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ÜMRANİYE PEDİATRİ DERGİSİ

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KARE

ÜMRANİYE PEDİATRİ DERGİSİ

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YAZARLARA BİLGİ

Ümraniye Pediatri Dergisi, uluslararası, periyodik ve açık erişimli akademik bir dergidir. Dergi; bağımsız, önyargısız ve çift-kör hakemlik ilkelerine uygun olarak Nisan, Ağustos ve Aralık aylarında yılda üç sayı yayınlanmaktadır. Derginin yayın dili Türkçe ve İngilizce'dir.

Değerlendirilmek üzere gönderilen yazılar Türkçe ya da İngilizce olarak kabul edilmekte ve yayınlanmaktadır.

Dergide makale değerlendirme ve yayın işlemleri için yazarlardan ücret talep edilmemektedir. Dergi arşivi www.umraniyepediatri.com üzerinden ücretsiz olarak okuyucuların erişimine açıktır.

Ümraniye Pediatri Dergisi çocuk sağlığı ve hastalıkları alanında yayınladığı özgün araştırma, nadir görülen olgu sunumları, derleme ve editöre mektup türündeki yazılar ile tıp bilimine katkı sağlamayı amaçlamaktadır. Derginin hedef kitlesi çocuk sağlığı ve hastalıkları konusunda çalışan uzmanlar, akademisyenler ve ilgili diğer dal uzmanlarıdır.

Derginin yazıları değerlendirme ve yayın süreçleri 'International Committee of Medical Journal Editors' (ICMJE), 'World Association of Medical Editors' (WAME), 'Council of Science Editors' (CSE), 'Committee on Publication Ethics' (COPE), 'European Association of Science Editors' (EASE), ve 'National Information Standards Organization' (NISO) kılavuzlarına uygun olarak şekillendirilmiş olup 'Principles of Transparency and Best Practice in Scholarly Publishing' (doaj.org/bestpractice) ilkelerine uygun olarak yürütülmektedir.

Bir yazının yayına kabul edilmesindeki en önemli ölçütler; özgünlük, yüksek bilimsel kalite ve atıf potansiyelidir. Ümraniye Pediatri Dergisi'ne gönderilen yazıların daha önce başka bir elektronik ya da basılı dergide, kitapta ya da farklı bir mecrada sunulmamış ya da yayınlanmamış olması gerekir. Toplantılarda sunulan çalışmalar için, sunum yapılan kongrenin tam adı, tarihi, şehri ve ülkesi belirtilmelidir.

Ümraniye Pediatri Dergisi'ne gönderilen tüm yazılar çift-kör hakem değerlendirme sürecinden geçmektedir. Tarafsız değerlendirme sağlayabilmek için her yazı alanlarında uzman en az iki dış-bağımsız hakem tarafından değerlendirilir. Dergi Yayın Kurulu üyeleri tarafından gönderilecek yazıların değerlendirme süreçleri, davet edilecek dış bağımsız editörler tarafından yürütülecektir. Bütün yazıların karar verme süreçlerinde son karar yetkisi Baş Editör'dedir.

Klinik ve deneysel çalışmalar, ilaç ile cihaz araştırmaları ve bazı olgu sunumları için World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013, www.wma.net) çerçevesinde hazırlanmış Etik Kurul raporu gerekmektedir. Türkiye'de yapılan bu tür çalışmalar için Sağlık Bakanlığı'nın 3359 numaralı Sağlık Hizmetleri Temel Kanunu'na uygun olarak Sağlık Bakanlığı'ndan izin alınması gereklidir. Etik Kurul raporu ya da eşdeğeri olan resmi bir yazı taranarak sisteme yüklenmelidir. İnsanlar üzerinde yapılmış deneysel çalışmaların sonuçlarını bildiren yazılarda, çalışmanın yapıldığı kişilere uygulanan yöntemlerin niteliği tümüyle açıklandıktan sonra, onaylarının alındığına ilişkin bir açıklamaya metin içinde yer verilmelidir. Hayvanlar üzerinde yapılan çalışmalarda ise, hayvanlara ağrı, acı ve rahatsızlık verilmemesi için alınan önlemler yazıda açık olarak belirtilmelidir. Hasta onamları, Etik Kurul raporunun alındığı kurumun adı, onay belgesinin numarası ve tarihi ana metin dosyasında yer alan Gereç ve Yöntemler başlığı altında yazılmalıdır. İnsanlarda yapılan tıbbi araştırmalarda Dünya Tıp Birliği'nin Helsinki Bildirgesine uyularak araştırmanın yapıldığı belirtilmelidir. Hastaların kimliklerinin gizliliğini korumak yazarların sorumluluğundadır. Hastaların kimliğini açığa çıkarabilecek fotoğraflar için hastadan ya da hastanın yasal vasilerinden alınan imzalı izinlerin de dergiye gönderilmesi gereklidir.

Bütün yazıların benzerlik denetimi iThenticate yazılımı aracılığıyla yapılmaktadır.

Yayın Kurulu, dergiye gönderilen çalışmalar hakkındaki intihal, atıf yönlendirmesi ve veri sahteciliği iddiaları ya/ya da şüpheleri karşısında COPE kılavuzunda belirtilen ilkelere göre hareket edecektir.

Yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık ölçütlerini karşılaması gerekmektedir. ICMJE, yazarların aşağıdaki 4 ölçütü karşılamasını önermektedir:

Çalışmanın düşüncesine/tasarımına ya da çalışma için verilerin toplanmasına, incelenmesine ve yorumlanmasına önemli ölçüde katkı sağlamış olmak; VE

Yazı taslağını hazırlamış ya da düşünsel içeriğin eleştirel incelemelerini yapmış olmak; VE

Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak; VE

Çalışmanın herhangi bir bölümünün geçerliliğine ve doğruluğuna ilişkin soruların uygun şekilde incelenip çözümlendiğini sağlamak amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Bir yazar, çalışmada katkı sağladığı kısımların sorumluluğunu almasının yanı sıra diğer yazarların çalışmanın hangi kısımlarından sorumlu olduğunu da saptayabilmelidir. Ayrıca, yazarlar birbirlerinin katkılarının bütünlüğüne güven duymalılardır.

Yazar olarak belirtilen herkes yazarlığın dört ölçütünü karşılamalı ve bu dört ölçütü karşılayan herkes yazar olarak tanımlanmalıdır. Dört ölçütün tamamını karşılamayan kişilere yazının başlık sayfasında teşekkür edilmelidir.

Sorumlu yazarlar; yazarlık haklarına uygun hareket etmek ve hayalet ya da lütuf yazarlığın önüne geçmek amacıyla yazıların yükleme sürecinde, www.umraniyepediatri.com adresinden erişilebilen Yazar Katkı Formu'nu imzalamalı ve bu formun taranmış şeklini yazıyla birlikte göndermelidir. Yayın Kurulu'nun gönderilen bir yazıda "lütuf yazarlık" olduğundan şüphelenmesi durumunda söz konusu yazı değerlendirme yapılmaksızın reddedilecektir.

Ümraniye Pediatri Dergisi gönderilen yazıların yazarları ile yazıların değerlendirme sürecinde olan kişilerin potansiyel çıkar çatışmasına ya da önyargıya yol açabilecek mali, kurumsal ve diğer ilişkilerini ya da potansiyel çıkar çatışmalarını bildirmelerini talep ve teşvik eder.

Bir çalışma için bir birey ya da kurumdan alınan her türlü mali destek ya da diğer destekler Yayın Kurulu'na bildirilmelidir. Potansiyel çıkar çatışmalarını bildirmek amacıyla ICMJE Potansiyel Çıkar Çatışmaları Formu katkı sağlayan tüm yazarlar tarafından ayrı ayrı doldurulmalıdır. Editörler, yazarlar ve hakemler ile ilgili potansiyel çıkar çatışmaları derginin Yayın Kurulu tarafından COPE ve ICMJE kılavuzları kapsamında çözülmektedir.

Derginin Yayın Kurulu, itiraz ve şikayet olaylarını, COPE rehberleri kapsamında işleme almaktadır. Yazarlar, itiraz ve şikayetleri için doğrudan Yayın Sekreterliği ile temasa geçebilirler. Gereksinim duyulduğunda Yayın Kurulu'nun kendi içinde çözemediği konular için tarafsız bir temsilci atanmaktadır. İtiraz ve şikayetlerle ilgili karar verme süreçlerinde son kararı Baş Editör verecektir.

Ümraniye Pediatri Dergisi her yazının www.umraniyepediatri.com adresinden erişilebilen Telif Hakkı Sözleşmesi ile beraber gönderilmesini talep eder. Yazarlar, yazıda yer alan resimler, tablolar ya da diğer her türlü içerik dahil daha önce yayınlanmış içeriği kullanırken telif hakkı sahibinden izin almalılardır. Bu konudaki yasal, mali ve cezai sorumluluk yazarlara aittir. Yazarlar, Telif Hakkı Sözleşmesini imzalayarak, Ümraniye Pediatri Dergisi'nde yayınlanacak yazıların Creative Commons 4.0 Uluslararası Atıf Lisansı (CC-BY-NC) kapsamında lisanslanacağını kabul ederler.

Dergide yayınlanan yazılarda ifade edilen görüşler Ümraniye Pediatri Dergisi, Baş Editör, Editörler, Yayın Kurulu ve Yayıncı'nın değil, yazar(lar)ın bakış açılarını yansıtır. Baş Editör, Editörler, Yayın Kurulu ve Yayıncı bu içeriklere dair hiçbir sorumluluk ya da yükümlülük kabul etmemektedir. Yayınlanan içerik ile ilgili tüm sorumluluk yazarlara aittir.

Yazıların Hazırlanması

Yazılar, ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje. org/icmje-recommendations.pdf) ile uyumlu olarak hazırlanmalıdır. Randomize çalışmalar CONSORT, gözlemsel çalışmalar STROBE, tanısal değerli çalışmalar STARD, sistematik derleme ve meta-analizler PRISMA, hayvan deneyli çalışmalar ARRIVE ve randomize olmayan davranış ve halk sağlığıyla ilgili çalışmalar TREND kılavuzlarına uyumlu olmalıdır.

Yazılar sadece www.umraniyepediatri.com adresinde yer alan derginin online yazı yükleme ve değerlendirme sistemi üzerinden gönderilebilir.

Gönderilen yazıların dergi yazım kurallarına uygunluğu ilk olarak dergi yayın kurulu tarafından kontrol edilecek, dergi yazım kurallarına uygun hazırlanmamış yazılar teknik düzeltme talepleri ile birlikte yazarlarına geri gönderilecektir.

Yazarların; Telif Hakkı Sözleşmesi, Yazar Katkı Formu ve ICMJE Potansiyel Çıkar Çatışmaları Formu'nu (bu form, tüm yazarlar tarafından doldurulmalıdır) ilk gönderim sırasında online yazıların yüklenme sistemine yüklemeleri gerekmektedir. Bu formlara www.umraniyepediatri.com adresinden erişilebilmektedir.

Başlık sayfası: Gönderilen tüm yazılar ile birlikte ayrı bir başlık sayfası da gönderilmelidir. Bu sayfa;

Yazının Türkçe ve İngilizce başlığını ve 50 karakteri geçmeyen kısa başlığını,

Yazarların isimlerini, kurumlarını, eğitim derecelerini, e-mail adreslerini ve ORCID ID numaralarını,

Mali destek bilgisi ve diğer destek kaynakları hakkında ayrıntılı bilgiyi,

Sorumlu yazarın ismi, adresi, telefonu (cep telefonu dahil), faks numarası ve e-posta adresini,

Yazıların hazırlama sürecine katkıda bulunan ama yazarlık ölçütlerini karşılamayan bireylerle ilgili bilgileri içermelidir.

Özet: Editöre Mektup ve Uzmanından Yorum türündeki yazılar dışında kalan tüm yazıların Türkçe ve İngilizce özetleri olmalıdır. Özgün Araştırma yazılarının özetleri "Amaç", "Gereç ve Yöntemler", "Bulgular" ve "Çıkarımlar" alt başlıklarını içerecek biçimde hazırlanmalıdır. Kelime kısıtlamaları için Tablo 1'i inceleyiniz.

Anahtar Sözcükler: Tüm yazılar en az 3 en fazla 10 anahtar kelimeyle birlikte gönderilmeli, anahtar sözcükler özetin hemen altına yazılmalıdır. Kısaltmalar anahtar sözcük olarak kullanılmamalıdır. Anahtar sözcükler National Library of Medicine (NLM) tarafından hazırlanan Medical Subject Headings (MeSH) veritabanından seçilmelidir.

Yazı Türleri

Yazı ana dosyaları Microsoft Office Word programı kullanarak hazırlanmalı ve türlerine göre aşağıdaki yapıda düzenlenmelidir.

Özgün Araştırma: Ana metin "Giriş", " Gereç ve Yöntemler", "Bulgular" ve "Tartışma" alt başlıklarını içermelidir. Özgün Araştırmalarla ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Sonucu desteklemek için istatiksel çözümleme genellikle gereklidir. İstatistiksel çözümleme, tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). İstatiksel çözümleme ile ilgili bilgi, Gereç ve Yöntemler bölümü içinde ayrı bir alt başlık olarak yazılmalı ve kullanılan yazılım kesinlikle tanımlanmalıdır. Araştırma makalelerinde örneklem sayısına karar verilirken yapılan hesaplamanın belirtilmesi gerekir. Sürekli değişkenlerin karşılaştırılmasında parametrik testler kullanıldığı zaman, verilerin ortalama±standart sapmalarıyla bildirilmesi gerekir. Parametrik olmayan testler için de ortanca (en düşük-en yüksek) ya da ortanca (25 ve 75. persantil) değerleri olarak bildirilmesi gerekir. İleri ve karmaşık istatistiksel çözümlemelerde, göreceli risk (RR-Relative Risk), olasılık (OR-Odds Ratio) ve tehlike (HR-Hazard Ratio) oranları, güven aralıkları (Confidence Intervals) ve p değerleri ile desteklenmelidir.

Birimler, uluslararası birim sistemi olan 'International System of Units' (SI)'a uygun olarak hazırlanmadır.

Uzmanından Yorum: Dergide yayınlanan bir araştırmanın, o konunun uzmanı olan ya da üst düzeyde değerlendirme yapan bir hakemi tarafından kısaca yorumlanması amacını taşımaktadır. Yazarları, dergi tarafından seçilip davet edilir. Uzmanından Yorum yazıları ile ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Derleme: Konusunda birikimi olan ve bu birikimleri uluslararası dizine yayın ve atıf sayısı olarak yansımış yazarlar Editörler Kurulu tarafından derleme yazmak üzere davet edilir. Derlemeler, bir bilgi ya da konunun klinikte kullanılması için vardığı son düzeyi anlatan, tartışan, değerlendiren ve gelecekte yapılacak olan çalışmalara yön veren bir şekilde hazırlanmalıdır. Ana metin "Giriş", "Klinik ve Araştırma Etkileri" ve "Sonuç" bölümlerini içermelidir. Derleme türündeki yazılarla ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Olgu Sunumu: Olgu sunumları için sınırlı sayıda yer ayrılmakta ve sadece nadir görülen tanı ve tedavisi güç olan hastalıklarla ilgili yeni bir yöntem öneren, kitaplarda yer verilmeyen bilgileri yansıtan, ilgi çekici ve öğretici özelliği olan olgular yayına kabul edilmektedir. Özette genel bilgiler değil olgu anlatılmalıdır. Ana metin; "Giriş", "Olgu" ve "Tartışma" alt başlıklarını içermelidir. Olgu sunumu türündeki yazılar için hasta(lar)dan ya da hastanın yasal vasilerinden bilgilendirilmiş yazılı hasta onamı alınması ve yazının başvurusu sırasında dergimize gönderilmesi zorunludur. Olgu Sunumlarıyla ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Editöre Mektup: Dergide daha önce yayınlanan bir yazının önemi, gözden kaçan bir ayrıntısı ya da eksik kısımları tartışabilir. Ayrıca derginin kapsamına giren alanlarda okurların ilgisini çekebilecek konular ve özellikle eğitici olgular hakkında da editöre mektup türünde yazılar yayınlanabilir. Okuyucular da yayınlanan yazılar hakkında yorum içeren editöre mektup türünde yazılarını sunabilirler. Editöre mektup türündeki yazılarda özet, anahtar sözcük, tablo, şekil ve diğer görseller kullanılmaz. Ana metin alt başlıksız olmalıdır. Hakkında mektup yazılan yayına ait cilt, yıl, sayı, sayfa numaraları, yazı başlığı ve yazarların adları açık bir şekilde belirtilmeli, kaynak listesinde yazılmalı ve metin içinde kaynak gösterilmelidir.

Tablolar

Tablolar ana dosyaya eklenmeli, kaynak listesi sonrasında sunulmalı ve ana metin içerisindeki geçiş sıralarına uygun olarak numaralandırılmadır. Tabloların üzerinde tanımlayıcı bir başlık yer almalı ve tablo içerisinde geçen kısaltmaların açılımları tablo altında alfabetik sıraya göre tanımlanmalıdır. Tablo dipnotlarında üst simge olarak harfler kullanılmalıdır. Tablolar Microsoft Office Word dosyası içinde "Tablo Ekle" komutu kullanılarak hazırlanmalı ve kolay okunabilir şekilde düzenlenmelidir. Tablolarda sunulan veriler ana metinde sunulan verilerin tekrarı olmamalı, ana metindeki verileri destekleyici nitelikte olmalılardır. Tablolarda kullanılan kısaltmalar tablo altlarında alfabetik sıraya göre tanımlanmalıdır.

Resim ve Resim Altyazıları

Resimler, grafikler ve fotoğraflar (TIFF ya da JPEG formatında) ayrı dosyalar şeklinde sisteme yüklenmelidir. Görseller bir Word dosyası dokümanı ya da ana doküman içerisinde sunulmamalıdır. Alt birimlere ayrılan görseller olduğunda, alt birimler tek bir görsel içerisinde verilmemelidir. Her bir alt birim sisteme ayrı bir dosya olarak yüklenmelidir. Resimler alt birimleri belli etme amacıyla etiketlenmemelidir (a, b, c vb.). Resimlerde altyazıları desteklemek için kalın ve ince oklar, ok başları, yıldızlar, asteriksler ve benzer işaretler kullanılabilir. Yazıların geri kalanında olduğu gibi resimlerde de çift-kör değerlendirmeyi sağlamak için kişi ve kurum bilgileri gizlenmelidir. Görsellerin çözünürlüğü en az 300DPI olmalıdır. Değerlendirme sürecindeki aksaklıkları önlemek için gönderilen bütün görsellerin çözünürlüğü net ve boyutu büyük (En küçük boyutlar 100x100 mm) olmalıdır. Resim altyazıları ana metnin sonunda yer almalıdır.

Özel Kurallar

Çift-kör hakem değerlendirmesinin yapılabilmesi için dergiye gönderilen yazı dosyaları ve görseller çalışmanın yapıldığı kurum ve kişilere ait bilgiler içermemelidir.

Türkçe ve İngilizce başlık ve kısa başlıklarda cümlenin ilk harfi büyük, diğer tüm harfler küçük olmalıdır. Başlık ve metinde eğer ":" dan sonra cümle geliyorsa ilk harfi büyük, cümle gelmiyor ise küçük harfle yazılmalıdır. Çok kullanılar sözcükler kısaltılabilir. Ancak özette kısaltma kullanılmamalıdır. Yazı içerisinde geçen tüm kısaltmalar ana metinde ilk kez kullanıldıkları yerde tanımlanarak kısaltma tanımın ardından parantez içerisinde verilmeli, yazı içinde cümle başlarında kısaltma kullanılmamalı, cümle içinde kısaltma kullanılmalıdır.

Ana metin içerisinde cihaz, yazılım, ilaç vb. ürünlerden bahsedildiğinde ürünün ismi, üreticisi, üretildiği şehir ve ülke bilgisini içeren ürün bilgisi parantez içinde verilmelidir; "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)". İlaç isimleri etken madde adı ile yazılmalıdır.

Tüm kaynak, tablo ve şekillere ana metin içinde uygun olan yerlerde sırayla numara verilerek kaynak gösterilmelidir. Tablo ve şekil başlıklarında ve bunların yazı içinde anılmasında Roma rakamları kullanılmamalıdır.

Dört ve üzeri haneli sayılarda binlik basamaklar arasında boşluk bırakılmalıdır [Örn: 1 000 000]. Çift haneli sayılar, yazı içinde rakamla, tek haneli sayılar ise yazıyla verilmelidir. Ancak değerleri belirten ifadelerde tek haneler rakamla verilmelidir (Örn: 1 cm). Yazı içinde ve tablolarda yüzdelik değerler virgülden sonra iki basamak, p değerleri virgülden sonra üç basamak olarak verilmelidir. Yazı, tablo ve şekillerde yer alan ondalık sayılar Türkçe yazılarda virgül ile İngilizce yazılarda nokta ile ayrılmalıdır.

Özgün araştırmaların kısıtlamaları, engelleri ve yetersizliklerinden Sonuç paragrafı öncesi "Tartışma" bölümünde bahsedilmelidir.

