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ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Trombositopeni Ön Tanısı ile Tetkik Edilen Çocukların Klinik ve Laboratuvar Bulgularının Retrospektif İncelenmesi

Clinical and Laboratory Analysis of Children Who Follow Up with Thrombocytopenia: A Retrospective Study

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Öz

Giriş: Trombositler pıhtı tıkacının oluştuğu hemostazın ilk fazında önemli rol oynayan hücrelerdir. Trombositlerin sayı veya fonksiyon bozuklukları kanamaya yol açabilir. Çocukluk çağında trombositopeni etiyolojisinden birçok durum sorumluyken en sık nedeni immun trombositopenilerdir. Çalışmanın amacı; trombositopeni gelişen çocuklarda, nedenleri araştırmak, tedavi ve takip stratejilerini değerlendirmek, tanıdaki ve tedavideki gecikmeleri azaltmak olarak belirlendi.

Gereç ve Yöntem: Çalışmamızda Ocak 2010-Aralık 2015 tarih aralığında kliniğimize başvuran D69.3, D69.4, D69.5, D69.6 İCD kodlarından en az biri verilmiş olan 1500 hasta değerlendirildi. Dahil edilme kriterlerine uymayan hastalar çalışma dışında bırakılınca toplam 440 hasta ile trombositopeni formu doldurulduru.

Bulgular: Çalışmamızda yıllık trombositopeni insidansı 100 000 hastada 8,4 ve İTP insidansı 5,1 olarak bulundu. Hastaların %59'u erkek, %41'i kız cinsiyete sahipti ve ortalama yaşı 6,6±2,1 yıl olarak hesaplandı. En sık trombositopeni nedeni %62 ile immun trombositopeni (İTP) olarak bulundu. İTP hastalarının %49,2'sinde geçirilmiş üst solunum yolu enfeksiyonu öyküsü mevcuttu. Aşı öyküsü sorgulandığında; 40 hastada son 6 hafta içinde aşı yaptırma öyküsü mevcuttu. İTP hastalarının %10,5'inde ilaç kullanımına bağlı trombositopeni saptandı. Tüm hastaların %6,1'inin yenidoğan döneminde olduğu görüldü. İTP hastalarının %53,1'ine tedavi verildi. İntravenöz immunglobulin tedavisine yanıt süresi 36,8±1,2 saat ve steroid tedavisine yanıt süresi 63,2±1,2 saat olarak bulundu. İTP hastalarının %80,6'sında trombosit normale dönme süresi 0-3 ay arasındaydı. Kronikleşme görülen 36 hastanın 25'inin birincil İTP ve 11'inin ikincil İTP olduğu görüldü.

Sonuç: Çocukluk çağında trombositopeni nadir saptanan bir laboratuvar sonucudur. Trombositopeni saptanan hastalarda iyi bir öykü, özgeçmiş-soygeçmiş incelemesi; detaylı fizik muayene ile doğru laboratuvar testleri kullanılarak konjenital trombositopeni sendromları, lösemi, immun trombositopeniler, aplastik anemi gibi kemik iliği supresyonu yapan hastalıklar ya da altta yatan enfeksiyonlar, solid maligniteler saptanabilmektedir. Tedavide hastaların birçoğunda trombosit düzeyinin komplikasyon geliştirmeden ilk 3 ayda kendiliğinden normale dönmesi göz önünde bulundurularak uygun hastalarda "izle ve bekle" stratejisinin uygulanması önemlidir.

Anahtar kelimeler
Çocukluk çağı trombositopenisi, immun trombositopeni, yenidoğan trombositopenisi

Keywords
Childhood thrombocytopenia, immune thrombocytopenia, newborn thrombocytopenia

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Abstract

Introduction: Platelets are cells that play an important role in the first phase of hemostasis, where the clot plug is formed. Disorders in the number or function of platelets can lead to bleeding. While many conditions are responsible for the etiology of thrombocytopenia in childhood, the most common cause is immune thrombocytopenia. The aim of the study was to investigate the causes, evaluate treatment and follow-up strategies, and reduce delays in diagnosis and treatment in children who develop thrombocytopenia.

Materials and Methods: In our study, 1500 patients who applied to our clinic between January 2010 and December 2015 and were given at least one of the ICD codes D69.3, D69.4, D69.5, and D69.6 were evaluated. When patients who did not meet the inclusion criteria were excluded from the study, a total of 440 patients were asked to fill out the thrombocytopenia form.

Results: In our study, the incidence of thrombocytopenia was 8.4: 100.000, and the incidence of ITP was 5.1. 59% of patients were male, and 41% were female. The mean age was 6.6±2.1 years. The most common cause of thrombocytopenia was found to be immune thrombocytopenia (ITP). 49.2% of ITP patients had a history of upper respiratory tract infection. 40 patients had a history of vaccination within the last 6 weeks. Drug-induced thrombocytopenia was detected in 10.5% of İTP patients. It was seen that 6.1% of all patients were in the neonatal period. Treatment was given to 53.1% of ITP patients. The response time to intravenous immunoglobulin and steroid treatments was 36.8±1.2 and 63.2±1.2 hours, respectively. Platelet recovery time was between 0-3 months in 80.6% of ITP patients. Of the 36 chronic İTP patients, 25 had primary ITP, and 11 had secondary ITP.

Conclusion: Thrombocytopenia is a rare laboratory result in childhood. In patients with thrombocytopenia, detailed history, physical examination, and correct laboratory tests can be used to detect congenital thrombocytopenia syndromes, leukemia, İTP, aplastic anemia or underlying infections, and solid malignancies. Considering that platelet levels return to normal spontaneously in the first three months without developing complications in most patients, it is important to apply the "watch and wait" strategy in appropriate patients.

Giriş

Trombositler pıhtı tıkacının oluştuğu hemostazın ilk fazında önemli rol oynayan hücrelerdir. 100.000/mm^3 altındaki değerler trombositopeni olarak kabul edilmektedir (1). Çocukluk çağında trombositopeni etiyolojisinden birçok durum sorumluyken en sık nedeni immun trombositopenilerdir (İTP) (1-2). Bu çalışmanın amacı; trombositopeni gelişen çocuklarda, nedenleri araştırmak, tedavi ve takip stratejilerini değerlendirmek, tanıdaki ve tedavideki gecikmeleri azaltmak olarak belirlendi.

Gereç ve Yöntem

Hasta Seçimi

Ocak 2010-Aralık 2015 tarih aralığında başvuran D69.3, D69.4, D69.5, D69. Altı İCD kodlarından en az biri verilmiş olan 1500 hasta değerlendirildi. 674 hastada trombositopeni olmaması nedeniyle çalışmaya alınmadı (hatalı tanı kodu). Trombositopeni saptanan 826 hastadan; 73 hastanın dosyasına ulaşılamamasından, 232 hasta aktif kemoterapi tedavisi almakta olduğundan ve 81 hasta malign olmayan kronik hematolojik hastalık nedenli takipli olduğu için çalışmadan çıkarıldı. Toplamda 440 hasta ile çalışma yapıldı. Birincil İTP hastalarından; üç hasta yatış gerektirdiği ve kliniğimizde yer olmaması dolayısıyla sevk edildiği, sekiz hasta takipten çıktığı için çalışmadan çıkarıldı. İkincil İTP hastalarından dört hasta takipten çıktığı için çalışmadan çıkarıldı. Geriye kalan 258 hastada İTP tanısı ile analiz tamamlandı.

Laboratuvar

Trombositopeni, 50-100.000/mm^3 arası hafif, 20.000-49.900/mm^3 arası orta, 10.000-19.900/mm^3 arası ağır ve 0-9.900/mm3 arası ciddi trombositopeni olarak değerlendirildi (3). Hastalarda lökosit ve hemoglobin değerleri "Lanzkowsky's Manual of Pediatric Hematology and Oncology 6th edition, 2016" referans değerlerine göre belirlendi (3). Hastalarda ortalama trombosit hacmi değerlendirilirken 6,5-11 femtolitre (fL) arası normal olarak, 6,5 fL altı düşük, 11 fL üstü değerler yüksek olarak alındı (3). Bursa Uludağ Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu Onayı (tarih: 16.02.2016, karar no: 2016-3/10) alındı.

İstatistiksel Analiz

İstatistiksel analizler IBM SPSS-23 paket programı kullanılarak yapıldı. Frekans analizleri, ikili gruplu kategorik değişkenler için Pearson ki-Kare ve Fisher's Exact testleri, çok gruplu kategorik değişkenler ikili bir değişken açısından artan veya azalan bir trend (eğilim) izleyip izlemediğini araştırmak için Mantel-Haensel doğrusal ilişki testi (ki-kare trend testi) kullanıldı. $p<0,05$ anlamlı olarak kabul edildi.

Bulgular

Ocak 2010-Aralık 2015 tarih aralığında merkezimize yapılan tüm başvurular ve trombositopeni olguları değerlendirildiğinde, trombositopeni insidansı 100.000 hastada 8,4 olarak bulundu. Çalışmaya alınan hastaların erkek-kız oranı 1,43:1 idi ve ortalama hasta yaşı 6,6±2,1 yıl olarak hesaplandı. Tanı dağılımının %60,7 İTP, %26,8 maligniteye ikincil trombositopeni, %6,1 yenidoğan trombositopenisi, %5 otoimmun hastalıklara bağlı trombositopeni, %0,7 immun yetmezlik nedeniyle trombositopeni ve %0,7 enfeksiyona ikincil trombositopeni olduğu görüldü (Tablo 1).

İmmun Trombositopeni (İTP)

İkiyüzellisekiz hastaya İTP tanısı konuldu. İTP insidansı 5,1:100.000 olarak bulundu. En sık başvuru şikâyeti dış merkezde trombositopeni saptanıp üst merkeze sevk edilmeydi (%45,7). Diğer en sık nedenler döküntü (%22,1) ve vücutta morluk saptanmasıydı (%15,9). Erkek-kız oranı 1,41:1 idi (birincil İTP 1,28:1, ikincil İTP 1,48:1). Olguların %46,1'i 2-10 yaş aralığında (oyun çocuğu) iken; %31'inin 28 gün-2 yaş (süt çocuğu) ve %22,9'unun 10 yaş üstünde (ergenlik ve adölesan çağ) olduğu görüldü. Başvurunun mevsimsel dağılımı ise sırayla yaz (%32,2), ilkbahar (%25,2), kış (%25,2) ve sonbahar (%17,4) olarak bulundu. Tüm İTP olgularının %83'ünde lökosit sayıları; %91,5'inde hemoglobin düzeyi normal aralıktaydı. Olguların %34,1'inde hafif, %23,3'ünde orta, %23,3'ünde ciddi ve %15,5'inde ağır trombositopeni saptandı. Olguların %65,5'i ikincil İTP, %34,5'i birincil İTP tanısı aldı. Viral serolojik tetkikler öykü ve fizik muayeneye göre çalışıldı (%57,8) ve yalnızca olguların %12,1'inde pozitif saptandı: Sitomegalovirus (CMV) IgM (n:7), Ebstein Barr virüs (EBV) IgM pozitifliği (n:7), Parvovirus IgM (n:5), suçiçeği IgM (n:2), Salmonella IgM (n:1) ve Kızamık IgM (n:1). İTP hastalarının %53,9'unda aile öyküsü, ek hastalık, özgeçmiş ve klinik seyir sorgulanarak otoimmun tetkikler çalışıldı. Hastaların %82 hastada negatif, %18 hastada pozitif olarak bulundu: Anti-nükleer antikor (ANA) (n:23), anti trombosit antikor (n:6), anti kardiyolipin IgM (n:5) ve anti çift zincir (ds) DNA (n:3). Yüz otuz dört (%52) İTP hastasında direk coombs testi yapıldı. Bu hastalardan sadece 2'sinde direk coombs pozitif olarak bulundu. Bu hastalar Evans sendromu açısından takibe alındı, izlemde hemolitik anemi görülmedi.

Tablo 1. Trombositopeni saptanıp çalışmaya alınan tüm hastaların tanılara göre dağılımı

	Hastalık	Olgu sayısı
İTP (n:267)*	Birincil İTP	97
	İkincil İTP	170
Malignite (n:118)	Akut Lenfoblastik Lösemi (ALL)	90
	Akut Myeloblastik Lösemi (AML)	22
	Juvenil Monomyelositer Lösemi (JMML)	2
	Kronik Myelositer Lösemi (KML)	1
	Lenfoma	1
	Nöroblastom	2
Yenidoğan (n:27)	Erken neonatal sepsis	10
	İtpli anne bebeği	5
	Alloimmun trombositopeni	2
	Koryoamniyonit	2
	Hepatit B aşı öyküsü	3
	Lupuslu anne bebeği	1
	Schwachman diamond	1
	Bernard Soulier hastalığı	1
	Wiskott Aldrich sendromu	1
	Karaciğerde hemanjiom	1
İmmun yetmezlikler (n:3)	Hiper İgM Send+ Noonan Sendromu	1
	Kostman hastalığı	1
	SCİD	1
Otoimmun hastalıklar (n:22)	Kobalamin C defekti	1
	SLE	2
	Siroz	1
	Psödotrombositopeni (EDTA Fenomeni)	5
	Bernard soulier hastalığı	2
	Aplastik anemi	11
Enfeksiyona ikincil (n:3)	Leishmaniazis	1
	Tüberküloza ikincil hemofagositik lenfohistiyositoz (HLH)	1
	Hemolitik üremik sendrom	1

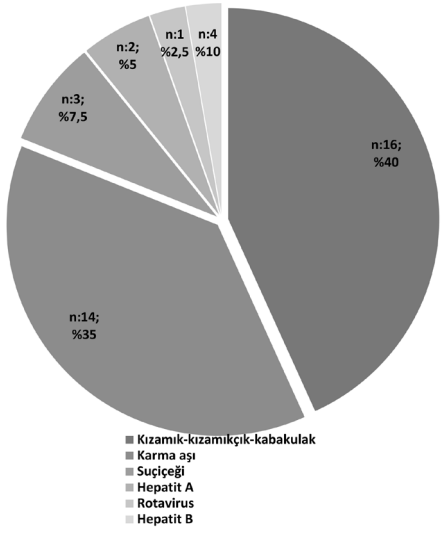
SCID: Ağır kombine immun yetmezlik, SLE: Sistemik lupus eritematozis, EDTA: Etilendiamin tetraasetik asit, *3 hasta yenidoğan döneminde gösterildi, 3 hasta kronik hastalık ve ikincil İTP olması nedenli kronik hastalığı ile tabloya alındı. Çalışmadan ayrılan İTP olguları nedeniyle istatistik 258 olgu ile tamamlandı

İTP hastalarında en sık saptanan fizik muayene bulgularını üst solunum yolu enfeksiyonu (ÜSYE) bulguları (%49,2) ve peteşi (%47,3) oluşturmaktaydı.

Aşı öyküsü sorgulandığında İTP olarak değerlendirilen 40 hastada son 6 hafta içinde aşı yaptırma öyküsü mevcuttu (%15,5). Bu aşıların %50 oranıyla canlı aşı (kızamık-kızamıkçık-kabakulak, suçiçeği, rotavirus) olduğu görüldü (Şekil 1). İki hastada aynı anda birden fazla aşının uygulanmış olduğu görüldü (Kızamık-kızamıkçık-kabakulak ve suçiçeği; difteri-aselüler boğmaca-tetanoz-inaktif polio-H. influenza tip B (beşli karma aşısı) ve rotavirus). Aşıya bağlı trombositopeni saptanan bu hastalarda daha sonraki aşı uygulamalarında trombositopeninin tekrarlamadığı görüldü. 27 İTP olgusunda (%10,5) ilaç kullanımına bağlı trombositopeni saptandı ve en sık sebebi antiepileptik ilaç kullanımıydı (%77,7). Bu hastalarda ilaç kesimi veya doz azaltımı ile trombositopenide düzelme saptandı ve izlemde tekrarlamadığı gözlendi.

Yenidoğan Trombositopenisi

Tüm hastaların %6,1'inin (n:27) yenidoğan döneminde olduğu görüldü. Erken neonatal sepsis saptanan 9, annesinde kronik İTP mevcut olan 5, alloimmun trombositopeni saptanan 2, annesinde koryoamniyonit öyküsü olan 2, son 15 gün içinde hepatit B aşısı öyküsü mevcut olan 3, lupuslu anne bebeği olarak değerlendirilen 1 ve karaciğerde hemanjiom saptanan hastanın trombosit normale dönme süresi 0-3 ay arasında (yeni tanı konmuş İTP) olduğu bulundu. Kandida sepsisi saptanan bir erken neonatal sepsis hastasının trombosit değerlerinin 5. ayda normale döndüğü görüldü (persistan İTP).



Şekil 1. Aşıya bağlı immun trombositopeni gelişen hastalarda uygulanan aşıların dağılımı

İmmun Trombositopenide Tedavi

İTP hastalarının 137'sine (%53,1); fizik muayenede yaş peteşi, mukozal kanama veya diğer kanama bulguları (uzamış âdet kanaması, burun kanaması, diş eti kanaması, hematüri) ve trombosit sayısı 10.000/mm^3 altında olup periferik yaymada bunun doğrulanması şartıyla tedavi verildiği görüldü. Hastalardan 77'sine (%29,8) intravenöz immunoglobulin (İVİG), 22'sine (%8,5) steroid ve 12'sine (%4,7) İVİG ve steroid tedavileri beraber verilmişti. Bir kronik İTP hastası Rituksimab (anti-CD20) tedavisi aldı. İVİG tedavisi verilen 77 hastanın 74'ünde İVİG yanıtı görüldü, 3 hastada yanıt alınamadı. Ortalama yanıt süresi 36,8±1,2 saat olarak bulundu. İVİG tedavisi verilen 1 hastada İVİG sonrası alerjik reaksiyon gelişti. On hastaya birden fazla İVİG tedavisi verilmesi gerekti. İki hastada öncelikle İVİG yanıtı olmayıp 2. dozda yanıt alındı. İki hastada önce İVİG sonra steroid tedavileri uygulandı ancak iki tedaviye de yanıt alınamadı. Bu 2 hastadan birine sonrasında Rituksimab tedavisi de denendi ancak bu tedaviye de yanıt alınamadı. İki hastada İVİG tedavisine yanıt alınmazken sonrasında verilen steroid tedavisine sırasıyla 48. ve 72. saatlerde yanıt alındı. Steroid tedavisi verilen 22 hastanın 18'inde steroid yanıtı görüldü. Ortalama yanıt süresi 63,2±1,2 saat olarak bulundu. Dört hastada steroid yanıtı alınamadı. İki hastada tedaviye yanıt süresi 10 günden uzun bulundu.

