li et al. (16) found this method particularly useful in detecting ectopic parathyroid adenomas. In our study, parathyroid pathology was identified by ultrasound in four out of five cases, while one case with normal ultrasound had a positive finding on scintigraphy. The combined use of both imaging techniques enhances diagnostic success. SPECT/CT examination was not needed in our cases.

In childhood cancers, bone complications are common. Mostoufi-Moab et al. (17) reported osteonecrosis in 2-10% of cases of acute lymphoblastic leukemia. Studies have shown that the frequency of hypercalcemia associated with malignant tumors ranges from 0.4% to 1.3%, with Ewing sarcoma, ALL, lymphoma, neuroblastoma, and Wilms tumor being malignancies associated with hypercalcemia (18,19). In our study, there were two patients diagnosed with ALL and one with osteosarcoma. Malignancy needs to be excluded, particularly in cases of PTH-independent hypercalcemia. In our study, calcium levels were similar in both groups, and mild or malignant calcium levels were not helpful in the diagnostic algorithm. Simultaneous measurement of PTH levels was the most essential diagnostic tool in our study.

Limited research exists on the relationship between primary hyperparathyroidism and hypophosphatemia. Two studies have emphasized the clinical significance of hypophosphatemia in this context. Additionally, simultaneous measurement of calcium and phosphorus levels is suggested to be more significant in diagnosing and treating primary hyperparathyroidism (20,21). In our study, phosphorus levels were lower in the PTH-dependent group, supporting our diagnosis. Knowing phosphorus levels can be helpful both in determining the etiology of hypercalcemia and in guiding treatment decisions.

Urolithiasis is a growing concern worldwide, with hypercalcemia being a significant cause of kidney stones. Işik et al. (22) reported hypervitaminosis D in 2% of 197 pediatric patients with urolithiasis and hypercalcemia in 27%. They emphasized that vitamin D intake greater than 400 IU/day could increase the risk of stone formation. In our study, vitamin D intoxication was found in 14.3% of patients, nephrocalcinosis in 14.3%, stones in 9.5%, and pelvicalyceal ectasia in 9.5%. The complications of hypercalcemia are significant, and its management requires careful consideration.

Primary hyperparathyroidism and parathyroid adenoma should be considered primarily in cases of advanced childhood hypercalcemia. Studies have shown an increased frequency of parathyroid adenomas in adolescents (23,24). Rampp et al. (25) reported that the most common pathology in adolescents with primary hyperparathyroidism was a single parathyroid adenoma (71%). Similarly, Hsu and Levine (26) found parathyroid adenoma in 12 out of 17 patients. Genetic and syndromic causes are rarer. Kollars et al. (12) found parathyroid adenoma in 34 out of 52 patients, with 16 having parathyroid hyperplasia, and 57% of hyperplasias were diagnosed with MEN-1. When encountering hypercalcemia in adolescents, adenoma should be considered, and further investigations should be performed. Consistent with the literature, we had five cases of parathyroid adenoma in our study, with a higher average age. Four of our cases had a single parathyroid adenoma, and one patient was diagnosed with MEN-1.

The parathyroid glands are initially visualized using ultrasound. In addition to ultrasonography, 99m Tc sestamibi scintigraphy is highly useful in detecting pathology (4). In a study by Kızılcan Çetin et al. (24), adenomas were detected with at least one of these methods. In our study, diagnosis was made with ultrasonography in four out of five cases and with scintigraphy in one case.

Adrenal insufficiency is a rare cause of hypercalcemia, and the mechanism is not fully understood. Sakao et al. reported that improvement occurs with steroid replacement (27). Schoelwer et al. (28) found elevated calcium levels in 82.5% of patients with congenital adrenal hyperplasia and hypercalcemia. Madihi et al. (29) found nephrocalcinosis in 3.3% of 120 patients with congenital adrenal hyperplasia, emphasizing the need for careful evaluation. In our study, 19% of our cases had hypercalcemia due to adrenal insufficiency, representing a considerable proportion.

Pseudohypoaldosteronism is another rare cause of hypercalcemia. While we had one case in our study, Babar and Tariq (30) reported a similar case. Aldosterone may stimulate PTH secretion indirectly by promoting hypercalciuria through its effects on the nephron, leading to secondary hyperparathyroidism. This mechanism has been proposed as a potential pathophysiological pathway explaining elevated PTH levels, particularly in cases of chronic aldosterone excess (31). Hypophosphatasia presents with hypercalcemia, hypercalciuria, and increased bone resorption. Demirbilek et al. (32) reported a case with hypophosphatasia and hypercalcemia. In our case, hypercalciuria, nephrocalcinosis, and hypercalcemia were present. Osteomyelitis is also a disease that causes hypercalcemia due to increased bone resorption. One patient in our study had osteomyelitis.

Calcium-sensing receptor mutations are an important genetic cause of hypercalcemia, often accompanied by hypophosphatemia, hypocalciuria, and hyperparathyroidism (33). Urgent treatment is required for malignant hypercalcemia, with successful use of cinacalcet in some cases (34). In our study, there was mild hypercalcemia, and no treatment other than hydration was needed. Close monitoring continues for any potential malignant elevation.

Treatment of hypercalcemia aims to prevent complications and correct the underlying cause. Mild cases do not require urgent treatment, while severe or persistent hypercalcemia requires hydration and may benefit from treatments such as furosemide, calcitonin, prednisolone, bisphosphonates, or hemodialysis (5,10). Bisphosphonates are often required in severe or persistent cases until the underlying condition is controlled. Surgical treatment is indicated for parathyroid adenomas after calcium levels stabilize. Early excision is crucial for malignant hypercalcemia. Phitayakorn and McHenry (35) found that bisphosphonates serve as a bridge before excision. In our study, four patients with parathyroid adenomas underwent surgery, with bisphosphonate treatment administered prior to surgery to normalize calcium levels. Pamidronate is the most commonly used bisphosphonate in childhood (5). Alagaratnam and Kurzawinski (36) reported parathyroidectomy as the treatment for parathyroid tumors. In a study by Çullas İlarslan et al. (11), four cases of malignancy-related hypercalcemia showed resistance to treatment and recurrent courses. In our study, 33.3% of cases required bisphosphonate therapy, and four out of five cases with adenoma underwent surgical treatment with no recurrence. We did not observe any cases of resistant or recurrent hypercalcemia.

Study Limitations

This study has several limitations, the most significant of which is the small sample size, making it difficult to compare different groups. Longer follow-up and a better understanding of the natural course of hypercalcemia and hypercalciuria could provide more detailed information on complications such as nephrolithiasis.

Conclusion

This study demonstrates that childhood hypercalcemia can be caused by various factors. The presence of complicated cases suggests that diagnosis may be delayed due to the asymptomatic progression of the condition. Mild cases are challenging to identify, and malignancies may go undiagnosed if no additional symptoms are present. Early diagnosis and emergency intervention are critical to preventing significant complications. Measurement of serum calcium levels is essential for children presenting with vague clinical findings, particularly when gastrointestinal symptoms are present. Early diagnosis and intervention are crucial to preventing severe complications.

Ethics

Ethical Approval: Our study was retrospective in design, and the study protocol was approved by the University of Health Sciences Türkiye, Başaksehir Cam ve Sakura City Hospital Ethics Committee (approval code: KAEK 2023.06.276). Between 01.06.2021 and 01.03.2023, 21 patients aged 0-18 years who presented with at least two high calcium measurements were included in the study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Investigation of Allergen Sensitization in Asthmatic Children Aged 3-6 and Their Relationship with Other Allergic Diseases

3-6 Yaş Grubu Astımlı Çocuklarda Alerjen Duyarlılıklarının Araştırılması ve Diğer Alerjik Hastalıklarla İlişkisi

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Abstract

Introduction: Sensitivity to inhalant allergens in asthmatic children is closely related to asthma symptoms and exacerbations. This study aimed to investigate various characteristics of allergen sensitivities and their association with other comorbid allergic diseases in children aged 3-6 years diagnosed with asthma.

Materials and Methods: A total of 239 children (3-6 years old) diagnosed with asthma were included in the study. Other allergic disease diagnoses accompanying asthma, allergen sensitivities (using skin prick and serum allergen-specific IgE tests), total IgE test results, and the age distribution of allergen sensitivities were analyzed retrospectively.

Findings: Sensitivity to at least one allergen was detected in 46.4% of asthmatic children and they were defined as atopic. In children with asthma, the prevalence of atopy was determined to be 38.4% in the 36-47 month age group, 47.3% in the 48-59 month age group, and 50% in the 60-72 month age group (p=0.39). In the entire study population, allergen sensitivities were most frequently detected against mites at 29.7% and pollens at 23%. In asthmatic children, inhalant allergen sensitivities tended to increase with age. Mites sensitivity rates were determined as 17.3% in the 36-47 month group, 31.2% in the 48-59 month group, and 35.1% in the 60-72 month group (p=0.073). The sensitivity rates to pollen were found to be 1.9% in the 36-47 month group, 13% in the 48-59 month group, and 44.6% in the 60-72 month group (p=0.001). It has been determined that sensitivity rates to food allergens tend to decrease with increasing age. In all three age groups, total IgE levels were found to be higher in children with atopic asthma compared to children without atopic asthma (p=0.000-0.002). The most common comorbid allergic diseases in asthmatic children were allergic rhinitis (44.4%), atopic dermatitis (25.1%), and allergic conjunctivitis (8.8%). In asthmatic children, sensitivity to dust mites (56.3% vs. 43.7%) and pollens (72.7% vs. 27.3%) was found to be higher in cases with comorbid allergic rhinitis compared to cases without allergic rhinitis.

Conclusion: In children with asthma, inhalant allergen sensitivities tend to increase with age, while food allergen sensitivities tend to decrease with age. Identifying allergen sensitivities and comorbid allergic diseases in children diagnosed with asthma is necessary; this should be considered during the diagnosis and treatment processes of these patients and should be re-evaluated during follow-up.

Keywords
Asthma, child, allergen, sensitivity, atopy, allergic rhinitis

Anahtar kelimeler
Astım, çocuk, alerjen, duyarlılık, atopi, alerjik rinit

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Öz

Giriş: Astımlı çocuklarda çeşitli inhalan alerjen duyarlılıkları, astım semptomları ve alevlenmeleri ile yakından ilişkilidir. Bu çalışmada, astım tanısı almış 3-6 yaş grubu çocuklarda alerjen duyarlılıklarının çeşitli özelliklerinin ve eşlik eden diğer alerjik hastalıklarla ilişkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Astım tanısı alan toplam 239 çocuk (3-6 yaş) hasta çalışmaya dahil edilmiştir. Astıma eşlik eden diğer alerjik hastalık tanıları, alerjen duyarlılıkları (alerjenlerle deri prick ve serum alerjen spesifik IgE testleri ile), total IgE test sonuçları, alerjen duyarlılıklarının yaşlara göre dağılımı, retrospektif olarak analiz edilmiştir.

Bulgular: Astımlı çocukların %46,4'ünde en az bir alerjene karşı duyarlılık saptandı ve atopik olarak tanımlandı. Astımlı çocuklarda yaş gruplarına göre atopi saptanma oranları sırasıyla; 36-47 ay grubunda %38,4, 48-59 ay grubunda %47,3 ve 60-72 ay grubunda %50 olarak tespit edilmiştir (p=0,39). Tüm çalışma populasyonunda alerjen duyarlılıkları en sık %29,7 oranında akarlara ve %23 oranında polenlere karşı saptandı. Astımlı çocuklarda inhalan alerjen duyarlılıkları yaş ile birlikte artış eğilimi göstermiştir. Akarlar için duyarlılık oranları; 36-47 ay grubunda %17,3, 48-59 ay grubunda %31,2 ve 60-72 ay grubunda %35,1 olarak tespit edilmiştir (p=0,073). Polenlere duyarlılıkları oranları; 36-47 ay grubunda %1,9, 48-59 ay grubunda %13 ve 60-72 ay grubunda %44,6 bulundu (p=0,001). Besin alerjenlerine duyarlılık oranlarının yaşla birlikte azalma eğiliminde olduğu tespit edilmiştir. Atopik astımlılarda her 3 yaş grubunda da, total IgE değerlerinin atopik bulunmayan çocuklara göre, daha yüksek olduğu görülmüştür (p=0,000-0,002). Astımlı çocuklarda en sık eşlik eden alerjik hastalıklar; alerjik rinit (%44,4), atopik dermatit (%25,1) ve alerjik konjonktivit %8,8 olarak belirlendi. Astımlı çocuklarda ek olarak alerjik rinitin birlikte bulunduğu olgularda, alerjik rinitin bulunmadığı olgulara kıyasla akarlara (%56,3'e karşı %43,7) ve polenlere (%72,7'ye karşı %27,3) duyarlılık oranlarının daha yüksek olduğu tespit edilmiştir.

Sonuç: Astımlı çocuklarda inhalan alerjen duyarlılıkları yaş ile birlikte artış eğilimi gösterirken, besin alerjen duyarlılıklarının yaş ile azalma eğiliminde olduğu görülmektedir. Astım tanılı çocuklarda alerjen duyarlılıklarının saptanması ve komorbid alerjik hastalıkların belirlenmesi gereklidir, bu hastaların tanı ve tedavi süreçlerinde göz önünde tutulması ve ek olarak izlemlerinde tekrar değerlendirilmesi gereken bir konu olduğu düşünülmüştür.

Introduction

Asthma is characterized by chronic inflammation of the airways in susceptible individuals; symptoms include shortness of breath, wheezing, chest tightness, and coughing, and are often exacerbated in relation to triggers (1,2). Major environmental factors that trigger asthma attacks include inhalant allergens, viral respiratory infections, and exercise-induced bronchoconstriction. Additionally, environmental pollutants such as air pollution, irritants, and cigarette smoke can worsen symptoms by increasing airway sensitivity (2). Current guidelines emphasize that reducing trigger exposure is important in asthma control (3).

Childhood asthma is a heterogeneous disease, and a significant portion of its phenotypes are associated with immunoglobulin E (IgE)-mediated sensitization to inhalant allergens (1,2). It is known that approximately 40-80% of childhood asthma cases are generally defined as allergic (atopic) asthma (4,5). Atopy is defined as the presence of sensitivity to at least one allergen in an individual and is closely associated with many allergic diseases, primarily asthma (6,7). A significant proportion of asthmatic children also have other allergic diseases such as allergic rhinitis, atopic dermatitis, and/or food allergies concurrently (6,7).

In the allergic (atopic) asthma phenotype, airway inflammation is associated with inhalant allergen sensitivity, which often begins in early childhood and can persist throughout life. Large epidemiological studies such as ISAAC have shown that the increase in the prevalence of childhood asthma, allergic rhinitis, and atopic dermatitis parallels the western lifestyle, changes in indoor allergen exposure, and global climate dynamics (8). Inhalant allergen (aeroallergen) sensitivity refers to the development of specific IgE against indoor mites, fungal spores, pollens, pet allergens, cockroaches, and other environmental allergens, and is closely related to both asthma development and disease severity (2,9,10). Inhalant allergen sensitivity develops as a result of the interaction of multiple factors such as environmental exposure level, genetic predisposition, epithelial barrier integrity, and early life infections (1,2).

Inhalant allergens are the most important environmental factors that trigger symptoms in childhood allergic asthma, allergic rhinitis, and allergic conjunctivitis (8). Inhalant allergen sensitivities frequently detected in cases of allergic asthma in childhood are reported to be house dust mites (*Dermatophagoides pteronyssinus*, *D. farinae*), pollens (grass, tree, and weed pollens), fungal spores (*Alternaria, Cladosporium,* etc.), cockroaches, and domestic animals (cats, dogs, horses, etc.) (9, 11-14). Determining allergen sensitivities is of great importance in identifying the allergic phenotype of asthma and planning appropriate treatment strategies (15). Skin prick tests with allergens and evaluation of serum allergen-specific IgE levels are commonly used diagnostic methods (16).

It has been reported that inhalant allergen sensitivities in asthmatic children show significant differences between regions and countries, depending on many factors such as genetics, living conditions, regional and geographical characteristics, climate and vegetation, urban/rural settlement, air pollution, lifestyle, and environmental features (9,12,13,17-22). Additionally, the prevalence of atopy and sensitivity to inhalant allergens in asthmatic children shows significant changes with age, generally tending to increase with age (10,23-25).

Current data on allergen sensitivities in asthmatic children aged 3-6 years in our region are limited. Therefore, this study aimed to investigate the frequency of general atopy, the prevalence of various inhalant allergen sensitivities, the age-related changes in these sensitivities, and the relationship between allergen sensitivities and other allergic diseases in children aged 3-6 years diagnosed with asthma.

Materials and Methods

In this study, data from 3-6 year old children diagnosed with asthma at the Department of Pediatric Allergy, Faculty of Medicine, Bursa Uludağ University, between May 1, 2020 and October 1, 2022 were examined. Asthma diagnosis in the patients included in the study was evaluated according to the 2020 GINA criteria (26). The diagnosis of other accompanying allergic diseases was made based on the patients' history, physical examination findings and laboratory test results. The case files were retrospectively reviewed; allergic disease diagnoses, skin prick test with allergens, serum allergen-specific IgE and total IgE test results were analyzed.

Skin prick tests with allergens were performed and evaluated in accordance with the EAACI skin prick test application recommendations, as required by the clinic's routine practice (27). Skin prick tests with allergens were performed on the volar surface of both forearms using standardized allergen extract solutions from Lofarma SpA (Milan, Italy). Skin prick tests were performed after discontinuing any medications that could affect the skin test results for the appropriate time. Each allergen was applied to the skin with separate sterile lancets; evaluation was made by comparing it with positive (histamine) and negative (saline) controls. The test result was considered positive if edema of ≥3 mm was detected 15-20 minutes after allergen application compared to the negative control (27). The allergens used in skin prick testing (as part of the clinic's routine standard practice for children aged 3-6 years) included house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*); grass pollens (grass mix, *Phleum pratense*, *Dactylis glomerata*, *Lolium perenne*, *Cynodon dactylon*, *Poa pratensis*); cereal pollens (*Secale cereale*, *Triticum sativum*, *Avena sativa*); tree pollens (tree mix, *Alnus glutinosa*, *Betula verrucosa*, *Olea europaea*); weed pollens (weed mix, *Artemisia vulgaris*, *Plantago lanceolata*, *Parietaria officinalis*, *Chenopodium album*); fungal spores (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*); cat, dog, cow's milk, egg white, egg yolk, peanut, hazelnut, and walnut.

Serum allergen-specific IgE and total IgE levels were measured using the IMMULITE 2000 XPi immunoassay system (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). In allergen-specific IgE testing, values ≥0.35 kU/L (Class I) were considered positive. The allergens included in the serum allergen-specific IgE assays were as follows: mite panel (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, *Blattella germanica*), grass pollen panel (*Phleum pratense*, *Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Poa pratensis*), *Olea europaea*, *Alternaria alternata*, cat, dog, cow's milk, egg white, egg yolk, peanut, hazelnut, and walnut.

When determining allergen sensitivity results, sensitivity to each allergen was considered present if at least one of the skin prick tests and/or serum allergen-specific IgE tests with the allergen was found to be positive. Additionally, when analyzing allergen sensitivity results, the presence of sensitivity to at least one allergen in a group (such as mites, pollen, grass pollen, etc.) was defined as the presence of general sensitivity for that group (e.g.,"mites general", "pollens general", "grass pollens general", etc.).

In statistical analyses, data were analyzed using SPSS (Statistical Package for the Social Sciences) 28.0 program. The normality of the data distribution was checked using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables, and as number and percentage (%) for categorical variables. Pearson chi-square, Fisher-Freeman-Halton, or Fisher's exact chi-square tests were used to compare categorical data; Mann-Whitney U and Kruskal-Wallis tests were used for non-parametric data. The statistical significance level was accepted as $p<0.05$.

Results

A total of 239 asthmatic children aged 3-6 years (36-72 months) were included in this study; 60.7% (n=145) were boys and 39.3% (n=94) were girls. The median age of the cases was calculated as 57 months (minimum: 36 - maximum: 72). No statistically significant difference was found between age groups in terms of gender distribution (p=0.688).

The distribution of other allergic diseases accompanying asthma in asthmatic children is given in Table 1. In 34.7% of the cases, only asthma was present as an allergic disease. Among the allergic diseases accompanying asthma, allergic rhinitis was the most common with 44.4%, followed by atopic dermatitis with 25.1%.

In 46.4% (n=111) of all children diagnosed with asthma, sensitivity to at least one allergen (inhalan or food) was detected, and these patients were defined as atopic. 53.6% (n=128) of asthmatic children were defined as non-atopic. The distribution of atopic and non-atopic cases among asthmatic children by age group (n=239) is given in Table 2. The rates of atopy detection by age group were 38.4% in the 36-47 month group, 47.3% in the 48-59 month group, and 50% in the 60-72 month group. The lowest rate of atopy detection was observed in the 36-47 month age group among asthmatic children; an increasing trend in the rate of atopy detection was observed with age, but the differences between age groups were not statistically significant (Table 2).

The results of allergen sensitivities detected in asthmatic children, and their comparisons across the entire study population and by age groups, are detailed in Table 3. The lowest rate of atopy ("any allergen" sensitivity: presence of sensitivity to at least one inhalant or food allergen) was observed in the 36-47 month age group of asthmatic children, with an increasing trend with age (p=0.39). In the entire study population of asthmatic children, allergen sensitivities were most frequently detected as mite general sensitivity (sensitivity to at least one of the allergens *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) at 29.7% and pollens general (sensitivity to at least one of the pollens of grass, tree, cereal, and weeds) at 23%. Within the pollen group general, grass pollen general sensitivity was the most frequently detected (8.8%). Sensitivities were found to pet allergens (cat and/or dog) (7.5%) and food allergens (sensitivity to at least one of the following allergens: cow's milk, egg white, egg yolk, peanuts, hazelnuts, walnuts) (5.9%). Among food allergens, egg white sensitivity was the most common (3.8%) (Table 3).

As a general trend in asthmatic children, sensitivity rates to inhalant allergens were found to increase with age (Table 3). For inhalant allergens, sensitivity rates for pollens general (p=0.001), grass pollens general (p=0.018), cereal pollens general (p=0.002), tree pollens general (p=0.006), and fungal spores general (p=0.014) increased significantly with age. A similar trend was observed for pets (cats and/or dogs) with increasing age, but the differences were not statistically significant (p=0.454). Sensitivity rates to food allergens, however, tended to decrease with age (p=0.405) (Table 3).

The rates of atopy detection in cases where any additional allergic disease is present alongside asthma are given separately for each disease in Table 4. In the presence of allergic rhinitis, atopic dermatitis, and allergic conjunctivitis accompanying asthma, the overall rates of atopy were found to be higher (although not statistically significant). In cases with accompanying angioedema, anaphylaxis, and food allergy, the rates of atopy were found to be statistically significantly higher (p=0.001-0.021) (Table 4).