Kaynaklar

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İndeksler

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REVIEW
Pediatrics

Artificial intelligence for the busy paediatrician

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ABSTRACT

Artificial intelligence (AI) is rapidly entering paediatric practice, yet clinicians often lack a concise, practical orientation. We summarise what paediatricians should know about contemporary AI in a compact and clinically useful context. We performed a narrative state-of-the-art review of peer-reviewed literature published between January 2017 and April 2026 (last search date: 30.04.2026) using PubMed, Scopus, and special issues on AI in paediatrics. Search terms combined "artificial intelligence," "machine learning," "deep learning," "large language models," and "natural language processing" with "paediatric/pediatric," "child," "neonatal," and paediatric subspecialty keywords. Priority was given to peer-reviewed studies, regulatory and ethics guidance, and recent reviews addressing clinical implementation, validation, bias, explainability, and governance. Because the review was narrative rather than systematic, no PRISMA flow diagram was prepared. Findings were organised around five clinical domains, with cross-cutting pitfalls synthesised. Mature applications include image-based diagnostics (radiology, ophthalmology, and dysmorphology), deterioration and sepsis prediction in the paediatric intensive care unit, asthma exacerbation forecasting, autism screening, accelerated rare-disease diagnosis from whole-genome data, precision dosing, and LLM-based clinical documentation and parental education tools. In selected narrow tasks under controlled test conditions, reported performance may approach, and in some studies overlap with, expert-level performance; however, generalisability is highly dependent on dataset quality, population similarity, and external validation. Conversely, paediatric AI faces unique threats: small and developmentally heterogeneous datasets, label scarcity, racial and gender bias, dataset shift, opaque "black box" reasoning, and complex consent for minors. Robust external validation in diverse paediatric populations remains the exception rather than the rule. AI is best understood as augmented intelligence that supports, rather than replaces, the paediatrician. Practical adoption requires AI literacy, structured evaluation of tools against age-stratified evidence, vigilance for bias, and explicit local governance. Paediatricians who engage early will help shape safe, equitable, child-specific AI.

Keywords: Artificial intelligence; clinical decision support systems; deep learning; diagnostic imaging; machine learning; natural language processing; paediatrics.

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Yoğun pediatristler için yapay zekâ

ÖZET

Yapay zekâ (YZ), günlük pediatri pratiğine hızla girmektedir; ancak yoğun rutinde klinisyenler kısa ve uygulanabilir bir kaynak bulmakta güçlük çekebilmektedir. Bu derleme, her pediatristin güncel YZ uygulamaları hakkında bilmek isteyebileceği kısa, klinik açıdan kullanışlı ve pratik bilgileri sunmayı amaçlamaktadır. Ocak 2017-Nisan 2026 (son tarama tarihi: 30 Nisan 2026) arasında yayımlanan hakemli literatürün anlatısal nitelikte güncel bir derlemesi yapıldı. PubMed, Scopus ve pediatrik YZ'ye ayrılmış güncel özel sayılar tarandı. Arama terimleri (İngilizce) "yapay zekâ", "makine öğrenmesi", "derin öğrenme", "büyük dil modelleri" ve "doğal dil işleme" kavramları ile "pediatri", "çocuk", "neonatal" ve pediatrik yan dal anahtar sözcükleri birleştirilerek oluşturuldu. Klinik uygulama, doğrulama, yanlılık, açıklanabilirlik ve yönetişimi ele alan hakemli çalışmalara, düzenleyici ve etik kılavuzlara ve güncel derlemelere öncelik verildi. Sistematik olmaktan çok anlatısal bir derleme amaçlandığından PRISMA akış diyagramı hazırlanmadı. Bulgular beş klinik alanda toplandı ve sentezlendi. Olgunluğa ulaşmış uygulamalar arasında görüntü temelli tanı (radyoloji, oftalmoloji, dismorfoloji), pediatrik yoğun bakımda kötüleşme ve sepsis öngörüsü, astım atağı tahmini, otizm taraması, tüm genom verisinden hızlandırılmış nadir hastalık tanısı, hassas dozlama ve büyük dil modeli tabanlı klinik dokümantasyon ile ebeveyn eğitimi araçları yer almaktadır. Dar tanımlı seçili görevlerde bildirilen performans, uzman düzeyine yaklaşabilmekte ve bazı çalışmalarda bu düzeyle örtüşebilmektedir; ancak genellenebilirlik veri kalitesine, popülasyon benzerliğine ve doğrulama (validasyon) süreçlerine büyük ölçüde bağlıdır. Buna karşın pediatrik YZ; küçük ve gelişimsel açıdan heterojen veri kümeleri, ırk ve cinsiyet yanlılıkları, veri kayması, şeffaflıktan yoksun "kara kutu" modeller ve reşit olmayanlarda karmaşık onam süreçleri gibi kendine özgü tehditlerle karşı karşıyadır. Farklılık ve çeşitlilik gösteren pediatrik popülasyonlarda dış doğrulama hâlâ kuraldan çok istisnadır. YZ, pediatristin yerine geçen değil, onu destekleyen artırılmış zekâ olarak anlaşılmalıdır. Pratik benimseme; YZ okuryazarlığı, araçların yaşa göre tabakalandırılmış kanıtlarla yapılandırılmış değerlendirilmesi, yanlılığa karşı dikkat ve duruma özgü yönetişim gerektirmektedir. YZ süreçlerine katılmak için gecikmeksizin çaba gösteren pediatristler, çocuklara özgü güvenli ve adil bir YZ'nin biçimlenmesine katkı sağlayacaktır.

Anahtar Kelimeler: Derin öğrenme; doğal dil işleme; klinik karar destek sistemleri; makine öğrenmesi; pediatri; tanısal görüntüleme; yapay zekâ.

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INTRODUCTION

Few topics have generated as much excitement, anxiety, and clinical inertia within paediatrics as artificial intelligence (AI). The general paediatrician is increasingly expected not only to interpret clinical data but also to understand rapidly evolving AI-related claims, tools, and risks: a regulator clears another algorithm; a national academy issues guidance on chatbots in clinic; a hospital pilots a sepsis predictor on the wards; a parent arrives with a printed exchange from a large language model (LLM) and a list of pointed questions about a rash. Within roughly a decade, AI has moved from the periphery of medicine to a position where it touches triage, imaging interpretation, electronic health record (EHR) documentation, dosing, and even how parents prepare for the visit (1–3).

Paediatrics carries unique features that intensify both the promise and the risk of AI. Children are not small adults: physiology, dosing, image appearance, disease epidemiology, and reference ranges all change with age and developmental stage. Paediatric datasets are smaller, rare outcomes are common, and the data labels available to train models often reflect the clinical world of adults rather than that of children (4, 5). Add to this the special obligations of paediatric care: guardianship, assent, lifelong consequences of misclassification, and the digital literacy of the family. It becomes clear that paediatricians cannot delegate the AI strategy.

This narrative state-of-the-art review is organised as a series of compact "AI bits": short, practical takeaways for the busy clinician. We first summarise the core terminology so that the rest of the article can be read fluently (Table 1 and Fig. 1). We then survey contemporary applications across five clinical domains, with selected high-quality examples. We close with the cross-cutting pitfalls of paediatric AI, an evaluation framework that fits into a clinic day (Fig. 2), and the educational and governance implications for the next five years. The aim of this work is orientation rather than exhaustive coverage. Once these pages have been read, the paediatrician should be in a position to scrutinise an AI claim, to put sharper questions to vendors and editors, and to judge whether a given tool earns its place in the daily workflow.

SEARCH STRATEGY AND SCOPE

Consistent with a narrative-review design, sources were identified through PubMed, Scopus, and recent special issues dedicated to AI in paediatrics, with hand-searching of the reference lists of pivotal reviews. The search window ran from January 2017 to April 2026, with the final pass completed on April 30, 2026. Within this window, the terms "artificial intelligence," "machine learning," "deep learning," "large language models," and "natural language processing" were paired with "paediatric/pediatric," "child," "children," "neonatal," and selected paediatric subspecialty keywords. Peer-reviewed paediatric studies, regulatory and

Table 1. Glossary of essential AI terminology for the practising paediatrician

Term	Plain-language definition	Paediatric example
Artificial intelligence (AI)	Umbrella term for computer systems that perform tasks usually requiring human cognition.	AI-enabled symptom checkers in primary care.
Machine learning (ML)	A subset of AI in which algorithms improve at a task through exposure to data.	Predicting hospitalisation risk in paediatric asthma.
Deep learning (DL)	ML using multilayer neural networks, especially powerful with images, signals and text.	Detecting fractures and pneumonia on chest radiographs.
Convolutional neural network (CNN)	DL architecture optimised for spatial pattern recognition in images.	Scoliosis quantification; retinopathy of prematurity grading.
Recurrent / transformer network	DL architectures for sequences and language; transformers underlie modern LLMs.	PICU vital-sign streams; ambient clinical scribes.
Natural language processing (NLP)	Techniques for understanding and generating human language.	Extracting child-abuse cues from unstructured paediatric notes.
Large language model (LLM)	Generative model trained on massive text; produces fluent answers and summaries.	Parental education on developmental dysplasia of the hip.
Generative AI	AI that creates new content (text, images, audio).	Drafting discharge summaries; synthetic paediatric data for teaching.
Reinforcement learning	Learning by trial-and-error rewarded for desired outcomes.	Closed-loop ventilator weaning in neonatal care.
Federated learning	Multi-site training where data stay local and only model updates are shared.	Pooling rare-disease cohorts across paediatric centres.
Explainable AI (XAI)	Methods that make model reasoning interpretable to humans.	Saliency maps highlighting suspicious regions on a chest film.
Augmented intelligence	Framing AI as a clinician's assistant rather than a replacement.	Decision support that flags abnormal newborn screen patterns.

ethics guidance, and recent reviews addressing clinical implementation, validation, bias, explainability, and governance were given priority. We used non-paediatric or non-peer-reviewed sources for definitional or contextual purposes.

The review is narrative rather than systematic; therefore, no formal PRISMA flow diagram was prepared, and we did not attempt a meta-analytic synthesis. Limitations of this approach are acknowledged: narrative reviews are subject to selection bias by design. The rapidly moving field implies that some emerging tools may not yet be reflected in the indexed literature at the time of writing.

CLINICAL AND RESEARCH IMPLICATIONS

AI Bits, Defined: A 60-Second Taxonomy

Artificial intelligence is a broad term for computer systems that perform tasks usually tied to human cognition, including pattern recognition, language understanding, and decision support (1, 6). Within AI, machine learning (ML) denotes algorithms that improve at a task by learning from data rather than explicit rules. Deep learning (DL) is a subset of ML that uses multilayer artificial neural networks; convolutional neural networks (CNNs) handle images well, while transformer-based networks underpin modern LLMs and increasingly handle a growing share of EHR time series (1, 5, 7). Natural language processing (NLP) is the family of techniques that enables computers to understand and generate human language, and it is the motor of clinical scribes, document summarisation, and chatbots (1, 8).

Two more terms now circulate in everyday clinical talk among researchers. Generative AI describes systems that produce new content (text, images, and code) and includes ChatGPT-class LLMs. Federated learning describes training methods in which models are updated across several hospitals without raw patient data leaving each site, a particularly attractive approach for rare paediatric diseases (4, 9, 10). Figure 1 places these terms in their nested relationship; Table 1 provides a glossary intended for daily use, and Figure 2 maps how each of these technologies enters and exits a paediatric clinical workflow.

Two practical clarifications matter for clinicians. First, what is often called "AI in medicine" today is, more precisely, augmented intelligence. As Bhargava and Knake have argued, this software serves as an assistant to the physician and not as a replacement for the physician (1, 2). Second, AI tools are narrow in scope. A model that detects retinopathy of prematurity is not the same as a model that predicts sepsis, and validation in one task or population does not carry over by default to another. This tight scope is a strength when kept in mind and a danger when forgotten.

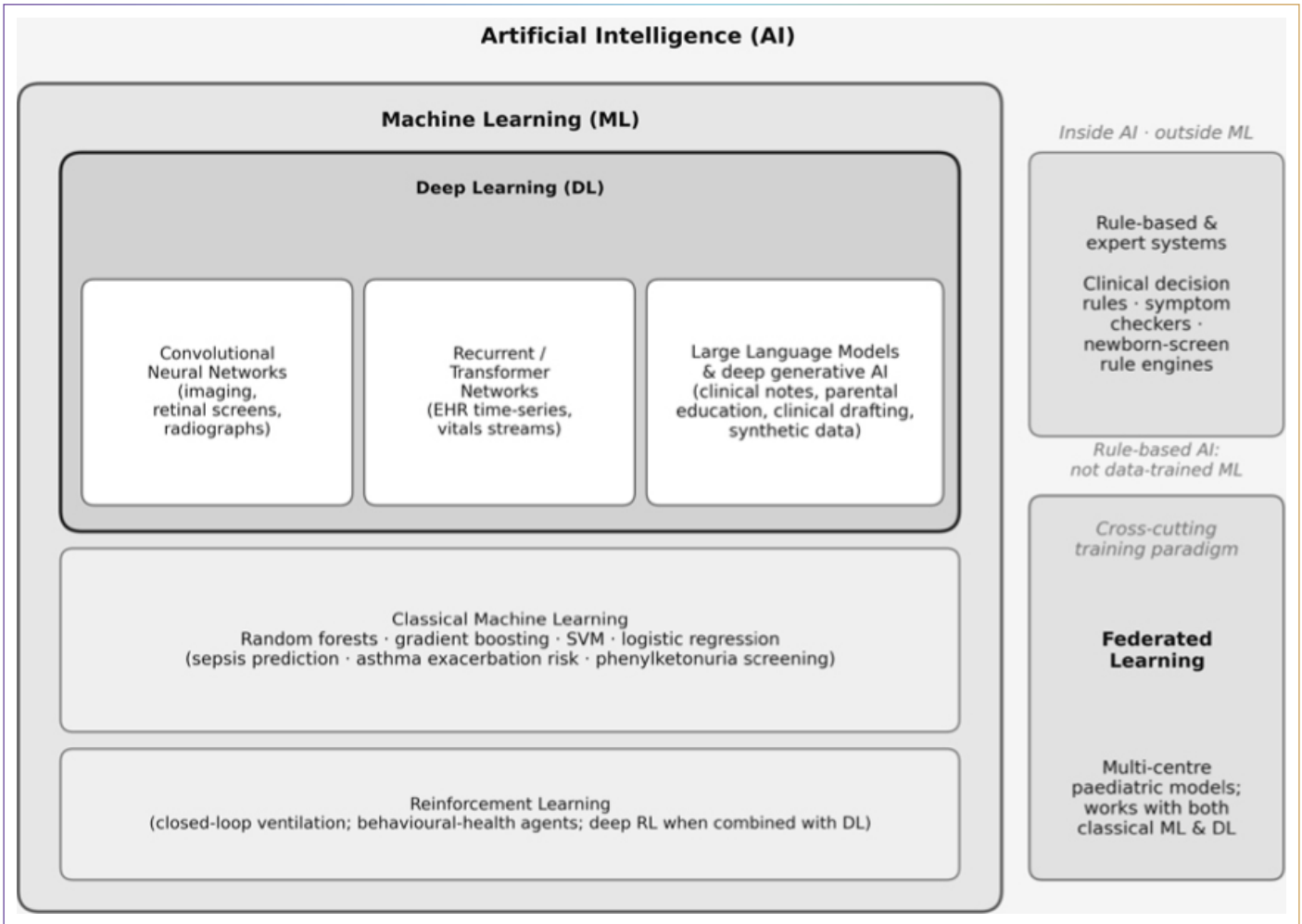

Figure 1. Conceptual taxonomy of artificial intelligence with paediatric examples.

Nested rectangles show that machine learning is a subset of artificial intelligence and deep learning is a subset of machine learning. Selected paediatric exemplars are listed for each level, including convolutional neural networks for imaging, transformer networks for electronic health record time series and large language models for parental education and clinical documentation.

Where AI Is Already Useful in Paediatric Practice

Imaging and Dysmorphology

Image interpretation is reported to be the most mature application of AI in paediatric medicine (Table 2). In selected narrow tasks, such as scoliosis quantification, fracture and physical injury detection, cystic fibrosis scoring on chest radiographs, identification of tuberculosis and bacterial pneumonia patterns, and automated grading in retinopathy of prematurity and paediatric cataract, deep CNNs have reported performance approaching that of paediatric subspecialists, with occasional reports of overlap under controlled test conditions; such comparisons depend strongly on the test set, scanner, and population used (3, 7, 11, 12). In dysmorphology, facial-image classifiers can suggest candidate genetic syndromes, such as trisomy 21, DiGeorge, and Goldenhar syndromes, from a single photograph, supporting earlier referral in regions with limited access to medical genetics (4, 7). The major caveats are that paediatric-specific training data remain scarce relative to adult datasets and that performance characteristics often degrade when the AI is exposed to portable radiographs, different scanners, or a different ethnic distribution than that on which it was trained (3, 4, 13).

Risk Prediction and the Paediatric Intensive Care Unit

AI-based early warning systems are advancing rapidly in critical care. Kamaleswaran and colleagues, working with nearly 500 children admitted to a paediatric intensive care unit (PICU), trained an ML algorithm that flagged severe sepsis up to eight hours earlier than the conventional electronic health record screen (3, 14). Even a modest lead time of this size may translate into earlier antibiotic administration and a measurable reduction in organ failure. Models for clinical deterioration, bronchopulmonary dysplasia (BPD) in preterm infants, and paediatric urinary tract infection (UTI) in febrile children are emerging from international consortia (5, 15). Closed-loop technology has also reached the bedside: technology-driven automated weaning of mechanical ventilation continuously titrates pressure to a clinician-chosen tidal volume target, illustrating how

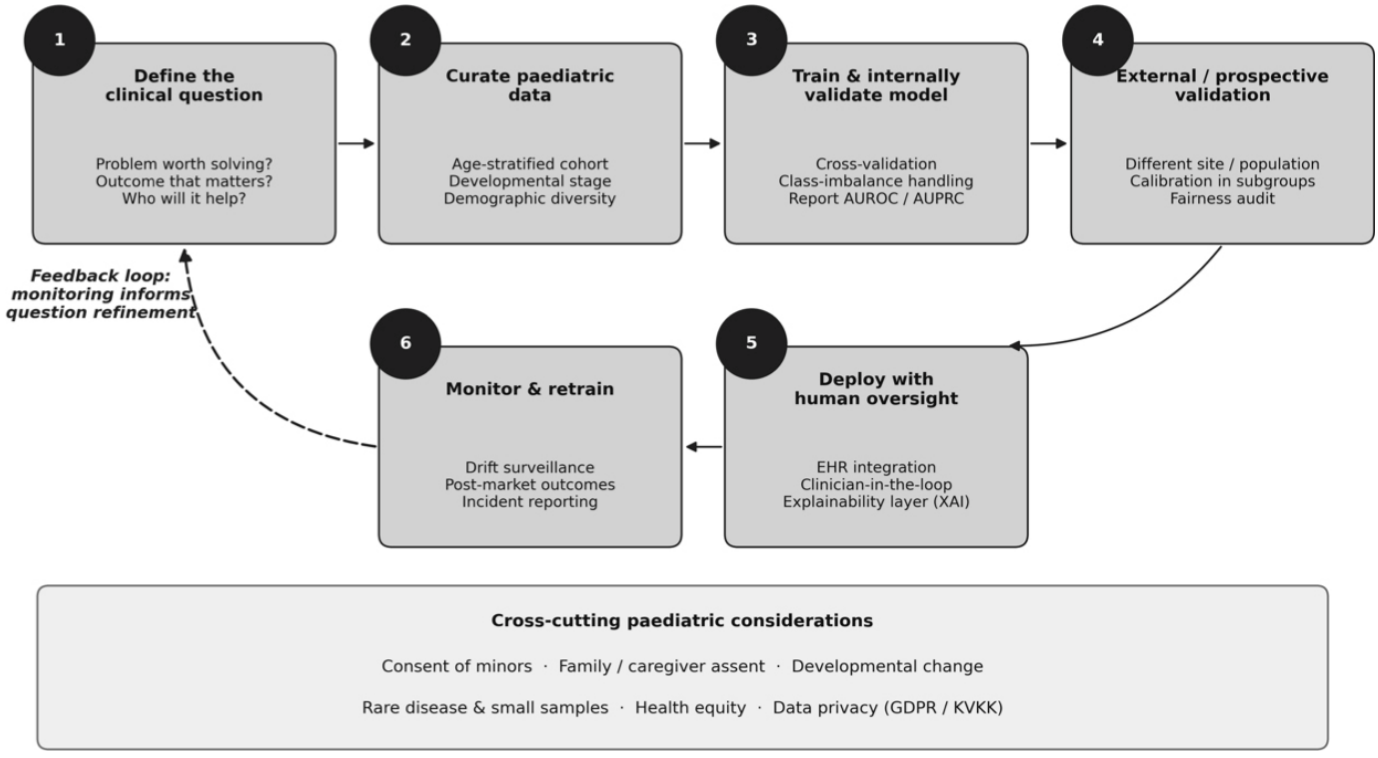

Figure 2. The paediatric AI lifecycle: a practical six-step framework for the paediatrician.

The cycle moves from defining the clinical question, through data curation, training and internal validation, external or prospective validation, deployment with human oversight and continuous post-market monitoring. A feedback loop returns lessons to the question-formulation step. Cross-cutting paediatric considerations should apply at every stage: consent of minors, family or caregiver assent, developmental change, rare diseases and small samples, equity and data privacy under GDPR and the Turkish Personal Data Protection Law (KVKK).

an algorithm can perform a structured task tirelessly when supervised (2). Paediatricians should ask whether such tools have been prospectively validated in a population resembling their own and how alerts are routed, displayed, and acted upon.