İmmun Trombositopenide Kronikleşme

İTP olgularının trombosit normale dönme süreleri; %80,6 0-3 ay (yeni tanı konmuş İTP), %5,4 3-12 ay (persistan İTP) ve %14 12 aydan daha uzun (kronik İTP) saptandı (2 olguda 12-24 ay). Kronikleşme görülen 36 hastanın 25'inin (%28,1) birincil İTP ve sadece 11'inin (%6,5) ikincil İTP olduğu görüldü. Birincil İTP olan olgularda kronikleşme oranı ikincil ITP olgularına göre anlamlı oranda daha fazla olduğu görüldü ($p<0.05$). İTP'nin kronikleşmesi hem İVİG hem steroid alan olgularda (%75), İVİG veya steroid den birini alanlara (%20) ve tedavi almayanlara (%7) göre anlamlı düzeyde yüksek olarak saptandı ($p<0,05$).

Tartışma

Çalışmamızda trombositopeni insidansı 8,4:100.000, İTP insidansı 5,1:100.000 olarak bulundu. Hastaların erkek-kız oranı 1,43:1 idi ve

ortalama hasta yaşı 6,6±2,1 yıl olarak hesaplandı. %60,7 oranla en sık trombositopeni nedeni İTP olarak bulundu. Literatürde de çocukluk çağı trombositopenisinin en sık nedeni olarak bildirilen İTP insidansı 2,2-6:100.000 olup çalışmamızla benzerdir (4-15). Türkiye veya Güney Marmara bölgesi için literatürde insidans verisi görülmemiştir. Fransa'da yapılan bir çalışmada İTP saptanma sıklığının 2 ve 14 yaşlarında pik yaptığı, en sık görülme yaşının 2-9 yaş aralığı olduğu ve 6 ay-4 yaş arasında kızlarda; ergenlik yaşında ise erkeklerde daha sık görüldüğü belirtilmiştir (10). Tayland'da yapılan çalışmada yine en sık görülme yaşının 6-10 yaş arası olduğu ve %62,8 oranıyla kız hastalarda daha sık görüldüğü belirtilmiştir (16). Evim ve ark. (17) Türkiye'de 201 hasta ile yaptığı çalışmada da kız hastalarda daha sık görüldüğü belirtilmiştir. Amerika'da 311 hasta ile yapılan çalışmada da %53 oranıyla kızlarda daha sık bulunmuştur (18). Frederiksen ve ark. (14) yaptığı bir çalışmada ise bebeklikten çocukluğa kadar erkek çocuklarda kız çocuklarına göre daha yaygın olduğu, ergenlikte ve genç yetişkinlerde ise tam tersinin geçerli olduğu bildirilmiştir. Bu yaş gruplarındaki kadınlarda daha sık görülmesinin ise otoimmüniteyi arttırabilen östrojenin etkisi olabileceği yorumu yapılmıştır (14-15,19). Başka bir çalışmada ise özellikle ikincil İTP'de kadın dominansının olmadığı vurgulanmıştır (20). Çalışmamızda ise İTP'nin erkeklerde görülme daha fazla iken, yaş aralığı literatürle uyumlu saptandı. İTP olgularımızda erkek cinsiyetin daha yüksek oranda saptanmasının, ikincil İTP olgularının çoğunlukta olması (%65,5), ortalama yaşın kız cinsiyet dominansının kaybolduğu 6,6±2,1 yıl olması ve çoğu olgunun 2 yaş üzerinde tanı (%69) alması nedeniyle olduğu düşünülmektedir. Literatürde İTP'nin en sık ortaya çıkış döneminin viral enfeksiyon etkisine bağlı olarak bahar ayları olduğu bildirilmiştir (15,21). Çalışmamızda İTP tanısı alan hastaların en sık başvurduğu mevsim %32,2 oranıyla yaz olarak bulundu ancak mevsimler arasında istatistiksel olarak anlamlı fark saptanmadı. Evim ve ark. (17) yaptığı çalışmada da mevsimsel farklılık saptanmadığı bildirilmiştir. Hastaların tam kan sayımı genel olarak değerlendirildiğinde lökosit ve hemoglobin sayıları çoğu hastada normal aralıktaydı (%83; %91,5) ve literatürle uyumlu bulundu (9,11,16,22). Birincil İTP altta yatan bir sebebe bağlı olmadan ortaya çıkan idiyopatik veya otoimmunite ile ilişkili olabilen immun trombositepeni olarak tanımlanmaktadır ve izole trombositopeni ile kendini göstermektedir. Çoklu humoral ve hücresel immün anormallikler, hızlandırılmış trombosit yıkımı ve baskılanmış trombosit üretimi ile sonuçlanır. Tanısı, diğer trombositopeni nedenlerinin klinik olarak dışlanması ile konulur (15,19-20). İkincil İTP'de ise genellikle ilaçlar, enfeksiyonlar, aşılar ve SLE gibi diğer otoimmün durumlar da dahil olmak üzere dış bir neden vardır (20). Çalışmamızda İTP olgularının çoğu (%65,5) ikincil İTP olarak değerlendirildi (En sık enfeksiyona, aşılamaya ve ilaç kullanımına ikincil). İTP hastalarının %7'sinde viral seroloji pozitifliği görüldü. Viral enfeksiyonlarda "moleküler benzerlik" nedeniyle trombositlere karşı antikor gelişmesi ve trombositlerin dolaşımdan temizlenmesi nedeniyle oluştuğuna dair çalışmalar bulunmaktadır. Özellikle EBV ve CMV enfeksiyonlarına bağlı trombositopeni belirtilmiştir ve çalışmamızla benzerdir (23-24). Çalışmamızda İTP hastalarının %18'inde otoimmun tetkikler pozitif olarak bulundu. İTP tanısı alan hastalarda SLE gibi diğer otoimmun hastalıklar ile birliktelik bildirilmiş olup (25), Hazzan ve ark. (26) yaptığı çalışmada ANA pozitifliği saptanan hastaların 4,2 yıl izleminde %3,6'sının SLE tanısı aldığı görülmüştür. Çalışmamızda benzer şekilde ANA pozitif saptanan 2 hastaya daha sonra SLE tanısı konulmuştur. Başka çalışmalarda ANA pozitifliği saptanan çocuk hastalarda kronikleşme ile daha ilişkili bulunduğu belirtilmiştir (27-28), çalışmamızda ise otoantikor pozitifliği ile kronikleşme açısından anlamlı ilişki saptanmadı. Çalışmamızda İTP olgularının %15,5'inde son 6 hafta içinde aşı yapılma öyküsü mevcuttu. Bu uygulanan aşıların %50 oranıyla canlı aşı (kızamık-kızamıkçık-kabakulak, suçiçeği, rotavirus) olduğu görüldü. Benzer bir çalışmada 12 hastada aşılama sonrası (6 olguda 2. doz hepatit B aşısı, 2 olguda birinci doz kızamık-kızamıkçık-kabakulak aşısı ve 1 olguda 1. doz suçiçeği aşısı) İTP geliştiği bildirilmiştir. (29). Kanada'da aşı sonrası İTP gelişen 107 hastada yapılan çalışmada özellikle kızamık-kızamıkçık-kabakulak aşısının neden olduğu belirtilmiştir (30). Literatürde kızamık-kızamıkçık-kabakulak aşısının canlı aşılar arasında en çok İTP yol açan aşı olduğu, 100.000 dozda yaklaşık 0,087-4'lük bir insidans saptandığı ve komplikasyon çoğunlukla çocuklarda görüldüğü bildirilmiştir (23,31-33). Benzer şekilde COVID-19 pandemisi sonrası mRNA COVİD-19 aşılarının da İTP'ye yol açtığı birçok yayında belirtilmiştir (34-37). Aşılama sonrası trombositopeni saptanan bu

hastalarda trombosit otoantikoru üretimi için en çok kabul gören hipotezler "moleküler benzerlik" ve "aşı antijenleri ile insan hücreleri arasındaki çapraz reaksiyon" olarak literatürde bildirilmiştir. Bu, otoreaktif B veya T lenfositlerin aktivasyonu, anti-platelet antikorlarının ortaya çıkması, epitop yayılması ve poliklonal bağışıklık reaksiyonu İTP ile sonuçlanmaktadır (29-33,37). Hastalarımızda daha sonraki aşı uygulamalarında trombositopeninin tekrarlamadığı görüldü; aşıların tekrarlayan dozlarının yapılmasında herhangi bir sakınca görülmedi. İmmun trombositopenik hastaların %10,5'inde ilaç kullanımına bağlı trombositopeni saptandı ve anti-epileptikler birinci sıradaydı. Bu hastalarda ilaç kesimi veya doz azaltımı ile trombositopenide düzelme saptandı ve izlemde tekrarlamadığı gözlendi. Bu klinik tecrübeye dayanılarak özellikle antiepileptik tedavi alan hastaların klinik bulguları olmasa bile aralıklı olarak tam kan sayımı tetkiklerini yapılmasının uygun olacağı düşünüldü. Çalışmamızda yenidoğan döneminde en sık sepsis nedeniyle trombositopeni saptandı ve yalnızca sepsis tedavisi ile trombosit sayısı normale döndü. Çalışmamıza alınan İTP olgularında tedavi olarak İVİG, steroid veya İVİG ve steroid tedavisi uygulanmıştı. İVİG tedavisi verilen 77 hastanın 74'ünde, steroid tedavisi verilen 22 hastanın ise 18'inde yanıt görüldü. Trombosit sayısı normale dönme süresi ise İVİG verilen hastalarda daha kısa olduğu saptandı (36,8±1,2 saat). Tüm bu veriler literatürle uyumlu olarak bulundu (17-19,38). Tüm İTP hastalarının %80,6'sında 0-6 ay, %5,4'ü 3-12 ayda trombosit sayısı normale döndü. %14 hastada ise 12 aydan uzun sürdü. Kronikleşme görülen 36 hastanın 25'inin (%28,1) birincil İTP ve sadece 11'inin (%6,5) ikincil İTP olduğu görüldü. Birincil ITP olan olgularda kronikleşme oranı İkincil ITP olgularına göre anlamlı oranda daha fazla olduğu görüldü ($p<0,05$). Kronikleşme hem İVİG hem steroid alanlarda, İVİG veya steroidden birini alanlara ve tedavi almayanlara göre anlamlı düzeyde yüksek olarak saptandı ($p<0,05$). Bu kronikleşme farkının hem İVİG hem de steroid tedavisi alan hastaların zaten tedaviye geç veya zor yanıt verdiği için ikinci ilaca ihtiyaç duyduğunu düşündürmektedir. Grimaldi-Bensouda tarafından yapılan bir çalışmada hastaların izleminde Amerika'da özellikle "izle ve bekle" stratejisinin uygulandığı belirtilmiştir (10). Çalışmamızda da kronikleşme görülen hastaların büyük çoğunluğunun farmakolojik tedavi almasına rağmen kronik seyretmiş olması, tedavisiz izlenen 121 (%46,9) hastanın trombosit düzeyinin komplikasyon geliştirmeden ilk 3 ayda kendiliğinden normale dönmesi ve verilen farmakolojik tedavilerin de yan etkilerinin olabilmesi nedeniyle "izle ve bekle" stratejisinin önemini bize bir kez daha göstermiştir.

Çalışmanın Kısıtlılıkları

Çalışma geriye dönük olarak dosya taraması ile yapılmıştır.

Sonuç

Sonuç olarak çocukluk çağında trombositopeni saptanan olgularda doğru anamnez alınmalı, detaylı fizik muayene yapılmalı ve tedavi planı yapılırken altta yatan neden iyi aydınlatılmalıdır. İTP olgularının birçoğunda trombosit düzeyinin komplikasyon geliştirmeden ilk 3 ayda kendiliğinden normale dönmesi göz önünde bulundurularak uygun hastalarda "izle ve bekle" stratejisinin uygulanması önemlidir.

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Kaynaklar

1. Mcguinn C, Bussel J. Lanzkowsky's manual of pediatric hematology and oncology. Elsevier Academic Press. 2016;6:239-78.
2. Robert SH, Kenneth AA, Henry MR. Hematology in clinical practice. 4th edition. 2009;4:319-79.
3. Mcguinn C, Bussel J. Disorders of platelets. Lanzkowsky's manual of pediatric hematology and oncology. 6th edition. Elsevier Academic Press. 2016;709-21.
4. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:4190-207.
5. Flaujac C, Boukour S, Cramer-Bordé E. Platelets and viruses: an ambivalent relationship. Cell Mol Life Sci. 2010;67:545-56.
6. Assinger A. Platelets and infection - an emerging role of platelets in viral infection. Front Immunol. 2014;5:649.
7. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions

and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-93.

8. Donato H, Picón A, Martinez M, Rapetti MC, Rosso A, Gomez S, et al. Demographic data, natural history, and prognostic factors of idiopathic thrombocytopenic purpura in children: a multicentered study from Argentina. Pediatr Blood Cancer. 2009;52:491-6.
9. Imbach P, Kühne T, Müller D, Berchtold W, Zimmerman S, Elalfy M, Buchanan GR. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). Pediatr Blood Cancer. 2006;46:351-6.
10. Grimaldi-Bensouda L, Nordon C, Leblanc T, Abenhaim L, Allali S, Armari-Alla C, et al. Childhood immune thrombocytopenia: a nationwide cohort study on condition management and outcomes. Pediatr Blood Cancer. 2017;64:e26389.
11. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. Am J Hematol. 2010;85:174-80.
12. Kühne T, Berchtold W, Michaels LA, Wu R, Donato H, Espina B, et al. Intercontinental Cooperative ITP Study Group. Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. Haematologica. 2011;96:1831-7.
13. Lee JY, Lee JH, Lee H, Kang B, Kim JW, Kim SH, et al. Epidemiology and management of primary immune thrombocytopenia: a nationwide population-based study in Korea. Thromb Res. 2017;155:86-91.
14. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood. 1999;94:909-13.
15. Pietras NM, Gupta N, Justiz Vaillant AA, Pearson-Shaver AL. Immune thrombocytopenia. 2024 May 5. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
16. Chotsampancharoen T, Sripornsawan P, Duangchoo S, Wongchanchailert M, McNeil E. Clinical outcome of childhood chronic immune thrombocytopenia: a 38-year experience from a single tertiary center in Thailand. Pediatr Blood Cancer. 2017;64:e26598.
17. Evim MS, Baytan B, Güneş AM. Childhood immune thrombocytopenia: long-term follow-up data evaluated by the criteria of the International Working Group on Immune Thrombocytopenic Purpura. Turk J Haematol. 2014;31:32-9.
18. Schultz CL, Mitra N, Schapira MM, Lambert MP. Influence of the American Society of Hematology guidelines on the management of newly diagnosed childhood immune thrombocytopenia. JAMA Pediatr. 2014;168:e142214.
19. Liu XG, Hou Y, Hou M. How we treat primary immune thrombocytopenia in adults. J Hematol Oncol. 2023;16:4.
20. González-López TJ, Provan D, Bárez A, Bernardo-Gutiérrez A, Bernat S, Martínez-Carballeira D, et al. Primary and secondary immune thrombocytopenia (ITP): Time for a rethink. Blood Rev. 2023;61:101112.
21. Sfaihi L, Kassar O, Medhaffar M, Kamoun T, Hadiji S, Aloulou H, et al. Thrombocytopénie immune primaire de L'Enfant: etude régionale dans le sud Tunisien [Primary immune thrombocytopenia in childhood: a regional study in the south of Tunisia]. Tunis Med. 2014;92:219-23.
22. Yildiz I, Ozdemir N, Celkan T, Soylu S, Karaman S, Canbolat A, et al. Initial management of childhood acute immune thrombocytopenia: single-center experience of 32 years. Pediatr Hematol Oncol. 2015;32:406-14.
23. Wu Z, Zhou J, Wei X, Wang X, Li Y, Peng B, Niu T. The role of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in immune thrombocytopenia. Hematology. 2013;18:295-9.
24. Amir A, Gilad O, Yacobovich J, Scheuerman O, Tamary H, Garty BZ. Post-varicella thrombocytopenic purpura. Acta Paediatr. 2010;99:1385-8.
25. Ktona E, Barbullushi M, Backa T, Idrizi A, Shpata V, Roshi E. Evaluation of thrombocytopenia in systemic lupus erythematosus and correlation with different organs damages. Mater Sociomed. 2014;26:122-4.
26. Hazzan R, Mukamel M, Yacobovich J, Yaniv I, Tamary H. Risk factors for future development of systemic lupus erythematosus in children with idiopathic thrombocytopenic purpura. Pediatr Blood Cancer. 2006;47:657-9.
27. Altintas A, Ozel A, Okur N, Okur N, Cil T, Pasa S, Ayyildiz O. Prevalence and clinical significance of elevated antinuclear antibody test in children and adult patients with idiopathic thrombocytopenic purpura. J Thromb Thrombolysis. 2007;24:163-8.
28. Heitink-Pollé KM, Nijsten J, Boonacker CW, de Haas M, Bruin MC. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Blood. 2014;124:3295-307.
29. O'Leary ST, Glanz JM, McClure DL, Akhtar A, Daley MF, Nakasato C, et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. Pediatrics. 2012;129:248-55.
30. Rajantie J, Zeller B, Treutiger I, Rosthöj S. NOPHO ITP working group and five national study groups. Vaccination associated thrombocytopenic purpura in children. Vaccine. 2007;25:1838-40.
31. Vrbensky JR, Moore JE, Arnold DM, Smith JW, Kelton JG, Nazy I. The sensitivity and specificity of platelet autoantibody testing in immune thrombocytopenia: a systematic review and meta-analysis of a diagnostic test. J Thromb Haemost. 2019;17:787-94.
32. Gan G, Liu H, Liang Z, Zhang G, Liu X, Ma L. Vaccine-associated thrombocytopenia. Thromb Res. 2022;220:12-20.
33. Yokomichi H, Tanaka-Taya K, Koshida R, Nakano T, Yasui Y, Mori M, et al. Immune thrombocytopenic purpura risk by live, inactivated and simultaneous vaccinations among Japanese adults, children and infants: a matched case-control study. Int J Hematol. 2020;112:105-14.
34. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2021;39:3329-32.
35. David P, Dotan A, Mahroum N, Shoenfeld Y. Immune Thrombocytopenic Purpura (ITP) triggered by COVID-19 infection and vaccination. Isr Med Assoc J. 2021;23:378-80.
36. Malayala SV, Mohan G, Vasireddy D, Atluri P. Purpuric rash and thrombocytopenia after the mRNA-1273 (Moderna) COVID-19 vaccine. Cureus. 2021;13:e14099.
37. Bidari A, Asgarian S, Pour Mohammad A, Naderi D, Anaraki SR, Gholizadeh Mesgarha M, et al. Immune thrombocytopenic purpura secondary to COVID-19 vaccination: a systematic review. Eur J Haematol. 2023;110:335-53.
38. Higashigawa M, Maeyama T, Yoshino A, Matsuda K, Ito M, Maji T, et al. Incidence of childhood primary immune thrombocytopenic purpura. Pediatr Int. 2015;57:1041-3.

ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Nicotine Addiction in Adolescents

Ergenlerde Nikotin Bağımlılığının Değerlendirilmesi

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Abstract

Introduction: Those who start smoking during adolescence have a higher risk of developing an addiction. This study aimed to evaluate cigarette addiction in the adolescents who smoke.

Materials and Methods: Cross-sectional, observational, single center study. Two hundred sixty middle and late-aged adolescents 14 years and over who presented to the adolescent and pediatric polyclinic and declared that they were smokers were included in the study.

Results: In our study, 81 (31.2%) were female and 179 (68.8%) were male. The mean age of the 260 adolescents was 17.0±1.5 years. The mean age at the first attempt was 13.9±2.3 years, and the mean age of starting regular smoking was 14.2±2.1 years. The age range at which the adolescents started smoking the most was 14-17 years (73%). According to the mFTQ test, approximately 70% of the adolescents and 90% according to the HONC test were nicotine dependent. Addiction scores of late-age adolescence were higher. We found that although males smoked more by percentage, sex was not associated with addiction. According to both tests related to addiction used in our study, as the number of cigarettes increases (mFTQ test: $p<0.0001$; HONC test: $p<0.001$) addiction also increases.

Conclusion: It was observed that there was a high rate of addiction among smokers. In addition, it was found that the age of starting smoking is low in our studyand the addiction increases as the age of starting smoking decreases.

Keywords
Adolescent, smoking, nicotine addiction, HONC, mFTQ

Anahtar kelimeler
Adölesan, sigara içme, nikotin bağımlılığı, HONC, mFTQ

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Öz

Giriş: Ergenlik döneminde sigaraya başlayanların bağımlılık geliştirme riski daha yüksektir. Bu çalışma sigara içen adölesanlarda sigara bağımlılığını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Kesitsel, gözlemsel, tek merkezli çalışma. Adölesan ve pediatri polikliniğine başvuran ve sigara içtiğini beyan eden 14 yaş ve üzeri, iki yüz altmış orta ve geç dönem adölesan çalışmaya dahil edildi.

Bulgular: Çalışmamızda 81 (%31,2) kişi kız, 179 (%68,8) kişi erkekti. 260 adölesanın yaş ortalaması 17,0 ± 1,5 yıldı. İlk denemedeki yaş ortalaması 13,9 ± 2,3 yıl, düzenli sigaraya başlama yaş ortalaması ise 14,2 ± 2,1 yıldı. Ergenlerin en çok sigaraya başladığı yaş aralığı 14-17 yaş aralığıydı (%73). mFTQ testine göre adölesanların yaklaşık %70'i, HONC testine göre ise %90'ı nikotine bağımlıydı. Geç ergenlik döneminde bağımlılık puanları daha yüksekti. Erkeklerin yüzde olarak daha fazla sigara içtiğini ancak cinsiyetin bağımlılıkla ilişkili olmadığını bulduk. Çalışmamızda bağımlılıkla ilgili kullanılan her iki teste göre; sigara içilen kişi sayısı arttıkça (mFTQ testi: $p<0,0001$; HONC testi: $p<0,001$) bağımlılık artmaktadır.

Sonuç: Sigara içenler arasında bağımlılık oranının yüksek olduğu gözlemlenmiştir. Ayrıca çalışmamızda sigaraya başlama yaşının düşük olduğu ve sigaraya başlama yaşı düştükçe bağımlılığın arttığı bulunmuştur.

Introduction

It is known that initiation and addiction to smoking often occur before the age of 20 years. Adolescence, which is considered the transition period from childhood to adulthood, is a period of rapid growth and development in which physical, psychological, social, and cognitive changes are experienced. During this period, adolescents see themselves as very strong physically and think that they will not be harmed, which leads them to engage in risky behaviors. It has been observed that cigarette addiction also begins in adolescence and continues in adulthood (1). In adolescents, the first dose of nicotine may leave a permanent mark on the brain and cause disruptions in the reward system in the brain. Nicotine withdrawal symptoms in adolescents can occur even with low cigarette consumption (2). This situation also paves the way for adolescents to become addicted more quickly. As noted in A Report of Surgeon General 2014, if people do not start smoking by the age of 26 years, they usually do not start thereafter (3).

Starting to smoke is the process in which psychodynamic factors are effective along with environmental and social conditions on the genetic background. The impact on the environment and society is undeniable. Individuals trying to find a place in society try to imitate role models. Considering the social learning theory, adolescents are affected by adults in two ways. The first is imitation. The second is to internalize the behavior of others. Reasons such as deterioration of balance in the family, substance addiction among parents, and neglect by the family lead individuals to substance addiction (4,5). In addition, peer and social influence and peer habits in adolescence are effective in starting and quitting smoking.

According to the World Health Organization, nicotine addiction is defined as follows: substance abuse, continuing to use the substance despite adverse effects, and the emergence of withdrawal symptoms in the person when trying to quit. According to the WHO, tobacco addiction is included in the international disease classification with F17 (6). According to DSM 5, nicotine addiction must have occurred in the last 12 months, and in order for addiction and withdrawal to be defined, the smoker must meet at least 2 of the 11 current addiction criteria (7). The World Health Organization reports that the main element in substance addiction is the individual's lack of control over the substance. DSM defines it as the loss of control over the amount and duration of substance use. The Hooked on Nicotine Test is another test that measures nicotine addiction. According to the HONC Test, the onset of addiction can be defined as the moment when the individual loses full autonomy over tobacco use. Autonomy theory does not assume that all symptoms of addiction are a result of the pharmacological effects of nicotine. Autonomy theory assumes that what appears to be a single clinical syndrome actually represents a mixture resulting from multiple independent mechanisms. Therefore, no single mechanistic theory can explain all the features of the clinical syndromes of addiction. The autonomy model allows the reconciliation of competing addiction theories into a single model (8,9). In our study, we planned to see the results of these two tests on addiction in our study group and to obtain better results by using both tests together.

Although there are studies on the frequency of smoking, there is no study investigating nicotine addiction and withdrawal symptoms in adolescents in our country. The present study aimed to evaluate the addiction status of adolescents who smoke.

Materials and Methods

Study Design

The study was conducted at adolescent polyclinic, and general pediatrics polyclinic. Approval was obtained from the Education Planning Board for the study to be conducted in the adolescent outpatient clinic and general pediatric polyclinic of our hospital. This was a single-center, cross-sectional study conducted between January 2018 and January 2019. This cross-sectional study was approved by the local Ethics Committee of Keçiören Training and Research Hospital (date: 13.12.2017, approval number:1561). Our study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki.

Two hundred sixty adolescents aged 14 years and over, middle and late-age adolescents who smoked and presented to the outpatient clinic were included. Adolescents were classified as middle-age (age 14-17 years) and late-age (17-21 years) (10). Smoker patients with chronic diseases were not included in the study. A questionnaire developed by the researchers was administered to all adolescents face-to-face to those who agreed to participate in the study.

In the first part of the survey, the adolescent's age, sex, education level, education and occupation of the parents, with whom they lived, the number of siblings, the number of people living at home, the monthly income level of the family, the amount of pocket money received from the family, the age at which they first tried smoking, their family awareness of smoking, smoking at home, and sports habits. In the second part of the questionnaire, they were asked about their school status (private, state, vocational school), whether their friends at school smoked, their smoking in and around school, and whether or not smoking bans could be applied in their school or institution. After they were allowed to answer the questionnaire questions, the Modified Fagerström Test for Nicotine Dependence (mFTQ) and Hooked on Nicotine Checklist (HONC) were administered (11-13). The HONC Test is scored from 0 to 10. 0 is considered no loss of autonomy, 10 is considered complete loss of autonomy. Up to 7 points in the HONC Test were considered dependent, 8 points and above were considered highly dependent. In the evaluation of the mFTQ Test, 0-2 points were defined as no dependency, 3-5 points as dependency, and 6 and above as highly dependent. Both test contents were given in Supplemental Files.

Statistical Analysis

The Statistical Package for the Social Sciences version 25.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics are given as numbers and percentages for qualitative variables, and as mean, median (25-75 percentile), standard deviation, minimum and maximum for quantitative variables. As univariate analyses, Student's t-test and one-way analysis of variance (one-way ANOVA) tests were used to compare group means. In cases of violation of the homogeneity assumption, Welch t and Welch ANOVA tests were used. The relationship between numerical variables was examined using Pearson's correlation test. Backward multiple regression analysis was used in multivariate analyses. The analysis of the data was evaluated to the level of significance of $p<0.05$ at 95% confidence intervals.

Results

The mean age of the 260 adolescents included in the study was 17.0±1.5 years, with 177 (68.1%) middle-age adolescents and 83 (31.9%) late-age adolescence. Two hundred (76.9%) of the adolescents lived with their parents, and 30 (11.5%) stated that they lived only with their mother or father due to the divorce of their parents. When the parental education levels of the adolescents were evaluated, it was determined that 89 (34.2%) of their mothers were high school graduates, 24 (9.2%) were university graduates, 114 (43.8%) of their fathers were high school graduates, and 39 (15%) were university graduates. The families of 164 (63.1%) adolescents knew that they smoked; the families of 96 (36.9%) adolescents were not aware of their smoking. One hundred twenty-two of the adolescents (46.9%) could smoke at home, and 138 (53.1%) stated that they did not smoke at home.

Two hundred thirty-eight (91.5%) adolescents stated that they had no health problems, and 22 (8.5%) said they did not have a chronic disease, but they were frequently sick (such as frequent upper respiratory tract infections, and allergies). One hundred thirty-one (50.4%) adolescents stated that they did sports, and 129 (49.6%) stated that they did not do any sports.

The mean age of regular smoking in adolescents was 14.2 (range, 6-20) years, and the mean age of first smoking was 14 (range, 5-20) years. The median number of cigarettes smoked per day was 10 (range, 5-20), and the median number of cigarettes smoked per week was 60 (range, 21-105). Among the adolescents in our study, the earliest age of starting smoking was 5 years, and the latest age was 18 years. The highest ratio to start smoking was between the ages of 14-17, and 73% of adolescents started smoking at an early age. Another remarkable finding was that 5.4% started smoking under the age of 10 years. Approximately 20% of adolescents started smoking between the ages of 10-13 years and only 2% started smoking after the age of 18 years.

There was no relationship between female and male gender with addiction according to the mFTQ

and HONC test (p=0.9559 for mFTQ and p=0.663 for HONC test). Addiction scores were found to be similar in both genders.

In our study, the number of cigarettes smoked by the subjects per day was found to be related to addiction in both tests. Addiction increased as the number of cigarettes smoked per day increased (p<0.001). Number of cigarettes used, and dependency relationship of both tests are shown in Table 1 and Table 2 separately.

When the factors that most affect smoking addiction in adolescents were examined, according to the mFTQ test, it was observed that the level of addiction increased with higher income levels of the family (p<0.001), high pocket money received from the family (p=0.001), the number of cigarettes smoked per day (p<0.001), and as the age of the adolescent increased (p<0.001). According to the mFTQ test scores, it was seen that the most effective factor in the addiction of adolescents was the number of cigarettes smoked per day. As the number of cigarettes smoked per day increased, addiction increased (rs=0.687, p<0.001). According to the HONC test, age, the total income of the family, pocket money received from the family, and the number of cigarettes smoked per day were statistically significant (p<0.001, p=0.018, p=0.001, and p<0.001). The relationship between the demographic data of the adolescents and addiction is given in Table 3.

After univariate analyses, backward stepwise regression analysis was performed with the variables found to be significant in terms of mFTQ scores (dependent variable). In this method, all variables are included in the model, then the variable with the lowest contribution to the model is removed and the model is rebuilt, this process continues until a meaningful model is obtained. The overall model was found to be significant (F=46.319, p<0.001). The model explains approximately 56% of the variance in the mFTQ score (dependent variable). If the statistics

Table 1. Demographic and addiction-related characteristics of adolescent smokers

Demographic characteristics		**Number of patients**	**Percentage (%)**
Gender	Female	81	31.2
	Male	179	68.8
Age (years)	Middle adolescence (14-17)	177	68.1
	Late adolescence (18-21)	83	31.9
Someone in the family who smokes	No	72	27.7
	Yes	188	72.3
Buy a pack of cigarettes	Yes	202	77.7
	No	58	22.3
Age of starting smoking	Under 10 years old	14	5.4
	10-13 years old	51	19.6
	14-17 years old	190	73.1
	18 years old and above	5	1.9
Number of cigarettes smoked per day	5 and below	90	34.6
	6-10	71	27.3
	11-15	29	11.2
	16 and above	70	26.9
Addiction according to mFTQ test	Not dependent	82	31.6
	Dependent	101	38.8
	Highly dependent	77	29.6
Addiction according to HONC test	Not dependent	29	11
	Dependent	138	53
	Highly dependent	93	36

HONC: Hooked on nicotine checklist, mFTQ: Modified fagerström test for nicotine dependence

Table 2. Examination of the relationship between the number of cigarettes used with addiction according to HONC test scores and mFTQ test scores			
Parameters	**Number of patients**	**HONC test scores**	
The relationship between the number of cigarettes and addiction			
6 or fewer cigarettes	90	2.6±2.4	**p<0.001***
6-10 cigarettes	71	6.0±3.1	
11-15 cigarettes	29	6.2±3.5	
16 or more cigarettes	70	7.7±2.6	
Parameters	**Number of patients**	**mFTQ test scores**	
The relationship between the number of cigarettes and addiction			
6 or fewer cigarettes	90	1.9±1.6	**p<0.001****
6-10 cigarettes	71	3.9±1.7	

Table 3. The relationship between the demographic data and addiction				
	mFTQ test score		**HONC test score**	
	Pearson r	**p-value**	**Pearson r**	**p-value**
mFTQ score	1.000	-	0.720	**<0.001***
HONC score	0.720	<0.001*	1.000	**-**
Age	0.283	<0.001*	0.267	**<0.001***
Family income	0.208	<0.001*	0.146	**0.018***
Pocket money	0.247	0.001*	0.197	**0.001***
Age at first smoking	-0.190	0.002*	-0.112	**0.041***
Dependency duration (from the first cigarette)	0.133	0.031*	0.056	**0.368***
Cigarettes smoked per day	0.687	<0.001*	0.543	**<0.001***
Modified fagerström test for nicotine dependence, HONC: Hooked on nicotine checklist, *Pearson's rank correlation coefficient				

obtained are interpreted, a one-unit increase in the age variable causes a 0.17-unit increase in the mFTQ score, and if there is a smoker in the family, a 0.42-unit increase in the mFTQ score. If the family knows that the adolescent smokes, there is a 0.93 unit increase in the mFTQ score, and each increase in the number of cigarettes smoked per day causes a 0.16 unit increase in the mFTQ score. In addition, the mFTQ score of those whose fathers have a high school education is 0.56 units higher than the score of those whose fathers are primary school graduates. The MFTQ scores of those whose fathers are university graduates are 0.66 units higher than the scores of those whose fathers are primary school graduates. The three most important variables that have the most significant impact on the mFTQ score are; Number of cigarettes smoked per day (Beta=0.52), knowing that the family smokes (Beta=0.19) and being able to smoke at home (Beta=0.13), respectively. The effects of demographic data on addiction according to the mFTQ test are shown in Table 4.

After univariate analyses, backward stepwise regression analysis was performed with the variables found to be significant in terms of mFTQ scores (dependent variable). In this method, all variables are included in the model, then the variable with the lowest contribution to the model is removed and the model is rebuilt, this process continues until a meaningful model is obtained. The overall model was found to be significant (F=33.368, p<0.001). The model explains approximately 44% of the variance in the HONC score (dependent variable). If the statistics obtained are interpreted, a one-unit increase in the age variable will result in a 0.268-unit increase in the HONC score, if there is a smoker in the family, a 1.023-unit increase in the HONC score, if the adolescent can afford to buy cigarettes, a -1.34-unit increase in the HONC score, and if the family knows that he smokes, a 1.54-unit increase in the HONC score. Each increase in the number of cigarettes smoked per day causes an increase of 0.159 units in the HONC score. The three most important variables that have the most significant impact on the HONC score are; Number of cigarettes smoked per day (Beta=0.34), knowing that the family smokes (Beta=0.21) and being able to buy cigarettes (Beta=0.16), respectively. The effects of demographic data on addiction according to the HONC test are shown in Table 5.

In our study, a strong correlation between the two tests was found at 0.720 in demonstrating cigarette addiction in adolescents.

Discussion

In this study, it was found that cigarette addiction in middle and late-age adolescents was 70% according to the mFTQ test and 90% according to the HONC test. According to both tests, it was determined that the most important factors affecting addiction were the number of cigarettes smoked per day, the amount of pocket money received from the family, and the high income of the family. It was determined that addiction increased when the family was aware of the smoking status and if the adolescent could smoke at home. In our study, it was observed that late-age adolescents were more dependent than middle-age adolescents. Addiction increased as the age of onset of smoking decreased. The mean age of regular smoking among the adolescents was 14.2±2.1 years, and the mean age of first smoking was 13.9±2.3 years. Surprisingly, the earliest age to start smoking was 5 years; 14 (5.4%) adolescents started smoking under the age of 10 years. The highest ratio to start smoking was between the ages of 14-17, and 73% of adolescents started smoking at such an early age.