Table 1. Distribution of other allergic diseases accompanying asthma in children with asthma

Diagnoses	n	%
Allergic rhinitis	106	44,4
Atopic dermatitis	60	25,1
Allergic conjunctivitis	21	8,8
Urticaria	18	7,5
Angioedema	6	2,5
Anaphylaxis	3	1,3
Food allergy	21	8,8
Only asthma	83	34,7

Data are given as n (%)

Table 2. Distribution of atopic and non-atopic cases by age group in children with asthma (n=239)

Characteristics	36-47 Months (n=52)		48-59 Months (n=93)		60-72 Months (n=94)		p[1]
	n	%	n	%	n	%	0,39[2] 0,37[3] 0,18[4] 0,71[5]
Atopic (n=111)	20	38,4	44	47,3	47	50	
Non-atopic (n=128)	32	61,6	49	52,7	47	50	

1: Pearson chi-square test
2: Age groups of 36-47 months, 48-59 months, and 60-72 months were compared.
3: Age groups of 36-47 months and 48-59 months were compared.
4: Age groups of 36-47 months and 60-72 months were compared.
5: Age groups of 48-59 months and 60-72 months were compared.
Data are given as n (%)

Table 3. Allergen sensitivities detected in all asthmatic children, their distribution and comparison by age group (n=239)

Allergens	**Total** (n=239)		**36-47 months** (n=52)		**48-59 months** (n=93)		**60-72 months** (n=94)		p
	n	%	n	%	n	%	n	%	
Any allergen[1]	111	**46,4**	20	38,4	44	47,3	47	50	0,39[3]
Mites general[2]	71	**29,7**	9	17,3	29	31,2	33	35,1	**0,073[3]**
D. pteronyssinus	70	29,2	9	17,3	29	31,2	32	34	0,091[3]
D. farinae	67	28	8	15,3	28	30,1	31	32,9	0,065[3]
Pollens general[2]	55	**23**	1	1,9	12	13	42	44,6	**0,001[3]**
Grass pollens general[2]	21	**8,8**	1	1,9	6	6,5	14	14,9	**0,018[3]**
Grasses miks	21	8,8	1	1,9	6	6,5	14	14,9	**0,018[3]**
Dactylis glomerata	13	5,4	1	1,9	4	4,3	8	8,5	0,360[4]
Lolium perenne	14	5,9	1	1,9	5	5,4	8	8,5	0,306[3]
Phleum pratense	10	4,2	1	1,9	4	4,3	5	5,3	0,839[4]
Cynodon dactylon	9	3,8	0	0	3	3,2	6	6,4	1,000[4]
Poa Pratensis	16	6,7	1	1,9	5	5,4	10	10,6	0,228[3]
Cereal pollens general[2]	13	**5,4**	0	0	2	2,2	11	11,7	**0,002[3]**
Secale cereale	12	5	0	0	2	2,2	10	10,6	**0,008[4]**
Triticum sativum	11	4,6	0	0	1	1,1	10	10,6	**0,008[4]**
Avena sativa	4	1,7	0	0	0	0	4	4,3	0,102[4]
Tree pollens general[2]	16	**6,7**	0	0	4	4,3	12	12,8	**0,006[4]**
Trees mix	16	6,7	0	0	4	4,3	12	12,8	**0,006[4]**
Alnus glutinosa	1	0,4	0	0	0	0	1	1,1	1,000[4]
Betula verrucosa	2	0,8	0	0	0	0	2	2,1	0,678[4]
Corylus avellana	1	0,4	0	0	0	0	1	1,1	1,000[4]
Olea europae	16	6,7	0	0	4	4,3	12	12,8	**0,006[4]**
Weed pollens general[2]	5	**2,1**	0	0	0	0	5	5,3	**0,026[4]**
Weeds mix	5	2,1	0	0	0	0	5	5,3	0,078[4]
Artemisia vulgaris	4	1,7	0	0	0	0	4	4,3	0,138[4]
Chenopodium album	1	0,4	0	0	0	0	1	1,1	1,000[4]
Plantago lanceolata	2	0,8	0	0	0	0	2	2,1	0,671[4]
Pets general[2]	18	**7,5**	2	3,8	7	7,6	9	9,6	0,454[3]
Cat	16	6,7	2	3,8	7	7,6	7	7,4	0,649[3]
Dog	3	1,3	0	0	0	0	3	3,2	0,238[4]
Foods general[2]	14	**5,9**	5	9,6	5	5,4	4	4,3	0,405[3]
Cow's milk	2	0,8	2	3,8	0	0	0	0	0,351[4]
Egg white	9	3,8	4	7,6	3	3,2	2	2,1	0,415[4]
Egg yolk	2	0,8	1	1,9	1	1,1	0	0	0,521[4]
Peanuts	5	2,1	2	3,8	1	1,1	2	2,1	0,455[4]
Hazelnuts	1	0,4	1	1,9	0	0	0	0	0,236[4]
Walnuts	3	1,3	2	3,8	1	1,1	0	0	0,414[4]

Table 3. Continued

Allergens	**Total** (n=239)		**36-47 months** (n=52)		**48-59 months** (n=93)		**60-72 months** (n=94)		p
	n	%	n	%	n	%	n	%	
Fungal spores general[2]	20	**8,3**	0	0	7	7,6	13	13,8	**0,014**[3]
Alternaria alternata	20	8,37	0	0	7	7,6	13	13,8	**0,014**[3]
Cladosporidium herbarum	1	0,4	0	0	0	0	1	1,1	1,000[4]
Aspergillus fumigatus	4	1,7	0	0	3	3,2	1	1,1	0,450[4]

1: Sensitivity to at least one inhalant or food allergen (presence of atopy)
2: Sensitivity to any of the allergens in this group
3: Pearson chi-square test.
4: Fisher's exact chi-square test.
Data are given as n (%).
Grasses mix*; Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, Festuca pratensis*
Trees mix; *Alnus glutinosa, Corylus avellana, Betula verrucosa*
Weeds mix; *Artemisia vulgaris, Plantago lanceolata, Chenopodium album, Parieteria officinalis*

Table 4. Rates of atopy detection in the presence of various allergic diseases accompanying asthma

	Total	Atopic		Non-atopic		p[1]
Diagnoses	n	n	%	n	%	
Allergic rhinitis	106	61	57,5	45	42,5	0,256
Atopic dermatitis	60	38	63,3	22	36,7	0,063
Allergic conjunctivitis	21	13	61,9	8	38,1	0,087
Urticaria	18	8	44,4	10	55,6	0,395
Angioedema	6	5	83,3	1	16,7	**0,001**
Anaphylaxis	3	2	66,6	1	33,4	**0,021**
Food allergy	21	15	71,4	6	28,6	**0,002**

1: Pearson chi-square test.
Data are given as n (%)

Allergic rhinitis was found to be the most common allergic disease accompanying asthma in children with asthma (Table 1). Table 5 shows the rates of allergen sensitivities in cases of asthma accompanied by allergic rhinitis. In pediatric patients with allergic rhinitis in addition to asthma, the sensitivities to allergen groups such as dust mites general, pollens general, grass pollens general, cereal pollens general, and tree pollens general were found to be statistically significantly higher (p=0.003-0.042). Sensitivities to fungal spores general and pet allergens general tended to be lower in the presence of allergic rhinitis (Table 5).

In the study population, serum total IgE levels of all asthmatic children aged 3-6 years were found to be in the range of 1-3057 IU/mL, with a median value of 65 IU/mL. The distribution of serum total IgE levels in patients according to age groups, with and without atopy, is shown in Table 6. In atopic patients, total IgE levels were found to be statistically significantly higher in all 3 age groups (p=0.000-0.002) (Table 6).

Discussion

This study evaluated the frequency of various allergen sensitivities in asthmatic children aged 3-6 years and the relationship of these sensitivities with age groups and related conditions such as concomitant allergic diseases, using current data. In the study population, it was observed that boys were more prevalent (male/female ratio=1.54) among asthmatic children aged 3-6 years. Studies on asthma epidemiology show that symptoms tend to start earlier in boys with asthma in childhood, that the incidence and prevalence of asthma in early childhood are higher in boys than in girls, and that the age of onset of asthma symptoms is generally earlier (28-31). A study conducted in the Bursa region in 2021 reported a male/female gender ratio of 1.4 in asthmatic children aged 5-18 years (32). A review of asthma prevalence in children in Middle Eastern countries showed that the male/female ratio was around 1.5 on average (33). A study conducted in Van, Manisa, Ankara, Antalya, and Trabzon found no statistically significant difference between genders (34). It has also been

Table 5. Allergen sensitivity rates when allergic rhinitis accompanies asthma (n=239)							
	Total (n=239)		**Allergic rhinitis (+)** (n=106)		**Allergic rhinitis (-)** (n=133)		**p**
Allergens	n	%	n	%	n	%	
Mites general[1]	71	29,7	40	56,3	31	43,7	**0,015**[2]
Pollens general[1]	55	23	40	72,7	15	27,3	**0,008**[2]
Grass pollens general[1]	21	8,8	15	71,6	6	28,4	**0,009**[2]
Tree pollens general[1]	16	6,7	11	68,7	5	31,3	**0,042**[2]
Cereal pollens general[1]	13	5,4	11	84,6	2	15,4	**0,003**[3]
Weed pollens general[1]	5	2,1	3	60	2	40	0,658[2]
Fungal spores general[1]	20	8,3	12	40	8	60	0,141[3]
Pets general[1]	18	7,5	7	38,9	11	61,1	0,628[2]
Foods general[1]	14	5,9	8	57,1	6	42,9	0,321[2]

1: Sensitivity to any of the allergens in this group
2: Pearson chi-square test.
3: Fisher's exact chi-square test.
Data are given as n (%) and % values are calculated according to allergens

Table 6. Comparison of serum total IgE levels in children with atopic and non-atopic asthma			
Age groups	**Total IgE** (IU/mL)		**p**[1]
36-48 months (n=52)	Atopic 115 (2:3057)	Non-atopic 16,5 (2:446)	0,002
48-60 months (n=93)	Atopic 159,5(2:1685)	Non-atopic 34 (2:1087)	0,000
60-72 months (n=94)	Atopic 166 (9:2642)	Non-atopic 37 (1:948)	0,000

1: Mann-Whitney U test.
Data are presented as median (minimum:maximum)

reported that asthma prevalence and atopy rates are higher in boys until school age, while an increase in asthma prevalence and atopy rates is observed in girls after puberty (30,31,33). In the literature, it is reported that many genetic, epigenetic, immunological, and environmental mechanisms, as well as changes in airway diameter and sex hormones, play a role in explaining this gender difference (35-37). It is thought that the relatively narrower airway diameters, higher viral infection load, and earlier and stronger Th2 response in boys in the early years may be related to this situation (29,37). In addition, environmental risk factors such as prematurity, low birth weight, prenatal exposure to cigarette smoke, obesity, and early childhood infections are reported to increase the risk of asthma in boys, combined with their already narrower airways and reduced expiratory flow (30,31,35,38). In adolescence and adulthood, it is suggested that factors such as obesity, physical activity level, air pollution, and occupational/household exposures may interact with sex hormones in girls, increasing the prevalence and severity of asthma (33,35,38).

In childhood, two or more of the following diseases can occur together and in significant proportions: allergic asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis. When the additional allergic diseases detected in children aged 3-6 years diagnosed with asthma in our study were examined, the presence of comorbid allergic diseases such as allergic rhinitis (44.4%), atopic dermatitis (25.1%), and allergic conjunctivitis (8.8%) was observed, respectively. Childhood asthma frequently occurs together with other allergic diseases due to "atopic burden" (39-43). Allergic rhinitis, in particular, is the most common comorbid condition affecting asthma control through the common Th2-inflammatory pathway of the upper and lower airways. A meta-analysis conducted on Chinese children reported the prevalence of allergic rhinitis in asthmatic children as 54.9% (39). Another multicenter study conducted in China reported the comorbidity of asthma and allergic rhinitis as 56.3% (40). In a pediatric study based on an allergy clinic, allergic rhinitis (AR) was detected in 70.5% of asthmatic children, suggesting that the rate may be higher in selected populations (41). In a study conducted in Japan on children aged 2-10 years, allergic rhinitis was detected in 83.8% of children diagnosed with asthma (42). The literature supports the strong co-occurrence of asthma and allergic rhinitis with numerous studies. Similarly, a systematic review conducted in Iran showed that the co-occurrence rates of allergic rhinitis in asthmatic children varied between 30-80% in

different studies (33). Additionally, allergic conjunctivitis, in the context of ocular allergy, can occur in significant proportions alongside allergic rhinitis. In a study of children diagnosed with asthma and/or allergic rhinitis, the frequency of allergic conjunctivitis was reported as 33.3% in the asthma group and 61.7% in the asthma+allergic rhinitis co-occurrence group (43). This finding is consistent with the information that allergic conjunctivitis is more common, especially in the presence of allergic rhinitis. In terms of skin involvement, atopic dermatitis is an early link in the "atopic march" and is bidirectional with asthma. The prevalence of atopic dermatitis in a pediatric asthma cohort was found to be 11.1% (41). In addition, another study reported the cumulative prevalence of asthma in patients with atopic dermatitis as 25.7% (44). In a study conducted in Bursa, asthma was observed in 20.2% and allergic rhinitis in 15.8% of pediatric cases with atopic dermatitis, and the co-occurrence of asthma and allergic rhinitis was reported in 19.3% (45). Careful evaluation of these allergic comorbidities is critically important in clinical practice for trigger control, treatment adherence, and symptom burden reduction. The incidence rates of childhood asthma, allergic rhinitis and allergic conjunctivitis, and atopic dermatitis may vary in different countries and societies depending on different factors (age, genetic factors, environmental factors, diagnostic methods used in studies, characteristics of the selected population, etc.) (18).

The presence of allergen sensitivity (atopy) is one of the important risk factors for the development of asthma (6,7). In our study, patients with asthma who tested positive in allergen skin prick tests and/or serum allergen-specific IgE tests were considered atopic, and the rate of atopic patients was found to be 46.4%, while the rate of non-atopic patients was 53.6%. Various studies investigating allergen sensitivity in asthmatic children in Turkey have reported sensitivity to at least one allergen in varying rates between 42-61% (23,46,47). Studies outside of Turkey have reported this rate to be approximately between 28-83% (48-50). Many studies in the literature have reported that inhalant allergen sensitivity increases significantly with age in childhood (10,23-25,49,51). Regarding the highly variable data reported in the literature, it is considered possible that different rates were obtained as a result of various characteristics of the populations selected in the studies, age group, study methods, regional, environmental and other possible factors. The rates of atopic cases detected in our study are generally consistent with the literature; however, it is thought that they may have been found to be slightly lower due to the age group being 3-6 years. The increasing trend in the incidence of atopy and inhalant allergen sensitivities with increasing age in the 48-59 month and 60-72 month age groups in our study group is considered as data supporting this possibility.

In our study, when allergen sensitivities of asthmatic children were examined, the highest rate of sensitivity to mites was observed (29.7%), followed by sensitivities to pollens (grass, cereal, weed, tree pollens) (23%), fungal spores (8.3%), and pet allergens (7.5%) (Table 3). In the literature, most studies investigating allergen sensitivity in children with asthma report that mites are the most frequently detected allergens in asthmatic children (10,52,53). In a study conducted in the Mediterranean region of Turkey, the distribution of allergen sensitivities in children diagnosed with asthma was reported as follows: mite sensitivity was most frequent (66%), followed by grass/cereal pollen mixture (51.2%), and then tree pollen mixture (50.9%) (53). In Ankara, it was reported that the most common allergen sensitivity in asthmatic children was pollen sensitivity (32%), followed by mite sensitivity (15.9%) (54). In Malatya, sensitivity to grass-cereal pollen mixture was found to be 48.9%, sensitivity to weed-pollen mixture was 48.5%, and sensitivity to mites was 40.2% in children diagnosed with asthma and allergic rhinitis (55). In a study of asthmatic children in Korea, sensitivity to mites was reported at a rate of 47.9% (10). A large cohort study in South China, based on real-life data and including 39,831 patients, reported that the most frequently detected aeroallergen in children was the mite (52). While sensitivity to mites was 28.1% in the entire cohort, this rate increased to 29.7% in children and to 55.3% in asthmatic children (52). Inhalant allergen sensitivities in asthmatic children; it is reported that there are significant differences between regions and countries depending on many factors such as genetics, age, living conditions, regional and geographical features, climate and vegetation, urban/rural settlement, air pollution, lifestyle, and environmental characteristics (17-20).

In this study, we observed that sensitivity to inhalant allergens (mite, grass, cereal and weed pollens, and fungal spores) increased significantly with age in asthmatic children, while sensitivity to food allergens gradually decreased. Similar age-dependent sensitization patterns have been reported in the literature. In an 18-year birth cohort study conducted on the Isle of Wight, the rate of atopy increased to 2% at age 1, 3% at age 2, 10% at age 4, 18-20% at age 10, and approximately 40% at age 18; it was shown that inhalant allergen sensitivity showed a regular increase with age (51). Similarly, according to the results of a child asthma cohort

in China, inhalant allergen sensitivity increased from 28% in the 3-5 age group to 55% in the 6-11 age group and to 62% in the 12-17 age group (49). In children, while inhalant allergen sensitivities increase with age, the decrease in food allergies over time is described as a natural part of the "atopic march". For example, in a multicenter study involving 5276 children, it was reported that cow's milk allergy decreased from 2.7% at age 1 to 0.5% at age 5; egg allergy decreased from 4.3% at age 1 to 0.8% at age 6 (7). Similarly, in a prospective cohort study, wheat allergy decreased from 1.8% at age 3 to 0.2% at age 6 (56). These data show that while food allergen sensitivities, which are dominant in early childhood, decrease significantly in later years, the increase in inhalant sensitivities with age reflects the expected course of immunological maturation, changes in environmental exposures, and the atopic march, which is similar to the data obtained in our study.

The sensitization rates to allergen groups such as mites general, pollens general, grass pollens general, cereal pollens general, and tree pollens general were found to be statistically significantly higher in children with asthma who also had allergic rhinitis. Additionally, while 46.4% of the general study population was diagnosed with asthma had sensitization to at least one allergen (inhalant or food) and were defined as atopic, this rate was found to be higher (57.5%) in those who also had allergic rhinitis (Table 4). Epidemiological studies show that sensitization rates to house dust mites, pollens, and animal dander are significantly higher in cases with both asthma and allergic rhinitis compared to children with asthma alone. In a multicenter study, inhalant allergen sensitization was found to be over 70% in children with both asthma and allergic rhinitis, while it was approximately 40-45% in those with asthma alone (57). In a comprehensive cohort study of 39,831 patients in southern China, house dust mite sensitivity was found to be 55.3% and grass pollen sensitivity 39.2% in children with asthma-allergic rhinitis comorbidity (52). For these reasons, it was considered that the significantly higher overall sensitivity to dust mites, grass pollen, tree pollen, and cereal pollen in asthmatic patients with concomitant allergic rhinitis in our study was consistent with current literature.

In this study, it was additionally found that children with atopic asthma had significantly higher total IgE levels than children without atopic asthma in all three age groups. Atopic asthma is characterized by a Th2-dominant immune system response in early childhood, during which a significant increase in total IgE levels is observed (58). Although not a general rule, total IgE is considered to be an indirect indicator of atopic sensitization in many cases and is found to be significantly higher in children with atopic asthma compared to their non-atopic or healthy peers. Similarly, data from the Tucson Children's Respiratory Study revealed that total IgE was higher in children with atopic asthma than in children with non-atopic wheezing (59). European-based studies have also shown that total IgE levels are statistically significantly higher in asthmatic children aged 3-6 years who have been sensitized to inhalant allergens compared to asthmatic children who have not been sensitized (58). In addition, it is emphasized that high total IgE levels in asthma are more frequently seen with accompanying atopic diseases such as allergic rhinitis and atopic dermatitis, and that these children have a higher risk of developing persistent asthma in later life (60). However, it is known that total IgE alone is not diagnostic; IgE levels can vary with age, parasitic infections, exposure to cigarette smoke, environmental factors, and comorbid conditions (61).

Study Limitations

The limitations of this study include its retrospective nature and the fact that it was conducted in only one healthcare facility. However, given that our institution specializes in allergic diseases, possesses standardized clinical and laboratory facilities, and is a tertiary healthcare center serving all relevant patients in the Bursa region, it can be considered that it contains sufficient data regarding the research results on allergen sensitizations in childhood asthma.

Conclusion

In this study, sensitivity to at least one allergen was detected in 46.4% of asthmatic children aged 3-6 years and was defined as atopic, with sensitivities most frequently found to be to mites (29.7%), pollens (23%), and fungal spores(8.3%). In asthmatic children, an increasing trend in the rate of atopy detection with age was observed (p=0.39). Inhalant allergen sensitivities in asthmatic children showed an increasing trend with age. Food allergen sensitivities, on the other hand, showed a decreasing trend with age. In asthmatic children, allergic diseases such as allergic rhinitis, atopic dermatitis, and allergic conjunctivitis were frequently observed to accompany asthma. In pediatric patients with both asthma and allergic rhinitis, significantly higher sensitivities to allergen groups such as dust mites, pollens, grass pollens, cereal pollens, and tree pollens have been found. In atopic asthmatics, total IgE levels were significantly higher in all three age groups compared to non-atopic children. Since inhalant allergen sensitivities in asthmatic children tend to increase with age, it was considered

necessary to re-evaluate these patients, especially in terms of the presence of inhalant allergen sensitivities (particularly in cases of additional allergic diseases), in parallel with increasing age. It is thought that the data obtained from this study will be useful in considering in the evaluation and follow-up of asthmatic pediatric patients.

Ethics

Ethics Committee Approval: The study received approval from the institution's ethics committee (Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision no. 2023-16/39 dated 01.08.2023).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Relationship between Disease Activity and Absolute Eosinophil Count and Serum IgE Level in Pediatric Patients with Eosinophilic Esophagitis

Eozinofilik Özefajitli Çocuk Hastalarda Hastalık Aktivitesi ile Mutlak Eozinofil Sayıları ve IgE Düzeyleri Arasındaki İlişki

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Abstract

Introduction: Clinical improvement does not reflect mucosal healing in the evaluation of response to treatment in eosinophilic esophagitis (EoE), and thus repeated endoscopies and eosinophil count on esophageal biopsy are still needed. Given that endoscopy is an invasive, risky, and costly method, noninvasive biomarkers that could practically indicate inflammation are needed to evaluate the treatment response.

Materials and Methods: The study included pediatric patients aged 0-18 years diagnosed with EoE. Age, gender, presenting complaints, comorbid allergic diseases, absolute eosinophil count (AEC), serum total IgE, and specific IgE (sIgE) levels were recorded retrospectively. All endoscopic examinations were performed by the same two experienced pediatric gastroenterologists. Biopsy samples were re-evaluated by two experienced pathologists.

Results: The study included 30 patients comprising 25 (83.3%) boys and 5 (16.7%) girls with a mean age of 6.93±4.47 (range, 2-16) years. Esophageal eosinophilic density established no significant correlation with total IgE level (p=0.75), while it was correlated with AEC (p=0.005, r=0.248). Both IgE (1843.1 kU/L vs. 420.8 kU/L, p<0.05) and AEC (1073.8/µL vs. 436.3/µL, p<0.05) were found to be significantly higher in patients with eosinophilic microabscess. In ROC analysis, AEC was found to have a predictive value in the diagnosis of EoE (AUC: 0.609, 95% CI: 0.51-0.71, p=0.022) at a cut-off value of 395/µL, with a sensitivity, specificity, PPV, and NPV of 58.1%, 64.2%, 47.5%, and 53.5%, respectively.

Conclusion: Although AEC appears to be a usable parameter in the follow-up of the patients, it is not sufficient as a biomarker alone for the prediction of EoE.

Öz

Giriş: Eozinofilik özofajitte (EoE) tedaviye yanıtı değerlendirmede, klinik iyileşme mukozal iyileşmeyi yansıtmamaktadır. Bu yüzden hala tekrarlayan endoskopiler yapılmakta ve biyopsi örneklerinden eozinofil sayılmaktadır. Endoskopinin invaziv, riskli ve pahalı bir yöntem olduğu düşünülürse tedaviye yanıtı değerlendirmek için noninvaziv ve inflamasyonu iyi yansıtan bir biyobelirtece ihtiyaç vardır.

Keywords
Eosinophilic esophagitis, absolute eosinophil count, serum IgE

Anahtar kelimeler
Eozinofilik özofajit, mutlak eozinofil sayısı, serum IgE

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Gereç ve Yöntem: Çalışmaya EoE tanısı almış 0-18 yaş arası pediatrik hastalar dahil edildi. Yaş, cinsiyet, başvuru şikayetleri, eşlik eden alerjik hastalıklar, mutlak eozinofil sayısı (AEC), serum toplam IgE ve spesifik IgE (sIgE) düzeyleri retrospektif olarak kaydedildi. Tüm endoskopik incelemeler aynı iki deneyimli pediatrik gastroenterolog tarafından yapıldı. Biyopsi örnekleri iki deneyimli patolog tarafından yeniden değerlendirildi.
Bulgular: Çalışmaya 25 (%83.3)' i erkek ve 5 (16.7)' i kız, yaş ortalaması 6.93±4.47 yıl (2-16 yaş) olan toplam 30 hasta alındı. Özefagial eozinofil yoğunluğu ile total IgE düzeyleri arasında korelasyon görülmezken (p=0.75), AEC ile korele olduğu tespit edildi (p=0.005, r=0.248). Eozinofilik mikroabsesi olan hastaların IgE (1843.1 kU/L vs 420.8 kU/L, p <0.05) ve AEC (1073.8 /µL vs 436.3 /µL, p <0.05) düzeyleri belirgin olarak daha yüksek bulundu. ROC analizi ile yapılan değerlendirme sonucunda AEC değerinin, EoE' i öngörmede tanısal değeri olduğu görüldü (AUC: 0.609, %95CI:0.51-0.71, p=0.022). Bu değer için önerilen sınır AEC değeri 395 /µL olup, sensitivite %58.1, spesifitesi %64.2, PPV%47.5, NPV %53.5 olarak bulundu.
Sonuç: AEC hastaların takibinde kullanılabilir bir parametre gibi görünse de, tek başına biyobelirteç olarak EoE'yi öngörmede yeterli değildir.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive immune-mediated disease characterized by antigen-driven type 2 inflammation (1). Its incidence is gradually increasing and its prevalence in children has been reported as 34.0 per 100,000 population (2). Although it affects individuals of all ages, it is more common in infants and young children. Young children mostly present to clinics with non-specific findings such as nausea, eating disorders, and growth retardation, whereas adolescents typically present with complaints of dysphagia and food retention due to progressive fibrosis (3). The diagnosis is usually made by the presence of a minimum of 15 intraepithelial eosinophils in at least one high-power field (hpf) in biopsy samples taken from the esophageal mucosa (4). Common treatment options include drug therapy, removal of dietary allergens, and esophageal dilation in cases with esophageal stricture (5).

Literature suggests that clinical improvement does not reflect mucosal healing in the evaluation of response to treatment in EoE, and thus repeated endoscopies and eosinophil count on esophageal biopsy are still needed (6). Given that endoscopy is an invasive, risky, and costly method, noninvasive biomarkers that could practically indicate inflammation are needed to evaluate the treatment response.

The aim of this study was to evaluate the utility of Absolute Eosinophil Count (AEC) and serum IgE level in the treatment and follow-up of pediatric patients with EoE.

Materials and Methods

The study included pediatric patients aged 0-18 years who applied to Karadeniz Technical University Medical School Pediatric Gastroenterology outpatient clinic with various complaints and were diagnosed with EoE between January 1, 2010 and December 31, 2023. For the diagnosis of EoE, a minimum of two biopsies were taken from the upper third (proximal), middle third, and lower third (distal) segments of the esophagus (7). Diagnosis was made based on the presence of a minimum of 15 intraepithelial eosinophils in at least one hpf in biopsy samples (4).