Chronic Disease and Behavioural Health

In asthma, ML has been used to predict hospitalisation risk from EHRs combined with weather, neighbourhood characteristics, and community viral load and to forecast the persistence of childhood asthma into later years (3). Smartphone microphones can substitute for office spirometry, and inhaler-mounted sensors fed into algorithms can identify environmental triggers and adherence gaps (3, 16). For autism spectrum disorder, the device evaluated by Megerian and colleagues, authorised by the United States Food and Drug Administration, combines caregiver questionnaires, short home videos, and primary-care input to assist diagnosis in children aged 18-72 months (3, 17). Such a tool may shorten a wait that, in many regions, still exceeds four years from the first parental concern and that falls hardest on girls and on Black, Latino, or rural children. For attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and post-traumatic stress disorder, ML models have shown promise for early screening, severity quantification, and identification of clinically meaningful subtypes (5, 18, 19). Finally, AI-driven cognitive behavioural therapy chatbots reduced depressive symptoms in a randomised trial in young adults, and their paediatric counterparts are being studied as bridges across mental health waitlists (3, 20).

Genetics, Rare Disease, and Metabolic Screening

Paediatric AI shines where the data are at their most challenging: in rare diseases. AI-augmented rapid whole-genome sequencing has been used to deliver provisional molecular diagnoses to critically ill neonates within hours rather than weeks, with measurable changes in management (3, 21). Pattern-recognition systems now help screen for phenylketonuria, mitochondrial disorders, and other inborn errors of metabolism without a false-positive penalty, and rare-disease auxiliary diagnosis platforms can shortlist candidate disorders from clinical phenotype data alone (5, 22). A large subset of rare diseases is hereditary and affects children; for these families, even a modest reduction in the diagnostic odyssey is meaningful.

Therapeutics, Dosing, and the Operating Room

Paediatric pharmacokinetics are a paradigm case for personalisation, since size and maturity drive dose far more than they do in adults. ML-based dosing models have been shown to outperform conventional approaches for selected antibiotics in children, including ceftaroline, by integrating weight, renal function, and organism susceptibility (5). In peri-operative care, an AI workflow tool was associated with a reduction in

Table 2. Selected paediatric AI applications by clinical domain

Domain	Representative tasks	Illustrative tools/studies	Maturity*
Imaging & dysmorphology	Fracture and physical injury detection; pneumonia and tuberculosis triage; scoliosis grading; retinopathy of prematurity; congenital cataract; syndrome facial recognition.	Paediatric chest-radiograph CNNs; retinal screening systems; FDNA Face2Gene-type platforms (3, 7, 11, 12).	Mature in narrow tasks; limited paediatric external validation.
Critical care & deterioration	Sepsis, septic shock, BPD, UTI, deterioration and mortality prediction; closed-loop ventilation.	PICU sepsis ML models with 8-h lead time; automated ventilator weaning algorithms (2, 3, 14, 15).	Several FDA-cleared adult tools; paediatric-specific evidence emerging.
Chronic disease & behavioural health	Asthma exacerbation and persistence prediction; smartphone spirometry; autism, ADHD, depression and PTSD support.	Smartphone-based spirometry; FDA-authorised AI device for autism (Canvas Dx); cognitive behavioural therapy chatbots (3, 17, 18, 20).	Selected products marketed; broader evidence still maturing.
Rare disease & genetics	Rapid whole-genome diagnosis in NICU/PICU; phenylketonuria and metabolic screening; phenotype-based rare-disease shortlisting.	Rapid whole-genome sequencing pipelines; RDAD systems; ML-based metabolic newborn-screening models (3, 21, 22).	Rapid clinical translation in tertiary centres.
Therapeutics & workflow	Precision dosing; perioperative opioid stewardship; ambient documentation; LLM-based parental education.	ML-based ceftaroline dosing; OR Advisor for opioid reduction; ChatGPT-class LLMs for parental information (3, 5, 23, 24).	Rapidly evolving; close human supervision required.

*: Maturity descriptions are qualitative; AUROC: Area under the receiver operating characteristic curve; BPD: Bronchopulmonary dysplasia; CNN: Convolutional neural network; FDA: Food and Drug Administration; LLM: Large language model; ML: Machine learning; NICU: Neonatal intensive care unit; PICU: Paediatric intensive care unit; RDAD: Rare Disease Auxiliary Diagnosis system; UTI: Urinary tract infection.

opioid administration from 85% of surgeries to <1% in a paediatric surgery centre, with implications for short-term recovery and long-term opioid exposure (3, 23). Across these examples, the algorithm augments the prescriber rather than replacing pharmacological judgment.

Documentation, Communication, and Parental Education

Generative AI—specifically LLMs such as ChatGPT and clinical equivalents—has shifted from novelty to daily use in only two years (24, 25). For paediatricians, three categories deserve attention. Ambient clinical documentation tools transcribe and summarise encounters, returning structured notes for human review and reducing keyboard time. Patient-facing chatbots can deliver explanations of paediatric conditions at an acceptable level of quality. In the comparative study by Li and colleagues, three contemporary LLMs answered standardised questions on developmental dysplasia of the hip with accuracy rates of 78-83% on independent specialist scoring, a result that places these tools as a supplement to, and never a substitute for, professional counselling (5, 24). Parents themselves now enter the consultation having already "consulted" a chatbot; mixed-methods studies of paediatric chronic-disease cohorts show that families show greater intention to use clinically curated chatbots than to use general-purpose LLMs, citing trust, credibility, and clinician involvement as decisive factors (5, 26). The principal risks are confident hallucinations, embedded bias, lack of paediatric calibration, and misinformation about vaccines and other public-health-sensitive topics (8, 25).

AI Bits for Paediatricians

Small Samples, Rare Outcomes, and Developmental Change

The defining mathematical fact about paediatric AI is data scarcity. Rare diseases, rare emergencies, and even common diseases, when stratified by narrow age bands, quickly produce datasets too small for confident generalisation (4, 5, 9, 11). Models trained on adolescents may underperform in toddlers, and a model trained on toddlers in 2018 may underperform in toddlers in 2026 because of changes in clinical practice, vaccination patterns, or coding habits, a phenomenon known as dataset shift (5, 9). Multicentre and federated learning approaches help, but no algorithm escapes the requirement for ongoing surveillance after deployment.

Bias, Equity, and "Algorithmic Ageism"

AI faithfully reproduces the patterns on which it is trained, including inequities (3, 9, 27). Demonstrated examples in paediatrics include diagnostic delays in autism for Black, Latino, female, and rural children embedded in screening tools and pulse oximetry algorithms that perform less accurately in children with darker skin (3). The remedy is not to refuse AI but to demand that vendors document the demographic composition of training and validation cohorts, that developers explicitly test for equity gaps, and that local users monitor performance by subgroup. Children additionally need protection from "algorithmic ageism": tools developed primarily for adults and silently extrapolated downward without revalidation.

Table 3. A five-minute appraisal checklist for an AI tool offered to a paediatric practice

Domain	Question to ask	Red flag if...
Clinical question	What exact decision will this AI improve, in which age group and at what stage of care?	Vendor describes a generic "platform" with no specific decision target.
Training data	How many paediatric cases were used? What is the age, sex, ethnicity, comorbidity and site distribution?	Training was adult-only or single-centre; no demographic breakdown is provided.
Validation	Was external or prospective paediatric validation performed? What are AUROC, calibration and subgroup performance?	Performance reported only on the training/test split from one institution.
Bias and equity	Has fairness been audited across race, sex, language, disability and socioeconomic strata?	No equity analysis; minority subgroups under-represented or unreported.
Workflow integration	How is the output displayed, who can override it and what is the expected alert burden?	"Always-on" alerts with no override pathway and unclear ownership.
Explainability	Can you understand, at the case level, why the model produced a given output?	Pure black box with no XAI layer or rationale.
Privacy and consent	Where do paediatric data flow? How is consent of the minor and family handled?	Data leave the institution to a vendor cloud without clear safeguards.
Post-deployment governance	Who monitors performance drift, equity and adverse events after go-live?	No defined owner, dashboard, or audit cadence.
Evidence base	Are peer-reviewed trials available with patient-oriented outcomes, ideally aligned with CONSORT-AI / TRIPOD-AI?	Only conference abstracts, vendor white papers, or in-silico claims.
Regulatory status	Is the tool authorised for the intended paediatric use by FDA, MHRA, EMA, or the Turkish Medicines and Medical Devices Agency?	Marketed as "CE-marked" only for adults but offered for paediatric care.

AI: Artificial intelligence; AUROC: Area under the receiver operating characteristic curve; CE: Conformité Européenne; CONSORT-AI: Consolidated Standards of Reporting Trials extension for AI; EMA: European Medicines Agency; FDA: Food and Drug Administration; MHRA: Medicines and Healthcare products Regulatory Agency; TRIPOD-AI: Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis extension for AI; XAI: Explainable AI.

The Black Box, Hallucinations, and Explainability

Many high-performing models, especially deep neural networks and LLMs, do not transparently disclose how they reach a conclusion. Saliency maps, counterfactual explanations, and rule extraction, collectively known as explainable AI (XAI), partially address this, but a clinician should never feel compelled to act on an output whose logic is opaque and that contradicts their clinical reasoning (5, 9). LLMs additionally produce hallucinations: smooth-sounding statements that are factually wrong, at times including fabricated references. Therefore, the clinical use of LLMs requires both human verification of factual claims and institutional policies that limit their unsupervised role in patient care (8, 25).

Privacy, Consent, and the Special Status of the Child

Children cannot meaningfully consent to the long-term reuse of their data, but the consequences of such reuse may follow them into adulthood. Several frameworks set out the basic rights that apply here: the European Union General Data Protection Regulation (GDPR), the EU AI Act, and Türkiye's Personal Data Protection Law (KVKK) (4, 28, 29). Among these rights, the right to erasure of personal data carries even greater weight when the data belong to a child. In Türkiye, the secondary regulation on the deletion, destruction, and anonymisation of personal data operationalises these rights and is directly relevant to paediatric data stewardship (29). Genetic, behavioural, and image data deserve heightened protection. Paediatricians act as custodians of paediatric data until the child grows into adult autonomy; this responsibility must be reflected in informed consent processes for any AI-related research or clinical use.

Regulatory and Clinical Maturity

More than 1000 AI-enabled medical devices have been authorised by the FDA according to the agency's public list, but the great majority were cleared for adult use, and few have undergone prospective paediatric trials with patient-oriented outcomes (3, 4, 30). Existing regulatory pathways were not built for self-updating algorithms; the FDA's proposed predetermined change control plans illustrate one direction, but local hospitals will still need clear governance structures, including model registries, performance dashboards, and incident reporting. The cautionary tale of an early symptom-checker chatbot that overstated its diagnostic accuracy in paediatric scenarios underlines the cost of premature commercialisation (5, 31).

HOW TO READ AN AI CLAIM IN FIVE STEPS

When confronted with a new AI tool, the paediatrician can run a five-step check that follows the same line of thinking used for any new test. To begin with, what is the exact clinical ques-

tion and target population, including age stratum? Second, on what data was the model trained, and is the demographic and developmental composition close to that of the local population? Third, has external or prospective validation been carried out in a paediatric cohort? If yes, how is performance reported: sensitivity, specificity, area under the receiver operating characteristic curve, calibration, and, where relevant, the results of fairness audits? Fourth, how does the tool integrate into the EHR and workflow, who acts on its outputs, and what is the alert burden? Fifth, what is the post-deployment monitoring plan for drift and harm? These five questions, summarised in Table 3, are deliberately compatible with a busy clinic schedule and align with the paediatric AI lifecycle shown in Figure 2.

In clinical research, the same logic applies during peer review and editorial work. Reporting standards such as STARD-AI, CONSORT-AI, SPIRIT-AI, TRIPOD-AI, and DECIDE-AI offer structured checklists; familiarity with these instruments allows paediatricians to comment on AI manuscripts even without a computer science background (4, 9, 31).

EDUCATION, GOVERNANCE, AND THE NEXT FIVE YEARS

Surveys consistently find that paediatric trainees and faculty report low confidence in AI literacy, despite high enthusiasm for its potential (3, 4, 32). Curriculum proposals such as MEd2030 explicitly add modules on biomedical informatics and AI, transdisciplinary collaboration, and the ethics of digital therapeutics; incremental local steps include adding AI critical appraisal sessions to journal clubs, requiring AI tool review as part of new-technology committees, and pairing each AI deployment with an outcome audit at six and twelve months (3, 32). At the institutional level, governance committees should include not only clinicians and informaticians but also patient and family representatives, ethicists, and equity champions (4, 5).

In Türkiye and the broader region, several near-term priorities are visible. Paediatric-specific reference datasets are scarce in Turkish-speaking populations and ought to be developed through multicentre collaboration. Local validation of imported algorithms should become the rule rather than the exception. The case is sharpest for radiology, ophthalmology, and growth-assessment tools, whose performance shifts with the acquisition hardware and the reference norms in use. Family-facing LLM use in vaccine counselling, infant nutrition, and adolescent mental health needs Turkish-language quality benchmarks. Finally, residency training programmes would benefit from a defined AI core competency, articulated within existing paediatrics curricula and assessed through structured cases.

CONCLUSIONS

AI is no longer a future technology in paediatrics; it is a present, uneven, and consequential reality. The most important shift required of the paediatrician is conceptual rather than technical: to read AI as augmented intelligence, narrow in scope and dependent on the quality of the data and labels behind it. The next shift is practical. We must apply the same disciplined questions to an algorithm that we already apply to a new diagnostic test or a new therapeutic approach: paediatric validation, equity audits, transparent reasoning, and clear post-deployment governance. The final shift is collective: to engage early with the design, evaluation, and regulation of paediatric AI so that algorithms come to reflect the realities of children's development, family context, and lifelong stakes. Paediatricians who do this will not merely use AI; they will shape it.

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ORIGINAL RESEARCH
Pediatric Endocrinology

Etiological distribution of cases of delayed puberty in a pediatric endocrinology outpatient clinic at a tertiary-care children's hospital

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ABSTRACT

Objective: Delayed puberty is a common condition with diverse causes, ranging from benign developmental delays to permanent hypogonadism. Accurate and timely diagnosis is essential to safeguard growth, psychosocial well-being, and fertility. This study aimed to identify the etiological distribution and diagnostic characteristics of patients diagnosed with delayed puberty at a pediatric endocrinology clinic.

Material and Methods: We retrospectively analyzed data from 180 patients diagnosed with delayed puberty at the Pediatric Endocrinology Clinic of Ankara Child Health and Diseases Hematology-Oncology Training and Research Hospital between 2005 and 2012. The parameters reviewed included chronological age, bone age, growth metrics, clinical findings, family history, and basal/stimulated gonadotropin levels. Patients were categorized into four main diagnostic groups: hypogonadotropic hypogonadism (HypoH), hypergonadotropic hypogonadism (HyperH), functional hypogonadotropic hypogonadism (FHH), and constitutional delay of puberty (CDP).

Results: Participants were aged 13–18 years. All diagnostic groups showed delayed bone age compared with chronological age, especially in the hypogonadotropic hypogonadism group. Height and BMI were reduced across groups, indicating impaired growth due to pubertal delay. Cases of constitutional delay of puberty often had a positive family history. Hypogonadotropic hypogonadism was the most common etiology in both sexes. Gonadotropin levels played a key role in the differential diagnosis. Benign causes were more prevalent in boys, whereas serious or permanent etiologies were more frequent in girls. Chromosomal analysis was necessary in selected cases.

Conclusion: This study highlights the clinical and etiological diversity among 180 cases of delayed puberty caused by 46 distinct conditions. Thorough history-taking, physical examination, bone age assessment, and hormonal evaluation are vital for accurate diagnosis. Prompt referral to pediatric endocrinology is crucial to prevent diagnostic and therapeutic delays.

Keywords: Delayed puberty; etiology; hypogonadism.

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Üçüncü basamak bir çocuk hastanesinin pediatrik endokrinoloji polikliniğinde gecikmiş ergenlik vakalarının etiyolojik dağılımı

ÖZET

Amaç: Ergenlik gecikmesi, iyi huylu gelişimsel gecikmelerden kalıcı hipogonadizme kadar çeşitli nedenlerle ortaya çıkabilen yaygın bir durumdur. Büyüme, psikososyal iyilik hali ve doğurganlığın korunması için doğru ve zamanında tanı şarttır. Bu çalışma, bir çocuk endokrinoloji kliniğinde ergenlik gecikmesi tanısı konulan hastaların etiyolojik dağılımını ve tanısal özelliklerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji-Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Endokrinoloji Kliniği'nde 2005–2012 yılları arasında ergenlik gecikmesi tanısı konulan 180 hastanın verileri retrospektif olarak analiz edildi. İncelenen parametreler arasında kronolojik yaş, kemik yaşı, büyüme ölçümleri, klinik bulgular, aile öyküsü ve bazal/uyarılmış gonadotropin düzeyleri yer aldı. Hastalar dört ana tanı grubuna ayrıldı: hipogonadotropik hipogonadizm (HypoH), hipergonadotropik hipogonadizm (HyperH), fonksiyonel hipogonadotropik hipogonadizm (FHH) ve konstitüsyonel ergenlik gecikmesi (CDP).

Bulgular: Katılımcılar 13–18 yaş aralığındaydı. Tüm tanı gruplarında, özellikle hipogonadotropik hipogonadizm grubunda, takvim yaşına kıyasla kemik yaşında gecikme görüldü. Boy ve BKİ tüm gruplarda azalmıştı ve bu durum pubertal gecikmeye bağlı büyüme bozukluğunu gösteriyordu. Konstitüsyonel ergenlik gecikmesi vakalarında genellikle pozitif aile öyküsü vardı. Her iki cinsiyette de en sık görülen etiyoloji hipogonadotropik hipogonadizmdi. Gonadotropin düzeyleri ayırıcı tanıda önemli bir rol oynadı. İyi huylu nedenler erkeklerde daha yaygınken, kızlarda ciddi veya kalıcı etiyolojiler daha sık görüldü. Seçilmiş vakalarda kromozom analizi gerekliydi.

Tartışma: Bu çalışma, 46 farklı duruma bağlı 180 ergenlik gecikmesi vakasındaki klinik ve etiyolojik çeşitliliği ortaya koymaktadır. Doğru tanı için kapsamlı öykü, fizik muayene, kemik yaşı değerlendirmesi ve hormonal değerlendirme hayati önem taşımaktadır. Tanı ve tedavi gecikmelerini önlemek için pediatrik endokrinolojiye derhal sevk edilmesi çok önemlidir.

Anahtar Kelimeler: Ergenlik gecikmesi; etiyoloji; hipogonadizm.

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INTRODUCTION

Puberty is a dynamic biological process marked by sexual and physical maturation and is influenced by genetic, environmental, nutritional, and socioeconomic factors. Delays in this process may result from individual variability or interactions among these factors (1).

In cases of suspected delayed puberty (DP), the primary clinical goal is to differentiate between physiological variants, in which growth and puberty are naturally slower, and pathological causes, in which the normal mechanisms triggering puberty are disrupted. Accurate diagnosis relies on anthropometric assessments, genital examination, and evaluation of secondary sexual characteristics and their progression over time (2).

Timely diagnosis and treatment are essential for supporting normal physical development, safeguarding psychosocial well-being, and preserving reproductive potential. Identifying the underlying causes and their distribution is key to guiding clinical evaluation, selecting appropriate tests, and making differential diagnoses (3).

This study aimed to identify etiological factors in patients presenting with DP at a tertiary care center, determine the distribution of diagnostic categories, and compare these groups based on clinical and laboratory findings. The findings are expected to contribute to a better clinical understanding of DP and improve diagnostic and management strategies for affected individuals.

MATERIAL AND METHODS

Study Population and Diagnostic Criteria

This retrospective observational study evaluated 180 patients (91 boys and 89 girls) diagnosed with DP who presented to the Pediatric Endocrinology Clinic at Ankara Children's Health and Diseases Hematology-Oncology Training and Research Hospital between December 1, 2005, and December 31, 2012. DP was defined using standard criteria: absence of breast development by age 13 years in girls and failure of testicular volume to reach 4 mL by age 14 years in boys.

Clinical Assessment and Anthropometry

Patients' medical histories were reviewed for prenatal and postnatal complications, birth weight, onset of pubertal delay, history of chronic illness, surgeries, medications, and nutritional habits. Family history of DP was also noted. Height was measured

using an AYRTON stadiometer and weight with a SECA® digital scale. Growth data were assessed using reference standards developed for Turkish children by Bundak et al. (4) Cases lacking adequate archival data for evaluation were excluded. Tanner-Marshall staging (5, 6) was used for pubertal evaluation, and bone age was assessed using the Greulich-Pyle atlas (7).

Laboratory Evaluations

Complete blood counts were performed using a Beckman Coulter Gen S analyzer. Biochemical parameters were measured with a Roche Hitachi Modular P800 using spectrophotometry. Screening for celiac disease included IgG and IgA anti-tTG antibodies analyzed via ELISA. Positive cases underwent stomach-duodenum biopsy for confirmation.

Hormonal Assays

Hormonal evaluations included thyroid function tests, insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), basal luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex steroids (estrogen/testosterone), prolactin, cortisol, and dehydroepiandrosterone sulfate (DHEA-S). These were analyzed using electrochemiluminescence on an Immulite 2000 autoanalyzer.

Patients without chronic illness, medication use, or nutritional deficiency and with low basal gonadotropin levels underwent a gonadotropin-releasing hormone (GnRH) stimulation test.

CDP was diagnosed in patients with bone age (BA) consistent with height but delayed relative to chronological age (CA), with no underlying chronic disease or endocrinopathy.

LHRH Stimulation Test: Initial blood samples were obtained for basal LH, FSH, and estrogen (E2) or total testosterone (TT). An intravenous LHRH dose of 60 mcg/m² (maximum 100 mcg/m²) was administered, and blood samples were collected at 30, 60, and 90 minutes after injection to assess stimulated hormone levels (8). Patients with a peak LH response <5 ng/mL and findings inconsistent with constitutional delay of puberty (CDP) were diagnosed with hypogonadotropic hypogonadism (HypoH). Although newer studies have proposed different thresholds, this cutoff was selected in accordance with the methodology applied during the study period. Chromosomal analysis was performed in patients with severe short stature, dysmorphic features, or clinical suspicion of chromosomal disorders, such as Turner syndrome or disorders of sex development.