Early experience with smoking addiction and sex-specific risks have been the focus of some research. It has been shown that smoking affects the reward pathway more in men than in women and that the sex factor is the main driver of the relationship between cigarette craving and early relapse (14). Pogun et al. (15) showed that adolescents were more sensitive to nicotine exposure and that sex was one of the foundations of addiction development. In the study of Sylvestere et al. (16) on 240 girls and 184 boys that investigated nicotine addiction between the sexes, adolescent girls tended to be regular smokers and nicotine addicts due to their biologic and sex-specific social characteristics, but the only thing that did not differ between the sexes was the age of the first cigarette. In our study, we found that sex did not play an important role in addiction.

Table 4. Effects of demographic data on addiction according to mFTQ test

	B	SH	Beta	T	p-value
Constant	-2.13	1.18		-1.80	0.072
Age	0.17	0.07	0.11	2.41	**0.016**
Family members are smokers, yes	0.42	0.23	0.08	1.809	0.072
If the adolescent's family knows about their smoking, yes	0.93	0.25	0.19	3.72	**<0.001**
Being able to smoke in the house, yes	0.60	0.26	0.13	2.32	**0.021**
Cigarettes smoked per day	0.16	0.01	0.52	10.9	**<0.001**
Father's education level high school, yes	0.56	0.22	0.12	2.53	**0.012**
Father's education level university, yes	0.66	0.3	0.10	2.203	**0.029**

Table 5. Effects of demographic data on addiction according to the HONC test

	B	SH	Beta	t	p-value
Constant	-1.97	2.201		-0.895	0.372
Age	0.268	0.113	0.119	2.38	**0.018**
Family members are smokers, yes	1.023	0.384	0.131	2.66	**0.008**
Buys a pack of cigarettes	-1.34	0.49	0.16	-2.74	**0.007**
If the adolescent's family knows that smokes, yes	1.54	0.39	0.21	3.96	**<0.001**
Went to the public school, yes	1.06	0.38	0.13	2.8	**0.005**
Cigarettes smoked per day	0.159	0.02	0.34	6.1	**<0.001**
Smoking ban at school	-0.988	0.34	-0.13	-2.9	**0.004**

Brain development continues throughout adolescence. The binding of nicotine to nicotinic acetylcholine receptors in the midbrain is more severe in adolescence. For this reason, adolescents are more vulnerable to nicotine addiction (1). Starting to smoke at an early age and experiencing the first nicotine exposure at an early age cause adolescents to become more addicted in their future lives. Studies in experimental animals have shown that as a result of nicotine exposure during adolescence, many genes affecting neuroplasticity in the brain are affected and cause permanent changes in nicotine-related brain regions (17,18). In the study of Kendler et al. (19) of 175 male-male and 69 female-female monozygotic twins, one twin started smoking 2 years earlier than the other and genetic and environmental factors were tried to be stabilized. It was shown that the earlier the twins started smoking, the higher their dependency in their later life than their twins who started smoking late. Lamin et al. (20) found that the age at the first cigarette attempt was 7-12 years (19.3%), 13-17 years old (63.2%), and 18-22 years (17.5%). When we separated the adolescents according to the smoking age range, 14 (5.4%) started smoking at the age of 10 years or younger, 51 (19.6%) started smoking between the ages of 11-13 years, 190 (73.1%) started aged 14-17 years, and five (1.9%) started aged 18 years and over. Similar to both studies, trying smoking and starting to use cigarettes regularly coincided with the middle adolescence period. In terms of public policy, we think that making access to cigarettes difficult for this age group, reducing the initiation of smoking, and delaying the age of starting smoking will reduce both the development of addiction and smoking-related morbidity and mortality.

In adolescents, the time between trying the first cigarette and starting regular cigarette smoking can be very short, and nicotine addiction can develop within weeks. Adolescents' nicotine addiction levels should be determined and timely intervention should be made. Different addiction scales are used to determine addiction levels in young people. In this regard, it is very important to better understand the relationship between nicotine addiction scales, understand the developmental stages of symptoms, and which symptoms are more associated with addiction. In our study, without defining the relationship between the internal dynamics of the HONC test and the mFTQ test with addiction, we analyzed the parameters that we investigated with the HONC test and the mFTQ test, both within themselves and between each other, and showed the relationship between both tests regarding addiction. There are few studies in the published literature examining the relationship between the HONC test and the mFTQ. In the study of Wellman et al. (21) with 1130 adult smokers, the correlation between the HONC test and the mFTQ was shown as 0.83. We think that the fact that the 6-item Fagerström adult test was used in the study of Wellman et al. (21) is the main source of the difference in compatibility between the two tests. The HONC test is more sensitive in detecting the onset of nicotine dependence, with 50% of occasional smokers and 100% of current smokers ticking at least one HONC test item in a youth study (22). Focusing on the mFTQ, a more sensitive and valid test can be defined by complementing the HONC test, which is more sensitive in catching young people with low nicotine addiction who are exposed to very low levels of tobacco use. In the study conducted by McPearson et al. (23) with 109 adolescent smokers aged 14-18 years (58% of whom were girls, and the mean age was 16.8±1.1 years), the condition of smoking at least 1 cigarette in the last 1 month was sought. It was determined that 95.5% of the participants said yes to at least one HONC test question. In our study, 88.8% of the participants answered yes to at least one of the HONC questions.

Another nicotine addiction that is not seen in our study population but is becoming more widespread in our country and the world is e-cigarette use. In the United States, adolescents use e-cigarettes and similar products more than other tobacco products (24). The availability of flavored products, social influences, and the effects of nicotine may affect adolescents' initiation and continuation of these products (25,26). In a study conducted by Audrain-McGovern et al. (27) in the state of Philadelphia with 1808 adolescents, internal and external factors that led to an increase in the number of days of e-cigarette use in 30 days and in the number of days of use in 30 months were investigated, and depression was determined to be the factor that caused the most increase in e-cigarette use. It was emphasized that two different adolescent groups should be focused on in the fight against e-cigarettes. A high-risk group that started using e-cigarettes early and another group with a low-risk profile that started

using e-cigarettes late. The timing and content of prevention studies should be different for each group.

Study Limitations

The most important limitation of the study was the detection of adolescents who smoked. We think most of the adolescent families weren't aware of their child's smoking. Since the patients came to the hospital with their families, we think that we were able to detect a small portion of the adolescents who smoked.

Conclusion

In conclusion, we showed in this study that most of the adolescents who smoked were at the addiction level and that the age of onset of smoking coincided with the middle adolescence period. We found that the factor most associated with addiction among smoking adolescents was the number of cigarettes smoked. We showed that mFTQ and HONC tests had a strong and significant relationship with smoking addiction among adolescents in our country. In both tests, we found that the number of cigarettes smoked and the family's awareness of their child's smoking was highly associated with addiction. This is the first study conducted in our country to measure addiction levels in adolescents using the mFTQ and HONC tests. In our study on addiction, we tried to minimize errors by using two different scales given the knowledge that each scale has its strengths and weaknesses in determining addiction, and we showed that these two scales gave consistent results in adolescents in our country. To reduce adolescents' access to cigarettes, the right steps should be taken to implement a ban on sales to those aged under 18 years and practices should be reconsidered to reduce their access to cigarettes. We think that peer education models should be widespread in schools to prevent adolescents from starting smoking and to reduce the frequency of smoking. Considering that trying to smoke in adolescence carries a greater risk of addiction, it would be useful to take precautions specific to this age period.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the local Ethics Committee of Keçiören Training and Research Hospital (date: 13.12.2017, approval number:1561). Our study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki.

Footnotes

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

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References

1. DiFranza JR, Savageau JA, Rigotti NA, Fletcher K, Ockene JK, McNeill AD, et al. Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. Tob Control. 2002;11:228-35.
2. Rubinstein ML, Shiffman S, Moscicki AB, Rait MA, Sen S, Benowitz NL. Nicotine metabolism and addiction among adolescent smokers. Addiction. 2013;108:406-12.
3. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US). 2014.
4. Jahoda G, Davies JB, Tagg S. Parents' alcohol consumption and children's knowledge of drinks and usage patterns. Br J Addict. 1980;75:297-303.
5. Campo AT, Rohner RP. Relationships between perceived parental acceptance-rejection, psychological adjustment, and substance abuse among young adults. Child Abuse Negl. 1992;16:429-40.
6. World Health Organization. The ICD-10 Classification of mental and behavioural disorders, diagnostic criteria for research. 1993.
7. American Psychiatric Association, Diagnostic and Statistical Manual of mental disorders. 2013.
8. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry. 1985;142:1259-64.
9. Kozlowski LT, Herman CP, The interaction of psychosocial and biological determinants of tobacco use: more on the boundary model. Journal of Applied Social Psychology, 1990;14:244-56.
10. Katzman DK, Neinstein LS, Callahan T, Gordon CM, Joffe A, Neinstein's adolescent and young adult health care: a practial guide (adolescent health care a practial guide) 2019.
11. Prokhorov AV, Hudmon KS, de Moor CA, Kelder SH, Conroy JL, Ordway N. Nicotine dependence, withdrawal symptoms, and adolescents' readiness to quit smoking. Nicotine Tob Res. 200;3:151-5.
12. Prokhorov AV, Pallonen UE, Fava JL, Ding L, Niaura R. Measuring nicotine dependence among high-risk adolescent smokers. Addict Behav. 1996;21:117-27.
13. Carpenter MJ, Baker NL, Gray KM, Upadhyaya HP. Assessment of nicotine dependence among adolescent and young adult smokers: a comparison of measures. Addict Behav. 2010;35:977-82.
14. al'Absi M, Nakajima M, Allen S, Lemieux A, Hatsukami D. Sex differences in hormonal responses to stress and smoking relapse: a prospective examination. Nicotine Tob Res. 2015;17:382-9.

15. Pogun S, Yararbas G, Nesil T, Kanit L. Sex differences in nicotine preference. J Neurosci Res. 2017;95:148-62.
16. Sylvestre MP, Chagnon M, Wellman RJ, Dugas EN, O'Loughlin J. Sex differences in attaining cigarette smoking and nicotine dependence milestones among novice smokers. Am J Epidemiol. 2018;187:1670-77.
17. Schochet TL, Kelley AE, Landry CF. Differential expression of arc mRNA and other plasticity-related genes induced by nicotine in adolescent rat forebrain. Neuroscience. 2005;135:285-97.
18. Doura MB, Luu TV, Lee NH, Perry DC. Persistent gene expression changes in ventral tegmental area of adolescent but not adult rats in response to chronic nicotine. Neuroscience. 2010;170:503-13.
19. Kendler KS, Myers J, Damaj MI, Chen X. Early smoking onset and risk for subsequent nicotine dependence: a monozygotic co-twin control study. Am J Psychiatry. 2013;170:408-13.
20. Lamin RAC, Othman N, Othman CN. Effect of smoking behavior on nicotine dependence level among adolescents. Procedia - Social and Behavioral Sciences. 2014;153:189-98.
21. Wellman RJ, Savageau JA, Godiwala S, Savageau N, Friedman K, Hazelton J, Difranza JR. A comparison of the hooked on nicotine checklist and the fagerström test for nicotine dependence in adult smokers. Nicotine Tob Res. 2006;8:575-80.
22. Wheeler KC, Fletcher KE, Wellman RJ, Difranza JR. Screening adolescents for nicotine dependence: the Hooked On Nicotine Checklist. J Adolesc Health. 2004;35:225-30.
23. MacPherson L, Strong DR, Myers MG. Using an item response model to examine the nicotine dependence construct as characterized by the HONC and the mFTQ among adolescent smokers. Addict Behav. 2008;33:880-94.
24. Jamal A, Park-Lee E, Birdsey J, West A, Cornelius M, Cooper MR, et al. Tobacco product use among Middle And High School Students - National Youth Tobacco Survey, United States, 2024. MMWR Morb Mortal Wkly Rep. 2024;73:917-24.
25. Apelberg BJ, Corey CG, Hoffman AC, Schroeder MJ, Husten CG, Caraballo RS, Backinger CL. Symptoms of tobacco dependence among middle and high school tobacco users: results from the 2012 National Youth Tobacco Survey. Am J Prev Med. 2014;47:4-14.
26. Gentzke AS, Wang TW, Cornelius M, Park-Lee E, Ren C, Sawdey MD, et al. Tobacco product use and associated factors among middle and high school students - National Youth Tobacco Survey, United States, 2021. MMWR Surveill Summ. 2022;71:1-29.
27. Audrain-McGovern J, Rodriguez D, Testa S, Alexander E, Pianin S. Adolescent e-cigarette onset and escalation: associations with internalizing and externalizing symptoms. J Adolesc Health. 2021;68:801-7.

ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Asthma Knowledge Level of Patients Over 11 Years of Age with Asthma Diagnosis

On Bir Yaş Üzeri Astım Tanılı Hastaların Astım Bilgi Düzeyinin Değerlendirilmesi

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Abstract

Introduction: Asthma is the most common respiratory disorder in children. Knowledge about asthma helps in achieving asthma control. Self-management of the disease includes adherence to medication, avoidance of trigger factors, and appropriate response to symptoms Education about asthma is essential to improve the health and reduce the negative impact on daily life.

Materials and Methods: In this study, 62 patients aged 14.04 ± 2.25 years, who had been followed up for at least 6 months at Dokuz Eylül University Pediatric Allergy and Immunology outpatient clinic, were included. A modified Asthma Self-Management Knowledge Questionnaire with 25 true or false questions was administered.

Results: The results of the study included the mean asthma control score of the patients to be 20.08 ± 4.50. Minimum and maximum score patients achieved on the questionnaire were 9 and 23 points, respectively. The effect of general asthma knowledge, asthma medication knowledge, and environmental factors knowledge on asthma control were found to be statistically significant. On the other hand, asthma exacerbation knowledge was not statistically significant. The findings of this study reveal that knowledge of environmental factors is the most influential factor on asthma control, whereas, the second most effective variable was the asthma medication knowledge.

Conclusion: Hence, asthma education programs must be tailored specifically to this age group, so that they can self-manage properly, avoid exposure to triggering factors appropriately, and hopefully live symptom free.

Öz

Giriş: Astım çocuklarda en sık görülen solunum yolu hastalığıdır. Astım hakkında bilgi sahibi olmak astım kontrolünün sağlanmasına yardımcı olur. Hastalığın öz yönetimi, ilaçlara uyumu, tetikleyici faktörlerden kaçınmayı ve semptomlara uygun yanıtı içerir. Astım hakkında eğitim, sağlığı iyileştirmek ve günlük yaşam üzerindeki olumsuz etkiyi azaltmak için esastır.

Gereç ve Yöntem: Çalışmamıza Dokuz Eylül Üniversitesi Çocuk Alerji ve İmmünoloji polikliniğinde en az 6 ay takip edilen, yaşları 14,04 ± 2,25 yıl olan 62 hasta dahil edildi. 25 doğru-yanlış sorudan oluşan Astım Öz Yönetim Bilgi Anketi uygulandı.

Keywords
Atopy, dose rescue medications, exacerbations, environmental triggers

Anahtar kelimeler
Atopi, kurtarıcı ilaçlar, alevlenme, çevresel tetikleyiciler

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Bulgular: Çalışmanın sonuçlarına göre hastaların astım kontrol puanı ortalaması 20,08 ± 4,50 olarak bulundu. Hastaların ankette aldıkları minimum ve maksimum puan sırasıyla 9 ve 23 oldu. Genel astım bilgisi, astım ilacı bilgisi ve çevresel faktörler bilgisinin astım kontrolü üzerindeki etkisi istatistiksel olarak anlamlı bulundu. Öte yandan, astım alevlenmesi bilgisi istatistiksel olarak anlamlı değildi.
Sonuç: Bu çalışmanın bulguları, çevresel faktörler bilgisinin astım kontrolünde en etkili faktör olduğunu, ikinci en etkili değişkenin ise astım ilacı bilgisi olduğunu ortaya koymaktadır. Bu nedenle, astım eğitim programları bu yaş grubuna özel olarak uyarlanmalıdır, böylece kendilerini düzgün bir şekilde yönetebilirler, tetikleyici faktörlere uygun şekilde maruz kalmaktan kaçınabilirler ve semptomsuz yaşayabilirler

Introduction

Asthma is the most common chronic disease among children and adolescents worldwide (1). Education is one of the cornerstones in achieving asthma control and is recommended in national and international guidelines (2). Self-management includes adherence to medication, avoidance of triggers, and appropriate response to symptoms, all of which are crucial for the well-being and asthma control of patients with chronic diseases (3). Lack of information about the disease among asthmatic patients and their family members may lead to inadequate treatment and disease control, frequent hospital admissions, high morbidity, and falling behind in school (4,5,6).

The primary aim of this study is to evaluate the asthma knowledge levels of children and adolescents over the age of 11 who have been diagnosed with asthma and to determine the impact of this knowledge on asthma control. As asthma is the most common chronic respiratory disease during childhood and adolescence, it is critical for patients and their families to have sufficient knowledge about the disease for its effective management.

In this study, patients' knowledge levels regarding general asthma information, asthma medications, environmental triggers, and asthma exacerbations were examined, and the contributions of this knowledge to asthma control were analyzed. The results of the study indicate that knowledge of environmental factors and medication use plays a significant role in improving asthma control. Based on these findings, it is aimed to tailor asthma education programs specifically for this age group and to enhance patients' self-management skills.