Age, gender, presenting complaints, comorbid allergic diseases, AEC, serum total IgE, and specific IgE (sIgE) levels (milk, egg, gluten, hazelnut) were recorded retrospectively from clinical notes. Hypereosinophilia was defined as AEC > 500/µL (8).

Skin prick testing (SPT) was conducted on the volar aspect of the forearm using standardized commercial allergen extracts and a 1-mm single-use lancet, in strict accordance with the guidelines established by the European Academy of Allergy and Clinical Immunology (EAACI). Histamine dihydrochloride (10 mg/mL) and physiological saline were employed as positive and negative controls, respectively. A test was considered positive if the mean wheal diameter was ≥3 mm greater than that of the negative control (9). Specific IgE (≥0.35 kU/L) was considered positive (9). Total IgE and food allergen-specific IgE (sIgE) levels were quantified in serum samples using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden).

All endoscopic examinations were performed by the same two experienced pediatric gastroenterologists and were evaluated macroscopically. Biopsy samples taken during endoscopy were re-evaluated by two experienced pathologists blinded to the clinical and laboratory characteristics of the patients.

A total of 10 sections of 4-6 mm thickness were taken from formalin-fixed paraffin-embedded esophageal tissue samples and Hematoxylin-Eosin (H&E) staining was used to evaluate the histological morphology of the samples. Histological examination of the samples was conducted using an Olympus BX51 microscope at x40 magnification (resulting in an area of microscopic field of 0.238 mm^2). Five fields of

view were counted from the area with peak eosinophilic density and the average of these five fields was taken. Presence of basal cell hyperplasia (BCH), polymorphonuclear leukocyte (PNL), and eosinophilic microabscess formation was evaluated in all sections (Figure 1).

Statistical Analysis

Data were analyzed using SPSS 26.0 for Windows (Armonk, NY: IBM Corp.). Descriptives were expressed as frequencies (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) and minimum-maximum for continuous variables. Normal distribution of variables was evaluated using Kolmogorov-Smirnov test. In independent groups, continuous variables were compared using Mann-Whitney U test since they did not show normal distribution. Correlations were assessed using Spearman's Correlation Coefficient. The diagnostic value of AEC (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) in predicting EoE was evaluated by Receiver Operating Characteristics (ROC) curve analysis. A p value of <0.05 was considered significant.

The study was conducted in accordance with the principles of the Declaration of Helsinki. An ethics committee approval was obtained from Karadeniz Technical University Scientific Research Ethics Committee (no: 2023/234, date: 07.12.2023).

Results

The study included 30 patients comprising 25 (83.3%) boys and 5 (16.7%) girls with a mean age of 6.93±4.47 (range, 2-16) years. A total of 147 endoscopy procedures were performed, with an average of 4.9±3.01 (range, 1-12) procedures. Most common presenting complaints included abdominal pain (40%) and dysphagia (30%). On endoscopic examination, esophageal mucosa was normal in 55 (37.4%) patients, while BCH was detected in 24 (16.3%), PNL in 18 (12.2%), and eosinophilic microabscess in 13 (8.8%) patients (Table 1).

Esophageal eosinophilic density established no significant correlation with total IgE level (p=0.75), while it was correlated with AEC (p=0.005, r=0.248). Both IgE (1843.1 kU/L vs. 420.8 kU/L, p<0.05) and AEC (1073.8/µL vs. 436.3/µL, p<0.05) were found to be significantly higher in patients with eosinophilic microabscess. No significant difference was found between patients with and without BCH with regard to IgE (251.6 kU/L vs. 624.5 kU/L, p=0.257) and AEC (712.1/µL vs. 450.3/µL, p=0.07) values. Although IgE (1537.3 kU/L vs. 466.9 kU/L, p=0.012) was found to be significantly higher in patients with PNL, no significant difference was detected between patients with and without PNL with regard to AEC (785.7/µL vs. 463.4/µL, p=0.073).

Esophageal eosinophilic density was significantly higher in patients with eosinophilic microabscess (76.6/hpf vs. 15.6/hpf, p<0.05) and BCH (47.4/hpf vs 15.6/hpf, p<0.05) compared to patients without, whereas it established no significant difference between patients with and without PNL (29.8/hpf vs. 19.6/hpf, respectively, p=0.196).

Both total IgE and AEC were significantly higher in patients with sIgE and/or skin prick test positivity than in patients without (p=0.049 vs. p=0.036, respectively). However, no significant difference was found between patients with and without sIgE and/or skin prick test positivity with regard to esophageal eosinophilic density (p=0.147).

At a cut-off value of >500/µL, the sensitivity, specificity, PPV, and NPV of AEC in the prediction of EoE were 62.7%, 46.3%, 57.5%, and 35.7%, respectively. No significant difference was detected between patients with and without hypereosinophilia with regard to esophageal eosinophilic density and treatment response (p=0.717 and p=1.00, respectively).

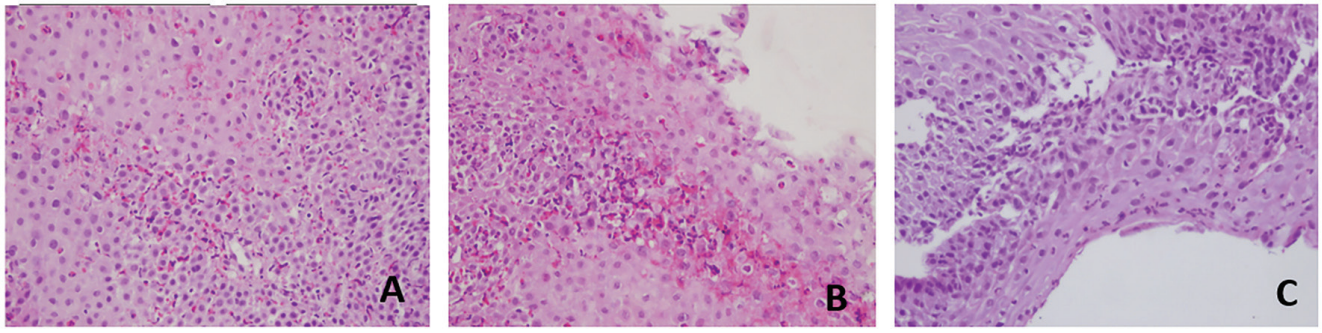

Figure 1. Histologic Characteristics of Eosinophilic Esophagitis. 1A. Eosinophilic leukocyte infiltration within stratified squamous epithelium (H&Ex400). 1B. Eosinophilic microabscess within stratified squamous epithelium (H&Ex400). 1C. Polymorphonuclear leukocytes infiltration within stratified squamous epithelium (H&Ex400)

Table 1. Demographic, clinic, endoscopic and histological characteristics of patients	
Parameters Mean±SD	
Age (years)	6.93±4.47
Gender (M) n (%)	25 (83.3)
Allergies (+) n (%)	10 (33.3)
Peak eosinophil count (/µL) Mean±SD	487.6±635.6
Total IgE level (kU/L) Mean±SD	556.9 ±1226.7
Specific IgE (+)	n (%)
Egg white	7 (23.3)
Egg yolk	5 (16.7)
Milk	8 (26.7)
Other food	4 (13.3)
Presenting complaints	n (%)
Abdominal pain	12 (40.0)
Dysphagia	9 (30.0)
Nausea	6 (20.0)
Vomiting	5 (16.7)
Loss of appetite	4 (13.3)
Anemia	3 (10.0)
Malnutrition	3 (10.0)
Constipation	2 (6.7)
Endoscopy	n (%)
Normal	55 (37.4)
Hyperemic	21 (14.3)
Trachealization	16 (10.9)
Linear interpolation	14 (9.5)
Nodular	11 (7.5)
White plaque	10 (6.8)
Erosive	9 (6.1)
Ulcer	7 (4.8)
Edematous	4 (2.7)
Histology	n (%)
Basal cell hyperplasia	24 (16.3)
Polymorphonuclear leukocyte	18 (12.2)
Eosinophilic microabscess	13 (8.8)

In ROC analysis, AEC was found to have a predictive value in the diagnosis of EoE (Area Under ROC Curve [AUC]: 0.609, 95% Confidence Interval [CI]: 0.51-0.71, p=0.022) at a cut-off value of 395/µL, with a sensitivity, specificity, PPV, and NPV of 58.1%, 64.2%, 47.5%, and 53.5%, respectively (Figure 2).

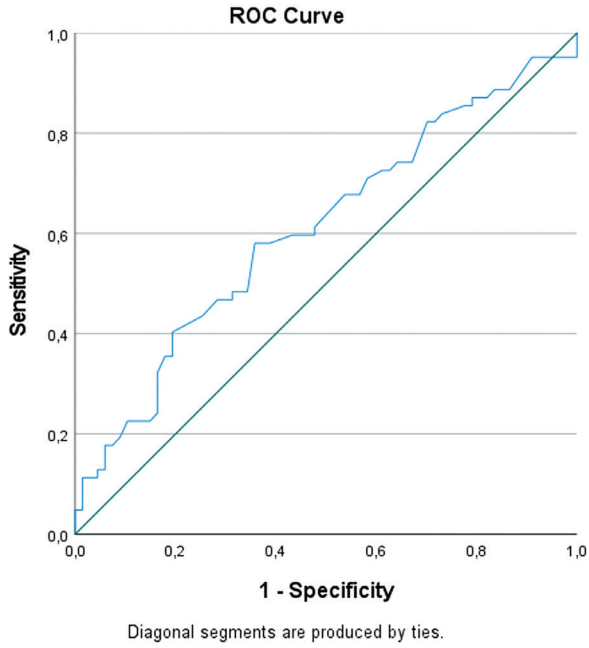

Figure 2. Diagnostic value of AEC in predicting EoE (AUC: 0.609, %95CI: 0.51-0.71, p=0.022)

Discussion

Eosinophilic esophagitis (EoE) is a disease with an increasing incidence, leading to reduced quality of life as well as severe long-term complications. Repeated endoscopic and histological examinations remain essential to evaluate treatment response. The present study evaluated the usability of AEC and serum IgE values in the follow-up of pediatric patients with EoE. Esophageal eosinophilic density established no significant correlation with total IgE, while it was correlated with AEC.

In the literature, there are numerous studies reporting on a correlation between AEC and esophageal eosinophilic density (10-12). The first report of eosinophilic esophagitis in Türkiye was published by Bakirtaş et al. (14) in 2012, and eosinophilia was detected in 4 of 7 patients (57.2%) (13). A study by Furuta et al. (5) reported that AEC decreased significantly after two weeks of budesonide treatment and that AEC was correlated with esophageal eosinophilic density. In another study, Rodríguez-Sánchez et al. (15) observed that AEC decreased in 22 patients who responded to a six-week diet treatment, while it did not decrease in six patients that did not respond to the treatment. In the same study, however, no significant correlation was found between AEC and esophageal eosinophilic density. In a study by Wechsler et al. (16), it was revealed that AEC and peak eosinophil count

(PEC) had a predictive value in the diagnosis of EoE. Schlag et al. (10) evaluated the correlation between esophageal eosinophilic density and several parameters including AEC, serum CCL-17, CCL-18, CCL-26, eosinophil-cationic-protein, and mast cell tryptase levels measured before and after budesonide treatment and reported that AEC showed the highest correlation. In the same study, the authors noted that AEC was also useful for assessing local disease activity and was significantly associated with histological remission.

To our knowledge, there is no established cut-off value for AEC to predict EoE or its prognosis. At a cut-off value of 300/µL, AEC has been shown to have a sensitivity and specificity of 88% and 56% in the prediction of histological remission (10). By contrast, a study by Min et al. (17) reported that a cut-off value of >150/µL had a sensitivity and specificity of 85% and 55%, while it had a sensitivity and specificity of 75% and 64% at a cut-off value of >200/µL, respectively. In our study, the optimal cut-off value was found to be 395/µL, with a sensitivity and specificity of 64.2% and 58.1%, respectively. Moreover, AEC was found to be correlated with esophageal eosinophilic density although the AUC (0.609) and correlation coefficient (r=0.248) were remarkably low. Taken together, all these findings implicate that AEC alone is not likely to evaluate the disease severity and replace endoscopy. On the other hand, it is known that esophageal eosinophilic density in EoE patients may vary depending on the seasons (18-19). Likewise, in our study, AEC showed variation between atopic and non-atopic patients. Additionally, AEC decreased after treatment, which we believe may be helpful in treatment response.

Some studies have attempted to improve the sensitivity and specificity of AEC alone by adding several other biomarkers. Among these, a study by Min et al. (17) reported that the use of eosinophil cationic protein (ECP) >30 ng/ml along with AEC >200 /µL increased the specificity to 77% while it decreased the sensitivity to 55%. The authors noted that the combined use of AEC and ECP was effective in the diagnosis of EoE. In a study by Thulin et al. (20), AEC was combined with eosinophil-derived neurotoxin (EDN), total and sIgG4, and sIgE to distinguish active EoE, EoE in remission, and healthy individuals. A combination of biomarkers (AEC, EDN, sIgE to egg white and wheat) and symptoms revealed an AUC of 0.92 in discriminating between the three groups. A study by Wechler et al. (16) reported that a combination of six serum biomarkers (galectin-10, ECP, EDN, Eotaxin 3, major basic protein-1 [MBP-1], and AEC) showed an AUC of 0.90, whereas another study indicated that a combination of 12 cytokines, AEC, and 15-hydroxyeicosatetraenoic acid (15(S)-HETE) had an AUC of up to 0.96 (21). Nevertheless, some other studies found that the use of parameters (ECP, EDN, MBP) in isolation was not sufficient to predict the diagnosis, and thus the studies attempted to predict the diagnosis by using data mining and machine learning techniques by adding some other different parameters (22,23).

In recent studies, these parameters have begun to be evaluated together with clinical findings. In an adult study conducted by Lingblom et al. (24), clinical findings (patients' reported outcomes) were combined with these parameters and the results suggested that this combination could be helpful in treatment monitoring. Nonetheless, there is need for further evidence to substantiate these findings. Moreover, multicenter studies involving more patients are needed to investigate the substitution of endoscopy with clinical, laboratory, endoscopic, and histopathological scoring systems.

Another issue to consider related to EoE is the correlation between histological findings and the prognosis. Hiremath et al. (25) indicated that histological scoring for EoE was correlated with histological findings (eosinophilic microabscess, BCH, eosinophilic inflammation, and dilated intercellular spaces). Choudhury et al. (26) found that esophageal eosinophilic density was higher in patients with BCH and eosinophilic microabscess regardless of the presence of neutrophils or lymphocytes. The authors also showed that esophageal eosinophilic density was correlated with AEC. In our study, although AEC was remarkably high particularly in patients with eosinophilic microabscess, esophageal eosinophilia density was higher in patients with eosinophilic microabscess and BCH. Additionally, esophageal eosinophilia density established a correlation with AEC in patients with eosinophilic microabscess, while there was no such correlation in patients with BCH and PNL. This finding may be due to the small number of patients in our study. Accordingly, further studies are needed on this subject to investigate whether the AEC cut-off value differs depending on the presence or absence of histological findings.

Study Limitations

Our study was limited in several ways. First, it had a small number of patients and thus active and remission patients could not be evaluated separately. Second, there was no healthy control group. Finally, the number of parameters examined was remarkably small. Given the retrospective nature of our study, further multicenter studies on this subject are needed.

Conclusion

In conclusion, EoE is a disease with an increasing incidence, requiring endoscopic and histological examination in the diagnosis and follow-up of the patients. Although AEC appears to be a usable parameter in the follow-up of the patients, it is not sufficient as a biomarker alone for the prediction of EoE. There is a need for scoring systems that could be used for evaluating other parameters and clinical findings together with endoscopic and histological findings.

Ethics

Ethical Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki. An ethics committee approval was obtained from Karadeniz Technical University Scientific Research Ethics Committee (no: 2023/234, date: 07.12.2023).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

An Evaluation of Two Different Surfactant Application Methods in Preterm Infants

Prematüre Bebeklerde İki Farklı Sürfaktan Uygulama Yönteminin Değerlendirilmesi

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Abstract

Introduction: Less invasive surfactant application (LISA) techniques are being investigated in order to reduce alveolar damage during exogenous surfactant application. This study analyses the therapeutic outcomes of the LISA and INSURE (INtubation SURfactant and Extubation) exogenous surfactant application techniques in premature babies.

Materials and Methods: Ninety-three premature babies born at the 36th week of pregnancy or earlier in the neonatal intensive care unit and administered surfactant using the INSURE (n=44) and LISA (n=49) methods were included in this prospective study. The two groups were evaluated in terms of treatment outcomes and the presence of complications of prematurity.

Results: The study population consisted of 37 (39.8%) girls and 56 (60.2%) boys. Twelve (27.3%) of the babies in Group 1 (the INSURE group) received Poractant, 24 (54.5%) Beractant, and eight (18.2%) Calfactant surfactant preparation. Poractant surfactant preparation was administered to all the babies in Group II (the LISA group). No significant differences were detected when the patients in groups I and II were compared in terms of repeat surfactant requirements, Clinical Risk of Babies (CRIB) scores, PaCO2, body temperature, days of mechanical ventilation, days of nasal continuous positive airway pressure, duration of use of oxygen hoods, and length of stay (p>0.05). No significant differences were also observed between the two groups in terms of complications developing during follow-up (pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia [BDP], intraventricular bleeding, and retinopathy of prematurity [ROP]) (p>0.05). However, the risk of BPD and ROP development was significantly greater in babies with high CRIB scores p=0,0003 and p=0,03).

Conclusion: Our comparison of the less invasive LISA and INSURE methods revealed no statistically significant difference in terms of treatment outcomes or complications. Further prospective studies involving new approaches and forms of treatment, their applicability, and larger numbers of cases are now needed.

Öz

Giriş: Ekzojen sürfaktan uygulaması sırasında alveolar hasarı azaltmak için daha az invaziv sürfaktan uygulama (LISA) teknikleri araştırılmaktadır. Bu çalışma, prematüre bebeklerde LISA ve INSURE (Entübasyon Sürfaktanı verilmesi Ekstübasyon) ekzojen sürfaktan uygulama tekniklerinin terapötik sonuçlarını analiz etmektedir.

Keywords
Respiratory distress syndrome, prematurity, surfactant, LISA, INSURE

Anahtar kelimeler
Solunum sıkıntısı sendromu, prematürelik, sürfaktan, LISA, INSURE

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Yöntem ve Gereçler: Bu prospektif çalışmaya, 36. gebelik haftasında veya daha erken bir zamanda yenidoğan yoğun bakım ünitesinde doğan ve INSURE (n=44) ve LISA (n=49) yöntemleri kullanılarak sürfaktan uygulanan doksan üç prematüre bebek dahil edildi. Daha sonra iki grup tedavi sonuçları ve prematüre komplikasyonlarının varlığı açısından değerlendirildi.

Bulgular: Çalışma popülasyonu 37 (%39,8) kız ve 56 (%60,2) erkek bebekten oluşuyordu. Grup 1'deki (INSURE grubu) bebeklerin 12'sine (%27,3) Poractant, 24'üne (%54,5) Beractant ve sekizine (%18,2) Calfactant sürfaktan preparatı uygulandı. Grup II'deki (LISA grubu) tüm bebeklere Poractant sürfaktan preparatı uygulandı. Grup I ve II'deki hastalar tekrarlayan sürfaktan gereksinimleri, Bebeklerde Klinik Risk (CRIB) skorları, PaCO2, vücut sıcaklığı, mekanik ventilasyon günü, nazal sürekli pozitif hava yolu basıncı günü, oksijen başlığı kullanım süresi ve hastanede kalış süresi açısından karşılaştırıldığında anlamlı bir fark saptanmadı (p>0,05). Takip sırasında gelişen komplikasyonlar (pnömotoraks, pulmoner hemoraji, bronkopulmoner displazi [BDP], intraventriküler kanama ve prematüre retinopatisi [ROP]) açısından da iki grup arasında anlamlı bir fark gözlenmedi (p>0,05). Ancak yüksek CRIB skorlu bebeklerde BPD ve ROP gelişme riski anlamlı olarak daha yüksekti (sırasıyla p=0,0003 ve p=0,03).

Sonuç: Daha az invaziv LISA ve INSURE yöntemlerinin karşılaştırması, tedavi sonuçları veya komplikasyonlar açısından istatistiksel olarak anlamlı bir fark ortaya koymadı. Yeni yaklaşımları ve tedavi biçimlerini, bunların uygulanabilirliğini ve daha fazla sayıda vakayı içeren daha fazla prospektif çalışmaya artık ihtiyaç duyulmaktadır.

Introduction

Respiratory distress syndrome (RDS) is a condition deriving from alveolar surfactant deficiency accompanying structural immaturity in the lungs. Despite major advances in treatment, it is still a major cause of severe morbidity and mortality in premature infants.. Early surfactant administration is widely employed in the treatment of RDS in preterm infants (1). The most widely employed technique for surfactant therapy is endotracheal intubation and short-term mechanical ventilation (INSURE, INtubation SURfactant and Extubation). However, premature babies' lungs are highly susceptible to mechanical ventilation-associated damage (2). A systematic review study reported that Less Invasive Surfactant Administration (LISA) reduced mechanical ventilation requirements and represented a better alternative compared to surfactant administration with mechanical ventilation via an endotracheal tube (3). Feeding tubes are easily available in all neonatal intensive care units (NICUs) and have been shown to be more reasonably priced than special catheters (4).

This study was planned to assess the effect of surfactant application via the INSURE and LISA methods on treatment and complications.

Materials and Methods

Preterm babies born at less than 36 weeks, administered surfactant by the two methods, and followed up between June 1, 2018, and October 1, 2019 in the NICU were included in this prospective study. Babies receiving surfactant via the INSURE method were classified as group I and those receiving surfactant via the LISA method as group II. Ninety-three babies were enrolled, 44 in Group I and 49 in Group II. Approval for the study was granted by the Atatürk University Medical Faculty ethical committee, Türkiye (decision no. 12, session 14, dated 30.05.2019). Informed consent was obtained from all individual participants included in the study.

Patients exhibiting postnatal tachypnea, grunting, retractions, and cyanosis, with hypoaeration, widespread reticulogranular opacity and air bronchograms on chest radiographs, were diagnosed with RDS. Surfactant was applied to patients with RDS when fraction of inspired oxygen (FiO_2) requirements were ≥40%. Babies with no regression in their clinical RDS findings and FiO_2 requirements persisting at ≥40% received repeat surfactant therapy at the intervals specified for each preparation.

Surfactant Preparation and Dosage

Three surfactant types were used;

1. Poractant (Curosurf®, Chiesi Farmaceutici SpA, Parma, Italy): Pharmaceutical type 80 mg/ml. Since studies have shown that an initial Poractant dose of 200 mg/kg is associated with lower mortality than a 100 mg/kg dose of the same preparation. The first dose was administered at 200 mg/kg, and when second and third doses were required, 100 mg/kg was given.
2. Beractant (Survanta®, AbbVie Inc. North Chicago, IL, USA): administered at a dosage of 100 mg/kg (25 mg/ml). The same dose was repeated when necessary.
3. Calfactant (Infasurf®, ONY Inc. Amherst, NY, USA): administered at 100 mg/kg (35 mg/ml). The same dose was repeated when necessary.

Methods of Application

Application Using the INSURE Method

Three different surfactant preparations were administered using the INSURE method to the babies in Group I. Endotracheal intubation was first performed, and the surfactant was then administered gradually through the tube in approximately one minute. Self-inflating balloon positive pressure ventilation was then applied for 30 seconds, after which the intubation tube was withdrawn and the baby was placed on continuous positive airway pressure (CPAP). In the INSURE method, surfactant preparations for a dose of 100 mg/kg were randomly selected from all three preparates.

Application Using the LISA Method

Poractant was administered to all the babies in Group II using the LISA method. The surfactant was administered by passing the vocal cord gap using a laryngoscope with the help of a LISAcath (130 mm long, 1.7 mm thick, Chiesi Farmaceutici SpA, Parma, Italy) with the baby on CPAP.

Mechanical ventilator requirements were classified as invasive and non-invasive mechanical ventilation . CPAP was defined as non-invasive, and endotracheal intubation as invasive mechanical ventilation.

Demographic data, type of delivery, birth weight, sex, APGAR score, surfactant administration method (INSURE or LISA), repeated surfactant administration requirements, pulmonary air-leak, whether or not intraventricular bleeding, BPD, and ROP developed, Clinical Risk of Babies (CRIB) score, duration of ventilator and oxygen therapy, and length of hospital stay were recorded.

Complications developing during observation were identified based on diagnostic criteria. Pulmonary air-leak was evaluated based on clinical and pulmonary findings, BPD using radiological National Institute of Child Health and Human Development criteria, intraventricular bleeding based on cranial ultrasonography and computed tomography/magnetic resonance imaging if required, ROP based on the international ROP classification, and CRIB scoring based on physiological parameters obtained in the first 12 hours (birth weight, birth week, presence of congenital malformation, the highest base deficit value in blood gas and the highest and lowest amount of FiO_2 administered). APGAR scores were calculated based on the baby's skin color, heart rate, muscle tone, and respiration in the first and fifth minutes after birth.