Growth Hormone Testing: In patients with suspected hypopituitarism and marked short stature, growth hormone (GH) stimulation tests were performed using L-DOPA or clonidine following testosterone priming (100 mg IM) (9).

Clonidine Test: A baseline sample was obtained, followed by 150 mcg/m² oral clonidine. Samples were collected at 30, 60, 90, and 120 minutes (9).

L-DOPA Test: L-DOPA was administered orally at 10 mg/kg (maximum 500 mg), and samples were collected at the same intervals. GH deficiency was diagnosed if peak levels were insufficient (9).

Radiological and Additional Evaluations

Patients with HypoH underwent pituitary MRI. Elevated basal FSH and LH levels indicated hypergonadotropic hypogonadism (HyperH).

The differentiation between constitutional delay of puberty (CDP), functional hypogonadotropic hypogonadism (FHH), and permanent hypogonadotropic hypogonadism (HypoH) was based on a combination of clinical, auxological, and biochemical parameters. These included bone age delay relative to chronological age, family history of delayed puberty, presence of chronic illness or nutritional deficiency, and response to GnRH stimulation testing. CDP was considered in patients with delayed bone age consistent with height, positive family history, and a pubertal response to GnRH stimulation, whereas HypoH was diagnosed in patients with persistently low gonadotropin responses and no evidence of reversible underlying conditions.

Patients with chronic illness or malnutrition but no permanent hypothalamic or pituitary damage were classified under functional hypogonadotropic hypogonadism (FHH). Malnutrition-related DP was diagnosed in individuals below the 10th percentile for weight-for-height and with documented nutritional deficiencies.

Nutritional and Hematological Causes

Iron Deficiency Anemia: Diagnosed in patients with low hemoglobin and hematocrit levels, microcytic indices, and elevated red cell distribution width (10).

Macrocytic Anemia: Diagnosed based on high mean corpuscular volume, low vitamin B12 and folate levels, and low hematological parameters (10).

Tayanç-Prasad Syndrome: Diagnosed in patients with growth retardation, hepatosplenomegaly, iron/zinc deficiency, and DP. These patients improved following supplementation (11).

Genetic and Structural Diagnoses: Two patients were diagnosed with Turner syndrome through karyotype analysis, prompted by severe short stature and the absence of elevated basal gonadotropin levels. Additional patients with abnormal LHRH responses (stimulated LH >5 ng/mL but low baseline levels) and abnormal pituitary imaging findings, such as microadenoma or partial empty sella, were categorized as unclassifiable.

An otolaryngologist evaluated cases of hypopituitarism for anosmia.

For analytical purposes, patients were categorized into four main diagnostic groups: hypogonadotropic hypogonadism (HypoH), hypergonadotropic hypogonadism (HyperH), functional hypogonadotropic hypogonadism (FHH), and constitutional delay of puberty (CDP).

Statistical Analysis

Data were analyzed using SPSS for Windows, version 16.0. Continuous variables were expressed as mean±standard deviation (min–max). Group comparisons for continuous variables were performed using Student's t-test for two groups or one-way ANOVA with LSD post hoc test for multiple groups.

Table 1. Gender differences in cases of delayed puberty

	Girls (n=89)	Boys (n=91)	p
Height SDS[a]	-2.4±1.9 (-6.7–2.1)	-2.5±1.6 (-7.3–1.5)	0.600
BMI SDS[a]	-0.95±1.85 (-4.9–3.7)	-1.01±2.1 (-8.2–2.6)	0.800
Weight SDS[a]	-2.1±2.3 (-6.3–3.8)	-2.1±2.2 (-9.8–2.5)	0.800
Pubic hair[b]	44.9%	27.5%	**0.015**
Axillary hair[b]	41.6%	36.3%	0.560
Parental history[b]	8 (9)	24 (26.4)	**0.002**
Sibling history[b]	16 (18)	3 (3.3)	**0.001**
CDP[b] n (%)	15 (16.9)	31 (34.1)	**<0.05**
FHH[b] n (%)	20 (22.5)	18 (19.8)	>0.05
HypoH[b] n (%)	29 (32.6)	32 (35.2)	>0.05
HyperH[b] n (%)	23 (25.8)	9 (9.9)	**<0.05**

a: Results are presented as the mean±standard deviation (minimum–maximum); b: Results are given as percentages; CDP: Constitutional delay of puberty; FHH: Functional hypogonadotropic hypogonadism; HyperH: Hypergonadotropic hypogonadism; HypoH: Hypogonadotropic hypogonadism.

For non-normally distributed data, the Kruskal–Wallis test was used. Categorical data were compared using the chi-squared test. For pairwise comparisons of non-normally distributed variables between two groups, the Mann–Whitney U test was used. A p-value <0.05 was considered statistically significant.

Ethical Approval

This study was derived from a pediatric residency thesis and represents a retrospective analysis of data collected in 2013 at Ankara Children's Health and Diseases Hematology and Oncology Training and Research Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee.

RESULTS

The following results were obtained from the evaluation of 180 cases. Of these cases, 50.6% were male (n=91).

The mean CA was 14.5±1.2 (13–18) years, and the median BA was 12±1.5 (9.5–18) years. The mean difference between CA and BA (CA-BA) was 2.4±2.2 (-3.8±7.0) (p<0.05).

Although the difference in CA between male and female cases was significant (p<0.05), the differences in BA and ΔCA-BA values were not significant (p>0.05).

A significant difference in ΔCA-BA was found in the comparison between HypoH and HyperH (p<0.05). Among female cases, a significant difference in ΔCA-BA was observed between HypoH and HyperH, as well as between HypoH and FHH (p<0.05). Among FHH cases, the difference in ΔCA-BA between female and male cases was significant (p<0.05).

Pubic hair was present in 36.1% of cases. The prevalence of pubic hair was significantly higher in girls than in boys (p<0.05). However, no significant difference was found in axillary hair between the two groups (p>0.05).

A history of DP was present in at least one parent in 17.8% of cases and in at least one sibling in 10.6% of cases. The history of DP among parents and siblings differed significantly by sex and diagnostic group (p<0.05).

We categorized cases into four groups based on DP etiology. The most common diagnosis was HypoH. Hypogonadotropic hypogonadism and FHH occurred at similar rates in both sexes. Hypergonadotropic hypogonadism was more common in girls, whereas CDP was more frequent in boys. Table 1 presents the characteristics by sex, and Table 2 presents the characteristics by diagnostic group.

A total of 46 diagnostic subgroups were identified. Tables 3, 4, and 5 show the subgroup distributions for HypoH, HyperH, and FHH, respectively. Idiopathic HypoH was the most frequent subgroup and was more common in males.

Of all cases, patients with HypoH presented latest. The CA of the HypoH group differed from that of the CDP group (p=0.003). Patients with HyperH were found to have a BA that was older than that of patients with CDP (p=0.026). There was no difference in BA between the other groups.

IGF-1 showed better SDS values in the HyperH group than in the other three diagnostic groups (p<0.05). IGFBP-3 SDS values differed significantly between the HyperH and HypoH groups (p=0.026). However, there was no significant difference in BMI SDS among the diagnostic groups (p>0.05).

The HyperH group had significantly higher basal LH and FSH values than the other groups (p<0.0001). The CDP and FHH groups exhibited a pubertal LHRH response. The HypoH group had a significantly lower peak LH response than the other groups (p<0.0001). The CDP group had a significantly higher LH peak than the FHH group (p=0.009).

In males, chronological age and peak LH levels differed significantly between the HypoH and CDP groups (p=0.019 and p=0.0001, respectively).

Table 2. Differences between diagnostic groups

	CDP	HypoH	FHH	HyperH
ΔTY-KY (years)				
All cases[a]	2.3±0.9	2.9±1.5	2.3±1.7	2.0±1.5
Girls[a]	2.3±0.7	3.1±1.5	1.5±1.5	2.1±1.4
Boys[a]	2.3±1.01	2.7±1.6	3.1±1.6	1.8±1.9
Parental history[b]	**47.8**%*	11.5%	5.3%	3.1%
Sibling history[b]	4.3%	13.1%	7.9%	**18.8**%*

a: Results are presented as the mean±standard deviation (minimum–maximum); b: Results are given as percentages; *: A parental history was more frequent in CDP cases, whereas a sibling history was more frequent in HyperH cases. CDP: Constitutional delay of puberty; FHH: Functional hypogonadotropic hypogonadism; HyperH: Hypergonadotropic hypogonadism; HypoH: Hypogonadotropic hypogonadism.

Table 3. Diagnosis subgroups of hypogonadotrophic hypogonadism

	All cases	Girls	Boys
Idiopathic hypoH	18 (29.5)	4 (13.7)	14 (44.2)
Panhypopituitarism	10 (16.6)	8 (27.5)	2 (6.2)
Thalassemia major	7 (11.5)	3 (10.3)	4 (12.5)
Pituitary microadenoma	6 (9.8)	5 (17.2)	1 (3.1)
Craniopharyngeoma	5 (8.2)	3 (10.3)	2 (6.2)
Syndromic cases[a]	3 (4.9)		3 (9.2)
Empty sella	2 (3.3)	2 (7)	
Partially empty sella	2 (3.3)		2 (6.2)
Head trauma	2 (3.3)	1 (3.5)	1 (3.1)
Chemotherapy	1 (1.6)		1 (3.1)
Hypoxic ischemic encephalopathy	1 (1.6)		1 (3.1)
Hypophysitis	1 (1.6)		1 (3.1)
Pars intermedia cyst	1 (1.6)	1 (3.5)	
Severe iron deficiency anemia	1 (1.6)	1 (3.5)	
Ovarian dysgenesis and pituitary hypoplasia	1 (1.6)	1 (3.5)	
Total	61 (100)	29(100)	32 (100)

a: Bardet Biedl Syndrome, Lesch-Nyhan Syndrome, Nail Patella Syndrome Results are given as number of cases (%)

There was a significant difference between the HypoH and FHH groups in terms of IGF-1 SDS (p=0.016) and peak LH levels (p=0.028).

There was a significant difference between the FHH and HyperH groups in terms of bone age (p=0.042).

There was a significant difference between the FHH and CDP groups in terms of IGFBP-3 SDS (p=0.038) and peak LH levels (p=0.0001).

Table 4. Diagnosis subgroups of hypergonadotrophic hypogonadism

	All cases	Girls	Boys
Sexual differentiation defects	12 (37.7)	11 (47.8)	1 (11.1)
Turner syndrome	7 (21.8)	7 (30.4)	
Klinefelter syndrome	2 (6.25)		2 (22.2)
Ovarian dysgenesis	2 (6.25)	2 (8.7)	
Bone marrow transplantation	2 (6.25)	2 (8.7)	
Testicular atrophy	2 (6.25)		2 (22.2)
Radiotherapy	1 (3.1)		1 (11.1)
Testicular rest tumor	1 (3.1)		1 (11.1)
Vanishing testis	1 (3.1)		1 (11.1)
Anorexia nervosa	1 (3.1)	1 (4.4)	
Mitochondrial disease	1 (3.1)		1 (11.1)
Total	32 (100)	23 (100)	9 (100)

Results are given as number of cases (%).

Table 5. Diagnosis subgroups of functional hypogonadotrophic hypogonadism

	All cases	Girls	Boys
Obesity	6 (16)	2 (10)	4 (22.3)
Celiac disease	3 (7.9)	3 (15)	
Thalassemia major	3 (7.9)	2 (10)	1 (5.55)
Malnutrition	3 (7.9)	1 (5)	2 (11.1)
Familial Mediterranean fever	3 (7.9)	2 (10)	1(5.55)
Diabetes mellitus (Type 1)	2 (5.3)	2 (10)	
Tayanç Prasad syndrome	2 (5.3)	1 (5)	1 (5.55)
Immunodeficiency	3 (7.9)	1 (5)	2 (11.1)
Bronchiectasis	2 (5.3)		2 (11.1)
Profound iron deficiency anemia	1 (2.6)	1 (5)	
Asthma	1 (2.6)	1 (5)	
Adrenal insufficiency	1 (2.6)	1 (5)	
Inflammatory bowel disease	1 (2.6)		1 (5.55)
Chronic renal failure	1 (2.6)	1 (5)	
Nephrotic syndrome	1 (2.6)		1 (5.55)
Autoimmune thyroiditis	1 (2.6)	1 (5)	
Cardiomyopathy	1 (2.6)		1 (5.55)
Renal tubular acidosis	1 (2.6)		1 (5.55)
Mitochondrial disease	1 (2.6)		1 (5.55)
Hypothyroidism	1 (2.6)	1 (5)	
Total	38 (100)	20 (100)	18 (100)

Results are given as number of cases (%).

With the exception of the HyperH group, there were no significant differences in BMI SDS or basal LH or FSH values between the diagnostic groups (p>0.05).

In females, significant differences were found between the HypoH and CDP cases in terms of BA (p=0.007), IGFBP-3 SDS (p=0.038), and peak LH values (p=0.0001).

Significant differences were observed between the HypoH and FHH groups in terms of IGF-1 SDS (p=0.025), IGFBP-3 SDS (p=0.015), and peak LH values (p=0.0001).

CA and BA were significantly lower in the CDP group than in the HyperH group (p=0.038 and p=0.019, respectively).

BA was significantly lower in the CDP group than in the FHH group (p=0.022).

DISCUSSION

Our study represents one of the largest DP case series in the literature (12–14), comprising a retrospective analysis of 180 patients who presented to our pediatric endocrinology clinic over a seven-year period. These cases were classified into 46 different diagnostic subgroups, allowing for a comprehensive evaluation of the wide range of etiological factors underlying DP.

The mean age at presentation was 14.5 years, with a significant sex-based difference: boys presented later than girls, a finding consistent with previous studies (12, 13). This highlights the importance of assessing testicular volume during routine pediatric evaluations, as early detection of pubertal onset in boys may otherwise be overlooked.

Among female patients, the mean age at presentation was 14 years, and approximately half had pubic hair. This may have led to misinterpretation by families, who could have assumed that pubertal development had already begun. However, in girls, pubic and axillary hair growth is primarily driven by adrenal androgens and does not necessarily indicate pubertal activation (2, 15). In contrast, pubic hair development in boys is typically linked to increased testicular volume and mediated by testicular androgens (15). The lower prevalence of pubic hair among male patients in our cohort may therefore reflect a deficiency in these androgens.

Across all diagnostic groups, bone age (BA) was delayed relative to chronological age (CA). The difference between CA and BA (ΔCA-BA) is a standard parameter for assessing bone maturation delay (13). Although no significant sex-based differences were observed in ΔCA-BA values, the greatest delay was noted in patients with hypogonadotropic hypogonadism (HypoH), particularly those with panhypopituitarism. In this subgroup, in addition to sex steroid deficiency, patients also exhibited deficits in thyroid hormone and growth hormone. They were also older at the time of presentation, suggesting that prolonged and profound hormone deficiencies contributed to the greater skeletal maturation delay observed.

Conversely, the most advanced BA was seen in the hypergonadotropic hypogonadism (HyperH) group. This is expected, as most HyperH cases are syndromic, and in such patients, CA and BA typically progress in parallel (13). Additionally, these individuals often maintain normal thyroid and growth hormone function, which may help preserve BA progression.

The role of estrogen in bone maturation, particularly in its biphasic effects on epiphyseal growth plates, is well documented. In girls with DP, estrogen deficiency can result in delayed BA and decreased growth velocity by altering growth hormone responsiveness (1). Although previous research has suggested that BA delay is often more pronounced in girls than in boys, our study did not find significant sex-based differences in BA, height SDS, weight SDS, or BMI SDS. These findings suggest that sex-specific effects of DP may not always be evident and could vary depending on population characteristics. Moreover, the impact of DP on growth is likely influenced by multiple hormonal and environmental factors.

A positive family history of DP was identified in 17.8% of parents and 10.6% of siblings. In the CDP group, parental history was particularly common (47.8%), whereas in the HyperH group, sibling history was more frequent (18.8%). Parental history was more often reported in male patients, whereas sibling history predominated among females. This may be due to the higher prevalence of HyperH among female cases, a condition that can be genetically transmitted, such as primary ovarian insufficiency, and can manifest similarly among siblings (16). On the other hand, the high prevalence of CDP among males, which is often inherited in an autosomal dominant fashion, may explain the increased parental history in this group (17).

Basal gonadotropin levels were central to diagnostic classification (18). The highest LH and FSH levels were observed in the HyperH group, whereas the lowest levels were found in the HypoH group. When basal levels were inconclusive, the LHRH stimulation test provided critical diagnostic clarity (9). A pubertal LH response was observed in the CDP and FHH groups, whereas the HypoH group had significantly blunted responses. Notably, patients with CDP had higher peak LH levels compared with the FHH group, a distinction that can aid in differentiating these conditions (15).

Although CDP is often cited as the most common cause of DP in both sexes (1, 2), our study found that HypoH was the most frequently diagnosed etiology. This likely reflects the referral nature of our tertiary care setting, which tends to receive more complex or pathological cases. CDP was the second most common diagnosis. HyperH, although the least frequent overall, was the second most prevalent diagnosis among female patients. Within the HyperH group, disorders of sex development (DSD) and Turner syndrome were predominant. Among males, CDP was the second most frequent cause. This distribution aligns with previous studies suggesting that pathological causes are more common among girls, whereas benign etiologies, such as CDP, are more typical in boys (12, 13).

Similarly, Galal et al., (14) in a 15-year retrospective analysis conducted at a tertiary center in Sudan, also identified HypoH and FHH as the most prevalent etiologies. They emphasized

the influence of socioeconomic status, nutritional factors, and genetic background, including high rates of consanguinity, on the distribution of DP causes.

A total of 46 distinct etiologies for DP were identified in our study. The most common was idiopathic hypogonadotropic hypogonadism (IHH). All patients with IHH were screened for anosmia, and those with suspicious findings were referred for otolaryngology evaluation. No cases of anosmia were confirmed. It is worth noting that, during the study period, genetic and molecular diagnostics were not widely available. Since then, advances in these technologies have allowed for more accurate identification of underlying causes in IHH cases (19).

Mean BMI SDS values were low across our cohort, indicating that body weight, like height, is negatively affected in patients with DP. No significant differences in BMI SDS were observed between diagnostic groups or sexes. In boys, decreased IGF-1 levels were particularly noted in the FHH group, suggesting that chronic illnesses may induce secondary growth hormone resistance. Among females, both IGF-1 and IGFBP-3 levels were significantly lower in the HypoH group compared with the FHH and HyperH groups. Many of these HypoH cases involved panhypopituitarism, and combined deficiencies of thyroid and growth hormones likely contributed to the observed reductions in IGF-1 and IGFBP-3.

Basal LH and FSH levels were diagnostically elevated in patients with HyperH, while remaining low in the other groups. However, before BA reaches approximately 12 years, when the hypothalamic-pituitary-gonadal (HPG) axis typically activates, it can be difficult to distinguish between CDP and HypoH (2, 3). In such cases, stimulated LH values following LHRH administration offer important diagnostic insight (8). In our CDP group, stimulated LH reached pubertal levels, and patients generally developed secondary sexual characteristics either spontaneously or after short-term sex steroid therapy. The subsequent rise in endogenous sex hormones after treatment cessation served as an indicator of ongoing gonadal function.

In patients with FHH, pubertal development sometimes commenced after treatment of the underlying chronic illness and temporary sex steroid administration, indicating the potential for endogenous activation. In contrast, patients in the HypoH group had persistently low LH levels both at baseline and after stimulation, necessitating lifelong hormone replacement due to permanent gonadotropin deficiency (2, 20). Distinguishing between CDP and HypoH is therefore essential for clinical decision-making (20).

Among female patients, HypoH and HyperH were the most frequent causes of DP, whereas CDP was the least common, consistent with findings in the literature (1, 2, 13). The higher prevalence of pathological etiologies in girls supports the need for thorough diagnostic workup and, where appropriate, chromosomal analysis. In our study, 18 of 22 female patients with HyperH (81.8%) had either DSD or Turner syndrome. These patients exhibited more advanced BA and higher IGF-1 and IGFBP-3 levels compared with the other groups, likely due to relatively normal growth hormone function and the presence of androgen excess, which is known to stimulate bone maturation.

Given our hospital's status as a tertiary referral center, the high number of patients and prevalence of complex conditions likely contributed to the predominance of permanent and functional hypogonadotropic causes in our cohort. IHH was the most commonly diagnosed condition, yet the lack of genetic testing during the study period limited our ability to differentiate between congenital and acquired forms (21). This constitutes a major limitation of the study. Future genetic research will enhance diagnostic precision and facilitate the early identification of at-risk family members.

Differentiating CDP from permanent HypoH remains a well-recognized clinical challenge, particularly in early adolescence, when the hypothalamic-pituitary-gonadal axis has not yet fully activated. In our study, this distinction was made based on clinical findings, bone age, family history, and GnRH stimulation test results. However, the absence of long-term follow-up data represents an important limitation. Some patients initially classified as IHH may later exhibit spontaneous pubertal development, leading to potential reclassification as CDP. Therefore, longitudinal follow-up is essential for confirming the definitive diagnosis in such cases.

CONCLUSION

In conclusion, this study is among the most comprehensive case series investigating the etiology of delayed puberty (DP) in a tertiary pediatric unit. Our findings provide valuable insight into the distribution of underlying causes and highlight the clinical and laboratory features that aid differential diagnosis. Accurate diagnosis and individualized assessment are essential for effectively managing adolescents with DP. Even in cases of permanent hypogonadism, appropriate treatment can significantly improve physical and psychosocial outcomes. Genetic studies are increasingly important in evaluating DP and are expected to play a critical role in the future management of hypogonadism.