Materials and Methods

Patients with asthma who had been followed up for at least 6 months at Dokuz Eylül University Pediatric Allergy and Immunology outpatient clinic were included in the study. Asthma diagnosis was made according to the Global Strategy for Asthma Management and Prevention report by the Global Initiative for Asthma. Patients' age, sex, time of asthma onset, presence of atopy, presence of atopy in the family, exposure to smoking, asthma control test score, and comorbid allergic diseases were documented. A 25-question questionnaire was administered to the patients. Although the Turkish validation of the Asthma Self-Management Knowledge Questionnaire has been performed for adults, it was modified and administered by three independent pediatric allergists in a language that children over 11 years of age could understand. The questionnaire includes 25 items with "true" or "false" responses about general asthma knowledge, asthma medications, asthma exacerbations, and environmental triggers. One point was given for each correct answer, and the total score indicated the patient's knowledge of asthma (7).

The asthma control test consists of five items: It evaluates (1) the effect of asthma on daily functioning, (2) the frequency of shortness of breath, (3) night-time/early awakenings due to asthma symptoms, (4) the use of rescue medication, and (5) the overall self-assessment of asthma control. All items refer to the past 4 weeks and are scaled from 1 to 5. The total score indicates asthma control with values of 25, 20–24, and <19 translating to excellent, good, and poor asthma control, respectively (8). An informed consent form was obtained from the patients and their families. For patients with atopy, a positive skin prick test of ≥3 mm was considered significant. The approval for this study was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (date: 27.04.2022, approval number: 2022/16-08).

Statistical Analysis

Descriptive statistics, including mean ± standard deviation (SD), were used to summarize continuous variables such as age, asthma knowledge, medication

knowledge, environmental factors knowledge, and exacerbation knowledge. For categorical variables (e.g., sex distribution, smoking exposure, and family history of atopy), frequencies and percentages were calculated.

To evaluate the relationships between level of asthma control and independent variables (general asthma knowledge, medication use knowledge, environmental factors knowledge, and asthma exacerbation knowledge), regression analysis was performed. Regression coefficients, standard errors, and p-values were reported to assess statistical significance. A p-value of <0.05 was considered statistically significant.

Results

The study included 62 patients, 37 of whom were male. The mean age of the patients was 14.04 ± 2.25 years. The time of asthma onset was 5.70 ± 3.27 years. Of the patients, 72.6% had no exposure to smoking, and 69.4% had a family history of atopy (Table 1). Sensitization to at least one allergen on a skin prick test was found in 87.1% of the patients. The main complaints at admission were cough and dyspnea 98.4%, accompanied by nasal congestion in 29% of the cases. Among the patients, 83.9% were using metered-dose inhalers, 30.6% were on montelukast, and 9.7% were on nasal corticosteroids. Additionally, 62.9% of the patients had atopic dermatitis and allergic rhinitis (Table 2). The mean asthma control score of the patients was 20.08 ± 4.50. The questionnaire scores ranged from a minimum of 9 to a maximum of 23, with a mean score of 16.56 ± 2.75. Only 6.5% of the patients responded correctly to all questions related to general asthma knowledge, asthma medication, environmental triggers, and asthma exacerbations (Table 3). Except for the score variable related to asthma exacerbation, other score types positively affected asthma control, increasing the control level. While the effect of general asthma knowledge ($p<0.05$), asthma medication knowledge ($p<0.01$), and environmental factors knowledge ($p<0.01$) on asthma control was statistically significant, asthma exacerbation knowledge was not significant (Table 4). A 1% increase in general asthma knowledge increased asthma control by approximately 0.39%. A 1% increase in asthma medication knowledge increased asthma control by approximately 0.72%. Lastly, a 1% increase in environmental factors knowledge increased asthma control by about 0.77%. The findings show that knowledge of environmental factors is the most influential factor on asthma control, followed by asthma medication knowledge (Figure 1).

Discussion

Although adequate asthma control can be achieved for most patients, the disease is often sub-optimally controlled. The reasons for this are multifactorial, including the patient's age, age of onset or severity of asthma, patient beliefs and coping strategies leading to decreased adherence to treatment, disease mechanisms, and lack of patient knowledge about management (9). Improving knowledge about asthma among individuals with the disease is an important component of self-management (10). Self-efficacy plays a key role in the prevention of asthma, improvement in asthma conditions, and sustainability of asthma control in children and adolescents (11). Previous data suggest that adolescents and young adults, in particular, are often unable to manage their asthma properly (12,13). To effectively personalize asthma education, it is necessary to identify gaps in asthma knowledge and self-management skills. An information questionnaire completed by the patient can be a useful tool to identify these gaps. Asthma self-management during adolescence becomes challenging due to poor treatment adherence. Recent studies have observed that digital applications and phone reminders improve treatment compliance in this age group alongside individual education (14).

Table 1. General characteristics of patients

Mean age	14.04 ± 2.25
Sex	Female 40.3% (n = 62)
Mean age at asthma onset	5.70 ± 3.27
No cigarette exposure	72.6%
Family history of atopy	69.4%
Those with concomitant allergic diseases	62.9%

Table 2. Medications used by patients for at least 6 months

Metered dose inhaler	83.9%
Nebul	4.8%
Montelukast	30.6%
Nasal corticosteroid	9.7%

Table 3. Survey results					
		General asthma knowledge	**Medication use knowledge**	**Environmental factors knowledge**	**Asthma exacerbations knowledge**
n	Valid	62	62	62	62
	Missing	0	0	0	0
Mean		5.0645	5.1290	4.4677	1.9194
Std. Deviation		1,23966	1,40822	88183	1.07579
Range		6.00	5.00	5.00	4.00
Minimum		1.00	3.00	1.00	00
Maximum		7.00	8.00	6.00	4.00
Sum		314.00	318.00	277.00	11900

Table 4. Relationship between survey results and ECT			
Independent Variables:	**Coef.**	**Std. Err.**	**p-value**
General asthma knowledge	0.39	0.16	**0.018**
Medication_use_knowledge	0.72	0.19	**0.000**
Environmental_factors_knowledge	0.77	0.20	**0.000**
Asthma_exacerbations_knowledge	0.02	0.13	0.855

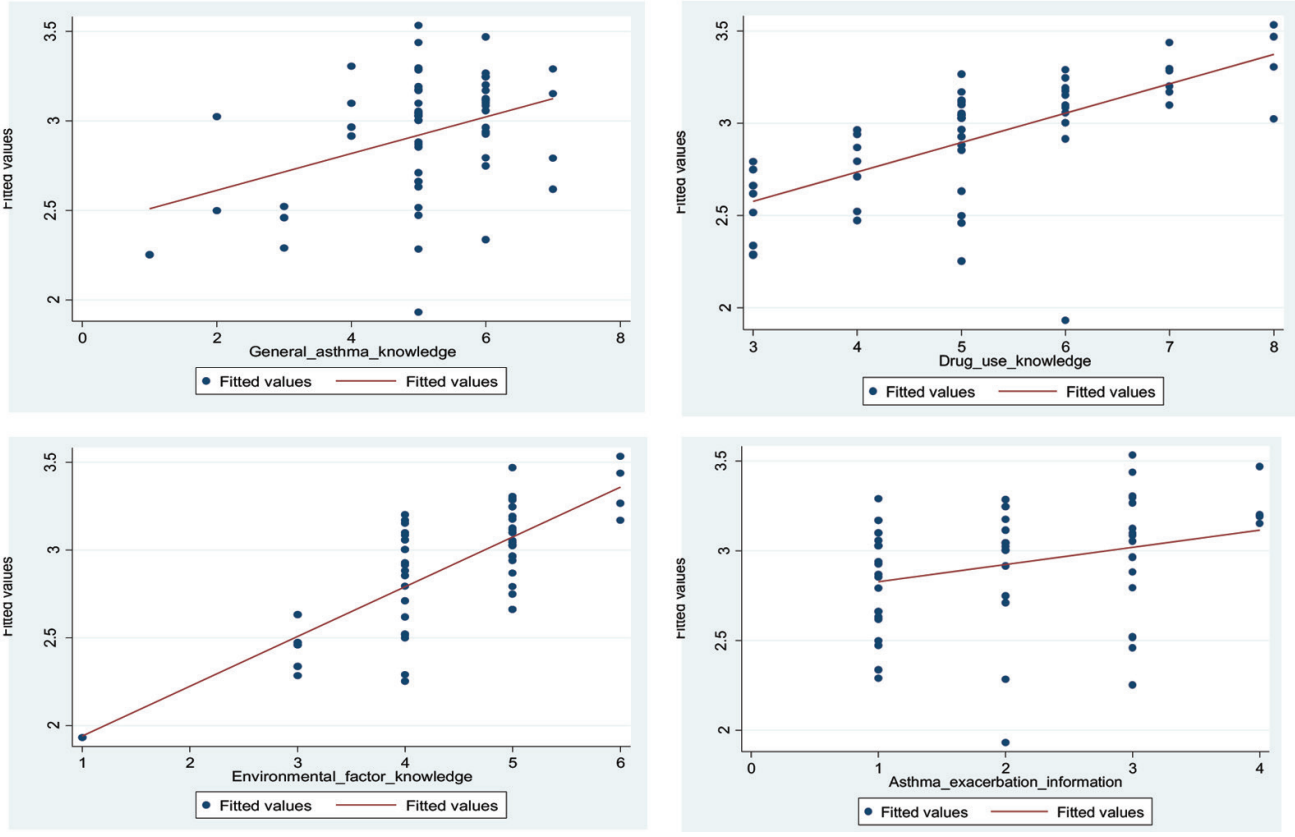

Figure 1. Relation of asthma control with various factors

In this study, patients were asked about their knowledge of asthma, medication use, environmental triggering factors, and asthma exacerbations. General knowledge of asthma, medication use, and environmental triggers was associated with asthma control, whereas knowledge of exacerbations was not. This may be because patients who are well-informed about their disease, take their medication regularly and correctly, and avoid triggers are less likely to experience exacerbations. Hence, their knowledge about exacerbations may be limited. Recent studies have shown that educational programs play a significant role in achieving asthma control. Children who received training on recognizing environmental triggers and proper use of inhaler devices showed a significant reduction in hospital admissions and symptom frequency (15).

Emphasizing the factors that most affect asthma control, as found in this survey, is crucial. It is widely accepted that asthma knowledge is necessary for effective self-management (16). However, managing asthma involves many complex tasks, requiring a vast amount of information (17). For example, patients need to understand the basic pathophysiology to comprehend why triggers can vary and why maintenance medications are necessary even in the absence of symptoms. They also need to learn to monitor lung function, recognize exacerbations early, dose rescue medications, and determine when emergency care is needed. Measuring knowledge in all these areas can be challenging. However, asthma attacks are likely to be less frequent if patients are educated about asthma, how to use medication, and how to avoid triggering factors during every clinical visit. Raising family awareness about recognizing asthma symptoms and taking early action has been shown to significantly reduce the frequency of asthma attacks (18).

A study conducted in Türkiye found a 40% decrease in emergency department visits among children whose families participated in educational programs. A study conducted in Türkiye revealed that indoor cigarette smoke and house dust mites are the most significant environmental risk factors affecting asthma control in children. Therefore, educating families on reducing exposure to environmental triggers is of utmost importance (19).

Study Limitations

Sample size: The study included only 62 patients, which limits the generalizability of the findings to the larger population of children and adolescents with asthma.

Cross-Sectional Design: As a cross-sectional study, it provides a snapshot of the relationship between asthma knowledge and control at a single point in time, without capturing longitudinal changes or causal relationships.

Self-Reported Data: The reliance on self-reported answers may introduce recall bias, particularly regarding adherence to medication and avoidance of triggers.

Unmeasured Confounding Factors: Other factors influencing asthma control, such as socioeconomic status, psychological factors, or detailed environmental exposures, were not included in the analysis.

Limited Scope of Education: The study emphasizes knowledge about asthma medications and environmental triggers but does not thoroughly explore other components of asthma education, such as the psychological impact or family support.

Generalizability to Other Age Groups: The findings are specific to children over 11 years old and may not apply to younger children or adults with asthma.

Conclusion

Education is essential to improve the health of young people with asthma and reduce the negative impact of the disease on their daily lives. The developmental tasks of adolescence require asthma education programs tailored specifically to this age group.

Ethics

Ethics Committee Approval: The approval for this study was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (date: 27.04.2022, approval number: 2022/16-08).

Footnotes

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

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

References

1. The global asthma report 2014. Global Asthma Network, Auckland. New Zealand 2014.
2. Global Initiative for Asthma – GINA. A pocket guide for health professionals updated. Available from: http://ginasthma.org/
3. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA. 2002;288:2469-75.
4. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) survey. Rev Panam Salud Publica. 2005;17:191-7.
5. Bruzzese JM, Bonner S, Vincent EJ, Sheares BJ, Mellins RB, Levison MJ, et al. Asthma education: the adolescent experience. Patient Educ Couns. 2004;55:396-406.
6. Bruzzese JM, Evans D, Kattan M. School-based asthma programs. J Allergy Clin Immunol. 2009;124:195-200.
7. Baygül A, Öztürk AB, Özyiğit LP, Keskin H, Karakaya G, Kalyoncu F, et al. The reliability and validation of the turkish version of the asthma self-management knowledge questionnaire. Turk Thorac J. 2017;18:125-30.
8. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, et al. The asthma control test and asthma control questionnaire for assessing asthma control: systematic review and meta-analysis. J Allergy Clin Immunol. 2013;131:695-703.
9. Soriano JB, Rabe KF, Vermeire PA. Predictors of poor asthma control in European adults. J Asthma. 2003;40:803-13.
10. McDonald VM, Gibson PG. Asthma self-management education. Chron Respir Dis. 2006;3:29-37.
11. Schlösser M, Havermans G. A self-efficacy scale for children and adolescents with asthma: construction and validation. J Asthma. 1992;29:99-108.
12. Rand CS, Wright RJ, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Mediators of asthma outcomes. J Allergy Clin Immunol. 2012;129:136-41.
13. Rhee H, Belyea MJ, Halterman JS. Adolescents' perception of asthma symptoms and health care utilization. J Pediatr Health Care. 2011;25:105-13.
14. Kaya E, Ergin H. Managing asthma in adolescence: challenges and solutions. Turk Klin Pediatr. 2023;32:45-52.
15. Güler N, Çetinkaya F. The importance of education in childhood asthma management. Turk Arch Pediatr. 2023;58:112-20.
16. van der Palen J, Klein JJ, Seydel ER. Are high generalised and asthma-specific self-efficacy predictive of adequate self-management behaviour among adult asthma patients? Patient Educ Couns. 1997;32:35-41.
17. Shegog R, Bartholomew LK, Parcel GS, Sockrider MM, Mâsse L, Abramson SL. Impact of a computer-assisted education program on factors related to asthma self-management behavior. J Am Med Inform Assoc. 2001;8:49-61.
18. Öztürk S, Çoban H. The impact of family awareness programs in preventing asthma attacks. J Pediatr Health Dis. 2022;15:172-9.
19. Demir A, Yılmaz B. The effects of environmental triggers on childhood asthma. J Chest Dis. 2022;30:256-64.

ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Assessment of Mean Platelet Volume in Children with Celiac Disease on a Gluten-Free Diet

Glutensiz Diyet Uygulanan Çölyak Hastalığı Olan Çocuklarda Ortalama Trombosit Hacminin Değerlendirilmesi

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Abstract

Introduction: Celiac disease (CD) is a systemic disorder due to gluten in genetically susceptible individuals and characterized by an immune-mediated response. Gluten, triggers a chronic inflammatory response that leads to progressive atrophy of the small intestine in individuals with CD. Mean platelet volume (MPV) is a marker of platelet activation and function, and is considered a marker of inflammation. The objective of our study was to investigate whether MPV values change after introducing a gluten-free diet (GFD) in children with CD.

Materials and Methods: The pediatric patients with CD admitted to our pediatric gastroenterology clinic at Konya Training and Research Hospital between November 2013 and May 2016 were enrolled retrospectively. In all of the cases, demographic characteristics complete blood count parameters, including hemoglobin, white blood cell, platelet count, MPV, mean corpuscular volume, neutrophil, lymphocyte, and vitamin B12 values were recorded. The values were evaluated at the time of diagnosis and after six months of a GFD for the children with CD and healthy control subjects.

Results: Thirty-three pediatric patients with CD and 44 healthy children with no history of CD in their families or relatives were enrollled. Although the MPV values of patients with CD were slightly higher after a GFD, in the comparison of the values at diagnosis and after a GFD, the difference was not statistically significant (p=0.068). No statistically significant difference was detected between the MPV values of patients with CD at diagnosis and the healthy children (p=0.851). A statistically significant increase was detected in the comparison of hemoglobin, vitamin B12, and MCV values at diagnosis and after a GFD in patients with CD (p<0.001, p=0.002, and p=0.027, respectively). A comparison of the platelet counts at the time of diagnosis and after a GFD revealed a statistically significant decrease (p=0.011).

Conclusion: MPV may not be a useful biomarker for monitoring GFD in children with CD.

Keywords
Children, mean platelet volume, gluten-free diet, celiac disease

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Çocuk, ortalama trombosit hacmi, glutensiz diyet, çölyak hastalığı

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Öz

Giriş: Çölyak hastalığı (ÇH) genetik olarak duyarlı bireylerde glutene bağlı ortaya çıkan immün aracılı sistemik bir hastalıktır. Gluten, ÇH olan bireylerde ince bağırsakta progresif atrofiye yol açan kronik bir enflamatuvar yanıtı tetikler. Ortalama trombosit hacmi (OTH), trombosit aktivasyonu ve fonksiyonunun bir göstergesidir, ve bir enflamasyon belirteci olarak kabul edilmektedir. ÇH tanısı konulmuş çocuklarda glutensiz diyet uygulandıktan sonra MPV değerlerinin değişip değişmediğini araştırmayı amaçladık.

Gereç ve Yöntem: Kasım 2013 ile Mayıs 2016 tarihleri arasında Konya Eğitim ve Araştırma Hastanesi Çocuk Gastroenteroloji Kliniği'ne başvuran ÇH tanısı alan çocuk hastalar retrospektif olarak incelendi. Tüm vakaların demografik özellikleri, hemoglobin, beyaz küre, trombosit sayısı, MPV, ortalama korpusküler hacim, nötrofil, lenfosit ve vitamin B12 değerleri kaydedildi. Sağlıklı kontrollerin ve hastaların tanı anındaki ve glutensiz diyetten 6 ay sonraki değerleri değerlendirildi.