Statistical Analysis

Statistical analyses were carried out on SPSS version 22 software. The data were expressed as mean, standard deviation, mean (minimum-maximum), number, and percentage values. Normality of distribution by groups was assessed using the One-Sample Kolmogorov-Smirnov test. $p > 0.05$ was regarded as representing normal distribution. Normally distributed data were analyzed using the One–Way ANOVA test, and non-normally distributed data with the Mann-Whitney U and chi-square tests. p values <0.05 were considered statistically significant.

Results

Ninety-three babies were included in the study, 49 randomly assigned to the LISA group and 44 to the INSURE group for surfactant administration. The babies in both groups were delivered via cesarean section. Birth weights in the babies in group II were significantly lower than in group I ($p=0.02$). No difference was observed between the groups in terms of frequencies of multiple births ($p=0.08$). Fifth-minute APGAR scores were lower in group I ($p=0.01$). The groups' demographic characteristics are shown in Table 1.

The surfactant preparations applied are shown in Table 2.

Twenty-five (56.8) babies in Group I received two doses of surfactant and 23 (46.9%) of those in group II. Three doses were administered to two (4.5%) patients in group 1 and seven (14.3%) in group II. No statistically significant difference was determined between the two groups in terms of repeat surfactant requirements ($p>0.05$) (Table 3). The babies receiving a first surfactant dose of 200 mg/kg and those given 100 mg/kg were compared within and between the groups. Nineteen (59.45) of the 32 babies receiving 100 mg/kg surfactant in group I required repeat surfactant administration compared to 23 (46.9%) of the 449 babies receiving surfactant at 200 mg/kg in group II. The difference was not statistically significant ($p=0.27$). Six (50%) of the 12 babies in Group I receiving an initial surfactant dosage of 200 mg/kg required repeat application, while 17 (51.3%) of the 32 babies beractant+calfactant at 100 mg/kg required repeat application. The difference was also not statistically significant ($p=0.85$) (Table 4).

No significant differences were determined between the groups in terms of duration of mechanical ventilation, duration of nasal CPAP, length of oxygen hood use, or length of hospital stay ($p=0.44$, $p=0.53$, $p=0.41$, and $p=0.59$,

respectively). The groups receiving surfactant by the LISA and INSURE methods were also analyzed in terms of complications developing during follow-up. No statistically significant differences were determined between the groups in terms of pneumothorax, pulmonary hemorrhage, BPD, intraventricular bleeding, or ROP (Table 3).

The mean duration of mechanical ventilation among the babies in group I was 0.42±1.44 days for those receiving Poractant, 0.96±3.68 days for those given Beractant, and 1.75±4.2 days for those given Calfactant. Durations of stay were 32.6±17.7 days for the babies receiving Poractant, 42.1±32.4 days for those given Beractant, and 32.5±20.28 days for those given Calfactant. The differences were not statistically significant (p=0.68, p=0.18, and p=0.51, respectively). BPD developed in three (25%) of the babies in group I given Poractant, eight (33.7%) of those given Beractant, and one (12.5%) of the eight babies receiving Calfactant. This was also not statistically significant (p=0.64). While no ROP developed in any of the babies given Poractant and Calfactant, it was observed in one (4%) of those receiving Calfactant. The difference was not significant (p=0.58) (Table 5).

Respiratory distress syndrome is a neonatal disease frequently seen in preterm babies. However, the risk of mortality and BPD decreased with the entry into use of surfactants in treatment (5). The present study investigated the effects on treatment and development of complications of surfactant administration using the INSURE and LISA methods in preterm babies born at less than 36 weeks. Recent studies have shown that LISA represents the best approach in preterm babies with surfactant requirements. However, our results revealed no superiority of LISA over INSURE. High-dose surfactant administration can reduce repeat surfactant requirements and potential complications in babies with RDS.

Table 1. The Patients' Demographic Characteristics

			n (%)	p
Gender	Group 1 (n=44)	Female	19 (43.2%)	0.23
		Male	25 (56.8%)	
	Group 2 (n=49)	Female	18 (36.7%)	
		Male	31 (63.3%)	
Multiple pregnancy	Group 1 (n=44)	No	38 (86.4%)	0.08
		Yes	6 (13.6%)	
	Group 2 (n=49)	No	39 (79.6%)	
		Yes	10 (20.4%)	
			Mean ± SD	**p**
Birth weight (g)	Group 1 (n=44)		1727.39±455.25	0.04
	Group 2 (n=49)		1506.33±668.96	
Birth week	Group 1 (n=44)		31.32±2.79	0.57
	Group 2 (n=49)		30.33±3.26	
1st minute APGAR	Group 1 (n=44)		4.66±1.14	0.62
	Group 2 (n=49)		5.06±1.19	
5th minute APGAR	Group 1 (n=44)		6.39±0.86	0.01
	Group 2 (n=49)		6.94±0.62	

SD: Standard deviation

Table 2. The Surfactant Preparations Applied in the Groups

	Poractant n(%)	Beractant n (%)	Calfactant n (%)
Group 1 (n=44)	12 (27.3)	24 (54.5)	8 (18.2)
Group 2 (n=49)	49 (100)	-	-

Table 3. The Two Groups' LISA and INSURE outcome variables				
		Single dose	Second dose	P
Surfactant	Group 1 (n=44)	19 (43.2%)	25 (56.8%)	0.34
	Group 2 (n=49)	26 (53.1%)	23 (46.9%)	
Days of mechanical ventilation Mean±SD	Group 1 (n=44)	6±6.5		0.44
	Group 2 (n=49)	5.6±4.8		
Days of nasal CPAP Mean±SD	Group 1 (n=44)	6.5±6.2		0.53
	Group 2 (n=49)	6.2±7.2		
Days of O_2 via hood Mean±SD	Group 1 (n=44)	7±6.2		0.41
	Group 2 (n=49)	9.8±5.7		
Length of admission Mean±SD	Group 1 (n=44)	37.8±27		0.59
	Group 2 (n=49)	41.5±30.3		
CPAP: Continuous Positive Airway Pressure				

Table 4. The Comparison of Repeat Dose Requirements among Babies Receiving Initial Surfactant Doses of 200 mg/kg and 100 mg/kg			
	Repeat surfactant administration not required n (%)	Repeat application required n (%)	P
Group 1, initial dose 100 mg/kg (n=32) (Beractant + Calfactant)	13 (40.6)	19 (59.4)	0.27
Group 2, initial dose 200 mg/kg (n=49) (Poractant)	26 (53.1)	23 (46.9)	
Group 1, initial dose 100 mg/kg (n=32) (Beractant + Calfactant)	15 (46.9)	17 (53.1)	0.85
Group 1, initial dose 200 mg/kg (n=12) (Poractant)	6 (50)	6 (50)	

Table 5. Risk Factors and Complication Development According to Surfactant Types in Group I				
		Mean ± SD		P
Days of mechanical ventilation	Poractant (n=12)	0.42±1.44		0.68
	Beractant (n-=24)	0.96±3.68		
	Calfactant (n=8)	1.75±4.2		
Length of stay	Poractant (n=12)	32.6±17.7		0.51
	Beractant (n=24)	42.1±32.4		
	Calfactant (n=8)	32.5±20.28		
		None n(%)	Present n(%)	P
BPD	Poractant (n=12)	9 (75)	3 (3)	0.64
	Beractant (n=24)	16 (66.7)	8 (33.7)	
	Calfactant (n=8)	7 (87.5)	1 (12.5)	
ROP	Poractant (n=12)	12 (100)	-	0.58
	Beractant (n=24)	23 (95.8)	1 (4.2)	
	Calfactant (n=8)	8 (100)	-	

SD: Standard deviation; BPD: Bronchopulmonary Dysplasia; ROP: Retinopathy of Prematurity

The groups administered surfactant via the LISA and INSURE methods were evaluated in terms of complications developing during follow-up. No significant differences were observed between the two groups in terms of development of pneumothorax, pulmonary hemorrhage, BPD, intraventricular bleeding, or ROP (Table 6)

Table 6. Complications Developing in the Study Groups				
		None(n,%)	Present(n,%)	p
Pneumothorax	Group 1 (n=44)	43 (97.7%)	1 (2.3%)	0.36
	Group 2 (n=49)	46 (93.9%)	3 (6.1%)	
Pulmonary hemorrhage	Group 1 (n=44)	44 (100%)	0	0.34
	Group 2 (n=49)	48 (98%)	1 (2%)	
Bronchopulmonary dysplasia	Group 1 (n=44)	32 (72.7%)	12 (27.3%)	0.59
	Group 2 (n=49)	38 (77.6%)	11 (22.4%)	
Intraventricular bleeding	Group 1 (n=44)	44 (100%)	0	0.34
	Group 2 (n=49)	48 (98%)	1 (2%)	
Retinopathy of prematurity	Group 1 (n=44)	43 (97.7%)	1 (2.3%)	0.21
	Group 2 (n=49)	45 (91.8%)	4 (8.2%)	

Although the treatment outcomes and complication rates were similar between the LISA and INSURE groups, it should be noted that the mean birth weight was significantly lower in the LISA group (1506 g vs. 1727 g, p=0.04). This difference might have influenced the comparability of clinical outcomes despite the lack of statistical significance in gestational age. Therefore, this heterogeneity should be considered as a potential limitation of our study.

Studies have shown that surfactant administration using the INSURE method significantly reduces patients' mechanical ventilation requirements(6,7). This method involving endotracheal intubation requires the use of sedation, and complications such as decreased SpO_2 and trauma may develop. In addition, this method requires positive pressure ventilation, albeit for a short period, following surfactant administration. A need for surfactant administration methods that do not require endotracheal intubation has therefore been reported (8). Less invasive surfactant administration techniques have been described for reducing intubation and associated complications (9-11). Studies have shown that surfactant use with non-invasive ventilation causes less alveolar damage than mechanical ventilation via an endotracheal tube (12). In their multi-center study, Kribs et al. (13) recorded a significant decrease in mechanical ventilation requirements and in the incidence of BPD in the first 72 hours in their LISA group. A randomized, controlled study comparing LISA and INSURE in babies with RDS born at 26-34 weeks reported no significant difference in total respiration support, but that invasive mechanical ventilation requirements were lower in the LISA group (14). In the present study, the length of stay in the mechanical ventilator was shorter in Group II than in Group I. However, no significant differences were observed between LISA and INSURE in terms of length of stay in the mechanical ventilator, duration of nasal CPAP, length of hood use, or length of hospital stay. The youth of the study population may very likely have affected the significance level of the findings.

Anand reported comparable incidences of BPD in the two groups, and a low general incidence of ROP [14]. A meta-analysis comparing surfactant administration using the LISA method and intubation techniques in preterm infants diagnosed with RDS concluded that surfactant therapy with LISA was beneficial since this reduced the combined outcome of BPD and mortality and also mechanical ventilation requirements. Lower pneumothorax rates were also achieved with LISA. Meta-analysis results identified no difference in mortality or other neonatal morbidity outcomes (15). A previous review study reported no significant association between BPD and the LISA technique (16). No significant finding in terms of BPD or ROP emerged between the LISA and INSURE methods in the present research, although a significant increase in BPD development was determined in patients requiring repeat surfactant administration.

Surfactant administration with the LISA technique allows the maintenance of uninterrupted nasal CPAP support and also prevents pulmonary damage that may occur due to loss of functional capacity in the lung and atelectasis (17). The distribution of the surfactant in pulmonary tissue when applied using the LISA technique depends on the infant's efforts to breathe spontaneously. Compared with the INSURE method, in which repeated positive pressure air is applied, the surfactant reaches the lung tissue and is integrated with

it more quickly with LISA (18,19). No significant difference was observed between the two techniques in terms of pneumothorax and pulmonary hemorrhage complication development in the present study.

In their recent systematic review study, Isayama et al. (3) described LISA as reducing the incidence of intraventricular bleeding and BPD in addition to lowering mechanical ventilation requirements. There was no significant difference in terms of the development of intraventricular bleeding between the two groups in the current research.

Recent studies have shown that LISA reduces the need and duration of mechanical ventilation, decreases CPAP failure, and lowers the rates of bronchopulmonary dysplasia, pneumothorax, intraventricular hemorrhage and mortality compared to the INSURE method (14,20). However, our study included different surfactant preparations and doses, which may influence the comparability of LISA and INSURE outcomes.

Augur et al. (11) reported a significantly higher second dose of surfactant requirement in a LISA group compared to an INSURE group (35.6% compared to 6.5%, $p = 0.003$). This may be due to the surfactant dose in the LISA procedure (100 mg/kg) being lower than that in the INSURE group (200 mg/kg). Anand et al. (14) reported no significant difference between the two groups in terms of second dose of surfactant requirements. No significant difference in surfactant requirements was also determined in the present research. Although repeat surfactant requirements were lower in the group receiving 200 mg/kg initially, the difference was not statistically significant. The need for repeated surfactant may be lower with a 200 mg/kg dose applied through a less invasive method 200 mg/kg. A decreased repeat surfactant requirement may be beneficial in terms of a decrease in secondary complications and in terms of lowering costs. Further studies with larger case numbers are now needed to address this.

Study Limitations

Although this study compared both the LISA and INSURE methods, different surfactant preparations and initial doses (poractant alfa 200 mg/kg and other preparations 100 mg/kg) were used. This heterogeneity may have influenced the outcomes and reduced comparability between the two methods. A more homogeneous analysis restricted to infants receiving poractant alfa would likely provide a clearer evaluation of the differences between LISA and INSURE. This study was conducted in a single center with a relatively small sample size, and included heterogeneous surfactant types and initial doses. These factors may have limited the statistical power and generalizability of the findings.

Conclusion

Due to the sensitive state of premature babies and the complications that may develop after any form of invasive intervention, less invasive and interventional procedures are becoming increasingly important. The number of studies comparing the INSURE and LISA techniques in the international literature and in Türkiye is quite low. The present study is one of the few to compare the two. No statistically significant difference was determined in terms of complications with the two techniques. Endotracheal surfactant administration techniques will continue to occupy an important place in premature babies, for whom less invasive interventions are being sought. Further prospective studies evaluating novel approaches and forms of treatment, and the applicability there of, together with larger case numbers, are now needed.

Ethics

Ethical Approval: Approval for the study was granted by the Atatürk University Medical Faculty ethical committee, Türkiye (decision no. 12, session 14, dated 30.05.2019).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Systemic-Immune Inflammation Index (SII) Provides Valuable Insights into the Severity of Acidosis and Asidosis Resolution Time in Children with Diabetic Ketoacidosis

Systemic-Immune İnflammation Index [SII], Diyabetik Ketoasidozlu Çocuklarda Asidoz Şiddetini Belirlemeye Yardımcıdır

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Abstract

Introduction: DKA is a life-threatening disease that occurs early in type 1 diabetes. A lack of diagnostic resources can delay DKA diagnosis in some centers. In chronic disorders, hematologic inflammatory indicators are gaining attention. These markers' impact on DKA diagnosis and severity was the purpose of this cross-sectional investigation.

Materials and Methods: The study included 54 DKA-diagnosed T1DM children and 50 healthy controls from a single center. From the total blood count, SII, SIRI, NLR, and PLR values were computed, and Platecrit, MPV and PDW values were recorded.DKA is categorized into three groups: mild, moderate, or severe DKA using ISPAD criteria. We then analyzed uninfected T1DM patients' independent DKA predictors. Variable diagnostic performance was determined via ROC curve analysis. Multivariate logistic regression analysis examined all significant parameters.

Results: SII, NLR, and Platecrit significantly predict DKA severity (X2[3]SII=2973.23, X2[3]PCT =0,063, X2[3]NLR=93.29; pSII: 0,0001,pPCT: 0,0001,pNLR: 0,01). SII was the best marker for recognizing severe acidosis and T1DM with 94.44% sensitivity, and 81.48% specificity [AUC: 0.925 and 0,875]. This is one of the first SII/SIRI investigations in DKA children.

Conclusion: SII, NLR, and Platecrit may accurately predict DKA severity, with SII being the most effective marker for diagnosing DM and recognizing severe acidosis. In resource-limited settings, SII may be a viable alternative to blood gas tests for severe acidosis assessment.

Keywords
Diabetic ketoacidosis, neutrophil-to-lymphocyte ratio, plateletcrit, platelet-to-lymphocyte ratio, systemic immune-inflammation index, type 1 diabetes mellitus

Anahtar kelimeler
Diyabetik ketoasidoz, nötrofil-lenfosit oranı, plateletcrit, platelet-lenfosit oranı, sistemik immün-enflamasyon indeksi, tip 1 diyabetes mellitus

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Öz

Giriş: DKA, tip 1 diyabette erken dönemde ortaya çıkan, hayatı tehdit eden bir hastalıktır. Bazı merkezlerde tanısal kaynak eksiklikleri, DKA tanısının gecikmesine neden olabilir. Kronik hastalıklarda, hematolojik inflamatuar göstergelere olan ilgi artmaktadır. Bu parametrelerin DKA tanısı ve şiddeti üzerindeki etkisi, bu kesitsel araştırmanın amacını oluşturmuştur.

Gereç ve Yöntem: Çalışma, tek bir merkezden 54 DKA tanısı almış T1DM çocukları ve 50 sağlıklı kontrolü içermektedir. Tam kan sayımından, SII, SIRI, NLR ve PLR değerleri hesaplanmış, Platecrit, MPV ve PDW değerleri kaydedilmiştir. DKA, ISPAD kriterlerine göre hafif, orta veya şiddetli olarak üç gruba ayrılmıştır. Ardından,

enfekte olmayan T1DM hastalarının bağımsız DKA prediktörleri analiz edilmiştir. Değişken tanısal performans, ROC eğrisi analizi ile belirlenmiştir. Çoklu lojistik regresyon analizi, tüm önemli parametreleri incelemiştir.
Bulgular: SII, NLR ve Platecrit, DKA şiddetini anlamlı şekilde öngörmektedir (X2[3]SII=2973.23, X2[3]PCT =0,063, X2[3]NLR=93.29; pSII: 0,0001, pPCT: 0,0001, pNLR: 0,01). SII, şiddetli asidoz ve T1DM tanısını tanımada en iyi belirteçti ve %94,44 hassasiyet ve %81,48 özgüllük ile [AUC: 0,925 ve 0,875] en yüksek performansı gösterdi. Bu, DKA çocuklarında yapılan ilk SII/SIRI araştırmalarından biridir
Sonuç: SII, NLR ve Platecrit, DKA şiddetini doğru şekilde tahmin edebilir, ancak SII, DM tanısı ve şiddetli asidozun tanınması için en etkili belirteçtir. Kaynakların sınırlı olduğu ortamlarda, SII şiddetli asidoz değerlendirmesi için kan gazı testlerine alternatif olarak uygun bir seçenek olabilir.

Introduction

Diabetic ketoacidosis (DKA) is a hyperglycemic emergency defined by hyperglycemia, ketosis, and metabolic acidosis (1,2). In children with type 1 diabetes mellitus (T1DM), this condition presents as the initial manifestation in 30-40% of cases (1,3). The most common complication associated with DKA is cerebral edema, which increases the risk of mortality and morbidity, primarily due to severe acidosis and osmotic diuresis (1,4-5). As the diagnosis of DKA is delayed, the risk of complications rises significantly, with mortality rates escalating to 24% as acidosis worsens. Therefore, early diagnosis of DKA and prompt treatment initiation are crucial for improving prognosis (5,6).

Limited diagnostic resources in some centers can lead to delays in DKA diagnosis. Consequently, there is a pressing need for reliable alternative biomarkers that can be easily assessed in all healthcare settings to recognize acidosis. The complete blood count (CBC) is a low-cost test that provides information on various cells involved in inflammation and can be performed in most centers. Hematological inflammatory parameters, such as the systemic immune response index (SIRI), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), can be derived from this test. The use of these biomarkers is currently recommended in the context of inflammatory, rheumatological, and cardiac diseases, as well as malignancies and obesity (6-10). Recent studies indicate that some inflammatory markers are elevated in patients with T1DM and are associated with glycemic control (11). Consequently, NLR has been identified as a new biomarker for recognizing DKA (12). However, SII, among other markers, has not been extensively studied with DKA, highlighting a research gap that necessitates further exploration to understand their potential roles in this condition. Currently, further research is needed to evaluate the sensitivity and specificity of these biomarkers. This study aims to evaluate the diagnostic and prognostic value of hematological inflammatory markers in children with DKA, particularly in assessing acidosis severity and potential correlations with hospital stay and recovery time.

Materials and Methods

Patient Recruitment

This study was conducted with 81 T1DM patients and 49 healthy controls followed at the Pediatric Endocrinology Clinic of Zonguldak Bülent Ecevit University between April 2022 and January 2024, following the principles of the Declaration of Helsinki. Ethical approval was received from the ethics committee at our university. (ethics no:2024/07-6). We retrospectively evaluated the patients' medical files.

T1DM patients were categorized into 2 groups, DKA and Non-DKA groups, according to the presentation at the time of diagnosis. Patients with a concurrent infection, concomitant autoimmune or external diseases, diabetes types other than type 1, syndromic appearance, or recurrent DKA episodes were excluded from the study.

T1DM and DKA were diagnosed by the guidelines established by the International Society for Pediatric and Adolescent Diabetes (ISPAD). For DKA diagnosis, the thresholds were defined as a plasma glucose level >200 mg/dL, a urine ketone level >+2, and an arterial pH value <7.3. Patients were classified into three groups based on DKA severity, using the ISPAD criteria: mild DKA ($7.20 \leq pH < 7.30$ or $10 \leq HCO3 < 15$ mmol/L), moderate DKA ($7.10 \leq pH < 7.20$ or $5 \leq HCO3 < 10$ mmol/L), and severe DKA ($pH < 7.10$ or $HCO3 < 5$ mmol/L). We evaluated blood gas analysis results, hyperglycemia levels, CBC parameters such as plateletcrit (PCT), mean platelet volume (MPV), platelet redistribution width (PDW), C-reactive protein (CRP), glycated hemoglobin (HbA1c), and C-peptide levels at the time of diagnosis to assess possible changes due to treatment. From the CBC parameters, PLR (platelet/lymphocyte), NLR (neutrophil/lymphocyte), and SII (platelet x neutrophil/lymphocyte) were calculated. The variability of inflammatory markers was evaluated between healthy controls and non-DKA and DKA

groups. At the same time, the sensitivity of hematological inflammation markers in determining the severity of DKA was evaluated. Receiver Operating Characteristic (ROC) curve analysis was performed to analyze the effectiveness of these markers. We reevaluated our data to determine the best marker and cutoff for detecting severe DKA, categorizing patients into two groups based on an arterial pH value <7.1 or HCO3 <5 mmol/L according to the clinical two-group classification of DKA.

The healthy control group was composed of children who applied to the clinic for growth and development evaluation but were found to be within normal limits according to the Turkish children's percentile curves.

Biochemical Assays

We collected the blood samples immediately before initiating the treatment during the patient's admission. In our hospital laboratories, we processed blood gas analysis and CBC parameters, routine biochemistry, and HbA1c levels. CBC parameters are studied with the Sysmex XN-550 (Sysmex Corporation, Kobe, Japan) automated system. We calculated hematological inflammatory parameters such as SII, NLR, and PLR from CBC data for all groups. For HbA1c measurement, we utilized a high-performance liquid chromatography kit (Lifotronic H9 Hemoglobin Analyzer).

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 19 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk Test was utilized to verify the normality of the data distribution. For normally distributed data, we employed the T-test and One–way ANOVA; for non-normally distributed data, we used the Mann-Whitney U test and the Kruskal-Wallis test.

To compare the hematological inflammatory parameters based on the severity of DKA, we applied the Kruskal-Wallis Test. Multiple comparisons were conducted via post hoc analysis utilizing Dunn's (1964) procedure along with Bonferroni adjustment. To evaluate the discriminative capacities of SII, NLR, and PCT in predicting the severity of ketoacidosis and for optimal marker detection, we performed an ROC curve analysis. We determined the optimal cut-off values by maximizing the Youden index (calculated as sensitivity + specificity - 1, ranging from 0 to 1) and the area under the curve (AUC). Spearman's correlation test examined the relationship between hematologic parameters and the duration of diabetes, whereas Pearson's correlation test was applied for the connection between parameters. P-values < 0.05 were considered statistically significant.

Results

Basal Characteristics of Patients

The study included 54 patients diagnosed with T1DM who presented with DKA, 27 patients with T1DM who were diagnosed with isolated hyperglycemia and/or ketosis but not with DKA, and 50 healthy controls. In the DKA group, the mean age was 8.89 ± 4.12 years, with 53.3% being male. The cases were divided into three groups based on the severity of DKA: mild DKA (n=17), moderate DKA (n=18), and severe DKA (n=19). There were no significant differences between the groups in terms of age and sex distribution (p=0.16; p=0.23). The standard deviation scores (SDS) for height, body weight, and body mass index (BMI) were significantly higher as the severity of acidosis increased (p=0.005, p=0.005, p=0.044, respectively). Blood gas analysis revealed significant differences in pH and HCO3 levels, as expected (p<0.001). There were no significant differences in the blood sugar and HbA1c levels among the groups. C-peptide levels were significantly lower as the severity of acidosis increased (p=0.003).

Association Between Inflammatory Parameters and DKA Severity

As shown in Table 1, we found significant differences in complete blood count parameters among the three groups. We observed that as DKA severity increased, total white blood cells, neutrophils, monocytes, and platelet count also significantly increased (p < 0.001).