Ethics Committee Approval: This study was derived from a pediatric residency thesis and represents a retrospective analysis of data collected in 2013 at Ankara Children's Health and Diseases Hematology and Oncology Training and Research Hospital. The study was approved by the local ethics committee.

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Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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Yazarlık Katkıları: Fikir – FD, Fİ; Tasarım – FD, Fİ; Denetlemeler – FD, Fİ; Kaynaklar – FD, Fİ; Malzemeler – FD, Fİ; Veri toplanması ve/veya işleme – FD, Fİ; Analiz ve/veya yorumlama – FD, Fİ; Literatür araştırması – FD, Fİ; Yazım – FD, Fİ; Eleştirel incelemeler – FD, Fİ.

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ORIGINAL RESEARCH
Pediatric Cardiology

Clinical and laboratory factors associated with carditis in acute rheumatic fever: A single-center retrospective study

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ABSTRACT

Objective: Acute rheumatic fever (ARF) is an immune-mediated inflammatory disease that develops following group A streptococcal infection. Carditis is the major determinant of morbidity and long-term sequelae. This study aimed to evaluate clinical and laboratory/electrocardiographic factors associated with carditis in children followed for ARF.

Material and Methods: In this single-center retrospective study, the records of children followed for ARF between January 2015 and August 2016 were reviewed. Carditis was assessed by echocardiography. Clinical variables (fever ≥38.5°C, mono/polyarthritis, mono/polyarthralgia) and laboratory/ECG parameters (erythrocyte sedimentation rate, C-reactive protein, antistreptolysin-O, mean platelet volume, PR interval) were compared between groups. Appropriate parametric/nonparametric tests were used. Univariate odds ratios were calculated. Due to the small sample size and collinearity, parsimonious logistic regression models (ESR+PR and CRP+PR) were fitted.

Results: Among 40 children, 22 (55%) had carditis. Fever ≥38.5°C, polyarthritis, and polyarthralgia were associated with carditis in the univariate analyses. Sedimentation, CRP, and PR interval were significantly higher in the carditis group. In the parsimonious model, ESR (per 10 mm/h increase) remained independently associated with carditis; PR interval showed an independent association in the sensitivity analysis.

Conclusion: Carditis in ARF was accompanied by a higher systemic inflammatory burden, ECG findings suggestive of conduction involvement, and a polyarticular clinical phenotype. Systematic clinical assessment and low-threshold echocardiography are essential for the early recognition of carditis.

Keywords: Acute rheumatic fever; carditis; echocardiography; erythrocyte sedimentation rate.

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Akut romatizmal ateşte kardit ile ilişkili klinik ve laboratuvar faktörler: Tek merkezli retrospektif çalışma

ÖZET

Amaç: Akut romatizmal ateş (ARA), A grubu β-hemolitik streptokok enfeksiyonunu takiben gelişen immün aracılı inflamatuvar bir hastalıktır ve en önemli uzun dönem sonucu romatizmal kalp hastalığıdır. Kardit, ARA'ya bağlı morbidite ve sekelin temel belirleyicisi olup erken dönemde saptanması yönetimi doğrudan etkiler. Bu çalışmada, ARA olgularında kardit varlığı ile ilişkili klinik ve laboratuvar/elektrokardiyografik göstergelerin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu tek merkezli retrospektif çalışmada, Ocak 2015–Ağustos 2016 döneminde ARA tanısı/şüphesi ile izlenen çocukların kayıtları incelendi. Kardit varlığı ekokardiyografi ile değerlendirildi. Klinik değişkenler (≥38,5°C ateş, mono/poliartrit, mono/poliartralji) ve laboratuvar/EKG parametreleri (eritrosit sedimentasyon hızı, C-reaktif protein, antistreptolizin-O, ortalama trombosit hacmi, PR aralığı) kardit varlığına göre karşılaştırıldı. Kategorik değişkenler için Ki-kare/Fisher testi, sürekli değişkenler için dağılıma uygun olarak bağımsız örneklem t-testi veya Mann–Whitney U testi kullanıldı. Kardit ile ilişkili faktörler için tek değişkenli olasılık oranları hesaplandı. Küçük örneklem ve değişkenler arası korelasyon nedeniyle parsimoniyöz lojistik regresyon modelleri (ESR+PR ve CRP+PR) kuruldu.

Bulgular: Toplam 40 olgunun 22'sinde (%55) kardit saptandı. Tek değişkenli analizde ≥38,5°C ateş, poliartrit ve poliartralji kardit ile ilişkiliydi. Karditli olgularda sedimentasyon, CRP ve PR aralığı anlamlı olarak daha yüksekti. Parsimoniyöz modelde sedimentasyon (10 mm/saat artış başına) kardit ile bağımsız ilişkiliydi; PR aralığı ise duyarlılık analizinde bağımsız ilişki gösterdi.

Tartışma: Bu kohortta kardit varlığı; yüksek inflamasyon yükü, iletim sistemi etkilenimini düşündüren EKG bulguları ve poli-eklem tutulumuyla karakterize klinik fenotip ile birlikte seyretti. ARA şüphesinde sistematik klinik değerlendirme ve düşük eşikte ekokardiyografi, karditin erken saptanması açısından önemlidir.

Anahtar Kelimeler: Akut romatizmal ateş; ekokardiyografi; eritrosit sedimentasyon hızı; kardit.

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GİRİŞ

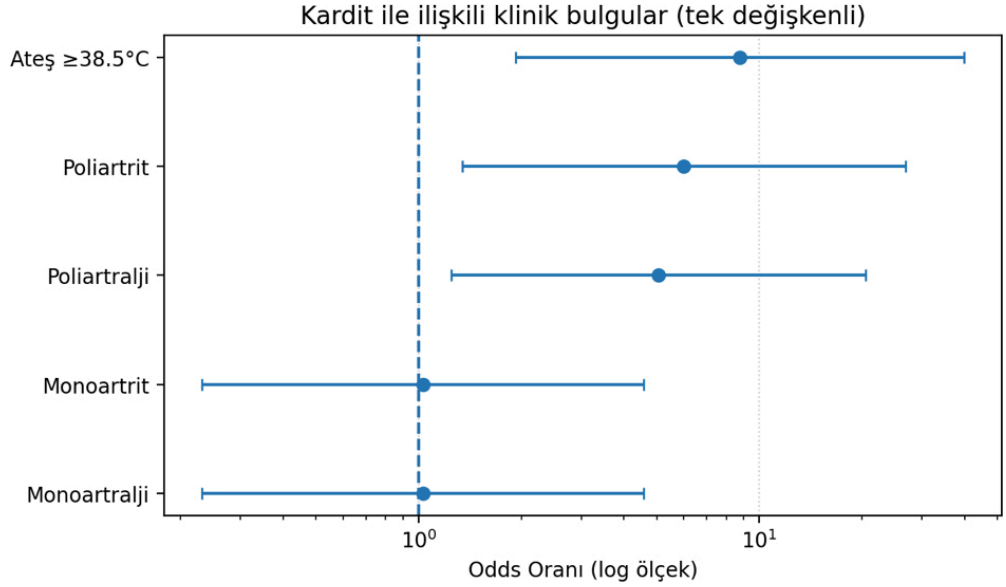
Akut romatizmal ateş (ARA), A grubu β-hemolitik streptokok (*Streptococcus pyogenes*) enfeksiyonunu takiben gelişen, çok sistemli ve immün aracılı inflamatuvar bir hastalıktır. ARA'nın en önemli uzun dönem sonucu romatizmal kalp hastalığı (RKH) olup özellikle endemik bölgelerde çocukluk çağında edinilmiş kalp hastalıklarının başlıca nedenleri arasında yer almaya devam etmektedir (1–3). Dünya Sağlık Örgütü (DSÖ), 2024 yılında yayımladığı kılavuzda ARA/RKH'nin önlenebilir bir hastalık yükü oluşturduğunu ve erken tanı ile sekonder profilaksinin önemini vurgulamaktadır (3).

ARA klinik spektrumu; artrit/artralji, kardit, kore, eritema marginatum ve subkutan nodüller gibi bulguları içeren geniş bir yelpazede seyredebilir. Morbidite ve mortalitenin belirleyicisi çoğunlukla kardiyak tutulumdur; kardit atağının şiddeti ve/veya yineleyen ataklar, kapaklarda kalıcı hasara ve ilerleyici RKH'ye yol açabilir (1, 2, 4). Bu nedenle, karditin erken dönemde saptanması tedavi yaklaşımını ve izlem stratejisini doğrudan etkilemektedir.

Tanısal yaklaşımda Jones kriterleri temel çerçeveyi oluşturur. Amerikan Kalp Derneği (AHA) tarafından 2015 yılında güncellenen Revize Jones kriterleri, düşük riskli ve orta/yüksek riskli popülasyonlar için ayrı tanı yolları tanımlamış, Doppler ekokardiyografiyi tüm şüpheli olgularda önermiş ve subklinik karditin majör kriter olarak kabul edilebileceğini belirtmiştir (5, 6). Ekokardiyografide patolojik regürjitasyonun tanımı ve standardizasyonu için Dünya Kalp Federasyonu'nun (WHF) ekokardiyografik kriterleri de pratikte önemli bir referans noktasıdır (7, 8).

Karditin her zaman belirgin oskültasyon bulgusu vermemesi, ilk başvuruda bulguların hızla değişebilmesi ve kaynak kısıtlı ortamlarda ekokardiyografiye erişimin gecikebilmesi nedeniyle, kardit olasılığını klinik ve laboratuvar parametreleriyle öngörebilmek klinik açıdan değerlidir. Akut faz reaktanları (eritrosit sedimentasyon hızı [ESH] ve C-reaktif protein [CRP]) ile iletim sistemi tutulumunu yansıtan PR aralığı uzaması, ARA aktivitesini gösteren parametreler olmakla birlikte, bu belirteçlerin kardit varlığı/şiddeti ile ilişkisine dair literatürde tutarsız sonuçlar bildirilmektedir (1, 2, 9). Bu bağlamda, tek merkezli seriler yerel klinik pratikte risk sınıflamasına yardımcı olabilecek ipuçları sağlayabilir.

Bu çalışmada, çocuk kliniğinde izlenen ARA olgularında kardit ile ilişkili klinik (ateş ve eklem bulguları) ve laboratuvar/elektrokardiyografik (ESH, CRP, ASO, MPV, PR aralığı) parametreleri



Şekil 1. Kardit ile ilişkili klinik değişkenler için tek değişkenli olasılık oranları (orman grafiği). OR ve %95 güven aralıkları gösterilmektedir.

değerlendirmeyi amaçladık. İkincil amaç olarak, aynı olgu grubunda DSÖ 2004 yaklaşımı ile 2015 Revize Jones kriterlerinin tanısal yakalama farklılıklarını betimlemeyi hedefledik.

GEREÇ VE YÖNTEMLER

Çalışma Tasarımı ve Çalışma Ortamı

Bu çalışma, tek merkezli, geriye dönük gözlemsel bir araştırmadır. Çalışma, Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği'nde yürütülmüştür. Hastane bilgi yönetim sistemi (HBYS/HİS) ve hasta dosyaları üzerinden, çalışma döneminde ARA tanısı ile izlenen olguların verileri geriye dönük olarak taranmıştır (Ocak 2015–Ağustos 2016).

Çalışma Popülasyonu

Dahil edilme ölçütleri şunlardı: (i) pediatri kliniğinde ARA tanısı ile izlenmiş olmak, (ii) çocukluk çağı (≤18 yaş) hastası olmak, (iii) klinik kayıtların Jones 2015 kriterlerinin uygulanmasına ve kardit varlığının değerlendirilmesine olanak verecek düzeyde tamamlanmış olması. Tekrarlayan ARA atağı ile başvuranlar, bilinen konjenital kalp hastalığı olanlar, önceden tanı almış romatizmal kalp hastalığı bulunanlar ve temel klinik/laboratuvar verileri eksik olan hastalar çalışma dışı bırakıldı. Nihai analiz, uygun kayıtları bulunan 40 olgu üzerinden gerçekleştirildi.

Tanısal Değerlendirme ve Tanımlar

ARA tanısı, 2015 Revize Jones kriterlerine göre (orta/yüksek riskli popülasyon yaklaşımı) yeniden gözden geçirildi (5). Streptokokal enfeksiyon kanıtı (örn. yükselmiş antistreptolizin O [ASO] titresi ve/veya klinik öykü) klinik kayıtlar üzerinden değerlendirildi. Aynı olgu grubu ayrıca DSÖ 2004 yaklaşımı çerçevesinde de sınıflandırıldı; böylece tanısal yakalama farklılıkları tanımlayıcı olarak karşılaştırıldı (3, 9).

Kardit, klinik kardit ve/veya subklinik kardit olarak değerlendirildi. Tüm olgularda iki boyutlu ve renkli Doppler ekokardiyografi bulguları incelendi. Subklinik kardit, oskültasyonda yeni üfürüm veya açık klinik kardit bulgusu olmaksızın ekokardiyografide patolojik kapak regürjitasyonunun saptanması şeklinde tanımlandı. Patolojik mitral/aort regürjitasyonu değerlendirmesinde standardizasyon amacıyla WHF ekokardiyografi kriterleri referans alındı (7, 8).

Eklem tutulumu, artrit (objektif şişlik ve/veya hareket kısıtlılığı/ısı artışı) ve artralji olarak ayrıldı; tutulan eklem sayısına göre monoartrit/monoartralji ve poliartrit/poliartralji şeklinde sınıflandırıldı. Vücut sıcaklığı, ≥38,5°C (yüksek ateş) ve <38,5°C olarak ikili sınıflandırıldı.

Veri Toplama

Demografik veriler (yaş, cinsiyet), başvuru yakınmaları ve klinik bulgular, majör/minör kriter bileşenleri ve tedavi özellikleri (penisilin, aspirin, kortikosteroid) HBYS ve hasta dosyalarından kaydedildi. Laboratuvar parametreleri olarak ESH (mm/saat), CRP (mg/dl), ASO (IU/ml) ve ortalama trombosit hacmi (MPV, fL) kaydedildi. Elektrokardiyografik değerlendirmede 12 derivasyonlu EKG'den PR aralığı (saniye) ölçümleri kaydedildi.

İstatistiksel Analiz

İstatistiksel analizler IBM SPSS Statistics yazılımı kullanılarak yapıldı (sürüm bilgisi eklenecektir). Sürekli değişkenlerin dağılımı Shapiro–Wilk testi ile değerlendirildi. Normal dağılım gösteren değişkenler ortalama±standart sapma, normal dağılmayan değişkenler medyan (minimum–maksimum) olarak özetlendi. İki grup karşılaştırmalarında uygun şekilde bağımsız örneklem t-testi veya Mann–Whitney U testi kullanıldı. Kategorik değişkenler sayı ve yüzde olarak verildi; gruplar arası karşılaştırmalarda Ki-kare testi veya beklenen hücre sayısına göre Fisher'in kesin testi uygulandı.

Tablo 1. Kardit varlığına göre demografik, laboratuvar ve EKG değişkenlerinin karşılaştırılması

Değişken	Kardit yok (n=18)	Kardit var (n=22)	Test	p
Yaş (yıl)	11.00±3.38	10.95±2.42	t=0.048	0.962
Sedimentasyon (mm/saat)	8.50 (6.25–23.75) 16.39±13.46	58.50 (38.25-79.25) 59.50±24.99	U=23.0	<0.001
CRP (mg/dl)	0.10 (0.10–0.45) 1.19±3.95	2.38 (0.53–7.85) 5.34±6.51	U=79.0	0.001
PR aralığı (sn)	0.12 (0.11–0.12) 0.12±0.02	0.16 (0.12–0.20) 0.17±0.05	U=67.5	<0.001
ASO (IU/ml)	216.50 (93.12–515.25) 301.10±264.01	39.00 (1.00–520.00) 221.91±282.98	U=260.5	0.088
MPV (fL)	7.17 (6.90–7.80) 7.52±1.27	7.39 (6.83–7.88) 7.62±1.34	U=192.0	0.881

CRP: C-reaktif protein; ASO: Anti-streptolisin O; MPV: Mean platelet volume (ortalama trombosit hacmi); t: Student's t-Test; U: Mann–Whitney U test; n: Hasta sayısı.

Tablo 2. Kardit varlığı ile ilişkili klinik bulgular: tek değişkenli analiz

Değişken (var=1)	Kardit yok n (%)	Kardit var n (%)	OR (%95 GA)	p	Test
Vücut sıcaklığı ≥38.5°C	3 (16.7)	14 (63.6)	8.75 (1.93–39.75)	0.003	χ^2
Poliartrit	3 (16.7)	12 (54.5)	6.00 (1.34–26.81)	0.014	χ^2
Poliartralji	4 (22.2)	13 (59.1)	5.06 (1.25–20.48)	0.019	χ^2
Monoartrit	4 (22.2)	5 (22.7)	1.03 (0.23–4.58)	1.000	Fisher
Monoartralji	4 (22.2)	5 (22.7)	1.03 (0.23–4.58)	1.000	Fisher

OR: Odds ratio; GA: Güven aralığı (confidence interval); χ^2: Ki-Kare Testi; Fisher: Fisher's Exact Test; n: Hasta sayısı.

Kardit ile ilişkili olası belirleyicileri değerlendirmek üzere tek değişkenli lojistik regresyon analizleri yapıldı; olasılık oranı (odds ratio, OR) ve %95 güven aralıkları (GA) raporlandı. Çok değişkenli lojistik regresyon analizine, tek değişkenli analizde anlamlı bulunan klinik ve laboratuvar değişkenleri dahil edildi. Akut faz reaktanları arasında olası çoklu doğrusal bağlantı (multicollinearity) nedeniyle ESH ve CRP aynı modele birlikte sokulmadı; ESH içeren ana model ve CRP içeren duyarlılık (sensitivity) modeli ayrı olarak kuruldu. PR aralığı, klinik yorumlanabilirliği artırmak ve katsayıların ölçek etkisini azaltmak amacıyla 10 ms (0,01 sn) artış başına olacak şekilde ölçeklendirilerek modele alındı. Tüm testlerde iki yönlü p<0,05 istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya toplam 40 olgu dâhil edildi; olguların 22'sinde (%55) kardit saptandı. Kardit varlığına göre yaş dağılımı benzerdi (Tablo 1).

Klinik bulguların kardit ile ilişkisi

Tek değişkenli analizde vücut sıcaklığının ≥38,5°C olması, poliartrit ve poliartralji varlığı kardit ile ilişkili bulundu (Tablo 2, Şekil 1). Yüksek ateş varlığında kardit olasılığı artmıştı (OR=8,75; %95 GA: 1,93–39,75; p=0,003). Benzer şekilde poliartrit (OR=6,00; %95 GA: 1,34–26,81; p=0,014) ve poliartralji (OR=5,06; %95 GA: 1,25–20,48; p=0,019) kardit ile ilişkiliydi. Monoartrit ve monoartralji ile kardit arasında anlamlı ilişki saptanmadı (Tablo 2).

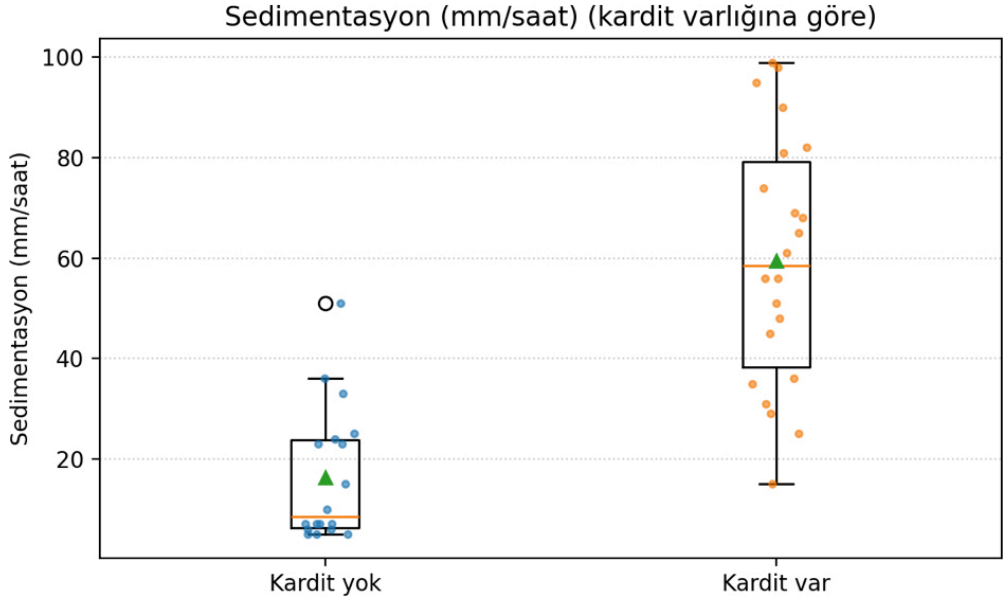
Laboratuvar ve EKG Bulguları

Kardit saptanan olgularda sedimentasyon ve CRP düzeyleri anlamlı olarak daha yüksekti (sedimentasyon U=23,0, p<0,001; CRP U=79,0, p=0,001; Tablo 1; Şekil 2, 3). PR aralığı kardit grubunda belirgin olarak uzundu (U=67,5, p<0,001; Tablo 1; Şekil 4). ASO ve MPV açısından gruplar arasında anlamlı farklılık izlenmedi (Tablo 1).