Bulgular: ÇH tanısı konulmuş 33 çocuk hasta ve ailelerinde veya akrabalarında ÇH öyküsü olmayan 44 sağlıklı çocuk çalışmamıza dahil edilmiştir. ÇH tanısı konulan hastaların OTH değerleri glutensiz diyet sonrasında biraz daha yüksek olsa da, tanı anındaki ve glutensiz diyet sonrasındaki OTH arasında istatistiksel olarak anlamlı fark yoktu (p=0,068). Yeni tanı almış hastalar ile sağlıklı kontrol grubu kıyaslandığında MPV değerleri arasında istatistiksel olarak anlamlı bir fark saptanmadı (p=0,851). ÇH tanısı alan hastaların hemoglobin, B12 vitamini ve MCV değerleri tanı anında ve glutensiz diyet sonrasında karşılaştırıldığında istatistiksel olarak anlamlı bir artış tespit edilmiştir (sırasıyla p<0.001, p=0.002 ve p=0.027). Tanı anındaki ve glutensiz diyet sonrasındaki trombosit sayıları karşılaştırıldığında istatistiksel olarak anlamlı bir düşüş saptanmıştır (p=0.011).

Sonuç: OTH, ÇH olan hastalarda glutensiz diyet yanıtını izlemek için yararlı bir biyobelirteç olmayabilir.

Introduction

Celiac disease (CD) is a systemic disorder triggered by gluten in genetically susceptible individuals and characterized by an immune-mediated response (1). Gluten, a protein complex found in barley, wheat, and rye, triggers a chronic inflammatory response that leads to progressive atrophy of the small intestine in individuals who suffer from CD (1,2). CD diagnosis is made based on the presence of clinical manifestations, human leukocyte antigen DQ2 or DQ8 haplotypes, and CD-specific antibodies as well as histological analysis of duodenal biopsies (3). CD-specific antibodies comprise endomysial antibodies, including autoantibodies against tissue transglutaminase type 2, and antibodies against deamidated forms of gliadin peptides (3). The modified Marsh classification is used for the histopathological diagnosis of CD (3). A lifelong gluten-free diet (GFD) is the fundamental aspect of CD treatment and requires follow-up (4). Early diagnosis and regular follow-up are crucial to protect against complications that can manifest in untreated patients with CD (1,5). Regarding follow-up, there are some limitations. The histological findings on a diet that includes gluten remain the gold standard for patients with CD, but it is an invasive method and is difficult to implement in children for routine follow-up (6). At present, celiac-specific serological tests constitute the first-line investigations for CD screening; however, there are certain limitations associated with their use in routine clinical practice (6). The antiendomysial antibody test is only conducted in laboratories with the requisite expertise, and the results are dependent on subjective interpretation of the test results (6). In the literature, the specificity of anti-tissue transglutaminase type 2 antibody varies considerably (even from kit to kit) from 89.5% to 98.8% (7).

Mean platelet volume (MPV) is a parameter assessed as part of a complete blood count, and generally, it is not noticed by physicians. Furthermore, MPV in a complete blood count represents a cost-effective marker. For diseases characterized by systemic or local inflammation, platelets play a significant role in their pathogenesis (8). MPV is a marker of platelet activation and function, and it has been demonstrated that larger platelets are more active (8). Furthermore, MPV is considered a marker of inflammation (8). In recent years, MPV has been established as an inflammatory marker with a demonstrated role in various systemic and gastrointestinal disorders, including amoebiasis (9), ulcerative colitis (10), allergic proctocolitis (11), acute appendicitis (12), irritable bowel syndrome (13), Crohn's disease (14), rotavirus gastroenteritis (8), and familial Mediterranean fever (15).

The objective of our study was to investigate whether MPV values change after introducing a GFD, as this may prove to be a useful biomarker in the diagnosis or follow-up of patients with CD. Therefore, we evaluated MPV values in patients with CD during diagnosis and after treatment with a GFD.

Materials and Methods

In this study, pediatric patients with CD admitted to our pediatric gastroenterology clinic at Konya Training

and Research Hospital between November 2013 and May 2016 were enrolled retrospectively. The inclusion criteria were children with CD aged 17 years and below who came for regular follow-up visits. The control group comprised healthy children with no history of CD in their families or relatives. The diagnosis of CD was made according to the guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (3). Patients with CD who did not come for follow-up after treatment and whose data were missing were excluded from the study group. The following datas were collected by using a computerized patient database: demographic characteristics (age and sex) and laboratory parameters, including white blood cell, hemoglobin, platelet count, MPV, mean corpuscular volume (MCV), neutrophil, lymphocyte, and vitamin B12 values. The values were recorded at the time of diagnosis and after six months of a GFD for the children with CD and healthy control subjects. The analysing of complete blood count parameters were conducted using the same coulter analyzer (Sysmex XE-2100, Sysmex Corporation, Kobe, Japan), on which general maintenance was performed and it was checked at regular intervals in the hospital's laboratory. Blood samples were taken in constant quantities in ethylenediaminetetraacetic acid–containing tubes. The samples were analyzed within two hours. Vitamin B12 titers were determined using the ADVIA Centaur XP (Siemens Diagnostics, Tarrytown, NY, USA) immunoassay autoanalyzer. The study was conducted in accordance with the principles outlined in the Helsinki Declaration and reviewed by the Selçuk University Ethical Review Board, and ethical approval was obtained from the Institutional Review Board (date: 09.06.2016, approval number: 2016/181).

Statistical Analysis

We analyzed the obtained data by using the IBM SPSS Statistics for Windows (version 22.0) program. The data are reported as mean ± standard deviation. The distribution of the parameters was controlled with the Kolmogorov-Smirnov test. We used the Mann-Whitney U test or Student's t-test to compare the groups. Regarding the study group, the Wilcoxon test or paired t-test was used to compare the parameters at the time of diagnosis and after introducing a GFD. The associations between parameters were assessed using Pearson's or Spearman's correlation test. The results were accepted to be significant when $p<0.05$.

Results

In this study, 33 patients with CD, comprising 21 girls (63.6%) and 12 boys (36.4%), were enrolled. There were 44 healthy children, consisting of 30 girls (68.1%) and 14 boys (31.9%), in the control group. The mean age of the children with CD was 9.7±0.7 years, while for the healthy children group, it was 9.5±0.8 years. There was no statistically significant difference in age between the healthy subjects and the children with CD (p=0.834).

Although the MPV values of children with CD were slightly higher after a GFD, in the comparison of the values at diagnosis and after a GFD, the difference was not statistically significant (p=0.068). No statistically significant difference was demonsrated between the MPV values of patients with CD at diagnosis and the healthy children (p=0.851) and similarly, there was no statistically significant difference between the children with CD after a GFD and the healty control group (p=0.171). On the other hand, a statistically significant increase was detected in the comparison of hemoglobin, vitamin B12, and MCV values at diagnosis and after a GFD in patients with CD ($p<0.001$, p=0.002, and p=0.027, respectively). A comparison of the platelet counts at the time of diagnosis and after a GFD revealed a statistically significant decrease (p=0.011). The laboratory and demographic features of children with CD at diagnosis and after a GFD are shown in Table 1. The laboratory and demographic features of the controls and the comparison with the CD group are shown in Table 2.

Discussion

CD has a multifactorial etiology, including environmental and genetic factors and an abnormal immune response (16). In the pathogenesis of CD, an abnormal immune response plays a crucial role, as such a response to deamidated gluten peptides stimulates inflammation and epithelial damage (16). In recent studies, researchers have demonstrated that platelets may be significant in the development of the adaptive immune response and have linked platelet activation to the pathophysiology of diseases characterized by inflammation (17,18). MPV

Table 1. The demographic and laboratory characteristics of patients at the time of diagnosis of CD and after gluten-free diet

Characteristics	Patients at the time of diagnosis of CD	Patients with CD after gluten-free diet	p-value
Number of patients	33		
Age, years (mean)	9.7±0.7		
Male: female ratio	12/21		
WBC (/mm^3)	8302.1±478.5	7652.7±452.3	0.088
Hb (gr/dL)	12.0±0.3	13.3±0.2	**<0.001**
MCV (fL)	76.7±1.5	79.5±0.9	**0.027**
Platelet count (/mm^3)	361818.2±16204.1	316909.1±11821.9	**0.011**
MPV (fL)	9.9±0.2	10.2±0.2	0.068
Neutrophile (/mm^3)	4328.7±334.3	3927.2±341.1	0.231
Lymphocyte (/mm^3)	3033.6±185.5	2946.6±185.9	0.308
Vit B12 (pg/mL)	394.8±33.0	479.1±25.5	**0.002**

CD: Celiac disease, WBC: White blood cell, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, Vit B12: Vitamin B12. Parametric values are expressed as means with standard deviation. Significance is determined by p<0.05 and shown with bold character

Table 2. The demographic and laboratory characteristics of controls and comparison with the CD group

		p-value	p-value
Characteristics	**Healthy controls**	**Control vs. patients with at the time of diagnosis of CD**	**Control vs. patients with after gluten-free diet**
Number of patients	44		
Age, years	9.5±0.8		
Male: female ratio	14/30		
WBC (/mm^3)	7927.2±455.2	0.649	0.555
Hb (gr/dL)	12.7±0.2	**0.035**	**0.037**
MCV (fL)	80.2±0.7	**0.042**	0.562
Platelet count (/mm^3)	321727.3±13734.4	**0.037**	0.878
MPV (fL)	9.9±0.2	0.851	0.171
Neutrophile (/mm^3)	4353.0±412.1	0.748	0.317
Lymphocyte (/mm^3)	2915.5±207.4	0.530	0.842
Vit B12 (pg/mL)	388.7±22.2	0.724	**0.010**

CD: Celiac disease, WBC: White blood cell, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, Vit B12: Vitamin B12. Parametric values are expressed as means with standard deviation. Significance is determined by p<0.05 and shown with bold characters

indicates platelet activation and is used as a measure of platelet size (19,20). Research has demonstrated MPV's importance as a marker for disease activity, inflammation, and the efficacy of anti-inflammatory treatment in various chronic inflammatory disorders (18). MPV reflects proinflammatory conditions involving various inflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF)-alpha (18). Overproduction of proinflammatory cytokines can suppress thrombocytes size by affecting megakaryopoiesis, resulting in the release of smaller thrombocytes by the bone marrow (18). On the other hand, in diseases associated with inflammation, it is thought that early platelet activation following inflammation leads to an increase in the release of young thrombocytes from the bone marrow into the bloodstream, thereby causing elevated MPV levels (12). It has been suggested that cytokine levels may

play a part in CD (21,22). In Manavalan et al. (21) study, individuals with active CD had higher levels of IL-1β, TNF-alpha, and IL-6 than healthy controls. Additionally, Kapoor et al. (22) demonstrated that IL-6 levels were significantly higher in newly diagnosed cases of CD than in healthy subjects and in patients with CD on a GFD. In children with CD, systemic levels of the cytokines IL-1β, IL-6, IL-8, IL-10, IL12p70, IL13, and TNF-alpha were increased compared to controls, but none of the systemic cytokines measured differed between the children with CD on a GFD and the controls (23). According to our hypothesis, we thought that MPV values might change due to reduced inflammation with GFD in CD and also MPV might be a beneficial biomarker in treatment follow-up.

Numerous studies have explored MPV as a marker in gastrointestinal disorders. In a study of 76 children with amoebiasis, MPV levels were significantly higher than in controls, and Çelik et al. (9) noted that MPV could be useful as an acute phase reactants. In 151 pediatric patients presenting with rotavirus gastroenteritis, Tanju et al. (8) found MPV values to be lower than in the control group, highlighting that MPV may be useful as a negative acute phase reactant. Furthermore, Chen et al. (10) found ulcerative colitis disease activity was negatively correlated with MPV, and they suggested that MPV is a potential biomarker for ulcerative colitis disease activity. However, Liu et al. (14) emphasized that MPV, a controversial marker in Crohn's disease, has no distinctive value in disease activity.

To date, several studies involving adults have investigated the role of MPV as an inflammatory marker in patients with CD (24,25). Purnak et al. (24) emphasized that MPV may be a usable marker for monitoring dietary compliance in adult patients with CD, they found significantly higher MPV levels in the CD group compared to healthy adults and, after the introduction of a GFD, a significant decrease in MPV from baseline levels in the CD group. Eighty-one patients with CD were enrolled in another study, and significantly higher MPV levels were observed in patients with CD compared to healthy controls (25). Following the introduction of a GFD, MPV levels were significantly lower in patients demonstrating dietary adherence compared to those who were nonadherent (25). A study involving 66 pediatric patients with CD evaluated the effects of a GFD and found a significant decrease in MPV after GFD introduction (26). In our study, after introducing a GFD, we observed a modest increase in MPV values from 9.9±0.2 to 10.2±0.2 fL in patients with CD. Furthermore, MPV values were within normal limits both before and after GFD. Contrary to our hypothesis that MPV levels might change as a result of a reduction in inflammation with a GFD in CD, the results of this study did not consistent with the hypothesis; we found no statistically significant difference in MPV values between patients at diagnosis and after GFD introduction. In addition, no relationship was found between the MPV values of the patient (pre- and post treatment) and control groups.

Thrombocytosis in CD may occur due to a potential underlying factor such as platelet increase due to inflammatory mediators (26). Gerceker et al. (25) illustrated that platelet counts were significantly higher in the CD patients with activation compared to the CD patients in remission group and also in healthy controls. In another adult study they found that platelet values at initial diagnosis were significantly higher in the CD group compared to healthy controls (24). Terlemez and Tokgöz (26) observed a significant decrease in platelet values of pediatric patients with CD after a GFD. In the present study, we found that platelet levels were significantly higher in the CD group at the time of diagnosis when compared to the CD group after GFD, and also that platelet levels were within normal limits before and after GFD.

In CD, chronic inflammation damages the villi in the small intestine, leading to malabsorption, resulting in anemia and micronutrient deficiencies such as vitamin B12 (26,27). Terlemez and Tokgöz (26) observed a significantly increase in hemoglobin and MCV values of pediatric patients with CD after a GFD. Gerceker et al. (25) showed us a slightly higher hemoglobin in healthy controls compared to patients with CD, but there was no statistically significant difference. Deora et al. (27) assessed pediatric patients with CD for micronutrient deficiencies at the time of diagnosis and 18 months after introducing a GFD. The results indicated that the incidence of vitamin B12 deficiency decreased significantly from baseline to after 18 months on a GFD (27). In another study, 48 pediatric patients with CD were evaluated for different periods on a GFD, but the researchers did not observe any differences in hemoglobin or vitamin

B12 values between the subjects with CD and the non-CD controls (28). Likewise, an adult study comparing newly diagnosed patients with CD with non-CD individuals found no significant differences in hematocrit, and vitamin B12 levels (29). In our study we observed that hemoglobin, MCV, and vitamin B12 levels significantly increased after GFD treatment compared with the levels at the time of diagnosis; however, hemoglobin, MCV and vitamin B12 levels were within normal limits in patients with CD before and after GFD.

Study Limitations

Due to the retrospective nature of this study, a notable limitation is the relatively small number of patients included and the lack of data pertaining to the cytokine levels and acute phase reactants within the study group.

Conclusion

In conclusion, MPV may not be a useful biomarker for monitoring GFD in children with CD. More comprehensive studies are required to clarify this issue.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles outlined in the Helsinki Declaration and reviewed by the Selçuk University Ethical Review Board, and ethical approval was obtained from the Institutional Review Board (date: 09.06.2016, approval number: 2016/181).

Footnotes

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

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References

1. Fasano A, Catassi C. Clinical practice. Celiac disease. N Engl J Med. 2012;367:2419-26.
2. Pinto-Sánchez MI, Verdu EF, Liu E, Bercik P, Green PH, Murray JA, et al. Gluten introduction to ınfant feeding and risk of celiac disease: systematic review and meta-analysis. J Pediatr. 2016;168:132-43.
3. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-60.
4. Ciacci C, Ciclitira P, Hadjivassiliou M, Kaukinen K, Ludvigsson JF, McGough N, et al. The gluten-free diet and its current application in coeliac disease and dermatitis herpetiformis. United European Gastroenterol J. 2015;3:121-35.
5. Schuppan D, Zimmer KP. The diagnosis and treatment of celiac disease. Dtsch Arztebl Int. 2013;110:835-46.
6. Singh P, Singh AD, Ahuja V, Makharia GK. Who to screen and how to screen for celiac disease. World J Gastroenterol. 2022;28:4493-507.
7. Mohta S, Agarwal A, Banyal V, Singh A, Bagchi S, Das P, et al. Falsely elevated anti-tissue transglutaminase antibodies in patients with immunoproliferative small intestinal diseases: a case series. Indian J Gastroenterol. 2023;42:713-7.
8. Tanju C, Ekrem G, Berksoy Emel A, Nur A. Mean platelet volume as a negative marker of inflammation in children with rotavirus gastroenteritis. Iran J Pediatr. 2014;24:617-22.
9. Çelik T, Güler E, Berksoy EA, Sorguç Y, Arslan N. Mean platelet volume in children with acute gastroenteritis caused by entamoeba histolytica. Turkiye Parazitol Derg. 2015;39:205-8.
10. Chen Z, Lu Y, Wu J, Zhang H. Clinical significance of blood platelets and mean platelet volume in patients with ulcerative colitis. J Int Med Res. 2021;49:3000605211009715.
11. Nacaroglu HT, Bahceci Erdem S, Durgun E, Karaman S, Baris Erdur C, et al. Markers of inflammation and tolerance development in allergic proctocolitis. Arch Argent Pediatr. 2018;116:e1-e7.
12. Ceylan B, Aslan T, Çınar A, Ruhkar Kurt A, Akkoyunlu Y. Can platelet indices be used as predictors of complication in subjects with appendicitis? Wien Klin Wochenschr. 2016;128:620-5.
13. Aktas G, Alcelik A, Tekce BK, Tekelioglu V, Sit M, Savli H. Red cell distribution width and mean platelet volume in patients with irritable bowel syndrome. Prz Gastroenterol. 2014;9:160-3.
14. Liu S, Ren J, Han G, Wang G, Gu G, Xia Q, et al. Mean platelet volume: a controversial marker of disease activity in Crohn's disease. Eur J Med Res. 2012;17:27.
15. Marzouk H, Lotfy HM, Farag Y, Rashed LA, El-Garf K. Mean platelet volume and splenomegaly as useful markers of subclinical activity in Egyptian children with familial mediterranean fever: a cross-sectional study. Int J Chronic Dis. 2015;2015:152616.
16. Cicerone C, Nenna R, Pontone S. Th17, intestinal microbiota and the abnormal immune response in the pathogenesis of celiac disease. Gastroenterol Hepatol Bed Bench. 2015;8:117-22.
17. Idzko M, Pitchford S, Page C. Role of platelets in allergic airway inflammation. J Allergy Clin Immunol. 2015;135:1416-23.
18. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17:47-58.
19. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets. 2002;13:301-6.
20. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of ınflammatory conditions. Mediators Inflamm. 2019;2019:9213074.
21. Manavalan JS, Hernandez L, Shah JG, Konikkara J, Naiyer AJ, Lee AR, et al. Serum cytokine elevations in celiac disease: association with disease presentation. Hum Immunol. 2010;71:50-7.