Among the hematological inflammatory parameters, SII, NLR, and PCT showed significant differences between the DKA groups (p<0.001), while PLR, PDW, and MPV levels were similar across the groups (Table 2).

As shown in Figure 1, all three parameters were significantly effective in predicting the severity of DKA (p<0.0001). The distributions of SII, PCT, and NLR scores were significantly different between groups ($X^2(3)^{SII}$ = 2973.23, $X^2(3)^{PCT}$ = 0.063, $X^2(3)^{NLR}$ = 93.293; p^{SII}= 0.0001, p^{PCT}= 0.0001, p^{NLR}=0.01).

Multiple comparisons were conducted via post hoc analysis utilizing Dunn's (1964) procedure along with Bonferroni adjustment. This post hoc analysis revealed statistically significant differences in the median scores of all three markers between those with severe DKA and those

Table 1. Laboratory and anthropometric findings in patients stratified by DKA severity				
	MILD DKA n=17	**MODERATE DKA n=18**	**SEVERE DKA n=19**	**p**
Age [years]	11.06 [6-17.66]	9.12 [0.91-16.91]	7.45 [2.58-13]	**0.026**
Height SDS	0.01±1.49	-0.13±0.86	1.01±0.86 [b]	**0.005**
Weight SDS	-1.12±0.77	-0.34±1.45	0.56±1.12 [b]	**0.005**
Body Mass Index SDS	-1.62±1.23	-0.29±1.77	-0.09±1.55	**0.044**
Serum pH	7.24±0.02[b]	7.16±0.02[a]	6.93±0.09[a,b]	**<0.001**
Serum HCO3	13.86±2.09[b]	10.15±1.32[a]	6.23±1.69[a,b]	**<0.001**
HbA1c [%]	12.2±1.49	10.9±2.22	12.26±1.99	0.134
Glucose [mg/dl]	484.9±172.88	437.76±174.05	462.94±86.8	0.176
C-peptide [ng/ml]	0.24±0.13	0.34±0.22	0.16±0.08[b]	**0.003**
WBCs [×10³/mm³]	8.76±3.21	10.18±3.28	25.33±8.8[a,b]	**<0.001**
Neutrophils [×10³/mm³]	5.79±2.61	6.74±2.84	20.46±6.86[a,b]	**<0.001**
Lymphocytes [×10³/mm³]	2.14±0.97	3.00±2.67	3.14±0.9	0.305
Monocytes [×10³/mm³]	0.56±0.27	0.58±0.37	3.37±7.39[a,b]	**<0.001**
Thrombocytes [×10³/mm³]	297.6±53.81	335.23±95.34	449.72±89.67[a,b]	**<0.001**
Acidosis recovery time (hours)	6,6±3,2 (3-14)	13,1 ±7,3 (5-36)	23,6±9,3(9-76)	**0,007**
Hospitalization stay (day)	9,1±2,5	7,5±4,0	10,1±4,3	**0,162**

Kruskal-Wallis Test and One Way ANOVA. Data are presented as mean±standard deviation, median [minimum, maximum], and percentage [%]. Statistically significant differences are indicated in bold and italicized with a p-value <0.05. HCO3: bicarbonate; HbA1c: glycated hemoglobin; WBC: white blood cell count; SDS: standard deviation score

Table 2. Comparison of hematologic inflammatory markers by DKA severity				
	Mild DKA n=17	**Moderate DKA n=18**	**Severe DKA n=19**	**p**
SII	981.98±705.04	1269.95±1005.03	3499.68±1442.64[a,b]	**<0.001**
NLR	3.21±2.15	4.17±3.57	7.9±3.29 [a,b]	**<0.001**
PLR	167.82±82.06	184.38±115.61	186.36±94.3	0.944
PCT [%]	0.25±0.005	0.29±0.08	0.38±0.06 [a,b]	**<0.001**
PDW	17.18±0.72	17.21±0.53	17.01±0.39	0.569
MPV [fL]	8.56±0.83	9.08±1.24	8.55±0.62	0.265

Kruskal-Wallis Test and One-Way ANOVA. Data are presented as mean±standard deviation and percentage [%]. Statistically significant differences are indicated in bold and italicized with a p-value <0.05. SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; MPV: mean platelet volume. Compared with the mild-DKA group, [a] $p < 0.016$. Compared with the moderate DKA group, [b] $p < 0.016$.

with moderate (p^{SII}= 0.0001, p^{PCT}= 0.003, p^{NLR}= 0.004), and mild DKA (p^{SII}= 0.0001, p^{PCT}= 0.0001, p^{NLR}= 0.02), but not between those with mild DKA and moderate DKA (p^{SII}= 1.00, p^{PCT}=0.28, p^{NLR}=1.00).

To demonstrate the diagnostic efficacy of SII, NLR, and PCT in predicting DKA severity, we performed an ROC curve analysis. When we reclassified the groups into mild-moderate DKA (pH > 7.1 or HCO3>5 mmol/L) and severe DKA (pH ≤ 7.1 or HCO3<5 mmol/L), we found that all three parameters were significantly effective in predicting DKA severity (p<0.0001) (Figure 1). Comparing the discriminative abilities of these three parameters for predicting DKA severity, we determined that SII was the most valuable parameter for discriminating severe acidosis from others. The statistical cut-off value for SII was determined to be 1612.29, with a sensitivity of 94.44% and a specificity of 81.48% (AUC=0.928) (Figure 1).

In the comparison of mild DKA, moderate DKA, and severe DKA groups, the acidosis resolution time was found to be significantly different (6.6±3.2 [3-14] hours, 13.1±7.3 [5-36] hours, and 23.6±9.3 [9-76] hours, respectively; p =

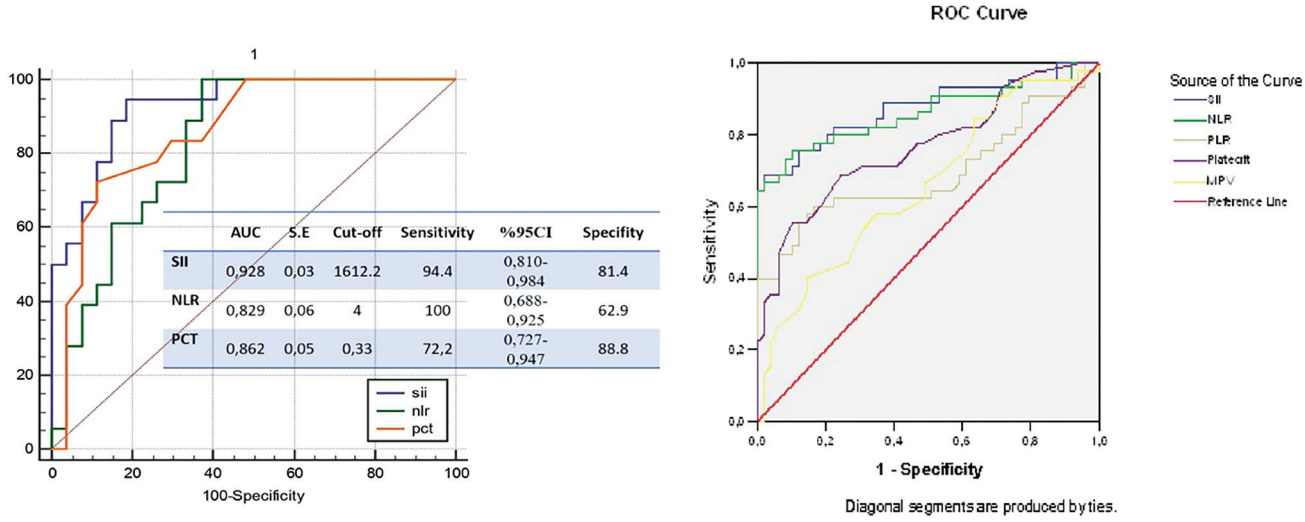

Figure 1. ROC curve analysis of inflammatory parameters in distinguishing DKA from healthy control and in determining DKA severity

ROC: Receiver operating characteristic, SII: systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PCT: plateletcrit, AUC: Area under the curve, S.E: Standard error, CI: confidence interval

P<0,0001 for all three markers

Table 3. Characteristics data and comparison of DKA group, Non-DKA T1DM group, and healthy controls

	DKA Group n=54	Non-DKA T1DM Group (n=27)	Control Group n=49	p
Age [years]	8.89±4.12	10,48±5,0	9.83±3.956	0.294
Height SDS	0.36±1.148[a]	0,49±1,12	-0.117±1.041	**0.037**
Weight SDS	-0.155±1.349	0,43±1,78	0.275±1.211	0.177
BMI SDS	-0.51±1.663[a]	0,07±1,94	0.405±1.095	**0.017**
WBC [×10³/mm³]	13.4 [3.6-45.6][a,b]	8,2 [4,9-16.9][c]	7.4 [3.9-12.6]	**<0.001**
Neutrophil [×10³/mm³]	10 [2-37.1][a,b]	4,9 [1.1-6.7].[c]	3.3 [0-7.5]	**<0.001**
Lymphocyte [×10³/mm³]	2.2 [0.5-9.2][b]	4,3 [2-10.8][a,c]	2.5 [0-5.3]	**<0.001**
Platelet [×10³/mm³]	348 [194-596][a,b]	290 [148-536].[c]	290 [164-549]	**<0.001**
SII	1612.29[221.9-6090][a,b]	442,3 [175-1957,5][c]	407.555 [82-1092.6]	**<0.001**
NLR	4.68 [0.62-14][a,b]	1,43 [0,63-7,0][c]	1.434 [0.5-3.95]	**<0.001**
PLR	154.1 [47.2-442][a,b]	95,1 [54,7-253,6][c]	119.629 [40.75-207]	**0.001**
Plateletcrit [%]	0.3202±0.0861[a,b]	0.247±0.030[c]	0.2433±0.0525	**<0.001**
MPV [fL]	8.7 [6.6-11.1][a]	8.4 [6.5-11][c]	8.2 [6.8-11.3]	**0.046**

Kruskal-Wallis Test and One Way ANOVA Data are presented as mean±standard deviation, median [minimum, maximum]. Statistically significant differences are indicated in bold and italicized with a p-value <0.05. WBC: white blood cell count; PLT: platelet count; SII: systemic immune-inflammation index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PCT: plateletcrit; MPV: mean platelet volume; SDS: standard deviation score. Compared with healthy controls, [a] $p < 0.016$. Compared with Non-DKA T1DM group, [b] $p < 0.016$. Compared with DKA group [c] $p<0.016$

0.007). However, no significant difference was observed in hospitalization time between the groups (9.1±2.5, 7.5±4.0, and 10.1±4.3 days, respectively; p = 0.162). (Table 2)

Upon categorizing the individuals into severe DKA and mild to moderate DKA, the median acidosis resolution time for the severe DKA group was 23.6 hours, substantially exceeding the 10 hours recorded for the mild-moderate DKA group (p=0.003). The median hospitalization duration in the severe DKA group was 10.1 days, whereas the other group had a median of 8 days (p= 0.09).

Table 4. ROC analysis of hematologic inflammatory markers for differentiating DKA patients from healthy controls						
	AUC	S.E	Cut-off	Sensitivity[%]	Specificity[%]	p
SII	0,875	0,038	673,2	75.5	87.7	**<0.0001**
NLR	0,860	0,041	2.12	77,7	83,6	**<0.0001**
PLR	0,693	0,058	134,6	62,2	77,6	**0.001**
Plateletcrit	0,767	0,049	0,27	68,8	75,5	**<0.0001**
MPV	0,656	0,056	8,65	57,7	63,5	**0.009**

ROC, receiver operating characteristic; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PCT, plateletcrit. PLR, platelet-to-lymphocyte ratio; MPV, mean platelet volume; AUC, area under the curve; S.E., standard error

Comparison of Inflammatory Markers Between DKA Patients, Non-DKA Patients, and Healthy Controls in T1DM

When comparing T1DM cases from both groups with healthy children, it was observed that all groups showed similar age and gender distributions. When comparing the three groups, significant differences were found in all parameters except for weight SDS, and age. In the comparison between Non-DKA T1DM and the healthy group, no significant changes were found in anthropometric and inflammatory parameters ($p>0.05$), except for lymphocyte levels ($p<0.001$). Post-hoc analysis revealed that this change was mostly observed between the DKA group and the healthy group.

Significant differences of weight values were found between the Non-DKA T1DM and DKA T1DM groups ($p=0.031$), white blood cells, platelets, PCT, neutrophils, lymphocytes, SII, NLR, and PLR (all $p <0.001$). No significant change was observed in MPV ($p= 0.43$).

In the anthropometric assessment between the DKA patients and the healthy control group, we found that height and BMI SDS were significant in distinguishing the DKA group ($p = 0.037$ and $p = 0.002$, respectively). The DKA group had significantly higher levels of white blood cells, neutrophils, lymphocytes, platelets, PCT, SII, NLR, and PLR compared to both the Non-DKA and healthy control groups. The MPV level showed a significant difference only between the DKA and healthy control groups (Table 3). In the ROC analysis, when we compared DKA patients with healthy controls in terms of inflammatory markers, SII was identified as the most valuable parameter for diagnosing DKA (AUC = 0.875, cut-off = 673.2, sensitivity = 75.5%, specificity = 87.7%) (Table 4) (Figure 1).

A significant correlation was found between DKA severity and acidosis resolution time ($p= 0.001$, $r= 0.55$), while no correlation was observed between hospitalization duration and DKA severity ($p= 0.27$). Among the inflammatory markers, a correlation was found between SII and acidosis resolution time ($p= 0.002$, $r=0.340$), but no relationship was observed with hospitalization duration ($p= 0.73$). No correlation was found between NLR and PLR with either acidosis resolution time ($p= 0.07$, $p= 0.67$, respectively) or hospitalization duration ($p= 0.58$, $p= 0.43$, respectively).

Discussion

In the current study, we found that specific inflammatory markers- particularly the SII, NLR, and Plateletcrit significantly correlate with the severity of DKA. SII is emerging as the most reliable indicator. SII's reliability is particularly high in distinguishing severe acidosis from mild and moderate cases. Notably, a cut-off value of 1612.29 for SII was identified, demonstrating significant predictive value for severe DKA, with high specificity and sensitivity.

As the most common hyperglycemic emergency, DKA is characterized not only by insulin deficiency but also by inflammatory processes activated as a stress response by the body. In this context, insulin deficiency triggers the release of counter-regulatory hormones such as glucagon, cortisol, and catecholamines, which in turn stimulate gluconeogenesis and ketogenesis in the liver. These hormonal changes enhance the inflammatory response by increasing the release of cytokines and other inflammatory mediators, thereby amplifying cellular stress and damage critical role in the pathophysiology of DKA. Elevated cytokine levels further worsen insulin resistance and disrupt metabolic balance (13). These interrelated processes contribute not only to the worsening of acidosis but also pave the way for complications. The inflammatory response's effects are more pronounced in DKA, especially in severe cases, leading to significant morbidity (14). Consequently, rapid and accurate recognition of DKA is crucial for initiating an effective treatment process.

Blood gas analysis is a common diagnostic tool for DKA, allowing for rapid assessment of a patient's acid-base status, with pH and bicarbonate parameters used for severity scoring. While blood gas analysis is the gold standard for assessing acid-base balance, challenges -such as delays

in sample collection, transport, analysis, and potential laboratory errors -can limit its effectiveness. This makes the availability of blood gas analysis a significant concern in various healthcare settings (13-15). These limitations have led to the exploration of alternative markers for assessment. The use of inflammatory markers to assess DKA severity has gained traction in recent research (11-12). Studies have shown that hematological inflammatory markers derived from CBC can serve as straightforward, practical, and cost-effective tools for predicting DKA severity. Researchers have particularly focused on markers like NLR, PLR, and SII, which have demonstrated their value across multiple studies in various inflammation-related immunological diseases (6-10,16).

The Systemic Immune-Inflammation Index derived from platelets, neutrophils, and lymphocytes, has emerged as a novel marker for inflammation and immune response, initially introduced by Hu et al. (17) in liver cancer. This index correlates significantly with disease severity and prognosis in both cancer and inflammatory conditions (9-10,16). A meta-analysis assessing the diagnostic role of SII in immunological diseases reviewed 16 studies, revealing elevated SII levels in affected individuals versus controls, achieving an AUC of 85% for diagnostic accuracy, with increased sensitivity during active disease (16). Comparative studies have identified SII as the most valuable parameter among various hematological indices (18,19), aligning with findings that indicate a stronger inflammatory response is linked to more severe clinical presentations. SII has demonstrated significant associations with clinical outcomes across different cancers and other disease states (19-21). Additionally, in patients with atherosclerosis, SII showed prognostic superiority over traditional risk factors, and in COVID-19 cases, it was independently linked to adverse outcomes (15,20). Aon et al. (21) reported that SII progressively increased with DKA severity, with the highest quartile identified as an independent risk factor, and the optimal SII cutoff for predicting DKA severity was determined to be 2524.24, demonstrating 85.3% specificity and 34.4% sensitivity. Their study focused on a group of young adults with an average age of 17. values. In the NHANES study, which evaluated its relationship with the prevalence of diabetes, it was shown that every 1 unit increase in SII in adults over the age of 20 increased the likelihood of diabetes by 4% (22). SII has been associated with other diabetes complications. SIRI and SII are potential biomarkers for early-onset atherosclerotic processes in diabetic children. To the best of our knowledge, this is the first study in children demonstrating the association between SII and DKA severity in T1DM. In our study, we determined an SII cut-off point of 1612.29, which provides 94.44% sensitivity and 81.48% specificity for the detection of severe acidosis. We showed that SII is the most reliable parameter when compared to other parameters.

In our study, we observed that the severity of DKA was strongly associated with the acidosis resolution time (p: 0.001, r: 0.55). This emphasizes that as the severity of DKA increases, the acidosis resolution time prolongs and that a more intensive approach is required in the treatment and follow-up of these patients. However, no significant correlation was found between the severity of DKA and the duration of hospitalization (p: 0.27), indicating that the duration of hospitalization may be affected by different factors. Aon et al. (21) similarly found no correlation between the length of hospitalization and the severity of DKA (21). Interestingly, among the inflammatory markers examined, SII (Systemic Immunity-Inflammation Index) stood out as an important factor. A correlation was found between SII and the acidosis resolution time (p: 0.002, r: 0.340), indicating that SII may be an important marker in assessing the severity and recovery time in DKA patients. However, no significant correlation was found between NLR (Neutrophil/Lymphocyte Ratio) and PLR (Platelet/Lymphocyte Ratio), and neither acidosis resolution time nor hospitalization duration (p= 0.07, p= 0.67 and p= 0.58, p= 0.43, respectively). These results suggest that, unlike SII, NLR and PLR may not be more reliable in predicting DKA clinical outcomes in this context. Our study is the only study examining this relationship and provides important contributions to the literature. Future studies should conduct more detailed investigations to confirm the role of inflammatory markers, especially SII, in the management and prognosis of DKA.

T1DM is one of the most prevalent chronic illnesses in the pediatric population (1-3). While the frequency of DKA in T1DM is 30-40%, in our country, it is seen up to 50% and most cases present with severe acidosis (2-5,15). The frequency of diagnosing DKA in T1DM has been rising significantly in recent years (3,4,22,23). This increase in diagnosis may be attributed to factors such as improved awareness among healthcare professionals, rising incidence rates of T1DM, and potentially delayed diagnosis of diabetes in younger populations (24-26). Our study indicates that most cases presenting with DKA had moderate to severe DKA in the northwest region of Turkey, which aligns with previous regional studies (20). This emphasizes the need for healthcare providers to be vigilant in recognizing the symptoms of both diabetes and DKA. Addressing the underlying causes is crucial for implementing

effective prevention strategies and improving clinical outcomes for patients with T1DM. Additionally, it highlights the importance of easily accessible tools for early diagnosis.

Research investigating the correlation between DKA and age has demonstrated that in univariate analysis, being less than 3 years old or older than 12 increases the probability of DKA at T1DM diagnosis. While some research indicates a slight relationship between age and the severity of DKA (23), similar to other studies, our study also demonstrated that younger children present with more severe acidosis (24). Because they often show less awareness of the symptoms of diabetes. This lack of recognition can delay diagnosis and treatment, leading to more pronounced metabolic disturbances, increasing their risk for complications, and necessitating more intensive management. Furthermore, while lower C-peptide levels are known to increase the risk of DKA in T1DM, we also determined that as C-peptide levels decrease, higher glucose levels are associated with increased DKA severity. C-peptide, as a marker of endogenous insulin secretion, indicates that a low C-peptide level reflects diminished β-cell function. In young children, low C-peptide levels are frequently associated with severe acidosis, aggressive diabetes, and delayed detection of diabetes symptoms. Enrolling in a prospective cohort that educated parents about diabetes symptoms reduced the risk of developing DKA at T1DM diagnosis in young children (24).

In studies investigating the risk factors associated with DKA, both leukocytosis and thrombocytosis be associated with severe metabolic acidosis (5,24). In our study, neutrophil, platelet, and monocyte counts were higher in the severe DKA group, while lymphocyte counts were relatively lower, though not statistically significant. Changes in the white blood cell percentage formula (an increase in neutrophils, monocytes, and total WBCs; a decrease in lymphocytes and eosinophils) matched those reported in the literature (12, 25).

The body's inflammatory response balance is mainly reflected in the neutrophil-to-lymphocyte ratio. NLR is considered a parameter that determines the severity of the inflammatory process; high NLR values indicate a stronger inflammatory response (25). While neutrophils act as active components of the inflammatory response, lymphocytes play a regulatory role and have a reducing effect. Both cell groups are regulated by the autonomic nervous system. Neutrophils are stimulated by sympathetic nerves through adrenergic receptors on their surfaces, while lymphocytes are affected by parasympathetic nerves through cholinergic receptors (26). In DKA patients, stimulation of the sympathetic nervous system results in enhanced neutrophil stimulation and the release of pro-inflammatory chemicals such as TNF-α, CRP, and IL-6 (26-27). Abnormalities in oxygenation caused by DKA cause episodes of hypoxemia, during which inflammatory responses may be triggered. Furthermore, hypoxia inhibits neutrophil apoptosis in DKA patients. WBCs activated by advanced glycation end-products produce pro-inflammatory cytokines (12). Acute hyperglycemia and fluctuations in blood sugar levels in diabetic patients lead to increased reactive oxygen species (ROS), causing damage to peripheral lymphocyte DNA and triggering apoptosis (27). According to studies, leukocytes in DM patients may produce more ROS, which increases oxidative DNA damage occurring in lymphocytes during hyperglycemia episodes (28,29). All these processes prepare the ground for the emergence of a systemic inflammatory response without infection.

The relationship between DKA severity and NLR has been examined in several studies (11-12,25). In a study involving newly diagnosed children with T1DM, the median NLR score increased as DKA severity increased. Correlation between NLR and cerebral edema has also been demonstrated (30). Our study also showed that NLR is a reliable marker for both diagnosing diabetes and determining acidosis severity. Compared to other studies, SII proved to be a better marker for recognizing DKA.

PLR, MPV, PDW, and PCT parameters derived from platelets are also important for inflammation (13,29-31). In individuals with diabetes, platelet hyperreactivity exists. This hyperreactivity causes platelets to become larger or more hyperfunctional due to prothrombinase activity.

In our study, all thrombocyte-derived markers except PCT were not significant in determining the severity of DKA; they were all useful in distinguishing T1DM from healthy cases. Various studies in the literature have reported differing results regarding these markers. While studies have shown that MPV and PCT can serve as poor prognostic indicators in colorectal cancer and pulmonary hypertension, there are relatively few studies specifically focused on PCT (31). Liu et al. (29) found that patients with PLR > 267.37 had a higher likelihood of readmission and death within 90 days in critically ill adult patients with DKA. MPV studies show conflicting results. Previous studies have suggested that MPV values reflect platelet activity in diabetic patients and are related to insulin resistance (32,33). Another study indicates that MPV can be a helpful risk marker for DKA diagnosis, even though it does not predict the severity of DKA (34). However, other studies noted that factors such as the time between blood sample collection and analysis, analysis techniques, and the use of anticoagulants could affect MPV, indicating

that there is no well-standardized test to measure platelet activity effectively (32).

Study Limitations

Although our study achieved important results regarding hematological inflammatory parameters, it also had some limitations. Firstly, our sample size was relatively small, especially in the non-DKA T1DM group, which may have limited the power of the analyses. Secondly, only values at the time of patient admission were considered, and longitudinal measurements could not be performed. Therefore, the dynamic trends of these parameters could not be monitored. Hence, multicenter studies with a larger patient population are needed, and we hope our study serves as a guiding resource for these future endeavors. Future studies should include larger patient cohorts to better differentiate the specific inflammatory response associated with ketoacidosis from the general inflammation in T1DM.

Its strengths are that only newly diagnosed DKA cases were included in the study; cases with known diagnoses were not included because it is one of the risk factors that increase the severity of DKA. Multiple markers were compared simultaneously and reliable results with high sensitivity and specificity were obtained.

Conclusion

In conclusion, our study underscores the significant correlation between SII and the severity of DKA. The findings indicate that elevated SII levels can serve as a reliable biomarker for predicting severe DKA, offering high sensitivity and specificity. This suggests that incorporating SII into routine clinical assessments may facilitate the earlier recognition of severe cases, enabling more proactive management strategies. Furthermore, understanding the inflammatory response in DKA could provide insights into the underlying pathophysiology, potentially guiding future therapeutic approaches. Overall, the utility of SII as a predictive tool highlights the importance of monitoring inflammatory markers in managing pediatric patients with T1DM and DKA. Further research is needed to establish standardized cutoff values and explore the broader implications of SII in various clinical contexts.