Çok Değişkenli Analiz

Örneklem büyüklüğü ve değişkenler arası korelasyon dikkate alınarak parsimoniyöz lojistik regresyon modelleri oluşturuldu (Tablo 3). Model A'da (ESR_10+PR_10ms) sedimentasyon (10 mm/saat artış başına) kardit ile bağımsız ilişkili bulundu (aOR=3,12; %95 GA: 1,36–7,16; p=0,007); PR aralığı (10 ms artış başına) sınırda anlamlıydı (aOR=1,96; %95 GA: 0,98–3,92; p=0,058). Duyarlılık analizinde (Model B: CRP+PR_10ms) PR aralığı bağımsız ilişkisini korurken (aOR=1,72; %95 GA: 1,13–2,61; p=0,012), CRP bağımsız bir belirleyici olarak kalmadı (p=0,223).

Bu kohortta kardit varlığı; yüksek ateş, poliartiküler klinik fenotip ve daha yüksek akut faz reaktanları ile birlikte seyretti. Ayrıntılı sayısal sonuçlar Tablo 1–3 ve Şekil 1–4'te sunulmuştur.



Şekil 2. Kardit varlığına göre eritrosit sedimentasyon hızı (mm/saat) dağılımı (kutu grafiği).

Tablo 3. Karditin bağımsız belirleyicileri: parsimoniyöz lojistik regresyon modelleri

Model/değişken	β	aOR	%95 GA	p
Model A (Sedimentasyon_10 + PR_10ms)				
Sedimentasyon (10 mm/saat artış başına)	1.139	3.12	1.36–7.16	0.007
PR aralığı (10 ms artış başına)	0.672	1.96	0.98–3.92	0.058
Model B (CRP + PR_10ms)				
CRP (1 mg/dl artış başına)	0.128	1.14	0.92–1.40	0.223
PR aralığı (10 ms artış başına)	0.539	1.72	1.13–2.61	0.012

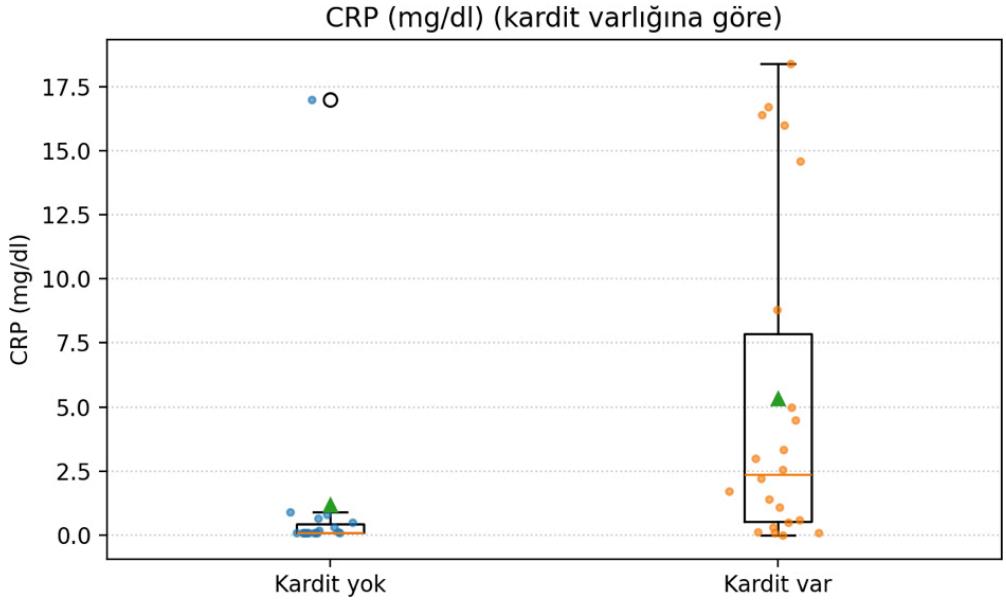
β: Regresyon katsayısı; aOR: Adjusted odds ratio; GA: Güven aralığı (confidence interval); CRP: C-reactive protein; p: P değeri.

TARTIŞMA

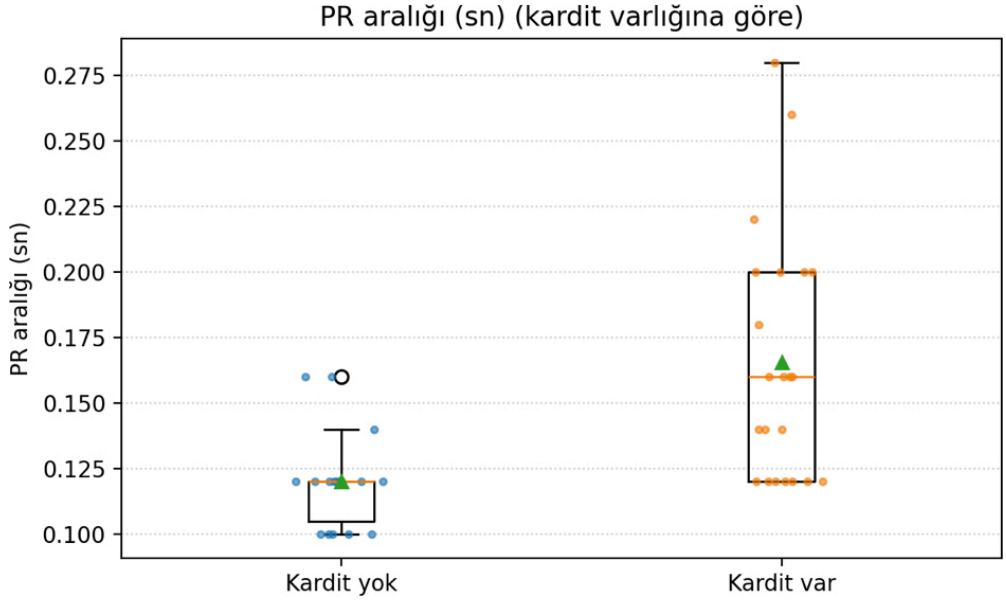
Bu tek merkezli retrospektif çalışmada, akut romatizmal ateş (ARA) olgularında kardit varlığı ile ilişkili klinik ve laboratuvar göstergeleri değerlendirilmiştir. Çalışmanın başlıca bulguları; kardit gelişen olgularda akut faz reaktanlarının belirgin derecede yüksek olması, iletim sistemi tutulumu ile uyumlu şekilde PR aralığının uzaması ve poli-eklem tutulumu (poliartrit/poliartralji) ile yüksek ateşin kardit ile ilişkili klinik bir fenotip oluşturmasıdır. Bu bulgular, ARA'nın tanısında klinik ipuçlarının ekokardiyografik değerlendirme ile birlikte yorumlanmasının önemini bir kez daha ortaya koymaktadır.

ARA, özellikle sosyoekonomik dezavantajlı popülasyonlarda ve gelişmekte olan ülkelerde romatizmal kalp hastalığına (RKH) neden olmaya devam etmektedir. Kardit, ARA'nın morbidite ve uzun dönem sekelinin temel belirleyicisi olup erken tanı ve uygun sekonder profilaksi, RKH yükünü azaltmada kritik rol oynar (2, 10). Amerikan Kalp Derneği'nin 2015 güncellemesi ile Doppler ekokardiyografide saptanan subklinik kardit tanı ölçütlerine dahil edilmiş; ayrıca yüksek riskli popülasyonlarda klinik spektrumun daha geniş olduğu (örn. poliartralji/monoartrit gibi) vurgulanmıştır (5). Klinik uygulama rehberleri de ARA şüphesi olan her olguda ekokardiyografinin kardit saptanması ve şiddetin derecelenmesi açısından temel inceleme olduğunu belirtmektedir (11, 12).

Çalışmamızda karditli olgularda sedimentasyon ve CRP'nin anlamlı olarak yüksek bulunması (Tablo 2), inflamatuvar aktivite ile kardiyak tutulum arasındaki ilişkiyi desteklemektedir. Bununla birlikte, sedimentasyon ve CRP'nin birbirleriyle korele biyobelirteçler olması ve farklı kinetik özellikler göstermesi (CRP'nin daha hızlı yükselip düşmesi; sedimentasyonun daha geç normalleşmesi) nedeniyle, karditi "tek başına" öngören özgül belirteçler olarak değil, hastalık aktivitesini ve sistemik inflamasyon yükünü yansıtan yardımcı parametreler olarak ele alınması daha uygundur (5, 10, 11). Revize edilmiş parsimoniyöz lojistik regresyon analizinde sedimentasyonun bağımsız ilişki göstermesi, sedimentasyonun klinik spektrum içinde daha stabil bir inflamasyon yükü göstergesi olabileceğini düşündürmektedir. CRP'nin duyarlılık analizinde bağımsız belirleyici olarak kalmaması ise örneklem büyüklüğü, ölçüm zamanlaması ve tedavi başlanma zamanı gibi faktörlerden etkilenebilen CRP kinetiği ile açıklanabilir.



Şekil 3. Kardit varlığına göre C-reaktif protein (mg/dl) dağılımı (kutu grafiği).



Şekil 4. Kardit varlığına göre PR aralığı (sn) dağılımı (kutu grafiği).

PR aralığının karditli grupta belirgin uzamış olması ve çok değişkenli analizde de etkisini koruması (özellikle duyarlılık analizinde) klinik açıdan dikkat çekicidir. PR uzaması, Jones kriterlerinde minör ölçütler arasında yer almakla birlikte kardit varlığında iletim sistemi etkileniminin bir yansıması olarak görülebilir (5, 11). Dolayısıyla, özellikle eklem bulgularıyla başvuran olgularda belirgin PR uzaması varlığı, kardiyak değerlendirmeyi (özellikle ekokardiyografi) hızlandırması gereken bir uyarı işareti olarak yorumlanabilir; ancak PR uzamasının karditin bir parçası olabileceği gerçeği göz önünde bulundurularak "prediktör" yerine "eşlik eden bulgu" şeklinde daha temkinli bir yorum tercih edilmelidir.

Eklem fenotipinin kardit ile ilişkisi yönünden, poliartrit ve poliartraljinin kardit ile anlamlı ilişkisi, yüksek riskli popülasyonlarda klinik spektrumun daha geniş olabileceğine dair güncellenmiş Jones kriterleri ile uyumludur (2). Bu bulgu, eklem yakınmalarıyla başvuran olgularda kardit olasılığının yalnızca "klinik üfürüm" varlığına indirgenmemesi gerektiğini, özellikle poli-eklem tutulumunun eşlik ettiği tabloda ekokardiyografinin düşük eşikte planlanmasının uygun olacağını düşündürür (12, 13). Ayrıca ≥38,5°C ateşin kardit ile tek değişkenli analizde güçlü ilişki göstermesi (Tablo 1), yüksek ateşin sistemik inflamasyon yükünü yansıtan bir klinik belirteç olabileceğini destekler. Bu yaklaşım, Jones kriterlerinde risk gruplarına göre ateş ve akut faz reaktanı eşiklerini tanımlayan çerçeve ile de uyumludur (11).

Antistreptolizin-O (ASO) düzeyinin kardit varlığına göre anlamlı farklılık göstermemesi, ASO'nun kardiyak tutulum şiddetini değil, geçirilmiş streptokok enfeksiyonuna ilişkin "kanıt" boyutunu daha iyi yansıttığını düşündürmektedir (5, 11). Bu nokta klinikte önemlidir; çünkü yalnızca yüksek ASO ve eklem yakınmaları ile ARA tanısı konulması veya gereksiz sekonder profilaksi başlanması, sahada sık karşılaşılan bir problemdir. Bir çalışmada, eklem şikâyeti ve yüksek ASO ile başvuran çocuklarda endikasyon dışı penisilin profilaksisinin yaygın olabileceği gösterilmiş; Jones kriterlerine dayalı kanıta dayalı yaklaşımın gerekliliği vurgulanmıştır (14). Bizim bulgularımız, eklem yakınmalarıyla başvuran olgularda kardit risk fenotipinin (poli-eklem tutulumu + yüksek inflamasyon belirteçleri + iletim bulguları) daha seçici bir yaklaşım geliştirmede yardımcı olabileceğini düşündürmektedir.

Hematolojik inflamasyon belirteçleri açısından MPV'nin gruplar arasında farklılık göstermemesi, MPV'nin ARA'da kardit varlığını ayırt etmede tutarlı bir belirteç olmayabileceğini destekler. Trombositlerin inflamasyondaki rolü literatürde ayrıntılı olarak tartışılmış olsa da MPV gibi trombosit indeksleri pre-analitik değişkenlerden etkilenebilmekte ve hastalık alt fenotipleri arasında heterojen sonuçlar verebilmektedir (15). Nitekim Özdemir ve arkadaşları, akut romatizmal karditte MPV ve PDW'nin anlamlı değişiklik göstermeyebileceğini bildirmiştir (16). Bu heterojen literatür, trombosit indekslerinin tek başına tanısal karar verdirici olmaktan ziyade yardımcı/araştırma amaçlı parametreler olarak değerlendirilmesi gerektiğine işaret etmektedir.

Çalışmamızın klinik çıkarımı, ARA şüphesiyle izlenen çocuklarda kardit olasılığını artıran örüntünün poli-eklem tutulumu, yüksek ateş, belirgin inflamasyon (özellikle yüksek sedimentasyon) ve PR uzaması birlikteliği olduğudur. Bu bulgular, karditin erken saptanması ve uygun antiinflamatuvar tedavi ile sekonder profilaksi planlanması açısından önemlidir (5, 10, 11). Ancak, kardit tanısında belirleyici yaklaşım ekokardiyografidir; akut faz reaktanları ve EKG bulguları ekokardiyografik değerlendirmeyi ikame etmez, yalnızca yönlendirir (12, 13).

Çalışmanın retrospektif ve tek merkezli tasarımı, örneklem büyüklüğünün sınırlı olması ve laboratuvar ölçümlerinin başvuru/tanı zamanlamasındaki heterojenlik, nedensellik çıkarımını kısıtlamaktadır. Ayrıca sedimentasyon ve CRP gibi parametreler, başvuru öncesi antiinflamatuvar/antibiyotik kullanımı ile etkilenebilir. Çok değişkenli analizde aşırı uyum riskini azaltmak için parsimoniyöz modeller tercih edilmiş olmakla birlikte, bulguların farklı merkezlerde ve daha geniş örneklemlerde doğrulanması gereklidir.

SONUÇ

Sonuç olarak, ARA olgularında kardit varlığı, daha yüksek inflamasyon yükü (özellikle yüksek sedimentasyon) ve iletim sistemi etkilenimi ile uyumlu EKG bulguları ile birlikte seyretmektedir. Poli-eklem tutulumu ve yüksek ateş gibi klinik özellikler, kardit olasılığını artıran bir fenotip oluşturabilir. Bu bulgular, eklem yakınmalarıyla başvuran çocuklarda Jones kriterlerine dayalı sistematik değerlendirmenin ve düşük eşikte ekokardiyografik incelemenin önemini desteklemektedir.

Etik Kurul Onayı: Bu çalışma, tek merkezli, geriye dönük gözlemsel bir araştırmadır. Çalışma, Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği'nde yürütülmüştür.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Yazarlar, yalnızca dil düzenleme ve metnin okunabilirliğini artırmak amacıyla yapay zeka destekli araçlardan yararlanmıştır. Veri analizi, yorumlama veya bilimsel içerik üretiminde yapay zeka kullanılmamıştır. Tüm içerik yazarlar tarafından gözden geçirilmiş ve onaylanmıştır.

Yazarlık Katkıları: Fikir – DT, NC, ŞG; Tasarım – DT, NC, ŞG; Denetlemeler – DT, NC, ŞG; Kaynaklar – DT, NC, ŞG; Malzemeler – DT, NC; Veri toplanması ve/veya işleme – DT, ŞG; Analiz ve/veya yorumlama – DT, NC; Literatür araştırması – DT, NC; Yazım – DT, NC, ŞG; Eleştirel incelemeler – ŞG, NC.

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Ethics Committee Approval: This study is a single-center, retrospective observational study. The study was conducted at the Department of Pediatrics at Ümraniye Training and Research Hospital, University of Health Sciences.

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ORIGINAL RESEARCH
Pediatric Cardiology

Levetiracetam compared with carbamazepine as monotherapy in children with focal epilepsy

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ABSTRACT

Objective: Carbamazepine (CBZ) has traditionally been used as a first-line agent for pediatric focal epilepsy, yet tolerability issues and potential drug–drug interactions have encouraged the broader use of newer antiseizure medications, including levetiracetam (LEV). Robust head-to-head data comparing LEV with CBZ as initial monotherapy in children remain scarce. In this study, LEV monotherapy was compared with CBZ, a well-established treatment for focal epilepsy, and its efficacy in seizure control and tolerability were evaluated.

Material and Methods: In this prospective, randomized clinical study, 80 children aged 2–14 years with newly diagnosed focal epilepsy meeting International League Against Epilepsy criteria were allocated to LEV (n=37) or CBZ (n=43) monotherapy. Seizure frequency, treatment response, drug resistance, and adverse events were evaluated at baseline and at 3, 6, and 12 months.

Results: Baseline demographic and clinical variables were comparable between groups. Seizure frequency declined significantly over time in both treatment arms. At 3 months, a numerically greater reduction was observed in the LEV group, although the between-group difference was not statistically significant ($p>0.05$); outcomes were similar at 6 months. By 12 months, seizure reduction was achieved in all patients receiving CBZ and in 86.7% of those receiving LEV, without a significant difference between groups ($p=0.155$). Drug resistance rates decreased across follow-up and did not differ significantly at 12 months. Adverse events occurred more often with CBZ, most notably somnolence and cutaneous reactions, whereas behavioral effects, particularly irritability, were more frequent with LEV. No serious hematologic or renal toxicity and no persistent hepatic adverse events were detected.

Conclusion: As initial monotherapy for newly diagnosed focal epilepsy in children, LEV and CBZ show comparable seizure-control efficacy. LEV may offer better overall tolerability, although behavioral symptoms require close surveillance. Both agents represent reasonable first-line options, with selection individualized according to patient-specific risk–benefit considerations.

Keywords: Carbamazepine; children; focal epilepsy; levetiracetam; monotherapy; randomized clinical trial.

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Fokal epilepsili çocuklarda monoterapi olarak levetirasetam ve karbamazepinin karşılaştırılması

ÖZET

Amaç: Karbamazepin (CBZ), pediatrik fokal epilepside geleneksel olarak birinci basamak tedavi olarak kullanılmaktadır; ancak tolere edilebilirlik sorunları ve olası ilaç–ilaç etkileşimleri, levetirasetam (LEV) dahil olmak üzere daha yeni nöbet ilaçlarının kullanımını teşvik etmiştir. Çocuklarda başlangıç monoterapisi olarak LEV ile CBZ'yi doğrudan karşılaştıran güçlü veriler ise sınırlıdır. Bu çalışmada, LEV monoterapisi, fokal epilepside iyi tanımlanmış bir tedavi olan CBZ ile karşılaştırılmış, nöbet kontrolündeki etkinliği ve tolere edilebilirliği değerlendirilmiştir.

Gereç ve Yöntemler: Bu prospektif, randomize klinik çalışmada, Uluslararası Epilepsi ile Savaş Birliği kriterlerine göre yeni tanı almış, fokal epilepsili 2–14 yaş arasındaki 80 çocuk LEV (n=37) veya CBZ (n=43) monoterapisi almak üzere randomize edilmiştir. Nöbet sıklığı, tedavi yanıtı, ilaç direnci ve advers olaylar başlangıçta ve 3., 6. ve 12. aylarda değerlendirilmiştir.

Bulgular: Başlangıçtaki demografik ve klinik özellikler açısından gruplar benzerdi. Nöbet sıklığı her iki tedavi kolunda da zaman içinde anlamlı biçimde azaldı. Üçüncü ayda LEV grubunda sayısal olarak daha belirgin bir azalma gözlenmiş olmakla birlikte, gruplar arasındaki fark istatistiksel olarak anlamlı değildi (p>0,05); altıncı ayda da benzer sonuçlar elde edildi. On ikinci ay sonunda CBZ alan tüm hastalarda ve LEV alan hastaların %86,7'sinde nöbet sıklığında azalma sağlandı; ancak iki grup arasında anlamlı fark saptanmadı (p=0,155). Takip süresince ilaç direnci oranlarında azalma görüldü ve 12. ayda gruplar arasında anlamlı farklılık bulunmadı. Advers olaylar CBZ grubunda daha sık gözlenmiş olup, özellikle somnolans ve kutanöz reaksiyonlar ön plandaydı. LEV grubunda ise irritabilite başta olmak üzere davranışsal yan etkiler daha sık bildirildi. Hiçbir hastada ciddi hematolojik ya da renal toksisite ve kalıcı hepatik advers etki saptanmadı.

Tartışma: Yeni tanı almış pediyatrik fokal epilepside başlangıç monoterapisi olarak levetirasetam ve karbamazepin benzer nöbet kontrolü etkinliği göstermektedir. Levetirasetam genel tolere edilebilirlik açısından bazı avantajlar sağlayabilir; ancak davranışsal yan etkiler açısından dikkatli izlem gereklidir. Her iki ajan da birinci basamak tedavi seçeneği olarak değerlendirilebilir ve tedavi seçimi hasta özellikleri ile risk–yarar dengesi göz önünde bulundurularak bireyselleştirilmelidir.

Anahtar Kelimeler: Çocuk; fokal epilepsi; karbamazepin; levetirasetam; monoterapi; randomize klinik çalışma.

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INTRODUCTION

Epidemiological data suggest that approximately 4–10% of children experience at least one seizure (febrile or afebrile) by 16 years of age. The cumulative lifetime incidence of epilepsy is estimated at around 3%, with more than half of all cases presenting during childhood. The annual prevalence ranges between 0.5% and 1.0% (1). The primary goal of epilepsy management in children is to achieve sustained seizure freedom while preserving normal growth, neurodevelopment, and overall systemic maturation (2).