22. Kapoor A, Patwari AK, Kumar P, Jain A, Narayan S. Serum soluble interleukin-2 receptor, interleukin-6 and tumor necrosis factor alpha as markers of celiac disease activity. Indian J Pediatr. 2013;80:108-13.
23. Björck S, Brundin C, Karlsson M, Agardh D. Reduced bone mineral density in children with screening-detected celiac disease. J Pediatr Gastroenterol Nutr. 2017;65:526-32.
24. Purnak T, Efe C, Yuksel O, Beyazit Y, Ozaslan E, Altiparmak E. Mean platelet volume could be a promising biomarker to monitor dietary compliance in celiac disease. Ups J Med Sci. 2011;116:208-11.
25. Gerceker E, Baykan AR, Cerrah S, Yuceyar H. Mean platelet volume can indicate dietary adherence and disease severity of celiac disease. North Clin Istanb. 2022;9:41-6.
26. Terlemez S, Tokgöz Y. Effects of gluten-free diet on hematological parameters in children with celiac disease. Kocatepe Medical Journal. 2018;19:126-30.
27. Deora V, Aylward N, Sokoro A, El-Matary W. Serum vitamins and minerals at diagnosis and follow-up in children with celiac disease. J Pediatr Gastroenterol Nutr. 2017;65:185-9.
28. Szaflarska-Popławska A, Dolińska A, Kuśmierek M. Nutritional ımbalances in polish children with coeliac disease on a strict gluten-free diet. Nutrients. 2022;14:3969.
29. Cabo Del Riego JM, Núñez-Iglesias MJ, Paz Carreira J, Blanco Hortas A, Álvarez Fernández T, Novío Mallón S, et al. Red cell distribution width as a predictive factor of celiac disease in middle and late adulthood and ıts potential utility as celiac disease screening criterion. Int J Environ Res Public Health. 2022;20:66.

ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Polikistik Over Sendromu Olan Ergenlerde Oksidatif Stres Parametrelerinin Değerlendirilmesi

Evaluation of Oxidative Stress Parameters in Adolescents with Polycystic Ovary Syndrome

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Öz

Giriş: Polikistik over sendromu (PKOS) etiyolojisi henüz tam olarak aydınlatılamamış olmakla birlikte, multifaktöriyel olduğu düşünülmektedir. Tartışılan mekanizmalardan biri de oksidatif stres artışıdır. Ancak literatürde, ergenlerde oksidatif stres artışına ilişkin bulgular tutarsızdır. Bu çalışmada PKOS'lu ergenlerde oksidatif stres parametrelerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Hastanemiz Ergen Sağlığı polikliniğine Eylül 2021-Mart 2023 tarihleri arasında başvuran ergenlerden, 12-18 yaş arasında olan ve en az 2 yıl önce menarş olan kız ergenler değerlendirilmiştir. PKOS tanısı alan ergenler çalışma grubuna, çalışma grubu ile yaş ve vücut kitle indeksi (VKİ) eşleştirilmiş sağlıklı ergenler kontrol grubuna dahil edilmiştir. Tüm katılımcılardan tıbbi ve menstrual öykü alınmış, fizik muayeneleri yapılmıştır. Katılımcılardan PKOS tanısı ve hiperandrojenizmi değerlendirmek üzere hormon tetkiki, inflamasyonu değerlendirmek için C-reaktif protein (CRP) ve oksidatif stres parametrelerini değerlendirmek için native tiyol, total tiyol ve iskemi modifiye albumin (İMA) düzeyleri çalışılmış; disülfid düzeyi, disülfid/native tiyol oranı, disülfid/total tiyol oranı ve native tiyol/total tiyol oranı hesaplanmıştır.

Bulgular: Çalışmaya 33 PKOS olan ve 43 sağlıklı ergen dahil edilmiştir. PKOS ve kontrol grubu karşılaştırıldığında, gruplar arasında oksidatif stres verileri ve İMA açısından anlamlı fark bulunmamıştır. Korelasyon analizinde, native tiyol ve total tiyol ile VKİ, bel çevresi, sistolik kan basıncı, diyastolik kan basıncı ve CRP arasında negatif korelasyon olduğu görülmüştür.

Sonuç: Çalışmamızda, PKOS ile kontrol grubu arasında oksidatif stres parametreleri açısından anlamlı bir fark saptanmazken, antioksidan kapasite ile metabolik ve inflamatuar parametreler arasında ters yönlü bir ilişki bulunmuştur. Bu sonuçlar, erişkin çalışmalarında bildirilen PKOS ile artmış oksidatif stres arasındaki anlamlı ilişki göz önünde bulundurulduğunda, bu ilişkinin PKOS etiyolojisinden çok, yaşın ilerlemesiyle birlikte belirgin hale gelen bir sonucu olduğu şeklinde yorumlanabilir.

Anahtar kelimeler
Polikistik over sendromu, oksidatif stres, ergenlik

Keywords
Polycystic ovary syndrome, oxidative stress, adolescence

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Abstract

Introduction: Although the etiology of polycystic ovary syndrome (PCOS) has not yet been fully elucidated, it is thought to be multifactorial. One of the debated mechanisms is the increase in oxidative stress. However, findings regarding oxidative stress increase in adolescents are inconsistent in the literature. This study aimed to evaluate oxidative stress parameters in adolescents with PCOS.

Materials and Methods: Adolescent girls aged 12-18 years, who presented to our Adolescent Health Outpatient Clinic between September 2021 and March 2023 and had menarche at least two years prior, were included in the study. Adolescents diagnosed with PCOS were included in the study group, while age- and body mass index (BMI)-matched healthy adolescents were included in the control group. A medical and menstrual history was obtained from all participants, and physical examinations were performed. Hormonal tests were conducted to assess PCOS diagnosis and hyperandrogenism, C-reactive protein (CRP) levels were measured to evaluate inflammation, and oxidative stress parameters were assessed by measuring native thiol, total thiol, and ischemia-modified albumin (IMA) levels. Additionally, disulfide levels, disulfide/native thiol ratio, disulfide/total thiol ratio, and native thiol/total thiol ratio were calculated.

Results: The study included 33 adolescents with PCOS and 43 healthy adolescents. No significant differences were found between the PCOS and control groups in terms of oxidative stress parameters or IMA levels. Correlation analysis revealed negative correlations between native thiol-total thiol levels and BMI, waist circumference, systolic blood pressure, diastolic blood pressure, and CRP.

Conclusion: In our study, no statistically significant difference was found in oxidative stress parameters between the PCOS and control groups. On the other hand, an inverse relationship was observed between antioxidant capacity and metabolic and inflammatory parameters. Considering the significant association reported in adult PCOS studies, these findings suggest that increased oxidative stress may be a consequence that becomes more pronounced with aging rather than a primary factor in the etiology of PCOS.

Giriş

Polikistik over sendromu (PKOS); hiperandrojenizm ve kronik anovulasyon ile karakterize, kadınlarda en sık görülen endokrinolojik bozukluktur (1). Ergenlerde PKOS prevalansı Amerikan Ulusal Sağlık Enstitüleri (National Institutes of Health, NIH) kriterlerine göre %3,39, Rotterdam kriterlerine göre %11,04, Androgen Excess Society (AES) kriterlerine göre %8,03 olarak bildirilmiştir (2).

PKOS patogenezinde hiperandrojenizm, insülin direnci, nöroendokrin değişiklikler, genetik, sempatik sinir sistemindeki değişiklikler, ovarian follikülogenezde bozulma ve overlerde oksidatif stres artışının yer aldığı düşünülmektedir (3). Oksidatif stres vücutta antioksidanların nötralize etme kapasitesini aşan düzeyde serbest radikal oluştuğunu gösteren bir dengesizlik durumudur. Süperoksit anyon radikalleri, hidrojen peroksit ve hidroksil radikalleri gibi çeşitli moleküllerden oluşan reaktif oksijen türleri, protein sentezi ve mitokondriyal metabolizma gibi metabolik süreçler sırasında hücreler tarafından üretilir. Reaktif oksijen türleri, reaktif nitrojen türleri ve diğer reaktif metabolik aracılar, antioksidan sistemlerin kapasitesini aşacak kadar artarsa, oksidatif strese neden olurlar. Oksidatif stres DNA, RNA, proteinler ve lipidleri içeren hücre komponentlerine toksik etki göstererek yaşlanma, hücre ölümü, metabolik sendrom ve pek çok bozukluğa neden olur (4-6).

Tiyoller, karbon atomuna sülfür (S) ve hidrojen (H) atomunun bağlanması ile oluşan sülfidril (-SH) grubu içeren organik bileşiklerdir ve -SH grupları nedeniyle oksidasyona karşı hassas antioksidanlardır. Reaktif oksijen türlerinin enzimatik olmayan eliminasyonunda rol oynarlar (6). Tiyoller, oksidasyon reaksiyonuna girer ve disülfid bağları oluştururlar. Disülfidler (-S-S-), iki tiyol grubu arasında oluşan en önemli dinamik, redoks duyarlı kovalent bağ sınıfıdır. Oluşan disülfid bağları yeniden tiyol gruplarına indirgenebilir; böylece dinamik tiyol-disülfid homeostazı korunur (7). Dinamik tiyol-disülfid homeostazı antioksidan koruma, detoksifikasyon, sinyal iletimi, enzimatik aktivitenin düzenlenmesi, apopitoz, bazı transkripsiyon faktörlerinin işlevi ve bazı hücresel sinyal mekanizmalarında önemli rol oynar (6).

İskemi modifiye albümin (İMA), albüminin iskemi nedeniyle yapısal değişikliğe uğramış formudur. İskemi ve oksidatif stres albüminin N-terminal bölgesinin kobalt, bakır ve nikel için bağlanma kapasitesini azaltır ve İMA'yı oluşturur. İMA'nın özellikle vasküler iskemiyle direk ilişkili hastalıklarda belirgin olarak artış gösterdiği bildirilmiştir (8).

PKOS'ta kronik düşük dereceli bir inflamasyon olduğu gösterilmiştir. Bu inflamasyonun göstergelerinden biri olan C-reaktif protein (CRP), interlökin-6 ve tümör nekroz faktörü-α tarafından uyarıldıktan sonra karaciğer tarafından üretilen bir

akut faz proteinidir. CRP aynı zamanda doğrudan yağ dokusu tarafından da üretilir. CRP'nin intravasküler inflamatuar sürecin bir belirteci olabileceği ve kardiyovasküler hastalıkların gelişimi için en önemli belirteçlerden biri olduğu düşünülmektedir (9).

PKOS'ta görülen anovulasyondan veya oosit değişikliklerinden, oksidatif stres ve düşük düzeyde inflamasyonu içeren pek çok mekanizmanın sorumlu olduğu düşünülmektedir. Fenkci ve ark. (10) PKOS'lu erişkin kadınlarda antioksidan kapasitenin azaldığını ve oksidatif stresin arttığını göstermişlerdir. Bir sistematik gözden geçirme ve meta-analizde, 2 tanesi ergenlerde yapılmış toplamda 68 çalışma değerlendirilmiş ve PKOS'ta oksidatif stresin arttığı gösterilmiştir. Ancak bu artışların çok yüksek olmadığı; PKOS için farklı tanı kriterlerinin kullanılması, farklı etnik köken ve ırktan hastaların dahil edilmesi, oksidatif stres değerlendirilmesinde farklı test yöntemleri ile farklı örneklerin kullanılması gibi nedenlerle dahil edilen çalışmaların heterojen olduğu vurgulanmıştır (11). Bu meta-analizde yer alan, ergenlerde yapılan 2 çalışmada ise oksidatif stres artışı gösterilememiştir. Bir çalışmada oksidatif stresle ilişkili olarak okside düşük yoğunluklu lipoprotein (LDL) ve asimetrik dimetil-arjinin düzeyleri, diğer çalışmada ise homosistein düzeyleri PKOS ve kontrol grubundaki ergenlerde karşılaştırılmış ve gruplar arasında fark saptanmamıştır (12,13).

Genç erişkinlerin dahil edildiği bir çalışmada ise oksidatif stres belirteçleri açısından, PKOS ve kontrol grupları arasında fark olmadığı gösterilmiş, bu sonuç hastaların genç, non-obez ve yeni tanı almış hastalar olmasına bağlanmıştır (14). Literatürde farklı sonuçları olan çok sayıda çalışma bulunmaktadır. Bu nedenle günümüzdeki bilgiler ışığında oksidatif stresin rutin olarak ölçülmesi ve antioksidan tedavi verilmesi önerilmemektedir (11).

Bu çalışmada, PKOS olan ergenlerde oksidatif stres parametreleri ölçülmüştür. Çalışmanın amacı, PKOS'lu ergenlerde oksidatif stresin artıp artmadığının değerlendirilmesidir.

Gereç ve Yöntem

Araştırmaya Eylül 2021-Mart 2023 tarihleri arasında hastanemiz Ergen Sağlığı polikliniğine başvuran, 12-18 yaş arasındaki ergenlerden, en az 2 yıl önce menarş olan, çalışmaya dahil olma kriterlerini karşılayan ve çalışmaya katılmaları için kendilerinden ve ailelerinden onam alınan 2 grup dahil edilmiştir. PKOS tanısı almış olan ergenler çalışma grubuna, PKOS grubu ile yaş ve vücut kitle indeksi (VKİ) eşleştirilmiş, düzenli adet gören ve hirsutizmi olmayan sağlıklı ergenler ise kontrol grubuna dahil edilmiştir.

Araştırmaya dahil edilmeme kriterleri ise şunlardır: Aile ya da ergenin çalışmaya katılmak istememesi; sigara kullanımı öyküsü; gebelik varlığı; kronik hastalık, hipertansiyon, diyabet, tiroid fonksiyonlarında bozukluk, Cushing sendromu, androjen sekrete eden tümör, geç başlangıçlı konjenital adrenal hiperplazi, hiperprolaktinemi varlığı; oral kontraseptif kullanımı.

PKOS tanısı 2015 Pediatrik Endokrin Derneği'nin kriterlerine uygun olarak, oligo/anovulasyon ve klinik ve/veya biokimyasal hiperandrojenizm varlığında, bu iki duruma neden olabilecek diğer nedenler ekarte edilerek konulmuştur (15). Çalışmaya menarştan sonra 2 yıl veya daha fazla zaman geçen katılımcılar dahil edildiğinden, ovulatuar disfonksiyon için menstrual siklusun sürekli olarak 21 günden kısa veya 45 günden uzun aralarla olması kriteri kabul edilmiştir.

Çalışma Protokolü

Tüm katılımcılardan ayrıntılı tıbbi öykü alınmış, menstrual öykü kapsamında hastaların menarş yaşı, menstrual siklus süresi ve adet kanama süresi öğrenilmiştir. Tüm katılımcıların sistemik fizik muayeneleri yapılmıştır. Her katılımcının vücut ağırlığı ve boyu ölçülerek VKİ hesaplanmıştır. VKİ (kg/m^2) vücut ağırlığı (kg), boyun karesine (m^2) bölünerek hesaplanmıştır. VKİ değerinin kaçıncı persentilde olduğu ve z skorları Hastalık Kontrol ve Önleme Merkezi'nin (Centers for Disease Control and Prevention, CDC) yaş ve cinsiyete göre VKİ eğrileri kullanılarak değerlendirilmiştir. Bel çevresi, göbek deliğinden geçecek şekilde, 10. kosta alt sınırı ile iliak kemiğin en üst kısmının ortasından ölçülmüştür. Kalça çevresi, kalçanın en geniş yerinden ölçülmüştür. Bel/kalça oranı hesaplanmıştır. Tüm katılımcıların kan basıncı hastanın ayakları yere basar pozisyonda otururken ölçülmüştür. Modifiye Ferriman-Gallwey skorlama sistemine göre, vücudun 9 bölgesindeki kıllanma miktarı 0-4 arasında skorlanmıştır. Toplam modifiye Ferriman-Gallwey skoru 8 ve üzerindeyse hirsutizm olarak kabul edilmiştir (16,17).

Çalışmaya katılan tüm ergenlerden PKOS ayırıcı tanısı için, hiperandrojenizmi ve inflamasyonu

değerlendirmek üzere kan alınmıştır. Total testosteron, dehidroepiandrosteron sülfat (DHEAS), seks hormonu bağlayıcı globulin (SHBG), folikül stimulan hormon (FSH), lüteinizan hormon (LH), estradiol (E_2), prolaktin, tiroid stimulan hormon (TSH), serbest T4 (sT4), 17-hidroksiprogesteron, CRP tetkikleri çalışılmak üzere kan alınmıştır.

Kan örnekleri foliküler fazın başında veya 3 aydır adet görmüyorsa herhangi bir zamanda sabah saat 09.00'da 12 saat açlık sonrası alınmıştır. FSH, LH, E_2, prolaktin, TSH ve sT4 iki basamaklı kemiluminesans mikropartikül immunoassay metodu ile; total testosteron, DHEAS kemiluminesans immunoassay metodu ile; SHBG ve 17-hidroksiprogesteron radyoimmunoassay metodu ile çalışılmıştır. CRP nefelometrik yöntemle çalışılmıştır. Biyokimyasal hiperandrojenizmi değerlendirmek için total testosteron düzeyi ve Serbest Androjen İndeksi (SAİ) kullanılmıştır. Total testosteron 55 ng/dL üzerindeyse veya SAİ 3,5 üzerindeyse hiperandrojenizm olarak kabul edilmiştir. SAİ, total testosteronu (nmol/L) SHBG'e (nmol/L) bölüp 100 ile çarparak hesaplanmıştır (18,19).