Ethics

Ethical Approval: This study was conducted with 81 T1DM patients and 49 healthy controls followed at the Pediatric Endocrinology Clinic of Zonguldak Bülent Ecevit University between April 2022 and January 2024, following the principles of the Declaration of Helsinki. Ethical approval was received from the ethics committee at our university. (ethics no:2024/07-6).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Investigation of Cat and Dog Allergen Sensitivities in Childhood Asthma

Çocukluk Çağı Astımında Kedi ve Köpek Allerjen Duyarlılıklarının Araştırılması

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Abstract

Introduction: Cat and dog allergens are among the inhalant allergens that are important risk factors for the development of allergic diseases in childhood. In recent years, there has been an increase in the adoption of pets (cats, dogs, etc.) and their care at home. Therefore, we aimed to investigate the prevalence and associated characteristics of cat and dog allergen sensitization in asthmatic children aged 0-18 in our region.

Materials and Methods: 880 asthmatic pediatric patients (0-18 years old) who admitted to the Faculty of Medicine, Department of Pediatric Allergy and were diagnosed with asthma were included in the study. Sensitization of asthmatic pediatric patients to cat allergen, dog allergen, and other inhalant allergens (based on skin prick test results), gender, age, serum total IgE levels, and the presence of other concomitant allergic diseases were retrospectively analyzed.

Findings: The study's inclusion of 880 children diagnosed with asthma had a 39% female (n= 343), 61% male (n=537) distribution. The most common allergic disease associated with asthma was allergic rhinitis (n= 402, 44.9%). Sensitivity to at least one inhalant allergen (presence of atopy) was detected by skin prick tests in 55.7% (n=490). Sensitivity to cat allergen was detected in 8.3% (n=73). The distribution of sensitivity to cat allergen by age was as follows: 3.7% in the 0-3 age, 6.7% in the 4-6 age,14.5% in the 7-12 age, 9.8% in the 13-18 age group. Sensitivity to dog allergen was found in 41(4.7%) children in the study population, with the distribution by age being: 2.4% in the 0-3 age, 2.7% in the 4-6 age, 8.7% in the 7-12 age, and 6.5% in the 13-18 age group. The rates of cat/dog sensitization were higher in boys but statistically significant difference was found only for dog allergens.

Conclusion: The prevalence of cat and dog allergies in asthmatic children in the Bursa region was found to be significantly high, requiring attention. The fact that cat and dog allergen sensitivities increase with age suggests that this situation should be taken into consideration in the follow-up of these patients and that patients should be re-evaluated in these respects as they age.

Keywords
Child, asthma, cat, dog, allergen, sensitization

Anahtar kelimeler
Çocuk, astım, kedi, köpek, alerjen, duyarlılık

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Öz

Giriş: Kedi ve köpek alerjenleri, çocukluk çağında alerjik hastalıkların gelişimi için önemli risk faktörleri olan inhalan alerjenler arasındadır. Son yıllarda evcil hayvan (kedi, köpek vs.) sahiplenerek evde bakma alışkanlıklarında artış gözlenmektedir. Bu nedenlerle bölgemizde 0-18 yaş astımlı çocuklarda kedi ve köpek alerjen duyarlılıklarının görülme sıklığının ve ilişkili özelliklerin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Tıp Fakültesi Çocuk Alerji Bilim Dalı'na başvuran ve astım tanısı konulan 880 astımlı çocuk hasta (0-18 yaş) dahil edildi. Astımlı çocuk hastaların kedi allerjeni, köpek allerjeni ve diğer inhalan alerjenlere duyarlılıkları (deri prick testleri sonuçlarına göre), cinsiyet, yaş, ve serum total IgE düzeyleri, eşlik eden diğer alerjik hastalıkların varlığı, retrospektif olarak incelendi.
Bulgular: Çalışmaya %39'u (n=343) kız, %61'i (n=537) erkek toplam 880 astım tanılı çocuk alındı. Astıma en sık eşlik eden alerjik hastalık alerjik rinit (n=402, %44,9) idi. Astımlı çocuklarda deri prik testleri ile en az bir inhalan alerjene duyarlılık durumu (atopi varlığı) %55,7 (n=490) oranında saptandı. Tüm çalışma popülasyonunda kedi alerjenine duyarlılık %8,3 (n=73) oranında saptandı. Kedi alerjenine duyarlılığın yaşlara göre dağılımı; 0-3 yaş grubunda %3,7, 4-6 yaş grubunda %6,7, 7-12 yaş grubunda %14,5, 13-18 yaş grubunda %9,8 oranlarında idi. Tüm çalışma popülasyonunda köpek alerjenine duyarlılık 41 (%4,7) çocukta bulundu, yaşlara göre dağılımı; 0-3 yaş grubunda %2,4, 4-6 yaş grubunda %2,7, 7-12 yaş grubunda %8,7, 13-18 yaş grubunda ise %6,5 oranlarında bulundu. Kedi ve/veya köpek allerjeni duyarlılığı saptanma oranlarının genel olarak yaş ile artma eğiliminde olduğu görülmüştür. Kedi ve/veya köpek duyarlılığı oranları erkek çocuklarda daha yüksek oranlarda idi, ancak sadece köpek alerjeni için istatistiksel anlamlı fark bulundu.
Sonuç: Bursa bölgesindeki astımlı çocuklarda kedi ve köpek allerjisi görülme oranlarının dikkate alınması gereken belirgin oranlarda bulunduğu saptandı. Kedi ve köpek alerjen duyarlılıklarının yaşla birlikte artması, bu hastaların takibinde bu durumun gözönünde tutulması ve hastaların bu açılardan yaş artışı ile birlikte tekrar değerlendirilmesi gerektiğini düşündürmüştür.

Introduction

Asthma is a chronic inflammatory disease of the airways characterized by reversible bronchoconstriction and is the most common chronic disease of childhood (1,2). Risk factors for asthma include genetic predisposition, atopic constitution, gender, obesity, and exposure to certain environmental factors. Allergens, viral infections, exercise, contact with irritants, and environmental air pollution can trigger symptoms (3,4).

Childhood asthma is primarily seen as allergic asthma, and various inhaled allergens play a significant role in asthma symptoms and flare-ups (5,6). Atopy refers to an immunological condition characterized by an individual's ability to produce specific immunoglobulin E (IgE) antibodies against allergens or to show positive sensitivity to the same allergens in a skin prick test (5,7,8). Since the IgE-mediated early-type hypersensitivity response is more pronounced in atopic individuals, the threshold value required for symptom development decreases when exposed to inhaled allergens (5). For this reason, atopy is considered one of the key determinants in both the onset of childhood allergic asthma and the increase in the frequency of flare-ups (9). Several studies have demonstrated that IgE sensitization to common aeroallergens, such as dust mites, pollen, and pet allergens, is associated with a more severe symptom profile, increased bronchial hyperreactivity, and higher healthcare utilization in children with asthma (8-10). Approximately 50-80% of asthma in childhood is classified as the atopic asthma phenotype; however, it has been reported that this atopy rate can vary depending on many individual and environmental factors (11). The onset of atopy is a multidimensional process shaped by the immune system's response to allergens from early life, environmental exposure patterns, and genetic characteristics (9).

Animal allergens, particularly those from cats and dogs, are significant risk factors for the development of allergic diseases in childhood (12). Cat and dog allergens (e.g., *Fel d 1, Can f 1*) can be spread into the environment through passive transfer via the clothing, hair, or fur of pet owners, even if the individual does not own a pet or has not had direct contact with one. Therefore, allergen exposure can occur anywhere for individuals who are sensitive (13,14). Cat and dog allergens (e.g., *Fel d 1, Can f 1*) can be spread into the environment through passive transfer via the clothing, hair, or fur of pet owners, even if the individual does not own a pet or has not had direct contact with one. Therefore, allergen exposure can occur anywhere for individuals who are sensitive (13,14). It has been reported that among inhaled allergens, sensitivity to cats and, to a slightly lesser extent, dogs is increasingly recognized as an important inhaled allergen in childhood asthma (15).

The prevalence of cat and dog sensitivity in childhood asthma is an increasingly prominent issue due to rising pet ownership and the frequency of atopy. It is reported that sensitivity rates to pet allergens in developed countries range from 10% to 30% of the general population, with cat/dog sensitivity accounting for a significant portion of this (16,17). This sensitization is a significant risk factor for asthmatic children in terms of both disease onset and severity. Community-based studies have reported that sensitization to cat and dog allergens (particularly *Fel d 1* and *Can f 1*) affects up to 25% of children and adults (17). However, when focusing on children with asthma, this rate increases significantly. The KiGGS cohort study, conducted in Germany, assessed specific IgE levels to inhaled allergens in approximately 13,000 children aged three to 17 years. The prevalence of cat and dog sensitivities was found to be

around 33% and 41%, respectively, in children diagnosed with asthma. These rates were significantly lower in children without asthma (18). This study shows that children with asthma are significantly more likely to be sensitive to cats and dogs than the general pediatric population. According to the KiGGS data, over one-third of children with asthma in the 7-13 age group are sensitive to cats, and nearly half are sensitive to dogs. The rate is lowest in younger age groups and highest in adolescents (18). This situation suggests that exposure to animal allergens is chronic and that the rate of sensitization accumulates with increasing age and maturation of the immune system (11,18).

In addition to this information, it has been observed that in recent years, it has become increasingly common in Turkey to adopt pets (cats, dogs, etc.) and care for them at home (19,20). Approximately 17% of the Turkish population owned a cat or dog in 2019, and this rate is reported to have approached 20% by 2023 **(21)**. The same study indicates that around 6,146,000 individuals in Turkey own cats or dogs (20). The significant effects of inhaled allergens, such as dust mites, cats, dogs, mice, cockroaches, and mold spores, on individuals with asthma and allergies are well known (22). Therefore, identifying potential allergens and taking the necessary precautions to avoid them is considered necessary in the management of childhood asthma (23).

Currently, there is a lack of information in the literature regarding the prevalence of cat and/or dog allergen sensitivity in asthmatic children in the Bursa region. For this reason, this study was designed to investigate the prevalence of sensitivity to cat and dog allergens, as well as other inhalant allergens, in children diagnosed with asthma who live in the Bursa region, and to examine related characteristics.

Materials and Methods

A total of 880 children between the ages of 0 and 18 who were diagnosed with asthma after applying to the Pediatric Allergy Department Outpatient Clinic at Bursa Uludağ University Faculty of Medicine between January 1, 2016, and June 30, 2019, were included in this retrospective study. The patients' gender, age at onset of asthma symptoms, additional allergic disease diagnoses, common allergens identified through skin prick (epidermal) tests, and serum total IgE levels were recorded. As a standard clinical routine, asthma diagnoses were made in all cases according to the GINA asthma diagnostic criteria (24,25).

Skin prick tests for allergens were performed and evaluated in the Pediatric Allergy Department Laboratory using ALK-Abello (Horsholm, Denmark) standard allergen kits and disposable Stallerpoint plastic lancets (Stallergenes, Antony, France), in accordance with EAACI recommendations (26). In skin prick tests, allergens were applied to the volar surfaces of both forearms, ensuring they did not touch each other, in accordance with standard practice. A different single-use lancet was used for each allergen, and the allergen was applied to the epidermis at a depth of 1 mm. Edema of at least 3 mm compared to the negative control was considered a positive test result 15 to 20 minutes after allergen application (26). All inhaled allergens administered to asthmatic children included in the study are shown in Table 4.

The presence of sensitivity to allergens was defined as individual results. Cases in which at least one positive result (sensitivity) to common allergens was detected in skin prick tests were defined as atopic. Additionally, when defining the results, the "pets general" result was defined as positive if sensitivity to at least one of the cat or dog allergens was detected (Table 1 and Table 4). Similarly, the "mites general" result was defined as positive when sensitivity to at least one mite allergen (at least one of the allergens *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*) was detected. (Table 1 and Table 4). The same method was used to define "general results" for each of the other allergen groups ("grass pollens general", "cereal pollens general", "tree pollens general", "cereal pollens general", "fungal spores general") (Table 1 and Table 4). Immulite 2000 (Diagnostic Products Corporation, Los Angeles, CA, USA) test kits were used for serum total IgE measurements, and results were reported in IU/mL.

The normality of continuous variables was examined in the statistical analysis of the data using the Shapiro-Wilk test. Age, age at diagnosis, and total IgE level were expressed as median (minimum, maximum) values. Categorical data were presented as n (%), and the Pearson Chi-Square and Fisher's Exact tests were used to analyze categorical data. The Mann-Whitney U test was used to compare total IgE measurements between groups. Data analysis was performed using the IBM SPSS Statistics 25 program, with an α level of 0.05 for statistical comparisons.

Results

Of the children with asthma included in the study, 39% (343 children) were female, and 61% (537 children) were male. The median age at diagnosis was 8.42 years, with a range of 1.75 to 18 years. The median age of onset of asthma symptoms was 3 years (min-max: 1- 16.6 years) in girls and 2 years (min-max: 1 - 17 years) in boys. Asthma symptoms

have been found to show significant differences in age of onset according to gender, with slightly earlier onset in boys ($p<0.001$). Among children with asthma, the most common accompanying allergic diseases were, in order: allergic rhinitis (45.6%), allergic conjunctivitis (18.8%), atopic dermatitis (15.1%), and food allergy (6%).

In skin prick tests performed with common inhalant allergens, sensitivity to at least one inhalant allergen (presence of atopy) was detected in 55.7% (n = 490) of patients, while 44.3% (n = 390) were determined to be non-atopic (no sensitivity to any inhalant allergen). The skin prick test results for cats, dogs, and other common inhalant allergens, categorized by patient age group, are presented in Table 1.

Among the entire study population of 880 children with asthma, cat allergen sensitivity was detected in 73 children (8.3%), and dog allergen sensitivity was detected in 41 children (4.7%). Among asthmatic children, sensitivity to cat allergens was higher than sensitivity to dog allergens in the entire study population and in all age groups (Table 1). When

Table 1. Results of allergen sensitivities detected by skin prick tests in the entire study population of children with asthma (n=880) and by age groups

	Ages 0-3 (n=246) **n (%)**	**Ages 4-6** (n=300) **n (%)**	**Ages 7-12** (n=242) **n (%)**	**Ages 13-18** (n=92) **n (%)**	**Total** (n=880) **n (%)**
Pets general*	11 (4.5)	22 (7.3)	39 (16.1)	10 (10.9)	82 (9.3)
Cat	9 (3.7)	20 (6.7)	35 (14.5)	9 (9.8)	73 (8.3)
Dog	6 (2.4)	8 (2.7)	21 (8.7)	6 (6.5)	41 (4.7)
Mites general*	62 (25.2)	110 (36.7)	133 (55)	46 (50)	351 (39.9)
Grass pollens general*	22 (8.9)	39 (13)	82 (33.9)	47 (51.1)	190 (21.6)
Cereal pollens general*	14 (5.7)	35 (11.7)	67 (27.7)	43 (46.7)	159 (18.1)
Tree pollens general*	10 (4.1)	27 (9)	36 (14.9)	20 (21.7)	93 (10.6)
Weed pollens general*	11 (4.5)	22 (7.3)	37 (15.3)	21 (22.8)	91 (10.3)
Fungal spores general*	22 (8.9)	37 (12.3)	44 (18.2)	17 (18.5)	120 (13.6)

Data are presented as n (%).
General*: Presence of sensitivity to at least one allergen in this group

Table 2. Comparison of cat allergen sensitivity rates in children with asthma according to age groups

	Cat allergen sensitivities		**p**	**Group comparisons**
	Positive (+) n (%)	**Negative (-) n (%)**		
Group 1 (Ages 0-3) (n=246)	9 (3.7)	237 (96.3)	**<0.001**	**Group** 1- **Group** 2: p=0.119 **Group** 1- **Group** 3: **p<0.001** **Group** 1- **Group** 4: p=0.052 **Group** 2- **Group** 3: **p=0.003** **Group** 2- **Group** 4: p=0.318 **Group** 3- **Group** 4: p=0.259
Group 2 (Ages 4-6) (n=300)	20 (6.7)	280 (93.3)		
Group 3 (Ages 7-12) (n=242)	35 (14.5)	207 (85.5)		
Group 4 (Ages 13-18) (n=92)	9 (9.8)	83 (90.2)		

Table 3. Comparison of dog allergen sensitivity rates in children with asthma according to age groups

	Dog Allergen Sensitivities		**p**	**Group Comparisons**
	Positive (+) n (%)	**Negative (-) n (%)**		
Group 1 (Ages 0-3) (n=246)	6 (2.4)	240 (97.6)	**0.002**	**Group** 1-**Group** 2: p=0.867 **Group** 1- **Group** 3: **p=0.003** **Group** 1- **Group** 4: p=0.096 **Group** 2- **Group** 3: **p=0.002** **Group** 2- **Group** 4: p=0.105 **Group** 3- **Group** 4: p=0.518
Group 2 (Ages 4-6) (n=300)	8 (2.7)	292 (97.3)		
Group 3 (Ages 7-12) (n=242)	21 (8.7)	221 (91.3)		
Group 4 (Ages 13-18) (n=92)	6 (6.5)	86 (93.5)		

sensitivity rates to cat allergens are examined by age group, the lowest rates are found in the 0-3 age group, showing an upward trend up to the 7-12 age group, and slightly lower rates in the 13-18 age group compared to the 7-12 age group. Sensitivity rates to dog allergens also showed a similar trend to cat sensitivity, increasing with age (Table 1).

Other inhalant allergen sensitivities detected in children with asthma, in order of prevalence, were: sensitivity to mites, 39.9%, grass pollen sensitivity was 21.6%, cereal pollen sensitivity was 18.1%, fungal spore sensitivity was 13.6%, tree pollen sensitivity was 10.6%, and weed pollen sensitivity was 10.3% (Table 1). Among all inhaled allergens, mite sensitivities

Table 4. Comparison of the rates of sensitivity to cats, dogs, and other inhalant allergens in children with asthma according to gender.

	Girls (n=540) n (%)	**Boys (n=340) n (%)**	**p**
Pets general*	24 (7.1)	58 (10.7)	0.067
Cat	24 (7.1)	49 (9.1)	0.291
Dog	9 (2.6)	32 (5.9)	**0.025**
Mites general*	118 (34.7)	233 (43.1)	**0.013**
D. pteronyssinus	108 (31.8)	211 (39.1)	**0.028**
D. farinae	107 (31.5)	213 (39.4)	**0.017**
Grass pollens general*	65 (19.1)	125 (23.1)	0.157
Grasses miks	64 (18.8)	117 (21.7)	0.310
Dactylis glomerata	53 (15.6)	112 (20.7)	0.057
Lolium perenne	12 (3.5)	32 (5.9)	0.112
Phleum pratense	54 (15.9)	98 (18.1)	0.387
Cynodon dactylon	50 (14.7)	102 (18.9)	0.110
Cereal pollens general*	51 (15)	108 (20)	0.061
Pollens mix	14 (4.1)	32 (5.9)	0.241
Secale cereale	49 (14.4)	104 (19.3)	0.065
Triticum sativum	45 (13.2)	98 (18.1)	0.054
Avena sativa	41 (12.1)	94 (17.4)	**0.032**
Tree pollens general*	27 (7.9)	66 (12.2)	**0.044**
Trees mix	11 (3.20)	28 (5.2)	0.171
Alnus glutinosa	6 (1.8)	12 (2.2)	0.641
Betula verrucosa	8 (2.4)	19 (3.5)	0.329
Olea europaea	21 (6.2)	58 (10.7)	**0.021**
Weed pollens general*	29 (8.5)	62 (11.5)	0.161
Weeds mix	18 (5.3)	40 (7.4)	0.219
Artemisia vulgaris	17 (5)	25 (4.6)	0.802
Plantago lanceolata	24 (7.1)	55 (10.2)	0.114
Parieteria officinalis	8 (2.4)	18 (3.3)	0.403
Fungal spores general*	39 (11.5)	81 (15)	0.137
Alternaria alternata	32 (9.4)	78 (14.4)	**0.028**
Cladosporidium herb.	3 (0.9)	12 (2.2)	0.135
Aspergillus fumigat.	7 (2.1)	23 (4.3)	0.080

Data are presented as n (%).
General*: Presence of sensitivity to at least one allergen in this group

Table 5. Relationship between sensitivity to cat and dog allergens and serum total IgE

Allergens	Sensitivity	Total IgE level	p[a]
Pets general*	Negatif (n=798)	79.8 (1.0:5310)	**<0.001**
	Pozitif (n=82)	318 (2.0:3549)	
Cat	Negatif (n=807)	88.2 (2.0:5290)	**<0.001**
	Pozitif (n=73)	325 (2.5:3540)	
Dog	Negatif (n=839)	71.8 (1.0:5310)	**<0.001**
	Pozitif (n=41)	310 (2.0:3549)	

The data is presented as the median (minimum: maximum).
General*: Presence of sensitivity to at least one allergen in this group
a: Mann-Whitney U test

were the most frequently detected allergen sensitivities in all age groups. Sensitivity rates to inhaled allergens were lowest in the 0-3 age group, and generally increased with age (Table 1).

The prevalence rates of cat and dog allergen sensitivity in asthmatic children, categorized by age group, are presented in Tables 2 and 3. The prevalence rates of cat allergen sensitivity in asthmatic children generally increased with age, compared to the 0-3 age group (Table 2). It has been determined that the detection rates of cat allergen sensitivity generally show statistically significant differences across age groups ($p< 0.001$). When age groups were compared with each other, it was determined that the rate of sensitivity to cats among patients aged 7-12 was statistically significantly higher than in the 0-3 and 4-6 age groups ($p< 0.001$ and $p= 0.003$, respectively). On the other hand, it was determined that the sensitivity rates of patients aged 13-18 to cats were higher than those of the 0-3 and 4-6 age groups; however, no statistically significant difference was found ($p= 0.052$ and $p= 0.318$, respectively). Additionally, a comparison between the 7-12 age group and the 13-18 age group revealed no statistically significant difference in sensitivity rates between the groups ($p= 0.259$) (Table 2).

The prevalence rates of dog allergy sensitivity also tend to increase with age, generally compared to the 0-3 age group (Table 3). The prevalence rates of dog allergen sensitivity also tended to increase with age, generally higher in older age groups compared to the 0-3 age group (Table 3). It was determined that dog allergen sensitivity generally showed statistically significant differences across age groups ($p = 0.002$). When age groups were compared with each other, it was determined that the rates of sensitivity to dogs among patients in the 7-12 age group were statistically significantly higher than those in the 0-3 and 4-6 age groups ($p = 0.003$ and $p = 0.002$, respectively). In terms of dog allergen sensitivity, no statistically significant difference was found between the 7-12 age group and the 13-18 age group ($p = 0.518$) (Table 3).

The comparison of detection rates for inhalant allergen sensitivities by gender is presented in Table 4. Cat allergen sensitivity was found to be higher in males than in females; however, no statistically significant difference was detected between the two groups ($p= 0.291$). The prevalence of dog allergen sensitivity was found to be statistically significantly higher in males than in females ($p = 0.025$). For other inhalant allergens, sensitivity rates generally tended to be higher in male children than in female children. However, these differences were statistically significant for only a small number of allergens (Table 4). It was determined that sensitivity to house dust mites, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus* was statistically significantly higher in males than in females ($p=0.013$, $p=0.028$, and $p=0.017$, respectively). Additionally, sensitivity to *Avena sativa* grain pollen ($p=0.032$), overall tree pollen sensitivity ($p=0.044$), *Olea europaea* sensitivity ($p=0.021$), and *Alternaria alternata* sensitivity ($p=0.028$) were also found to be statistically significantly higher in males (Table 4).

Table 5 shows changes in serum total IgE measurements according to the presence of cat and dog allergen sensitivities. Total IgE levels were found to be statistically significantly higher in cases of sensitivity to cat or dog allergens than in cases where sensitivity to these allergens was negative. The presence of sensitivity to cat or dog allergens was also found to be associated with higher total IgE levels.

Discussion

This study examined the sensitivity rates to cat and dog allergens, as well as various inhalant allergens, in pediatric patients diagnosed with asthma. IgE-mediated sensitivity to cat and dog allergens (especially *Fel d 1* and *Can f 1*) in children with asthma is an important factor in both the onset of the disease and the frequency of symptom exacerbations (22,23). Data collected from a wide range of provinces across Turkey reveals that pet ownership is rapidly becoming widespread. A national survey of 519 cat and/or dog owners found that 82.9% of participants acquired their pet within the last 10 years, with the majority being cat owners (19). These data suggest that a significant portion of the current cat and/or dog population stems from relatively recent adoptions, and that there has been a notable proliferation in recent years (19).