Antiseizure medications (ASMs) are commonly categorized into first-generation and newer-generation agents (3, 4). Despite the availability of numerous ASMs, nearly half of patients fail to achieve sufficient seizure control with initial monotherapy, and approximately 35% eventually require alternative or more effective treatment strategies (4). In addition, the broad pharmacological profiles of many ASMs and their potential for significant adverse effects make long-term management challenging. Therefore, there remains a continued need for therapies that provide improved efficacy while maintaining better tolerability.

Since its introduction to clinical practice in the early 2000s, levetiracetam (LEV) has been widely used as a newer-generation ASM with broad efficacy and reported safety in various epilepsy syndromes (5, 6). Among first-generation ASMs, carbamazepine (CBZ) has long been considered a first-line treatment for focal epilepsy. However, due to its considerable adverse-effect profile and frequent drug–drug interactions, its use as long-term monotherapy for focal seizures has become less favored in recent years (7, 8). By keeping voltage-gated sodium channels in an inactivated configuration for longer, CBZ decreases high-frequency, repetitive firing in postsynaptic neurons, which underlies its antiepileptic activity. In addition, it inhibits presynaptic neurotransmitter release, leading to suppression of synaptic transmission (9, 10). Common adverse effects of CBZ include somnolence, nausea, vomiting, ataxia, and headache, as well as hepatic and hematological complications, which are typically dose-dependent and more frequently observed during the initial treatment period. Accordingly, regular clinical assessments and laboratory follow-up are required (11).

Levetiracetam was first introduced in 1999 as an effective second-generation ASM and was initially approved as adjunctive therapy for focal seizures in adolescents (12). Its mechanism of action involves binding to synaptic vesicle protein 2A, thereby modulating neurotransmitter release through inhibition of calcium mobilization from intracellular neuronal stores (13). Data derived from double-blind, placebo-controlled studies indicate the efficacy of LEV in both adult and pediatric populations (14, 15). Nevertheless, its safety and efficacy in infants remain less clearly established (16). Although LEV monotherapy or add-on therapy has been associated with mental health-related adverse effects, including mood symptoms, irritability, and paranoid ideation, in a subset of adult patients, it has also been reported to decrease seizure burden and improve quality of life (13, 17). Major advantages of LEV include twice-daily dosing, a favorable tolerability profile, minimal drug–drug interactions, and no requirement for routine serum level monitoring, all of which support its widespread use in epilepsy management (18).

A growing body of literature has focused on LEV monotherapy in childhood epilepsies, including both focal and generalized seizure types (19). Smaller studies have suggested that LEV may be effective when transitioning patients from polytherapy to monotherapy (20). However, randomized controlled trials (RCTs) directly comparing LEV and CBZ monotherapy in children with focal seizures remain limited. Available evidence suggests that LEV monotherapy demonstrates efficacy comparable to that of other ASMs, particularly CBZ, while potentially offering a more favorable adverse-effect profile. Nevertheless, larger-scale RCTs have been recommended to more accurately assess both efficacy and tolerability (21, 22).

In light of the limited number of comparative studies and the clinical importance of selecting the most appropriate ASM for focal seizures in childhood, we conducted this prospective, randomized study to evaluate and compare the efficacy and adverse-effect profiles of LEV and CBZ as monotherapy.

MATERIAL AND METHODS

Ethical Approval

Ethical approval for this study was obtained from the Şişli Etfal Training and Research Hospital Ethics Committee on May 11, 2009 (approval no. 71). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Population and Eligibility Criteria

This study enrolled 80 children aged 2–14 years with newly diagnosed focal epilepsy. All participants had experienced at least two unprovoked seizure events, with an interval of over 24 hours between episodes, and fulfilled the diagnostic criteria of the International League Against Epilepsy (ILAE) (23). Additional inclusion criteria were a normal brain magnetic resonance imaging (MRI) study and confirmation of the diagnosis by electroencephalography (EEG).

Exclusion criteria comprised seizure types not classified as focal according to ILAE definitions, a history of brain injury within the preceding 3 months, known renal, hepatic, or hematological disorders, prior use of antiseizure or psychiatric medications, and refusal to participate by parents or legal guardians.

Enrollment and Baseline Assessment

Patients were selected based on clinical history and neurological examination. Participation was voluntary, and written informed consent was obtained from parents or legal guardians before enrollment. Following neurological examination and EEG evaluation, children with unprovoked seizures were identified. At study entry, a structured questionnaire was completed to collect demographic data and seizure-related characteristics, including seizure type, seizure frequency, seizure duration, and the presence of adverse effects.

All patients underwent baseline EEG, complete blood count (CBC), liver function tests (LFTs), serum creatinine (Cr), and blood urea nitrogen (BUN) assessments as part of the standard clinical evaluation.

Randomization and Treatment Protocol

After confirming eligibility, participants were randomized to one of two treatment groups: the levetiracetam group (LEV; n=37) or the carbamazepine group (CBZ; n=43). In both groups, medications were administered twice daily in either syrup or tablet form, according to the child's age and parental preference.

In the CBZ group, treatment was initiated at a dose of 10 mg/kg/day and increased by 10 mg/kg/day at weekly intervals until the standard maintenance dose of 30 mg/kg/day was reached and maintained. In the LEV group, treatment was similarly initiated at 10 mg/kg/day and titrated weekly by 10 mg/kg/day to a standard dose of 30 mg/kg/day. The maximum allowed doses were 40 mg/kg/day for LEV and 35 mg/kg/day for CBZ (24, 25).

The treatment strategy consisted of dose titration until seizure freedom was achieved. Parents were informed in advance about potential adverse effects and were instructed to maintain a seizure diary documenting seizure characteristics, seizure frequency, seizure duration, medication adherence, and possible adverse events (e.g., somnolence, agitation, nausea, and dermatological reactions).

Follow-up and Outcome Assessment

Parents were advised to contact the study team immediately in the event of serious adverse effects outside scheduled visits. Physical examinations were carried out at each follow-up visit to evaluate potential adverse effects, and routine laboratory tests (CBC and liver and renal function tests) were repeated. Seizure diaries were reviewed at each visit, and relevant data were recorded.

Patients who required discontinuation of treatment due to serious adverse effects or at the treating physician's discretion were withdrawn from the study. After the 3rd-, 6th-, and 12th-month visits, physical examination findings, EEG results, seizure frequency, and adverse-effect rates were compared between the two treatment groups.

Table 1. Comparison of groups according to demographic characteristics

	Levetiracetam (n=37)	Carbamazepine (n=43)	p
Age, (Mean±SD)	8.66±3.45	8.02±3.52	0.417*
Body weight (kg) (Mean±SD)	25.63±10.72	26.09±11.01	0.852*
Gender, n (%)			0.591**
Female	15 (40.5)	20 (46.5)	
Male	22 (59.5)	23 (53.5)	

SD: Standard deviation; *: Student's t-Test; **: Chi-Square Test.

Seizure characteristics, seizure frequency, seizure duration, and adverse effects were evaluated at baseline and at the 3-, 6-, and 12-month follow-up visits. The analyses were conducted using a per-protocol approach, including only patients with available data at the relevant follow-up visit.

Statistical Analysis

Statistical analyses were performed using NCSS 2007 (Number Cruncher Statistical System) and PASS 2008 (Utah, USA). Continuous variables are summarized as mean±standard deviation. Between-group comparisons of independent samples were carried out using Student's t test for normally distributed data and the Mann–Whitney U test when distributional assumptions were not satisfied. Within-group (paired) comparisons were assessed with the paired t test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square test, Fisher's exact test, or, where applicable, the McNemar test. All tests were two-tailed, and statistical significance was set at $p<0.05$.

RESULTS

Study Population and Baseline Characteristics

A total of 80 children were enrolled during the study period and subsequently randomized to the levetiracetam (LEV, n=37) or carbamazepine (CBZ, n=43) groups. During the follow-up period, some patients had missing data or were lost to follow-up; therefore, analyses were performed using the data available at the relevant time points. No statistically significant between-group differences were observed in terms of baseline demographic or clinical characteristics.

Based on clinical history, a broad spectrum of focal seizure types was observed, including focal aware seizures, focal seizures with impaired awareness, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic–clonic seizures. In some patients, precise seizure classification was not possible because seizures were infrequent, occurred exclusively during sleep, were unwitnessed, or were reported by unreliable observers. Nevertheless, no specific epilepsy syndrome or structural abnormality was identified in any patient, including those classified as non-responders.

Table 2. Treatment outcome measures

Seizure frequency	Levetiracetam n (%)	Carbamazepine n (%)	p
Month 3			0.061
Decrease	36 (97.3)	36 (83.7)	
Increase	1 (2.7)	1 (2.7)	
No change	0 (0)	6 (14.0)	
Month 6			0.962
Decrease	30 (81.1)	35 (81.4)	
Increase	4 (10.8)	4 (9.3)	
No change	3 (8.1)	4 (9.3)	
Month 12			0.155
Decrease	26 (86.7)	26 (100)	
Increase	3 (10.0)	0 (0)	
No change	1 (3.3)	0 (0)	

Chi-Square Test.

Patient Characteristics

Prior to the initiation of monotherapy, patients had been treated exclusively with benzodiazepines for acute postictal management, and no other antiseizure medications had been administered. The two treatment groups were comparable with respect to baseline demographic characteristics (Table 1). However, only 70% of the patients were able to complete the 12-month evaluation.

Treatment Efficacy

Seizure incidence between scheduled follow-up visits was compared between treatment groups at 3, 6, and 12 months (Table 2). At the 3-month assessment, patients receiving LEV showed a numerically greater reduction in seizure frequency than those treated with CBZ; however, the between-group difference did not reach statistical significance ($p>0.05$). By month 6, seizure frequency had decreased to a comparable degree in both groups ($p>0.05$). At 12 months, a reduction in seizure frequency was observed in 26/30 patients (86.7%) in the LEV group and in 26/26 patients (100%) in the CBZ group; however, the observed difference did not achieve statistical significance ($p=0.155$).

Table 3. Evaluation of treatment resistance

Drug resistance	Levetiracetam n (%)	Carbamazepine n (%)	p
Month 6			0.240*
Absent	29 (%78)	39 (%90)	
Present	8 (%22)	4 (%10)	
Month 12			0.407*
Absent	28 (%93)	26 (%100)	
Present	2 (%7)	0 (%0)	
Treatment Outcomes at Month 6 vs. Month 12			0.317**

*: Chi-Square Test; **: McNemar Test.

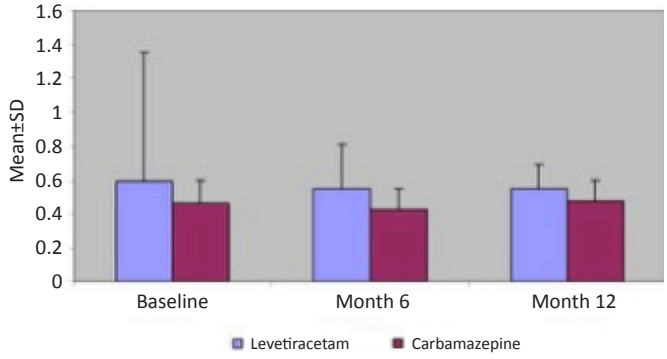

Figure 1. Distribution of serum creatinine levels.

Because of loss to follow-up and missing data, the number of evaluable patients differed across follow-up visits, particularly at month 12.

Assessment of Treatment Resistance

In this study, treatment resistance was defined based on clinical management decisions, specifically discontinuation of the drug or the addition of another medication to the treatment regimen.

The evaluation of treatment resistance is presented in Table 3. No statistically significant difference was observed between the LEV and CBZ groups in terms of the distribution of treatment resistance at 6 months (p=0.240). Similarly, no significant difference was found between the groups at 12 months (p=0.407). In the within-group analysis, the distribution of treatment resistance between the 6- and 12-month assessments was compared using the McNemar test, and no significant change was detected (p=0.317).

Although the proportion of patients classified as treatment-resistant appeared lower at 12 months than at 6 months, this comparison should be interpreted cautiously because the number of patients with available follow-up data differed between time points.

Treatment-related Adverse Events

No hematological or renal complications were reported in either group. Hepatic complications were observed as elevations in liver enzyme levels exceeding three times the upper limit of normal during the first month of treatment. Liver function tests returned to normal within one week after discontinuation of the medication.

Transient liver enzyme elevations were observed during the first month in some patients and resolved after drug discontinuation. No persistent hepatic, hematological, or renal complications were detected during long-term follow-up. Serum creatinine levels remained stable throughout the study period in the LEV group. In the CBZ group, a mild but statistically significant decrease in creatinine levels was observed at 6 months; however, this difference became clinically negligible by the 12-month follow-up (Fig. 1). Overall, both medications appeared safe with respect to long-term renal function.

In the LEV group, irritability was the most commonly reported adverse event, affecting 36% of patients at the 12-month assessment. Inattention and social withdrawal were infrequent throughout follow-up and were no longer observed in the LEV group by month 12. At 3, 6, and 12 months, the distribution of psychological adverse effects differed significantly between the LEV and CBZ groups (p<0.05) (Table 4).

DISCUSSION

Levetiracetam (LEV) has emerged as a promising first-line antiseizure medication for newly diagnosed epilepsy due to its rapid and sustained efficacy in both adults and children with focal-onset seizures, favorable tolerability profile, predictable

Table 4. Distribution of behavioral adverse effects during follow-up

	3-month		6-month		12-month	
	LEV (n=37)	CBZ (n=43)	LEV (n=37)	CBZ (n=43)	LEV (n=30)	CBZ (n=26)
Irritability	13 (35.1)	6 (13.9)	12 (32.4)	3 (6.9)	11 (36.6)	2 (7.6)
Inattention	1 (2.7)	1 (2.3)	1 (2.7)	1 (2.3)	0 (0)	1 (3.8)
Social withdrawal	1 (2.7)	1 (2.3)	1 (2.7)	1 (2.3)	0 (0)	0 (0)
p	0.036		0.007		0.021	

Fisher's exact test. LEV: Levetiracetam; CBZ: Carbamazepine.

pharmacokinetics, absence of enzyme-inducing properties, and limited potential for clinically relevant drug interactions. Despite these advantages, data regarding the efficacy and safety of LEV as monotherapy in childhood epilepsies remain limited, as most available studies have evaluated LEV primarily as adjunctive therapy. Consequently, evidence supporting its use as initial monotherapy in pediatric focal epilepsy is still relatively scarce (26–29).

In this study, we evaluated levetiracetam (LEV) and carbamazepine (CBZ) as first-line monotherapy in children with newly diagnosed focal epilepsy, with particular emphasis on seizure-related outcomes and tolerability. Overall, seizure control achieved with LEV was comparable to that observed with CBZ. Although seizure control appeared numerically higher in the LEV group across the first 3 months, the observed between-group difference did not achieve statistical significance.

Consistent with our findings, previous studies have reported that LEV and CBZ monotherapies demonstrate comparable efficacy and are generally well tolerated for treating pediatric focal epilepsy. In contrast, one study suggested that LEV may be more effective than CBZ in achieving seizure control in childhood focal epilepsies, which is not in agreement with our results (30). Moreover, a randomized controlled clinical trial conducted in adult patients observed no statistically significant efficacy difference between LEV and CBZ as therapy for focal seizures; however, seizure freedom was achieved more rapidly and was sustained for longer durations in adults (31). These more rapid and pronounced treatment responses in adults may be attributable to age-related differences in metabolic rates and physiological characteristics when compared with pediatric populations (21, 32).

Several studies conducted in both adult and pediatric populations have suggested that LEV monotherapy may be effective even at relatively low doses in controlling focal seizures (33–35). In our cohort, treatment with LEV was initiated at 20 mg/kg/day, with dose escalation permitted up to 40 mg/kg/day until seizure freedom was achieved. Notably, none of the patients required discontinuation of LEV due to serious adverse events.

A retrospective chart review evaluating treatment failure rates among children and adolescents receiving LEV, valproate, or oxcarbazepine monotherapy reported higher failure rates with LEV as initial treatment compared with the other agents. This was attributed to insufficient efficacy in generalized and focal epilepsies, respectively. In addition, findings from the SANAD study did not support the use of LEV or zonisamide as first-line treatment in focal epilepsy, instead recommending lamotrigine as the preferred initial therapy. Another study involving 52 patients aged 6 months to 16 years with partial or generalized epilepsy noted a >50% seizure-frequency reduction in roughly half of the cohort and a 25–50% reduction in the remaining half, while in two patients, the drug was withdrawn because of adverse reactions (36–38). The heterogeneity of these results may be explained by methodological differences across studies. In particular, the retrospective design of many studies precluded randomization, and the wide range of LEV doses used in focal epilepsy (27.1–108 mg/kg/day) limited meaningful comparisons of treatment efficacy. In contrast, in our study, a reduction exceeding 50% in seizure frequency was attained by 97.3% of patients at 3 months, 81.1% at 6 months, and 86.7% after one year of follow-up in the LEV group. These findings support LEV as an effective and safe monotherapy option in childhood focal epilepsy. Long-term follow-up revealed low resistance rates and high overall response rates with both medications. Although resistance appeared slightly higher in the LEV group early in treatment, this difference was no longer evident by the 12-month follow-up.

A population-based real-world study using linked healthcare databases from Ontario reported an incidence of acute kidney injury of 30 cases per 10,000 patient-months within the first 30 days after LEV initiation. Similarly, a large claims-based study in the United States demonstrated only a marginal increase in the risk of acute renal failure following LEV initiation compared with other antiseizure medications in previously untreated patients (39, 40) Both LEV and CBZ appeared to be safe with respect to gastrointestinal and renal function during long-term use. Neither medication exerted a clinically significant effect on serum creatinine levels in our cohort.

LEV is generally well tolerated, with behavioral changes and irritability being the most commonly reported adverse effects. The lowest incidence of adverse effects has been reported at doses around 40 mg/kg/day. Psychomotor slowing has been described at higher doses (approximately 65 mg/kg/day) and has been shown to resolve with dose reduction to 50 mg/kg/day. Previous studies have reported significantly higher rates of irritability in LEV-treated patients compared with those receiving CBZ, whereas somnolence has been more frequently observed in the CBZ group (21, 30, 38). In our study, behavioral changes and irritability were also the most frequently observed adverse effects in the LEV group, and the distribution of psychological adverse effects at 3, 6, and 12 months differed significantly between treatment groups ($p<0.05$). As the maximum LEV dose used in our cohort was 30 mg/kg/day, psychomotor slowing was not observed. Importantly, none of our patients discontinued treatment due to adverse effects, underscoring the importance of close behavioral monitoring during LEV therapy.

The strengths of this study include its randomized design, the relatively limited number of randomized clinical trials conducted in pediatric focal epilepsy, the use of a single standardized CBZ formulation, and the achievement of homogeneity between treatment groups. However, several limitations should be acknowledged, including the inability to measure serum levels of the study drugs LEV and CBZ and the lack of systematic assessment of psychological variables such as depression and anxiety. Future prospective research with larger cohorts, extended follow-up, and a more comprehensive assessment of psychological outcomes is needed to support stronger, more definitive clinical conclusions.

CONCLUSION

Our study demonstrates that LEV and CBZ monotherapies exhibit comparable efficacy and safety profiles in children recently diagnosed with focal epilepsy. The favorable tolerability and absence of serious adverse effects associated with LEV support its use as a safe treatment option in pediatric patients. Although careful monitoring for behavioral adverse effects is recommended, both medications appear to be safe with respect to renal and hepatic function during long-term use. Larger, long-term prospective investigations are required to corroborate our observations and build on these results.

Ethics Committee Approval: This study was approved by the Ethics Committee of Şişli Etfal Training and Research Hospital (Date: May 11, 2009, Decision No. 71).

Informed Consent: Written informed consent was obtained from the patient(s) and/or their legal guardian(s) for participation and publication.

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Yazarlık Katkıları: Fikir – İK; Tasarım – İK; Denetlemeler – İK; Kaynaklar – İK, BK; Malzemeler – İK; Veri toplanması ve/veya işleme – BK; Analiz ve/veya yorumlama – İK, BK; Literatür araştırması – BK; Yazım – BK; Eleştirel incelemeler – İK.

Hakemli inceleme: Harici olarak hakemli.

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CASE REPORT
Pediatric Gastroenterology

An asymptomatic case presenting with persistent transaminase elevation: Duchenne muscular dystrophy

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ABSTRACT

A two-year-old male patient was referred to our outpatient clinic due to elevated transaminase levels lasting for approximately one year. Physical examination was normal, but a significant elevation in creatine kinase (CK) was detected along with elevated AST and ALT levels (CK: 7296 U/L). Abdominal ultrasonography revealed no pathology. Although Gowers' sign was absent on physical examination, the significantly elevated CK level suggested a muscle disease, prompting further investigation. Genetic analysis revealed a hemizygous deletion (exon 8-11 deletion) in the Duchenne muscular dystrophy (DMD) gene, leading to a diagnosis of DMD. This case highlights the importance of considering muscle diseases in the differential diagnosis of persistent transaminase elevation and significant CK elevation, even without Gowers' sign on physical examination, both to prevent unnecessary investigations and to enable early diagnosis and treatment.

Keywords: Child; creatine kinase; Duchenne muscular dystrophy; hypertransaminasemia.

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Persistan transaminaz yüksekliği ile seyreden asemptomatik bir vaka: Duchenne musküler distrofi

ÖZET

İki yaşında erkek hasta, yaklaşık bir yıldır devam eden transaminaz yüksekliği nedeniyle polikliniğimize yönlendirilmişti. Fizik muayenesi normal olan hastada AST ve ALT yüksekliğine eşlik eden belirgin kreatin kinaz (CK) yüksekliği saptandı (CK: 7296 U/L). Abdominal ultrasonografide patoloji saptanmadı. Hastanın fizik muayenesinde Gowers belirtisi yoktu; ancak belirgin CK düzeyi yüksekliği nedeniyle hastada kas hastalığı düşünüldü ve buna yönelik ileri inceleme yapıldı. Genetik analizde Duchenne musküler distrofi (DMD) geninde hemizigot delesyon (ekzon 8-11 delesyonu) saptanarak hastaya DMD tanısı konuldu. Persistan transaminaz yüksekliği ve belirgin CK yüksekliği durumunda, fizik muayenede Gowers belirtisi saptanmasa bile ayırıcı tanıda kas hastalıklarının düşünülmesi gerektiğini vurgulayan bu olgu, hem gereksiz tetkiklerin önlenmesi hem de erken tanı ve tedavi açısından önem taşımaktadır.

Anahtar Kelimeler: Çocuk; Duchenne musküler distrofi; hipertransaminazemi; kreatin kinaz.

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GİRİŞ

Duchenne musküler distrofi (DMD), distrofin protein eksikliği ile karakterize, X'e bağlı resesif geçişli ve progresif kas dejenerasyonu ile seyreden en yaygın kas distrofisidir (1). Hastalık genellikle erken çocukluk döneminde kas güçsüzlüğü ile ortaya çıkmakla birlikte, bazı olgularda ilk bulgu biyokimyasal anormallikler olabilir.

Transaminazlar yalnızca hepatositlerde değil, aynı zamanda iskelet kasında da bulunduğundan kas hasarı durumlarında da yükselebilir (2, 3). Bu nedenle DMD gibi kas hastalıkları, özellikle asemptomatik olgularda, yanlışlıkla karaciğer hastalığı olarak değerlendirilebilmekte ve tanıda gecikmeler yaşanabilmektedir. İlaca bağlı transaminaz yüksekliği ön tanısıyla yaklaşık bir yıldır takip edilen, fizik muayenesinde Gowers belirtisi olmayan ve erken dönemde DMD tanısı alan iki yaşındaki bu olgunun sunulmasının amacı, açıklanamayan transaminaz yüksekliğinin ayırıcı tanısında asemptomatik olgularda bile DMD'nin düşünülmesi gerektiğini vurgulamaktır.

OLGU SUNUMU

İki yaşında erkek hasta, ilaca bağlı transaminaz yüksekliği nedeniyle başka bir merkezde yaklaşık bir yıl takip edilmiş ve transaminaz düzeylerinde gerileme olmaması nedeniyle karaciğer hastalığı ön tanısı ile polikliniğimize yönlendirilmişti. Hastanın fizik muayenesinde herhangi bir patoloji saptanmadı ve Gowers belirtisi yoktu. Özgeçmişinde özellik yoktu. Soygeçmişinde anne ve baba arasında ikinci derece akrabalık mevcuttu.

Hastanın yaklaşık bir yıl önce yapılan tetkiklerinde AST: 143 U/L ve ALT: 280 U/L saptanmış ve ilaca bağlı olabileceği düşünülerek hasta bir yıl boyunca başka bir merkezde takibe alınmıştı. Transaminaz yüksekliğinin devam etmesi üzerine hasta ileri tetkik amacıyla polikliniğimize yönlendirilmişti.

Laboratuvar incelemelerinde AST: 204 U/L, ALT: 286 U/L ve kreatin kinaz (CK): 7296 U/L idi. Abdominal ultrasonografide patoloji saptanmadı. Belirgin CK yüksekliği olması üzerine hasta kas hastalığı ön tanısı ile çocuk nöroloji bölümüne yönlendirildi. Ancak çocuk nöroloji bölümü tarafından hastanın fizik muayenesinde özellik saptanmaması nedeniyle kas hastalığı düşünülmemişti.

Tarafımızca hastada karaciğer hastalığı düşünülmedi; öncelikle kas hastalığı düşünüldü ve hasta genetik bölümüne yönlendirildi. Yapılan genetik analizde DMD geninin 8-11. ekzonlarında hemizigot delesyon saptandı ve hastaya DMD tanısı konuldu. Hasta ileri takip ve tedavi planlaması amacıyla çocuk nöroloji kliniğine yönlendirildi.

Bu makale için hastanın ailesinden yazılı hasta onamı alınmıştır.

TARTIŞMA

Çocukluk çağında hipertransaminazemi sık karşılaşılan bir durumdur ve etiyolojisi oldukça geniştir (3). Yüksek transaminaz düzeyleri, karaciğer dışı kaynaklar düşünüldüğünde en sık kas hastalıklarının ve hemolizin bir belirtisi olabilir. Beraberinde belirgin düzeyde CK yüksekliği de varsa bu durum kas yıkımına işaret eder (3). Bu hastalarda bilirubin ve GGT düzeyleri de normal seviyededir (4). CK seviyesindeki yükselmeye ayrıca ilaçlar veya toksinlerin neden olduğu hücresel nekroz ve yoğun egzersiz de neden olabilir (5, 6).

Kas hücre hasarı, AST ve ALT düzeylerinde belirgin artışa neden olabilir. Bu nedenle özellikle açıklanamayan transaminaz yüksekliğinde ilk aşamada CK düzeyinin değerlendirilmesi kritik öneme sahiptir (2, 7). DMD gibi kas distrofilerinde CK düzeyleri genel-

likle belirgin şekilde yüksektir ve bu durum tanı için önemli bir ipucu sağlar (8). DMD'nin erken döneminde klinik bulgular belirsiz olabilir ve fizik muayene normal saptanabilir. Bu nedenle yalnızca klinik bulgulara dayanarak tanı koymak zor olabilir. Literatürde, DMD tanısı alan hastaların bir kısmının ilk olarak hipertransaminazemi nedeniyle değerlendirildiği bildirilmiştir (2, 7, 8).

Bu olgu, persistan transaminaz yüksekliği olan asemptomatik hastalarda öncelikle kas hastalıklarının ayırıcı tanıda düşünülmesi gerektiğini göstermektedir. Erken dönemde CK düzeyi ölçümünün yapılması, gereksiz hepatolojik tetkiklerin önlenmesine ve tanının hızlandırılmasına katkı sağlar.

SONUÇ

Persistan transaminaz yüksekliği ile başvuran asemptomatik çocuk hastalarda, özellikle tabloya belirgin CK yüksekliği de eşlik ediyorsa, kas distrofileri mutlaka ayırıcı tanıda düşünülmelidir. Erken tanı, hastaların uygun şekilde yönlendirilmesi ve yönetimi açısından büyük önem taşımaktadır.

Etik Kurul Onayı: Bu, tek bir vaka raporudur ve bu nedenle kurum politikaları uyarınca etik kurul onayı gerekli görülmemiştir.

Hasta Onamı (veya gönüllü onamı): Bu makale için hastanın ailesinden yazılı hasta onamı alınmıştır.

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Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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Peer-review: Externally peer-reviewed.

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CASE REPORT
Pediatric Gastroenterology

Acute necrotizing pancreatitis in an adolescent patient: A case report

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ABSTRACT

Acute necrotizing pancreatitis (ANP) is a severe form of acute pancreatitis (AP) characterized by necrosis in the pancreatic parenchyma and/or peripancreatic tissue, carrying a high risk of morbidity and mortality. This case report aims to highlight the importance of conservative treatment and a multidisciplinary approach in acute necrotizing pancreatitis. A seventeen-year-old male patient presented with severe abdominal pain and recurrent vomiting. Physical examination revealed only epigastric tenderness. Laboratory investigations revealed significantly elevated serum amylase and lipase levels. Ultrasonography showed findings consistent with AP. Due to a gradual increase in CRP levels and persistent epigastric tenderness, contrast-enhanced abdominal CT revealed increased pancreatic edema and hypodense areas in the trunk and tail sections of the pancreas that did not enhance with contrast. Based on the clinical, laboratory, and radiological findings, the patient was diagnosed with ANP. The patient was treated conservatively with intensive therapy and close clinical monitoring.

Keywords: Acute necrotizing pancreatitis; acute pancreatitis; children.

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Adolesan bir hastada akut nekrotizan pankreatit: Bir vaka sunumu

ÖZET

Akut nekrotizan pankreatit (ANP), pankreas parankiminde ve/veya peripankreatik dokuda nekroz ile karakterize, yüksek morbidite ve mortalite riski taşıyan akut pankreatitin (AP) şiddetli bir formudur. Bu vaka sunumunda, akut nekrotizan pankreatitte konservatif tedavinin ve multidisipliner yaklaşımın önemininin vurgulanması amaçlanmaktadır. On yedi yaşında bir erkek hasta, şiddetli karın ağrısı ve tekrarlayan kusma şikayetiyle başvurdu. Fizik muayenesinde yalnızca epigastrik hassasiyet mevcuttu. Laboratuvar incelemelerinde serum amilaz ve lipaz düzeylerinde belirgin bir yükselme saptandı. Ultrasonografide AP ile uyumlu bulgular saptandı. CRP düzeylerinde kademeli bir artış ve devam eden epigastrik hassasiyet nedeniyle kontrastlı abdominal BT çekildi. BT'de pankreas ödeminde artış ve pankreasın gövde ve kuyruk kısımlarında kontrast tutmayan hipodens alanlar görüldü. Klinik, laboratuvar ve radyolojik bulgulara dayanarak hastaya ANP tanısı konuldu. Hasta yoğun tedavi ve yakın klinik takip ile konservatif olarak tedavi edildi.

Anahtar Kelimeler: Akut nekrotizan pankreatit; akut pankreatit; çocuklar.

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INTRODUCTION

Acute pancreatitis (AP) is a clinical syndrome characterized by acute inflammation of the pancreas, accompanied by abdominal pain and elevated pancreatic enzyme levels. The incidence of AP in children has been reported to increase in recent years (1). The incidence of acute pancreatitis in children is estimated to be approximately 33–74 per 100,000 children per year (1).

The etiology of AP in children differs from that in adults. Biliary tract diseases, drugs, systemic diseases, metabolic disorders, trauma, and genetic causes are the most common etiological factors (1, 2). The etiology is idiopathic in a significant number of cases.

The clinical spectrum of AP ranges from mild edematous pancreatitis to acute necrotizing pancreatitis, characterized by necrosis of the pancreas and surrounding tissues (3). It is estimated that less than 1% of children with acute pancreatitis develop necrotizing pancreatitis (4, 5). Necrotizing pancreatitis is characterized by necrosis of pancreatic or peripancreatic tissue and is associated with serious local and systemic complications (1, 6).

The aim of this case report is to present a case of acute necrotizing pancreatitis that developed and progressed severely in an adolescent patient and to highlight acute necrotizing pancreatitis and the importance of a multidisciplinary treatment approach.

CASE REPORT

A seventeen-year-old male patient presented with complaints of severe epigastric pain and recurrent vomiting that had started suddenly the previous day. It was learned that the pain radiated to the back and worsened with meals. His medical history included no known chronic illnesses, regular medication use, trauma, or alcohol consumption. There was no family history of pancreatitis or metabolic disease.

Physical examination revealed that the patient's general condition was fair, and vital signs were stable (blood pressure: 120/70 mmHg, heart rate: 88/min, temperature: 36.8°C). Abdominal examination showed no pathology except for epigastric tenderness. Other system examinations were normal.

At the time of admission, laboratory tests revealed serum amylase of 600 U/L, lipase of 3144 U/L, C-reactive protein (CRP) of 6 mg/L, and a white blood cell count of 16.59 × 10^3/μL. Liver function tests, total bilirubin, kidney function tests, electrolytes, triglyceride, and calcium levels were within normal limits. The etiological workup was unremarkable. However, serum IgG4 levels could not be measured to evaluate for autoimmune pancreatitis.

Ultrasonography revealed that the head of the pancreas measured 23 mm in the anteroposterior direction and showed a minimally hypoechoic heterogeneous appearance; no free fluid was detected in the abdominal cavity. Contrast-enhanced upper abdominal computed tomography (CT) showed a slightly thickened and edematous pancreas with free fluid in the peripancreatic space; the findings were consistent with acute pancreatitis (Fig. 1).

The patient was followed up with a preliminary diagnosis of AP. Oral intake was stopped, and intravenous fluid replacement (2500 cc/m^2/day) was initiated. Intravenous paracetamol was administered for analgesia, along with a proton pump inhibitor, and cefotaxime was given empirically as an antibiotic after

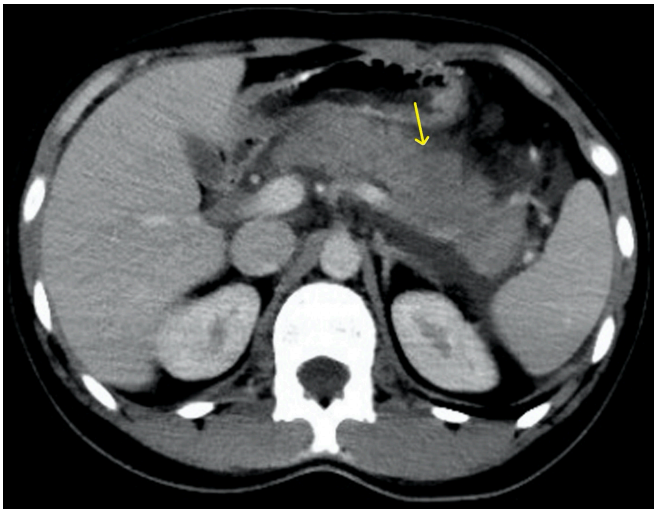

Figure 1. Contrast-enhanced abdominal CT demonstrates diffuse pancreatic enlargement and edema with prominent peripancreatic fat stranding and fluid collections. Heterogeneous hypodense areas at the pancreatic body–tail junction, consistent with parenchymal necrosis, are indicated by yellow arrows.

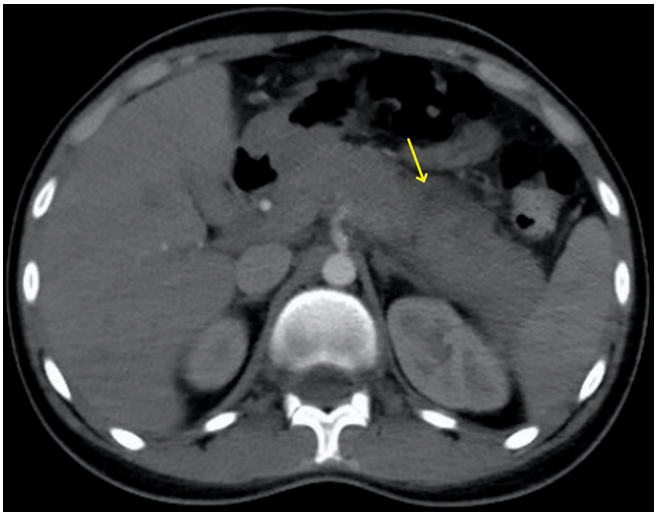

Figure 2. Follow-up contrast-enhanced CT shows increased conspicuity and clearer demarcation of the hypodense necrotic pancreatic areas (yellow arrows), with persistent peripancreatic inflammatory changes.

blood and urine cultures were obtained. On the second day of hospitalization, CRP increased to 39.9 mg/L, amylase increased to 899.7 U/L, while lipase decreased to 2031 U/L.

On the fifth day, the patient was suspected of having infective necrotizing pancreatitis due to the lack of improvement in clinical findings, an increase in CRP to 168.4 mg/L, and the emergence of necrotizing pancreatitis findings on control abdominal CT (Fig. 2). After blood and urine cultures were obtained, antibiotic treatment was changed to vancomycin, meropenem, and metronidazole. After evaluation by pediatric surgery, no urgent surgical indication was considered for the patient.

Due to the persistently elevated CRP levels (206.5 mg/L on day four) and the risk of progression of necrotizing pancreatitis, amikacin was added to the treatment. Additionally, low-dose somatostatin was initiated to reduce pancreatic secretion and prevent damage to surrounding tissues. Since the patient was unable to take oral medication, lipid-free total parenteral nutrition (TPN) was started.

During follow-up, CRP levels began to decrease, and amylase and lipase values returned to normal. Daily assessments by pediatric surgery revealed no abscess, pseudocyst, or condition requiring necrosectomy. Pancreatic anomaly was ruled out by magnetic resonance cholangiopancreatography (MRCP). Due to the presence of necrotizing pancreatitis, a pediatric endocrinology consultation was performed. No hypoglycemic or hyperglycemic episodes were observed during follow-up.

Somatostatin treatment was gradually tapered off and discontinued as clinical improvement progressed. Oral intake was gradually initiated on the eleventh day and was well tolerated. CRP decreased to 6.8 mg/L prior to discharge; amylase/lipase levels were 85/136 U/L on the day of discharge.

At the end of the two-week follow-up and treatment period, the patient's general condition was good, vital signs were stable, oral intake was adequate, abdominal examination was normal, and there was no epigastric tenderness. He was discharged with instructions to return for an outpatient follow-up in one week. Post-discharge follow-up of pancreatic function and endocrine status was planned.

Written informed consent was obtained from the patient's legal guardian for the publication of this case report.

DISCUSSION

It has been reported that there has been a significant increase in pediatric acute pancreatitis cases in recent years due to advances in diagnostic methods and increased awareness (1). Although most cases of AP are mild, necrotizing pancreatitis is seen in a small percentage of patients and is a cause of significant mortality and morbidity (1). Necrotizing pancreatitis is characterized by the development of necrosis in the pancreatic parenchyma or peripancreatic tissue and may lead to serious clinical consequences. This condition carries a significant risk, particularly in terms of systemic inflammatory response, organ failure, and the development of infected necrosis (7).

It is thought that pancreatic microcirculatory disorders, enzymatic autodigestion, and inflammatory cytokines play a role in the pathogenesis of necrotizing pancreatitis (8). This process leads to ischemia and cellular damage in the pancreatic tissue, causing necrosis.

Contrast-enhanced CT is an important imaging method for the diagnosis of necrotizing pancreatitis. Pancreatic areas that do not show contrast enhancement are interpreted as favoring necrosis (5, 9). In the presented case, areas in the pancreatic parenchyma that did not show contrast enhancement were detected on CT examination, supporting the diagnosis of necrotizing

pancreatitis. In addition, MRCP is a valuable approach for ruling out possible congenital anomalies and determining etiological factors. No anomalies were detected in our case on MRCP.

The cornerstone of acute necrotizing pancreatitis treatment is intensive supportive care. Aggressive intravenous fluid therapy administered early is critical for preserving pancreatic microcirculation and preventing organ failure (1, 10). In addition, appropriate analgesia, electrolyte balance, nutritional support, and early diagnosis of complications are essential components of treatment.

It has been shown that early enteral nutrition can reduce the risk of infection by protecting intestinal barrier function (1). However, initial parenteral nutritional support may be required in severe clinical conditions such as necrotizing pancreatitis. In our case, discontinuation of oral intake and the application of TPN contributed to the functional rest of the pancreas.

The development of infected necrosis is one of the most serious complications of necrotizing pancreatitis. Although the use of prophylactic antibiotics is controversial, empirical broad-spectrum antibiotic therapy is recommended in cases where infected necrosis is suspected (1, 8). In our case, the progressive increase in CRP levels and imaging findings suggested the risk of infected necrosis. Because acute infected necrotizing pancreatitis can lead to serious morbidity and mortality in children, aggressive treatment is necessary upon diagnosis; therefore, combination therapy with multiple antibiotics and lipid-free total parenteral nutrition are initiated early.

Somatostatin and its analogues can help rest the pancreas by suppressing pancreatic secretion. Although routine use is not recommended, it may be considered as an addition to treatment in selected severe cases (9). The use of somatostatin was preferred considering the severity of the clinical picture in our patient.

A significant proportion of necrotizing pancreatitis cases can be managed with conservative treatment. Surgical or interventional treatment is usually considered in patients who develop infected necrosis, persistent organ failure, or symptomatic collections (1). Early diagnosis, intensive supportive therapy, a multidisciplinary approach, and thorough clinical monitoring allowed for clinical improvement in the presented case without major sequelae. This demonstrates the importance of early diagnosis and a multidisciplinary approach in pediatric acute necrotizing pancreatitis.

CONCLUSION

Acute necrotizing pancreatitis is a rare but serious disease associated with high mortality and morbidity. Therefore, it should be diagnosed early and followed up and treated with a multidisciplinary approach.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient's legal guardian for the publication of this case report.

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Etik Kurul Onayı: Bu, tek bir vaka raporudur ve bu nedenle kurum politikaları uyarınca etik kurul onayı gerekli görülmemiştir.

Hasta Onamı (veya gönüllü onamı): Bu vaka raporunun yayınlanması için hastanın yasal vasisinden yazılı bilgilendirilmiş onam alınmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Yazarlar, yalnızca dil düzeltmesi ve dilbilgisi iyileştirmeleri amacıyla kullanılan yapay zekanın sağladığı yardıma teşekkür ederler.

Yazarlık Katkıları: Fikir – AÜ, ARF, YŞ; Tasarım – AÜ, ARF, YŞ; Denetlemeler – YŞ; Kaynaklar – AÜ, ARF, DY, RBP, YŞ; Malzemeler – AÜ, ARF, DY, RBP, YŞ; Veri toplanması ve/veya işleme – AÜ, ARF, DY, RBP, YŞ; Analiz ve/veya yorumlama – AÜ, ARF, DY, RBP, YŞ; Literatür araştırması – AÜ, ARF, YŞ; Yazım – AÜ, ARF, YŞ; Eleştirel incelemeler – RBP, YŞ.

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