Inhalant allergen sensitivity is one of the major risk factors for the development of asthma (9,11,22). The presence of atopy in children with asthma is one of the most important biological markers determining both the phenotype and clinical course of the disease (9). The emergence of atopy is a multidimensional process shaped by the immune system's response to allergens from early life, environmental exposure patterns, and genetic characteristics. According to the literature, approximately 50-80% of pediatric asthma can be classified under the atopic asthma phenotype; however, this rate varies depending on many individual and environmental factors (11,22). In this study, the prevalence of atopy (the presence of sensitivity to at least one inhaled allergen) was determined to be 55.7% in all asthmatic children in the study group based on skin prick tests with inhaled allergens. This rate is similar to research results reported from other regions in Turkey. In a 16-year study of pediatric patients aged 1-18 years diagnosed with asthma in Istanbul, the atopy rate was reported to be 61% (27)besides history and physical examination, many in vivo and in vitro laboratory tests are used. Skin prick test (SPT. In the Eastern Black Sea region, a study conducted on children aged 3-17 found that 35.9% of children with asthma had allergen sensitivity (28). The prevalence of atopy in children with asthma was reported as 60.3% and 61.1% in two separate studies conducted in Ankara province, and as 42.9% in Diyarbakır province (29,30,31). Other studies on the prevalence of inhalant allergen sensitivity (atopy) in children with asthma found rates of 41.2% and 72.5% in two separate studies in China (32,33)pediatric asthma is becoming more prevalent. Despite a growing body of evidence, there remains a significant unmet need for adequate management of childhood asthma. The Subspecialty Group of Respiratory Diseases of the Society of Pediatrics, the Chinese Medical Association, and the editorial board of the Chinese Journal of Pediatrics have recently updated the "Guidelines for diagnosis and optimal management of asthma in children," first published in 2008. Methods: This article reviews the major updates to the guidelines and covers the main recommendations for diagnosis, assessment, and treatment of pediatric asthma in China. Key regional data on epidemiology, clinical features, disease burden, knowledge among children and parents, and risk factors including pollution are provided to contextualize the recommendations. Results: The major updates to the guidelines include: (1. Studies conducted in different regions of Australia reported rates of 68-88%, while in England, the rate was reported as 44.1% (34,35). The prevalence of inhaled allergens and atopy in children with asthma may vary depending on factors such as age, genetic characteristics, regional characteristics, climate, geographical characteristics, living conditions, and environmental characteristics, which in turn influence the variety and intensity of allergens to which they are exposed (11,22).

In our study, cat allergen sensitivity was generally found to be higher than dog allergen sensitivity in children with asthma across the entire study population and in all age groups (Table 1). It has been reported that cat allergies are generally more common than dog allergies in children with asthma, and that various immunological and environmental factors are among the possible reasons for this situation (36-38). Among the reasons that can lead to this situation, it is reported that the biophysical properties of the primary cat allergen *Fel d 1* are significant. *Fel d 1* binds to tiny particles, remains suspended in the air for a long time, easily adheres to textiles, and thus creates widespread environmental exposure through schools, nurseries, and public areas, even if there are no cats in the home (39). Similarly, the ease with which cat allergens attach to textiles and clothing increases passive transport, allowing cat allergens to be found everywhere and raising the risk of sensitization in children (36,37). Secondly, in cat and dog allergies, sensitization patterns and IgE levels differ. Specific IgE levels for cat allergy in asthmatic children were found to be higher than in patients with rhinitis alone, demonstrating that sensitization at this molecular level is more strongly associated with the asthma phenotype (12,39). Additionally, some epidemiological studies have reported that exposure to indoor cats is a more substantial risk factor for asthma, with a higher prevalence of asthma and asthma-like symptoms in children sensitive to cat allergens (37,38).

Cat (*Fel d 1, Fel d 4*) and dog (*Can f 1 and 6*) allergens are among the major inhalant allergens involved in the development of asthma and allergic rhinitis in childhood. Numerous studies have reported that sensitivity to these allergens varies according to age, geography, exposure to pets, and gender (40,41). This study found that cat and/or dog allergen sensitivity also showed statistically significant differences across age groups. In subgroup analyses, a marked increase in sensitivity was observed after the 0-3 age group, reaching the highest rates in the 7-12 age group and slightly lower rates in the 13-18 age group. Generally, sensitivity to inhaled allergens (atopy) tends to increase with age (18,42). It is also known that the duration and intensity of allergen exposure may play a role in the development of inhalant allergen sensitivity (11). Comparative studies conducted in various countries have shown that atopic sensitivity increases linearly as the allergen load increases (11,18,42).

In our country, the practice of keeping pets in homes has increased significantly over the last decade (19-21). If these trends continue, new studies conducted in the coming years may indicate whether allergen exposure rates will increase among 13-to 18-year-olds. If these trends continue, new studies conducted in the coming years may indicate whether allergen exposure rates will increase among 13-to 18-year-olds (43). A study conducted in Istanbul reported an increase in pet sensitivity with age among asthmatic children aged 1 to 18 (27). Additionally, a study conducted in China among asthmatic patients aged 5 to 65 found that sensitivity to cats and dogs increased with age (44). A study conducted in Boston on children with aeroallergen sensitivity found that sensitivity to cats and dogs increases with age (45). Based on these data, various factors, including allergen exposure, age, genetics, and environment, are thought to influence the rates of sensitization to cat and/or dog allergens (11).

This study found that the age at which asthma symptoms began differed significantly by gender among children with asthma, with symptoms typically starting slightly earlier in boys. The earlier onset of asthma symptoms in boys is consistent with well-established gender differences in asthma epidemiology. Studies have reported higher incidence and prevalence rates of asthma in boys during childhood, as well as an earlier age of onset (46-48). The prevalence of asthma and atopy rates is higher in males until school age. After adolescence, however, an increase in favor of females has been reported (48). It has been reported that this condition in male children at an early age may be related to their relatively narrower airway diameters, higher viral infection load, and earlier and stronger Th2 response (49-51). The higher incidence of lower respiratory tract infections and bronchiolitis episodes in male infants is another factor supporting the "early-onset asthma" phenotype with recurrent wheezing in early childhood (52). In contrast, it has been reported that the more favorable airway diameter/lung growth ratio in girls, along with the partially protective effect of sex hormones that modulate the Th2 response of the immune system during the prepubertal period, may contribute to symptoms appearing at a later age on average (53,54).

In the present study, we found that the rates of sensitization to inhalant allergens (cat, dog, mites, pollen, and mold spores) in children with asthma tended to be higher in boys than in girls. It has been reported that inhalant allergen sensitivity in children with asthma may generally show some differences based on gender (54-56). Epidemiological data show that inhalant allergen sensitivities are more common in boys during early and middle childhood and in girls during adolescence and beyond (40,41,45,54-56). A study conducted in Boston on children with aeroallergen sensitivity reported that boys had significantly higher rates of sensitivity to all inhaled allergens compared to girls, particularly to dog and grass pollen (45). Additionally, in Sweden, serial measurements conducted in the BAMSE birth cohort between the ages of 4 and 24 reported that male gender is an independent risk factor for IgE sensitivity to both cat and dog allergens (40). This difference is believed to result from the development of the immune system, the interaction of hormonal processes with age, and the effects of environmental exposure on aging (54-56). Additionally, it has been reported that skin barrier integrity is lower in male infants and that this may play a critical role in sensitization during early life (56). Additionally, the higher incidence of viral infections such as respiratory syncytial virüs and rhinovirüs in boys in the first 3 age groups may increase allergen sensitivity by deepening epithelial damage (57). The 4-6 age group is a period when the immune system is still maturing. It has been reported that Th2 dominance is more prevalent in boys than in girls at this age. It has been noted that atopic sensitivity is notably higher in boys with indoor inhalant allergens (mites, mold spores) (40,58). At the same time, boys' greater behavioral exposure to outdoor allergens (pollen, fungal spores, etc.) may contribute to allergen sensitization. During the 7-12 age period, when gender differences are pronounced, it has been shown that total IgE levels in boys are significantly higher than in girls in this age group (40,55). With puberty, hormonal effects become more pronounced between the ages of 13-18. While the effect of estrogen in increasing mast cell activation can lead to an increase in allergic sensitivity in girls in the post-pubertal period; it has been suggested that the role of testosterone in suppressing airway inflammation may reduce sensitivity in boys (54,59). It has also been reported that atopic diseases may be seen at higher rates in girls after puberty compared to boys (54,59). For these reasons, gender differences in allergen sensitivity change during later adolescence. Some studies even report that girls catch up to boys, reaching higher rates of sensitivity (54,59).

In our study, when the inhalant allergen sensitivities observed in asthmatic children were examined individually, mites were the highest at 39.9%, followed by grass pollens at 21.6%, cereal pollens at 18.1%, and fungal spores at 13.6%. Depending on differences in climate conditions, vegetation, and living conditions between countries, as well as between regions within the same country, inhalant

allergen sensitivities may occur at varying rates (11). In a study conducted in the Mediterranean region of Turkey, the distribution of allergen sensitivities among children diagnosed with asthma was reported as follows: dust mites (66%), grass/grain pollen mixture (51.2%), and tree pollen mixture (50.9%) (60). A study conducted on children with asthma in Ankara reported that pollen sensitivity was the most common (32%), followed by sensitivity to mites (15.9%) (61). In another study conducted in Malatya, sensitivities were detected in children diagnosed with asthma and allergic rhinitis at rates of 48.9% for grass-cereal pollen mixture, 48.5% for weed-pollen mixture, and 40.2% for mites. (62). In another study conducted in Mersin, mites were reported at the highest rates in asthmatic children (*Dermatophagoides pteronyssinus* 67.9%, *Dermatophagoides farinae* 67.2%), followed by *Alternaria alternata* (19.4%) (63). In patients presenting with chronic cough in the Gaziantep region, skin prick test results showed that the most common positive reactions were to grass pollen (50.4%), mites (24.6%), and cereal pollen (23.3%), respectively (64). In Canada, sensitivities to dust mites (84.2%), cats (76.5%), and dogs (63%) were identified among cases of asthma and allergic rhinitis (65). In a study conducted in three separate regions in Australia, it was reported that mite sensitivity was again the most prominent factor (34). In our study, consistent with the literature in general, the highest level of mite sensitivity was detected, and it was thought that this situation could be related to the humid and temperate climate in our region, as well as living conditions. It is clear that the prevalence of atopy and the distribution of inhaled allergens in childhood asthma are multifactorial, shaped by a complex process involving age, genetic makeup, living conditions, geographical or regional characteristics, regional climate, environmental conditions, and allergen exposure load (11).

In the present study, sensitization rates to inhalant allergens other than cat and dog allergens were found to generally increase with advancing age. Similar results to those found in our study have been reported in numerous studies in the literature. A study of schoolchildren and adolescents in Korea found that pollen sensitivity increases with age (66). In a study conducted in Italy, where asthmatic children were divided into four groups-ages 1-3, 4-6, 7-9, and 10-17, it was found that pollen sensitivity increased with age (67). Similarly, a study conducted in Ankara on children aged 2-5, 6-11, and 12-18 found that pollen sensitivity increases with age (43). Additionally, a similar study conducted in Adana reported that pollen sensitivity in children increases with age (68). Age is one of the most significant factors in determining atopy. While sensitivity to inhaled allergens is relatively low in the preschool period, IgE-mediated sensitivity to allergens such as pollen, mites, cats, and dogs increases significantly during school age and adolescence (42). The BAMSE and ISAAC cohorts show that the prevalence of atopy has increased significantly, particularly among children aged 6 to 14 years (42). In this study, allergic rhinitis was detected in 45.6% of children diagnosed with asthma among the allergic diseases accompanying asthma. Asthma and allergic rhinitis are two atopic diseases that often occur together in children because they have similar immunological mechanisms and environmental triggers (11,69). Studies have shown that between 40% and 60% of children diagnosed with asthma are also affected by allergic rhinitis (11,69). In this context, the finding that allergic rhinitis was detected in 45.6% of children with asthma in our study is consistent with the literature (11,69).

In this study, it was observed that total IgE levels were statistically significantly higher in asthmatic children with positive sensitivities to cat and dog allergens (consistent with the existing literature on this subject). It is known that total IgE can be influenced by factors such as race, genetics, environmental conditions, and the presence of other accompanying diseases (70,71). A direct correlation has been found between total IgE levels and asthma severity in patients with asthma (70). Total IgE, unlike specific IgE, reflects the entire IgE pool but is a highly nonspecific marker; nevertheless, numerous studies have shown that total IgE levels generally increase as the burden of inhalant allergen sensitivity increases (72,73). According to the results of studies in the literature, children with asthma who are sensitive to cat/dog extracts or their molecular components (*Fel d 1, Fel d 4, Can f 1, Can f 6,* etc.) tend to have higher total IgE, more pronounced eosinophilia, and more severe asthma symptoms than both healthy controls and asthmatics without pet (cat and/or dog) sensitivity (12,72,74-76). A study conducted in adult asthmatic patients in our country has found that skin prick test positivity for aeroallergens is associated with elevated total IgE levels (77). In another study conducted on children with asthma, a relationship was found between high total IgE levels and sensitivity to dust mites, pollen, and pet allergens, but no relationship was found with fungal allergens (78). Additionally, another multicenter study reported that the presence of sensitivity to Dermatophagoides pteronyssinus and Dermatophagoides farinae, cat, Alternaria, tree pollen mixture, and grass pollen mixture was associated with increased total IgE levels (79).

Study Limitations

The main limitation of our study was that it was retrospective and conducted in a single center. However, because the institution is a tertiary healthcare center to which all relevant patients in the Bursa region apply, and because the study was conducted on a large population, it was considered to contain reliable data on pediatric asthmatic patients living in the region.

Conclusion

Inhaled allergen sensitivities play a significant role in childhood asthma. It was determined that the incidence rates of cat and dog allergies in asthmatic children in the Bursa region are significant enough to warrant consideration and evaluation. Cat allergen sensitivity was found to be higher than dog allergen sensitivity in children with asthma across the total study population and in all age groups. This situation is thought to be related to various immunological mechanisms and differences in allergen sensitization patterns, as well as environmental factors. Cat allergies are likely more common than dog allergies due to the characteristics of cat allergens, greater exposure, and other reasons. The increase in sensitivity to cat and dog allergens with age suggests that this situation should be considered when following up with these patients and that they should be reevaluated in this regard.

Ethics

Ethics Committee Approval: Approval was received from the Medical Ethics Committee of Bursa Uludağ University Faculty of Medicine (decision numbered 2019-21/37).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT OLGU SUNUMU

Case Report of Rickets Due to Vitamin D Deficiency Associated Ichthyosis

İktiyozis İlişkili Vitamin D Eksikliğine Bağlı Rikets Olgu Sunumu

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Abstract

Exposure of keratinocytes in the skin to sunlight is an important source of vitamin D. Vitamin D deficiency can occur in skin diseases involving keratinization disorders such as ichthyosis. In this case, aged six years and six months, ichthyosis-related symptoms include erythema, widespread desquamation and xerosis throughout the body, along with rickets-related frontal bossing, widening of the wrists and Harrison's groove. The investigations revealed that rickets was associated with vitamin D deficiency. This report emphasizes the need for screening for vitamin D deficiency and prophylaxis in patients with chronic skin diseases.

Öz

Ciltteki keratinositlerin güneş ışığına maruz kalması önemli bir vitamin D kaynağıdır. Vitamin D eksikliği, iktiyoz gibi keratinizasyon bozukluklarını içeren cilt hastalıklarında görülebilir. Bu altı yaş altı aylık olguda, iktiyozise bağlı vücutta yaygın kızarıklık, pullanma ve kurulukla beraber raşitizmle ilişkili alın çıkıntısı, bileklerde genişleme ve Harrison oluğu tespit edilmiştir. Olguda yapılan tetkikler sonucu vitamin D eksikliğine bağlı rikets olduğu saptandı. Bu olgu raporu kronik cilt hastalıkları olan hastalarda vitamin D eksikliği taraması ve profilaksisinin gerekliliğini vurgulamaktadır.

Keywords
Ichthyosis, vitamin D, rickets, hypocalcemia

Anahtar kelimeler
İktiyozis, Vitamin D, rikets, hipokalsemi

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Introduction

Rickets is a clinical condition characterized by a mineralization defect of the epiphyseal plates. Pathological conditions affecting vitamin D, calcium, and phosphorus metabolism, which are essential for mineralization, can lead to rickets. The most common cause is vitamin D deficiency (1). Clinical findings are mostly seen in the skeletal system, such as forearm deformities in crawling children, "O" or "X" shaped legs in toddlers, "rachitic rosary" due to enlargement at the costochondral junctions, prominence in the frontal part of the skull, and delayed tooth eruption. Extra-skeletal findings such as muscle weakness, hypotonia, tetany, laryngospasm, and growth retardation may also occur (2).

The main source of vitamin D is the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3) in keratinocytes after exposure to sunlight (3). Therefore, various skin diseases, especially keratinization disorders, can impair

vitamin D metabolism and lead to vitamin D deficiency. Cases of vitamin D deficiency have been reported in many skin diseases such as atopic dermatitis, xeroderma pigmentosum, and ichthyosis (4). Here, a case of rickets due to ichthyosis vulgaris is presented due to its rarity.

Case Report

A 6-year and 6-month-old male patient presented to the pediatric neurology outpatient clinic with complaints of inability to walk. On physical examination, his body weight was 13.2 kg (SDS Z score -4.2), and height was 95 cm (SDS Z score: -4.9). On head and neck examination, there was mild erythema on the face, ectropion, and widespread, superficial, white powdery scales. The frontal region of the skull was prominent. Only the two upper incisors and molars were present, and the teeth were hypoplastic. Pectus carinatum deformity, Harrison's groove, and widening of the wrists were observed. There was widespread desquamation and xerosis throughout the body. Neurological examination revealed spasticity in both lower extremities, while other system examinations were normal. The patient's physical examination findings are shown in Figure 1 and Figure 2.

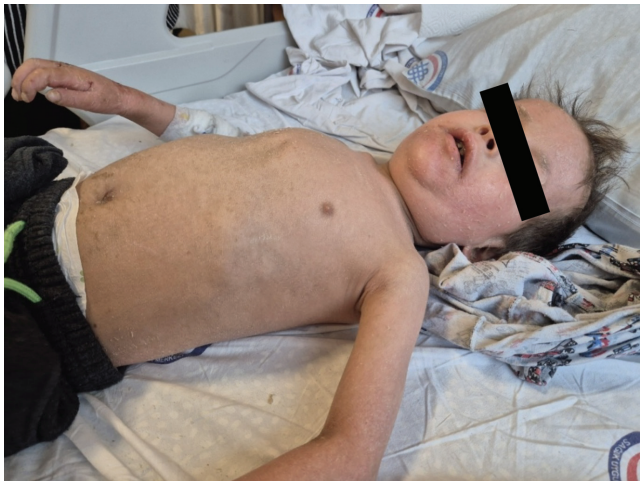

Figure 1. Widespread desquamation and xerosis throughout the body

In his medical history, it was learned that he was born at 33 weeks by normal delivery, weighing 1800 grams, and was hospitalized in the neonatal intensive care unit for one month due to prematurity. He was diagnosed with ichthyosis vulgaris in the neonatal period and had been receiving psoretin treatment for 3 years. The patient, who used bilateral cochlear implants due to hearing loss, was being followed by pediatric neurology and pediatric genetics units at another center. There was no consanguinity between the parents. His siblings were alive and healthy.

Laboratory tests revealed alkaline phosphatase 1179 U/L (142-335), calcium 6.02 mg/dl (8.8-10.8), albumin 4.19 mg/dl (3.5-5.2), phosphorus 3.78 mg/dl (3.3-5.6), magnesium 1.76 mg/dl (1.6-2.6), parathyroid hormone 597 ng/l, and 25-hydroxy vitamin D 3.26 mg/L. X-ray of the left wrist showed a cup-shaped appearance and fraying. Bone age was compatible with 3.5-4 years (Figure 3).

Based on the current examination and laboratory findings, the patient was evaluated as having rickets due to vitamin D deficiency. After a single dose of intravenous

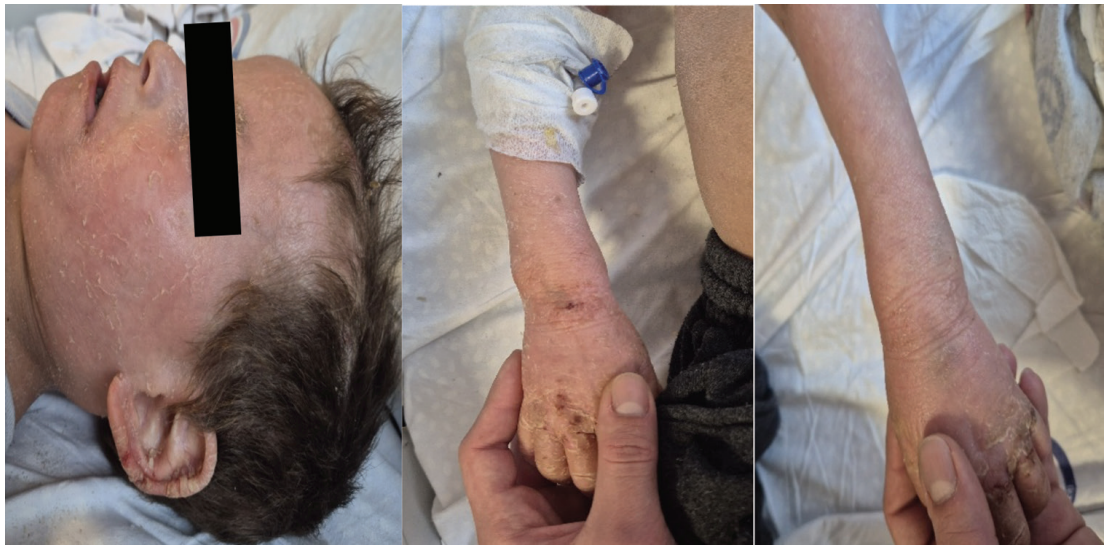

Figure 2. Frontal bossing and widening of the wrists

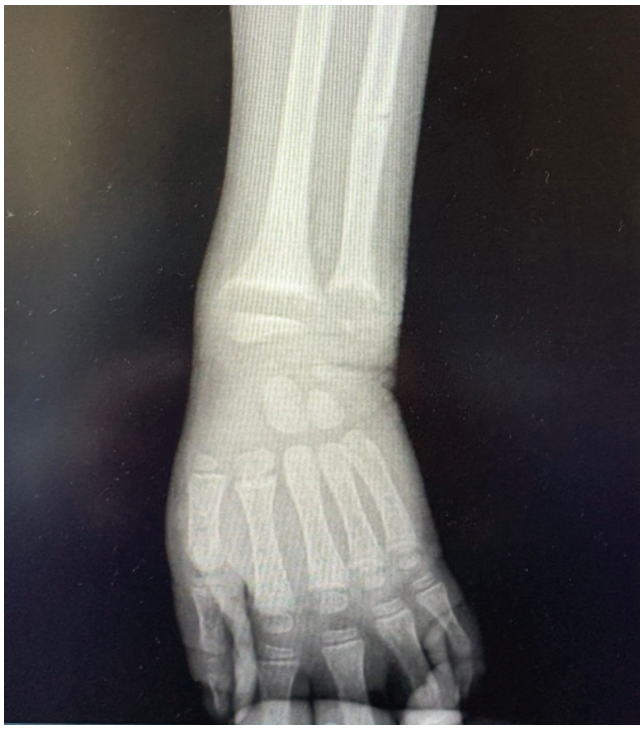

Figure 3. X ray of upper limb showed marked cupping and fraying of distal metaphyses

calcium, 75 mg/kg elemental calcium and 5000 IU/day vitamin D supplementation were started. Upon normalization of calcium levels in follow-up blood tests, the patient was discharged with oral treatments arranged and routine follow-ups planned. At the one-month follow-up, calcium was 9.3 mg/dl, alkaline phosphatase 739 U/L (142-335), and parathyroid hormone 114 ng/l.

Discussion

Here, a rare case of rickets due to ichthyosis vulgaris is discussed. The most common cause of rickets worldwide is vitamin D deficiency. The most common risk factors for vitamin D deficiency are winter and spring seasons, dark skin color, covered clothing, reduced sun exposure, insufficient dietary intake, and malabsorption. Nutritional causes and low sun exposure are the most prominent factors (5). One of the important steps in vitamin D metabolism begins in the skin. Even if sun exposure and nutrition are normal, vitamin D deficiency can develop in pathological skin conditions (4,6). Numerous studies have demonstrated an association between low vitamin D levels and conditions such as vitiligo, psoriasis, rosacea and, in particular, atopic dermatitis in children (6-8). In this case, rickets due to ichthyosis was considered.

Ichthyoses are a group of skin keratinization disorders characterized by dry, rough skin and prominent scaling. They exhibit an autosomal semi-dominant inheritance pattern with a milder phenotype in heterozygotes due to loss-of-function mutations in the filaggrin gene (FLG). Clinical findings include xerosis, keratosis pilaris, palmar hyperlinearity, and a predisposition to atopic disorders (9). Risk factors for the development of rickets in patients with ichthyosis include impaired vitamin D synthesis in diseased epidermis, poor penetration of ultraviolet B rays into the epidermis due to widespread scaling, reduced sun exposure due to discomfort from sunlight, dark skin, loss of calcium through the skin, and the use of systemic retinoids that reduce intestinal calcium absorption (4). Ichthyosis has its own risk factors and shows some differences from nutritional rickets. Known differences include consanguinity between parents, similar skin lesions in siblings, and discomfort from sun and heat (10). In this case, consistent with the literature, there were risk factors such as skin findings, retinoid use, consanguinity between parents, discomfort from sunlight, and features distinguishing it from nutritional rickets.

No typical skin lesions are associated with vitamin D deficiency. However, alopecia is observed in vitamin D-dependent rickets type 2. The most important difference between these two pathological conditions is that 1,25-dihydroxyvitamin D levels are high in vitamin D-dependent rickets and, despite treatment for rickets, the alopecia does not improve (11). Vitamin D deficiency has been demonstrated in inflammatory skin diseases characterised by itching, such as ichthyosis, and numerous studies have reported the potential benefits of using vitamin D topically or systemically (6).

In children with rickets, secondary hyperparathyroidism develops due to decreased vitamin D and hypocalcemia. Among the different combinations of threshold levels of serum 25-hydroxyvitamin D and parathyroid hormone, the risk of developing rickets in children with congenital ichthyosis is higher when serum 25-hydroxyvitamin D is ≤8 ng/ml and parathyroid hormone is ≥75 pg/ml (12). In this case, consistent with the literature, parathyroid hormone was 597 ng/l and 25-hydroxyvitamin D was 3.26 ng/ml.

It is recommended that patients with ichthyosis be advised about adequate sun exposure, have their vitamin D levels checked even in the absence of clinical signs of rickets, and receive lifelong “rickets prophylaxis” with periodic vitamin D supplementation(4,10).

Conclusion

Because the risk of developing rickets is quite high in cases of ichthyosis vulgaris, vitamin D levels should be monitored during follow-up. Preventing serious complications with oral treatment or prophylaxis is easier than dealing with the complications of rickets.

Footnotes

Conflict of Interest: The authors reported no potential conflict of interest.

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CASE REPORT OLGU SUNUMU

Wilms' Tumor in a Child with Cystic Fibrosis: A Case Report and Review of the Literature

Kistik Fibrozisli Bir Çocukta Wilms Tümörü: Olgu Sunumu ve Literatür Taraması

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Abstract

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder. While gastrointestinal and pulmonary complications are frequent in CF, the coexistence of malignancy is rare. We aimed to present a case of bilateral Wilms' tumor (BWT) in a child with CF and to review the relevant literature. A female child diagnosed with CF in the neonatal period was referred to our clinic at the age of 2 years, when bilateral Wilms' tumor was detected. Clinical history, laboratory findings, and imaging results were evaluated, and the diagnostic, therapeutic, and follow-up process were described in detail. In addition, a literature review was performed to identify similar cases.In addition to the typical clinical manifestations of CF, abdominal imaging revealed bilateral Wilms' tumor. The clinical course and treatment process of the patient were reported. Literature review demonstrated that the coexistence of CF and Wilms' tumor is extremely rare, with only a limited number of cases described. Although malignancy is rare in children with CF, it should not be overlooked. This case highlights the unusual coexistence of CF and Wilms' tumor and emphasizes that reporting such cases provides a valuable contribution to the literature. Clinicians should consider the possibility of malignancy during the long-term follow-up of patients with CF, particularly as survival improves.

Öz

Kistik fibroz (KF), yaşamı sınırlayan en yaygın otozomal resesif hastalıktır. KF'de gastrointestinal ve pulmoner komplikasyonlar sık görülürken, malignite birlikteliği nadirdir. KF'li bir çocukta bilateral Wilms tümörü (BWT) olgusunu sunmayı ve ilgili literatürü incelemeyi amaçladık. Yenidoğan döneminde KF tanısı almış bir kız çocuğu, 2 yaşındayken bilateral Wilms tümörü tespit edilmesi üzerine kliniğimize sevk edildi. Klinik öykü, laboratuvar bulguları ve görüntüleme sonuçları değerlendirildi ve tanı, tedavi ve takip süreci ayrıntılı olarak anlatıldı. Ayrıca benzer vakaları belirlemek için literatür taraması yapıldı. KF'nin tipik klinik bulgularına ek olarak, abdominal görüntülemede bilateral Wilms tümörü saptandı. Hastanın klinik seyri ve tedavi süreci raporlandı. Literatür taraması, KF ve Wilms tümörü birlikteliğinin son derece nadir olduğunu ve sınırlı sayıda vakanın tanımlandığını

Keywords
Wilms' tumor, child, cystic fibrosis

Anahtar kelimeler
Wilms tümörü, çocuk, kistik fibroz

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göstermiştir. Kistik fibrozisli çocuklarda malignite nadir görülse de göz ardı edilmemelidir. Bu olgu, Kistik fibrozis ve Wilms tümörünün alışılmadık bir şekilde bir arada bulunmasını vurgulamakta ve bu tür olguların bildirilmesinin literatüre değerli bir katkı sağladığını vurgulamaktadır. Klinisyenler, özellikle sağ kalım arttıkça, Kistik fibrozisli hastaların uzun dönem takibinde malignite olasılığını göz önünde bulundurmalıdır.

Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease affecting the pancreas, intestine and hepatobiliary system, and respiratory tract in Caucasians. CF is caused by different mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. With the use of modulators aimed at correcting the CFTR protein, the prognosis of CF has improved markedly over the past 20 years. In this way, the number of patients reaching adulthood is increasing. Approximately 85% of patients with CF have pancreatic insufficiency at birth. Gastroesophageal reflux disease (GERD) is more common in patients with CF but is thought to adversely affect lung health. Distal small bowel obstruction syndrome (DIOS), caused by meconium-like stool plugs, occurs at any age after the neonatal period and affects 15-20% of patients with CF (1). With the increasing survival rate, many patients with CF, especially gastrointestinal system cancers, are more common in advanced age compared with the normal population. Recently, it has been reported that different types of cancer are seen during the follow-up of patients CF in the pediatric age group (2,3). In this report, by reviewing the literature, we evaluated a bilateral Wilms tumor (BWT) detected in a 2-year-old girl who was followed up for CF.

Case Report

A female patient, who has been followed up with the diagnosis of CF since the neonatal period, was referred to our clinic when she was aged 2 years when bilateral hydronephrosis and a mass in both kidneys were detected in a routine abdominal ultrasonography follow-up.

When the first "immune reactive trypsinogen testing" (IRT) was found as 102 µg/L and the second IRT as 83 µg/L for the CF screening program in the neonatal period, the patient was given a sweat test. The patient was followed up when the chlorine amount was intermediate (43 eq/L) in the sweat chlorine test. In the blood tests performed during the follow-up of the patient (Na: 127 mmol/L, Cl: 96 mmol/L, Ph: 7.53, HCO3: 29 mmol/L), genetic analysis was performed and when the G85E/F1052V gene mutation was found to be a compound heterozygous mutation, she was diagnosed as having CF and treatment was started. It was confirmed through gene analysis that both parents were CF carriers.

Newborn CF screening thresholds for immunoreactive trypsinogen (IRT) vary across programs; representative fixed cutoffs are typically around 60–65 ng/mL (≈96th percentile), while some use fixed cutoffs spanning 50–100 ng/mL or floating percentiles (≈95th–99.5th). In our patient, IRT values were 102 and 83 µg/L (i.e., ng/mL), exceeding common screening thresholds.

In the physical examination of the patient, a mass was palpated in both flank regions. In abdominal ultrasonography, hydronephrosis was present in both kidneys and the larger one on the right was 4x4.5 cm. It was seen that there were multiple kidney masses on the left, the largest of which was 5x6 cm. In abdominal magnetic resonance imaging (MRI), multiple masses were detected in both kidneys (Figure 1, A-D).

She was started on chemotherapy with vincristine, actinomycin-D, and doxorubicin. Since the patient responded well, the Oncology Board decided to continue treatment beyond the usual 6–12 week window, and surgery was performed at week 25.

At that time, a left nephrectomy was performed due to multiple tumor masses, and nephron-sparing surgery was carried out on the right kidney. Pathology confirmed a regressive-type Wilms Tumor without anaplasia. Radiotherapy was applied to the left kidney lodge, while it was not administered to the right. The patient is followed up in the 3rd month after surgery, disease-free and without signs of kidney failure.

Pathology results confirmed a regressive-type Wilms Tumor without anaplasia (Figure 2). There was no tumor tissue in the surgical margins. A total of 10.8 Gy radiotherapy was applied to the left kidney lodge of the patient after the surgery. Radiotherapy was not administered to the right kidney lodge. The patient is followed up in the 3rd month after the surgery, free of disease and without signs of kidney failure.

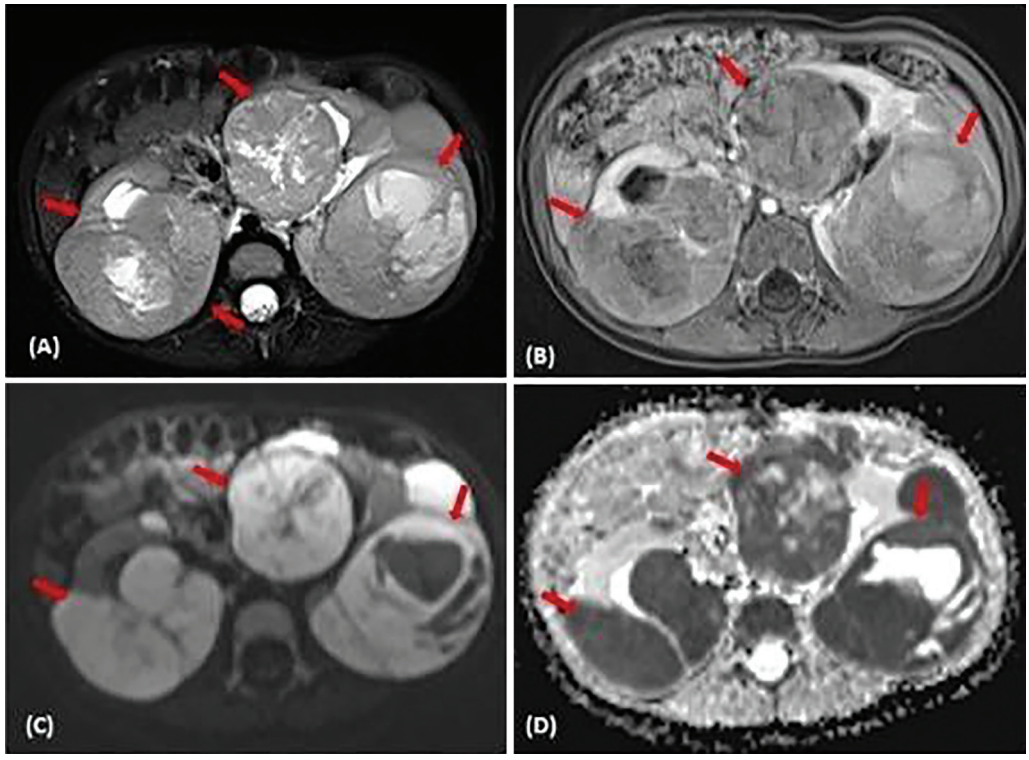

Figure 1. A-D. In both kidneys, the largest 38x45 mm on the right and 48x58 mm on the left, multiple parenchymal exophytic extensions in the collecting system with cystic and solid areas causing local dilatation and deformation, isointense with the kidney parenchyma in T2-weighted images (A), showing mild contrast enhancement on contrast-enhanced T1-weighted images (B), and marked diffusion restriction on diffusion-weighted images (C, D) solid space-occupying mass lesions are observed (red arrows)

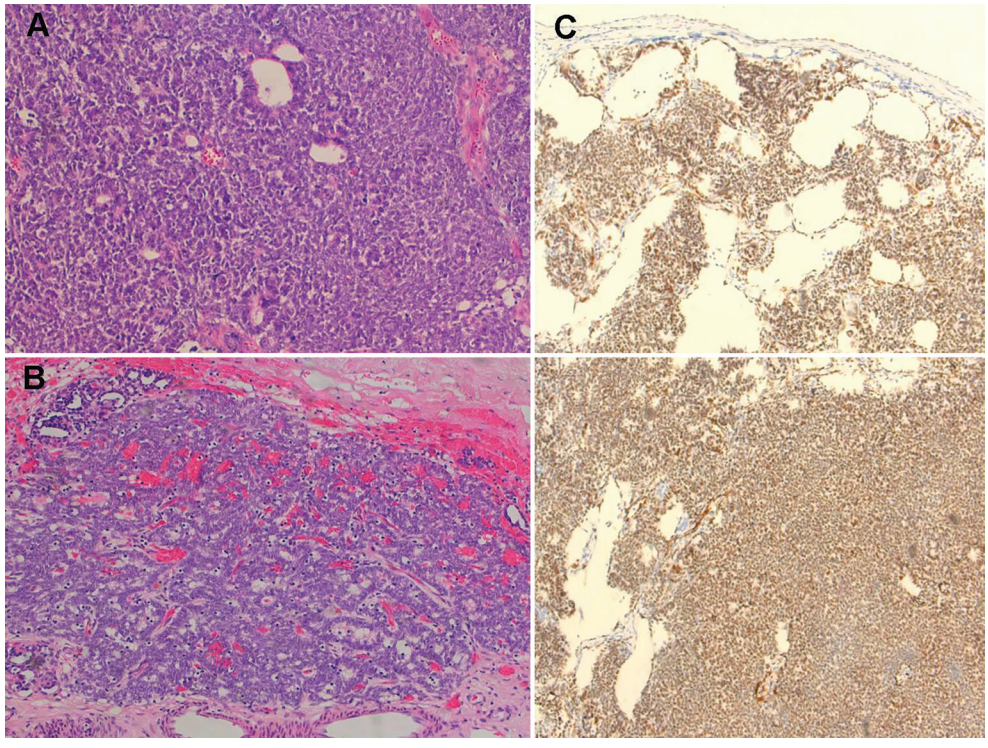

Figure 2. A: Extensive blastemal component in tumor tissue (Hematoxylin-eosin, original magnification, X40) B: Extensive epithelial component in tumor tissue (Hematoxylin-eosin, original magnification, X40)

C: Diffuse nuclear staining of tumor cells (Immunohistochemistry, WT-1 stain, original magnification, X20)

Discussion

CF is known to increase the risk of gastrointestinal cancers when compared with the general population, including specific cancers of the small intestine, colon, biliary tract, and pancreas. A screening strategy for gastrointestinal cancer needs to be developed in these patients (4).

Recent studies (2022–2024) have confirmed that while overall cancer risk in CF is increasing, non-GI malignancies such as Wilms tumor remain exceptionally rare. Updated reports emphasize the need for individualized management in bilateral Wilms tumor (BWT), with surgery generally recommended at week 6–12; in our case, the Tumor Board extended chemotherapy to week 25 due to ongoing favorable response. Importantly, no lung metastases were detected, and our follow-up period remains short (3 months), which is a limitation.

A study, which showed that there are various types of cancer in people with CF and its prevalence as 1.1%, stated that these types of cancer occur at a younger age than the general population. Although GI cancer is the most common, it still accounts for only 22% of total cancers (5). Although some studies did not demonstrate the relationship between existing cancer and CF (2), other authors noted that most of their patients had some degree of pancreatic insufficiency and impaired intestinal motility, and persistent pathologic changes associated with increased cell turnover. It has been shown that these changes can cause cancer and the incidence of non-gastrointestinal cancers is high (6). The coexistence of CF and Wilms tumor has been reported in only two patients in the literature, and the patients died in the early period (7). Our patient was diagnosed as having BWTs when she was aged only 2 years and she had no gastrointestinal tract symptoms.

Prospective evaluation of serum amylase and lipase measurements in all patients with newly diagnosed non-Hodgin lymphoma has been reported to be of interest to define the incidence of subclinical pancreatic disease and should bring to mind undiagnosed CF disease (8). Our patient had no signs of pancreatitis and her amylase lipase values were normal.

The coexistence of CF and acute lymphocytic leukemia (ALL) is rare and few cases have been reported in the literature (9-11). For ALL in patients with CF, the treatment of patients with severely impaired lung function should be individualized and, because teniposide clearance rates may be higher than population averages, assessment of systemic drug exposure and dose adjustment based on these findings are recommended (10). It has also been stated that some immune modulation and anti-inflammatory treatments given together with leukemia treatment are effective in lung problems caused by CF (11). Our patient had no lung problems that required treatment yet.

In another study on cancers accompanying congenital anomalies, it was stated that the possible leukemogenic effect of chloramphenicol, which is used in the treatment of CF in children with leukemia and Wilms tumor, should be considered and further studies should be conducted (7). Today, chloramphenicol is no longer used for the treatment of CF. Our patient was on medication containing only high doses of pancreatic enzymes for CF.

In the literature, cases of testicular, brain, and thyroid cancers, and neuroblastoma have also been reportedly seen with CF. The negative effects of the agents given during cancer treatment on the lung are important in patients with CF (6,12). Our patient had no lung disease due to chemotherapeutic drugs during the treatment period.

For BWTs, both the Current Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP) recommend preoperative chemotherapy, NSS, and subsequent treatment (13). Appropriate chemotherapy was given to our patient before the surgery, and radiotherapy was given after the surgery.

The COG and SIOP protocols mandate the removal of the entire tumor as well as lymph node sampling. Ipsilateral nephrectomy is usually performed and therefore NSS is reserved for BWT because of the size of unilateral tumors (and the fact that protocols mandate pre-chemo only of SIOP, not COG). Pre-administered chemotherapy allows the tumor to shrink significantly and makes it technically easier to separate the tumor from the surrounding normal renal parenchyma. The approach chosen should allow exposure of the retroperitoneum to facilitate tumor excision and lymph node sampling. A transperitoneal approach via a chevron incision can be used. It is necessary to protect the adrenal gland as long as it does not compromise oncologic control or other aspects of surgical quality (14). Laparoscopic partial nephrectomy for Wilms tumors has been reported, although there have been reports of large peritoneal spread by the tumor following minimally invasive NSS (15-17). Currently, the open surgical approach for NSS in patients with BWT remains the standard. Our patient first underwent a left total nephrectomy because there was more than one tumor mass in the left kidney, and NSS was not possible. Afterward, approximately 1.5 cm of tumor tissue in the mid-lower pole of the right posterior face was removed with NSS, and the double-J stent, which was placed after the opened pelvis

was repaired, was removed in the 3rd postoperative week. Both adrenal glands were not removed. There was no complication related to the surgical procedure. Renal failure did not develop.

Gastrointestinal system cancers can be seen in advanced age with CF. The association of non-GI system cancers with CF has been reported very rarely. Moreover, the appearance of these cancers at an early age indicates that patients with CF should be followed closely and with a multidisciplinary team. The association of CF Wilms' tumor has been reported in only a few cases in the literature. We state that since our patient had BWT, the diagnosis and treatment process were successfully managed and it is pleasing that she continued her life without developing kidney failure with NSS.

Conclusion

To date, only two cases of Wilms tumor associated with CF have been explicitly reported in the literature. Miller (1969) described two children with CF who developed Wilms tumor, both of whom died in the early period. Subsequent epidemiological reports discussed cancer risk in CF but did not provide further well-documented WT cases. Our patient therefore represents one of the very few surviving cases with detailed diagnostic and therapeutic follow-up, highlighting the exceptional rarity of this comorbidity.

Footnotes

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LETTER TO THE EDITOR EDİTÖRE MEKTUP

Burkitt Lymphoma with Severe Lactic Acidosis

Ağır Laktik Asidozlu Burkitt Lenfoma

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Dear Editor,

The prognosis of Burkitt lymphoma mainly depends on histopathology, the degree of involvement, and the characteristics of the patient (1). Reports indicating that lactic acidosis in patients diagnosed with malignancy is resolved only with chemotherapy are rare. Burkitt's lymphoma is the fastest growing human tumor, with a cell doubling time of 24–48 hours, so treatment should be started quickly without delay (2). There is a significant risk of tumor lysis syndrome when treating Burkitt lymphoma (3).

An 11-year-old boy who was followed up for autism with no other known disease was investigated in Iraq with a preliminary diagnosis of pancreatitis, with complaints of abdominal pain and vomiting that started 2 weeks prior. Hepatosplenomegaly and lymphadenopathy were not detected. However, fever, abdominal pain, vomiting, and positive inflammatory markers were observed. Mitral regurgitation was detected on the echocardiogram, and adrenaline infusions of 0.1 µg/kg/min and 0.5 µg/kg/minute milrinone were started.

The laboratory findings revealed a mild increase in C-reactive protein at 14.6 µm g/L. The initial complete blood count revealed cytopenia with anaemia (7.8 g/dL) and thrombocytopenia (49×10^9/L) without blast cells in the peripheral smear. Immunoglobulin and albumin levels were low. Triglyceride, D-dimer, ferritin, and lactate dehydrogenase levels were high. Troponin-T, BNP, amylase, and lipase levels were normal. Thyroid ultrasound revealed a hypoechoic lesion in the left thyroid lobe. Abdominal computed tomography revealed hypoechoic lesions 20×10 mm and 11×8 mm in size in the pancreas and diffuse soft tissue densities around the mesentery and superior mesenteric artery vein. When bone marrow aspiration was performed on the patient, 90% blasts were detected, and Burkitt lymphoma was diagnosed (Figure 1). The patient was evaluated as having stage 4 disease according to the Ann Arbor Staging System. The first curative chemotherapy with cyclophosphamide, vincristine, and steroid chemotherapy plan was made according to the Child Oncology Group ANHL01P1 Protocol. Electrolytes were checked at frequent intervals. Aggressive fluid hydration, allopurinol, and rasburicase treatment were used to prevent tumor lysis syndrome.

Keywords
Burkitt lymphoma, lactic acidosis, hypoglycemia

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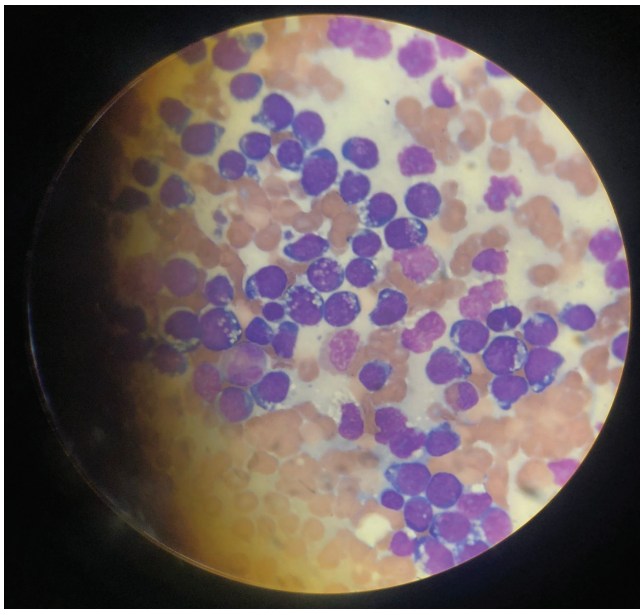

Figure 1. The patient's bone marrow aspiration image (bone marrow aspirate and biopsy slides) revealed complete effacement of the normal bone marrow architecture by sheets of monomorphic-looking cells. At high-power magnification, the medium-large neoplastic cells had a FAB L3 morphology, round or oval nuclei, finely stippled nuclear chromatin, multiple nucleoli and a thin rim of deeply basophilic cytoplasm containing numerous prominent vacuoles. Hematoxylin-eosin stain)

After the patient was admitted to the intensive care unit, the lactate levels in the blood gases first increased and then decreased with chemotherapy (6.7–8.9–13.7–12.2–16–14.3–10.2–6.9–15–20–20–20–23–25–25–23–20–15–10–8.4–4–2.6 mmol/L). When the patient's lactate level was 25 mmol/L, the patient's lactate level rapidly decreased after chemotherapy started. The lactate level decreased to 2.6 mmol/L 48 hours after chemotherapy started.

One of the most unusual features of our patient was severe lactate elevation and accompanying hypoglycemia. There are rare cases of lactic acidosis and hypoglycemia in non-Hodgkin lymphomas in the literature (4,5). Cancer cells can continue glycolysis even in the presence of high oxygen and therefore produce high levels of lactate. Insulin-like growth factors and their receptors, which are overexpressed by some cancer cells, can mimic many of the activities of insulin. A review of the literature revealed that lactic acidosis in patients diagnosed with malignancy is resolved only with chemotherapy (5).

Literature-Based Pathophysiological Mechanisms

The pathophysiology of type B lactic acidosis in pediatric malignancies is multifactorial. The central mechanism is tumor-driven metabolic reprogramming, classically described as the Warburg effect. In this process, malignant cells preferentially utilize aerobic glycolysis over oxidative phosphorylation even in the presence of adequate oxygen, leading to excessive lactate production. This is further amplified by the upregulation of key enzymes, including pyruvate kinase M2, lactate dehydrogenase A, and pyruvate dehydrogenase kinase 1, which accelerate glycolytic flux toward lactate accumulation (6).

In addition, impaired clearance exacerbates systemic acidosis. Malignant infiltration of the liver and kidneys significantly reduces lactate metabolism and excretion (6,7). Thiamine deficiency, often overlooked in critically ill oncology patients receiving inadequate nutrition or prolonged parenteral support, further impairs pyruvate oxidation by blocking its conversion to acetyl-CoA. Importantly, supplementation with thiamine has been shown to result in rapid reversal of severe lactic acidosis in such contexts (8). Taken together, these mechanisms underscore the multifactorial nature of malignancy-associated lactic acidosis, highlighting both tumor-intrinsic metabolic alterations and reversible cofactors that must be addressed to optimize patient outcomes.

In conclusion, lactic acidosis is frequently observed in circulatory failure and hypoxemia in critically ill children, but it rarely occurs for different causes, such as in our patient. Lactic acidosis in patients diagnosed with malignancy can be resolved only with chemotherapy.

Footnotes

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