Oksidatif stresi değerlendirmek amacıyla, çalışmaya katılan tüm ergenlerden native tiyol, total tiyol, disülfid ve İMA ölçümü için kan alınmıştır. Tüm katılımcılardan 5 mL açlık kan örneği sarı kapaklı biyokimya tüplerine alınmış, en geç yarım saat içinde 1600 g'de 10 dakika santrifüj edildikten sonra serumları eppendorfa ayrılmış ve örnekler çalışılacağı zamana kadar derin dondurucuda -80 °C'de saklanmıştır. Tüm örneklerin alınması tamamlandığında, dondurulmuş serum örnekleri Ankara Şehir Hastanesi, Tıbbi Biyokimya Laboratuvarı'na çalışılmak üzere götürülmüştür. Tiyol-disülfid homeostazı testleri, Erel ve Neselioğlu tarafından tanımlanan otomatik spektrofotometrik yöntemle ölçülmüştür (7). Bu yöntemde, kanda hem tiyol hem de disülfid seviyeleri ölçülmektedir. Dinamik disülfid miktarı, total tiyol ve native tiyol arasındaki farkın yarısıdır. Native tiyol ve total tiyol ölçümleri yapıldıktan sonra dinamik tiyol-disülfid homeostazını değerlendirmek için disülfid miktarı, disülfidin native tiyole oranı, disülfidin total tiyole oranı ve native tiyolün total tiyole oranı hesaplanmıştır. Disülfid artışı ve disülfid lehine artan oranlar oksidatif stresi göstermektedir. Tiyol artışı ve tiyol lehine artan oranlar ise tiyol-disülfid homeostazının antioksidan yöne kaydığını göstermektedir (5). İMA varlığını tespit etmek için Albümin Kobalt Bağlama Testi kullanılmıştır. Sonuçlar absorbans birimleri (ABSU) olarak ifade edilmiştir (20).

İstatistiksel Analiz

Kategorik değişkenler sayı ve % ile tanımlanırken, sürekli değişkenler (yaş vb.) aritmetik ortalama, standart sapma, ortanca, minimum ve maksimum değerler kullanılarak tanımlanmıştır.

Sürekli değişkenler PKOS ve Kontrol gruplarında parametrik test varsayımları sağlanıyorsa Student's t testi, sağlanmıyorsa Mann-Whitney U testi kullanılarak karşılaştırılmıştır. Parametrik test varsayımlarından en önemlisi normal dağılıma uygunluk olup verilerin gruplarda normal dağılıma uygunluğu Shapiro Wilk testi ile test edilmiştir. En az bir grupta verilerin normal dağılıma uygunluğu sağlanmıyorsa parametrik olmayan test tercih edilmiştir. Değişkenler arasındaki ilişki, Pearson korelasyon analizi kullanılarak değerlendirilmiştir. Pearson korelasyon katsayısı (r) 0 ile 1 arasında değişen bir sayıdır. 0'a yakın olan değerler düşük korelasyonu, +1'e yakın olan değerler pozitif ve yüksek korelasyonu, -1'e yakın değerler ise negatif ve yüksek korelasyonu gösterir. R katsayısı şu şekilde yorumlanabilir:

0,01-0,29: düşük düzeyde ilişki
0,30-0,70: orta düzeyde ilişki
0,71-0,99: yüksek düzeyde ilişki

Verilerin analizi SPSS 20.0 paket programı kullanılarak yapılmış olup $p<0,05$ istatistiksel anlamlı düzey olarak alınmıştır. İstatistiksel analizler %95 güven aralığı ile gerçekleştirilmiş olup, sonuçlar buna göre raporlanmıştır.

Bulgular

Çalışmaya 33 tane PKOS, 43 tane kontrol olmak üzere toplam 76 ergen dahil edilmiştir.

Antropometrik ve Menstrual Veriler

Yaş, antropometrik ölçüm, ve menstrual bilgilerin PKOS ve kontrol gruplarında karşılaştırılması Tablo 1'de verilmiştir. PKOS grubunda boy ortalaması (163,8±6,4 cm) kontrol grubundan (160,9±5,2 cm) yaklaşık olarak 3 cm daha uzun olmakla birlikte, vücut ağırlığı, VKİ ve VKİ persentil değeri ortalaması açısından iki grup arasında istatistiksel olarak fark saptanmamıştır (sırasıyla $p<0,05$, $p=0,112$, $p=0,297$, $p=0,504$). Bel/kalça oranı PKOS grubunda daha yüksek

bulunmuştur (p<0,01), ancak bel ve kalça çevresi açısından iki grup arasında istatistiksel olarak anlamlı fark saptanmamıştır (sırasıyla p=0,055, p=0,352).

Sistemik İnflamasyon Verisi

CRP değeri ortancası PKOS grubunda 0,2(0,1-0,8) mg/dL ve kontrol grubunda 0,2(0,1-0,8) mg/dL olarak bulunmuştur (p=0,507).

Oksidatif Strese İlişkin Veriler

Oksidatif stres parametrelerine bakıldığında, antioksidan etkisi olan native ve total tiyol ortalamasının PKOS grubunda kontrol grubuna göre daha düşük olduğu, ancak bunun istatistiksel olarak anlamlı bir fark olmadığı görülmüştür (sırasıyla p=0,210, p=0,154). PKOS ve kontrol gruplarının, oksidatif stres parametreleri ve İMA açısından karşılaştırması Tablo 2'de verilmiştir.

Korelasyon Analizi

Korelasyon analizinde, native tiyol ile VKİ (r=-0,325, p<0,01), bel çevresi (r=-0,319, p<0,01), sistolik kan basıncı (r=-0,237, p<0,05), diyastolik kan basıncı (r=-0,275, p<0,05) ve CRP (r=-0,384, p<0,01) arasında negatif korelasyon olduğu görülmüştür. Total tiyol ile VKİ (r=-0,356, p<0,01), bel çevresi (r=-0,339, p<0,01), sistolik kan basıncı (r=-0,239, p<0,05), diyastolik kan basıncı (r=-0,310, p<0,01) ve CRP (r=-0,379, p<0,01) arasında da negatif korelasyon saptanmıştır (Tablo 3).

Tartışma

PKOS, etiyopatogenezinde pek çok nedenle birlikte oksidatif stres artışının yer aldığı düşünülen kompleks bir bozukluktur. Çalışmamızda oksidatif stres parametreleri açısından PKOS ve kontrol grubu arasında istatistiksel açıdan anlamlı fark saptanmamıştır; ancak antioksidan etkisi olan native ve total tiyollerin PKOS grubunda kontrol grubuna göre daha düşük olduğu görülmüştür. Erişkin çalışmalarında ve meta-analizlerinde oksidatif stres artışı gösterilmesine karşın (4,10,11,21), bizim çalışmamızda olduğu gibi, ergenlerde ve genç erişkinlerde yapılan kısıtlı sayıda çalışmada oksidatif stresin arttığı gösterilememiştir (12,13,22,23).

Tablo 1. PKOS ve kontrol gruplarında yaş, antropometrik ölçüm, kan basıncı ve menstrual bilgilerin karşılaştırılması

	PKOS (n=33)		**Kontrol (n=43)**		
	Ortalama ± Standart sapma	**Güven aralığı %95**	**Ortalama ± Standart sapma**	**Güven aralığı %95**	**p-value**
Yaş (yıl)	15,7±0,8	[15,427-15,973]	15,4±1,3	[15,011-15,789]	0,215
Vücut ağırlığı (kg)	69,9±19,4	[63,281-76,519]	63,6±14,8	[59,176-68,024]	0,112
Boy (cm)	163,8±6,4	[161,616-165,984]	160,9±5,2	[159,346-162,454]	**<0,05**
VKİ (kg/m^2)	25,9±6,4	[23,716-28,084]	24,5±5,2	[22,946-26,054]	0,297
VKİ persentili	74,7±27,2	[65,420-83,980]	70,4±28,0	[62,031-78,769]	0,504
VKİ z skoru	0,95±1,01	[0,605-1,295]	0,79±1,02	[0,485-1,095]	0,500
Bel çevresi (cm)	81,4±15,5	[76,112-86,688]	75,2±12,3	[71,524-78,876]	0,055
Kalça çevresi (cm)	102,1±12,4	[97,869-106,331]	99,7±10,0	[96,711-102,689]	0,352
Bel/kalça oranı	0,79±0,06	[0,770-0,810]	0,75±0,06	[0,732-0,768]	**<0,01**
SKB (mmHg)	117,7±9,8	[114,356-121,044]	116,4±7,6	[114,128-118,672]	0,505
DKB (mmHg)	78,0±7,0	[75,612-80,388]	75,3±5,9	[73,537-77,063]	0,074
Menars yaşı (yıl)	12,2±1,1	[11,825-12,575]	11,7±1,2	[11,341-12,059]	0,057
Adet kanama süresi (gün)	6,1±1,3	[5,656-6,544]	5,7±1,2	[5,341-6,059]	0,145
	Ortanca (min-maks)		**Ortanca (min-maks)**		
Menstrual siklus süresi (gün)	90 (45-365)	[90-135]	30 (25-40)	[30-32]	**<0,001**
mFG skoru	11 (2-19)	[9-12]	2 (0-5)	[0-2]	**<0,001**

DKB: Diyastolik kan basıncı, mFG: Modifiye Ferriman-Gallwey, SKB: Sistolik kan basıncı, PKOS: Polikistik over sendromu, VKİ: Vücut kitle indeksi

Tablo 2. PKOS ve kontrol grubunda oksidatif stres verilerinin karşılaştırılması					
	PKOS (n=33)		**Kontrol (n=43)**		
	Ortalama ± Standart sapma	**Güven aralığı %95**	**Ortalama ± Standart sapma**	**Güven aralığı %95**	**p-value**
Native tiyol	604,1±61,6	[583,083-625,117]	621,2±55,5	[604,612-637,788]	0,210
Total tiyol	645,2±55,3	[626,332-664,068]	663,4±53,9	[647,290-679,510]	0,154
Disülfid	20,6±6,1	[18,519-22,681]	21,1±5,4	[19,486-22,714]	0,676
Disülfid/native Tiyol x100	3,5±1,3	[3,056-3,944]	3,4±0,9	[3,131-3,669]	0,816
Disülfid/total tiyol x 100	3,2±1,1	[2,825-3,575]	3,2±0,8	[2,961-3,439]	0,858
Native tiyol/total tiyol x 100	93,5±2,2	[92,749-94,251]	93,6±1,7	[93,092-94,108]	0,861
	Ortanca (min-maks)		**Ortanca (min-maks)**		
İMA	0,67(0,66-0,70)	[0,67-0,68]	0,67(0,64-0,70)	[0,67-0,68]	0,983
İMA: İskemi modifiye albumin, PKOS: Polikistik over sendromu					

PKOS kronik inflamasyon ve doku düzeyinde oksidatif stres artışı ile ilişkilendirilmektedir. Ancak bu ilişkinin laboratuvar yöntemleri ile gösterilmesi, örnek alınma zamanı ile de ilgili olabilir. Çünkü antioksidan kapasitenin başlangıçta reaktif oksijen türleri tarafından aşılabileceği, ancak devam eden oksidatif strese yanıt olarak zamanla artabileceği düşünülmektedir (24).

Yetişkin bireylerde, özellikle yaş ve hastalık süresi arttıkça oksidatif stres düzeylerinde belirgin bir artış gözlenirken, ergen bireylerde ve hastalık tanısı alındığı ilk dönemde bu artışın gözlemlenmemesi, oksidatif stresin hastalığın etiyolojik bir faktöründen ziyade, hastalık süresi ve komorbiditelerin artışıyla ilişkili sekonder bir süreç olabileceğini düşündürmektedir. Ergenlerin ve genç yetişkinlerin dahil edildiği bir çalışmada, PKOS ve kontrol grupları arasında tiyol, disülfid ve İMA düzeyleri açısından fark olmadığı gösterilmiştir. Öte yandan serum CRP düzeyleri ile native tiyol, total tiyol düzeyleri arasında negatif korelasyon saptanmıştır (22). PKOS'a bağlı değişiklikler ve komorbiditeler, vücutta oksidanların artışına ve antioksidan kapasitenin yetersiz kalarak vücutta oksidatif stresin artışına neden olabilir. Bizim çalışmamızda da yeni tanı almış, yaş ortalaması küçük bir hasta grubu değerlendirildiğinden gruplar arasında fark saptanmamış olabilir. PKOS'ta hastalık süresi uzadıkça komorbiditeler arttığı için oksidatif stres de yaşla ve hastalık süresi ile artıyor gibi görünmektedir. Ayrıca VKİ, bel çevresi, sistolik ve diyastolik kan basıncı gibi metabolik sendrom bulguları ve CRP gibi inflamasyon belirteçleri ile antioksidan seviyelerinin, yani native ve total tiyol seviyelerinin, negatif korelasyonu da bu düşünceyi desteklemektedir.

PKOS ve oksidatif stres belirteçleri arasındaki ilişkinin VKİ ve adiposite ilişkili olabileceği de öne sürülmüştür. Fazla kilolu genç erişkin PKOS ve kontrol grubunun karşılaştırıldığı bir çalışmada, gruplar arasında oksidan ve antioksidan kapasite açısından fark olmadığı gösterilmiştir (23). Hastaların VKİ'ye göre 4 gruba ayrıldığı, genç erişkinleri kapsayan başka bir çalışmada, antioksidan düzeyinin göstergesi olan tiyollerin obez PKOS grubunda obez kontrol grubuna göre daha yüksek olduğu, oksidan düzeyinin göstergesi olan disülfidin ise obez PKOS grubunda obez kontrollerden düşük olduğu gösterilmiştir. Obez olmayan PKOS ve kontrol gruplarında da benzer sonuçlar gözlenmiştir. Yazarlar beklenenin aksine, yüksek oksidatif stres yerine yüksek antioksidan seviyelerinin, PKOS'un etiyopatogenezinde önemli bir rol oynayabileceğini belirtmişlerdir. Yüksek serum tiyol seviyelerinin, özellikle obez PKOS hastalarında belirgin olduğunu ve bu durumun, anovülasyon, çoklu folikül gelişimi ve apopitoz gibi mekanizmalardan veya obeziteden kaynaklanan oksidatif yüke karşı bir kompansasyon yanıtı olabileceğini vurgulamışlardır (25). Yine katılımcıların 4 grupta incelendiği, ergenlerde yapılan bir çalışmada farklı olarak native ve total tiyolün fazla kilolu PKOS grubunda, normal kilolu PKOS ve kontrollere göre daha düşük olduğu ancak fazla kilolu kontrolle arada anlamlı fark olmadığı gösterilmiştir.

Tablo 3. Oksidatif stres ile antropometrik ölçüm, kan basıncı, androjen ve inflamatuar belirtecin korelasyon analizi

		Ort.	SS	1	2	3	4	5	6	7	8	9	10	11
1	VKİ	25,12	5,75	1										
2	Bel çevresi	77,86	14,04	0,939**	1									
3	Bel/kalça oranı	0,77	0,064	0,715**	0,862**	1								
4	SKB	116,97	8,57	0,685**	0,699**	0,622**	1							
5	DKB	76,51	6,48	0,678**	0,704**	0,658**	0,822**	1						
6	T.testosteron	36,84	19,93	0,221	0,358**	0,393**	0,183	0,271*	1					
7	CRP	0,305	0,2	0,373**	0,328**	0,331**	0,299*	0,323**	0,054	1				
8	Native tiyol	613,78	58,45	-0,325**	-0,319**	-0,188	-0,237*	-0,275*	-0,181	-0,384**	1			
9	Total tiyol	655,51	54,89	-0,356**	-0,339**	-0,202	-0,239*	-0,310**	-0,193	-0,379**	0,982**	1		
10	Disülfid	20,87	5,7	-0,045	0	-0,005	0,063	-0,082	-0,001	0,14	-0,400**	-0,219	1	
11	İMA	0,67	0,011	-0,07	-0,075	-0,085	-0,036	-0,171	-0,056	0,089	-0,404**	-0,378**	0,25*	1

**p<0,01, *p<0,05. CRP: C-reaktif protein, DKB: Diyastolik kan basıncı, İMA: İskemi modifiye albümin, Ort: Ortalama, SKB: Sistolik kan basıncı, SS: Standart sapma, T: Total, VKİ: Vücut kitle indeksi

Disülfid düzeyi, disülfid/native tiyol oranı, disülfid/total tiyol oranı ve native tiyol/total tiyol oranları arasında ise anlamlı fark saptanmamıştır (26). Bizim çalışmamızda da native tiyol ve total tiyol ile VKİ ve bel çevresi, arasında orta güçte ters yönlü bir korelasyon saptanmıştır. Bu bulgular adiposite artışı ile antioksidan kapasitenin azaldığı yönünde yorumlanabilir. Literatürde farklı tanı kriterlerine göre PKOS tanısı konulan hastalarda, farklı testlerle değerlendirilen oksidatif stres parametreleri ölçümü tutarsız sonuçlar vermektedir. Yaş, tanı ve oksidatif stres ölçüm zamanı, eşlik eden obezite veya PKOS komorbiditeleri varlığı da sonuçları değiştirmektedir. Sonuçlardaki bu farklılık, çalışmaların heterojen olmasından kaynaklanabileceği gibi, doku düzeyinde etkili olan oksidatif stresin dolaşımda iyi ifade edilmemesi veya gösterilememesi nedeniyle olabilir.

Çalışmamızda PKOS ve kontrol grupları arasında, sistemik inflamasyonu gösteren CRP değerinde farklılık saptanmamıştır. PKOS'lu erişkin kadınlarda inflamasyon belirteçlerinin değerlendirildiği ve 31 çalışmanın dahil edildiği bir sistematik gözden geçirme ve meta-analizde, PKOS'lu kadınlarda ortalama serum CRP düzeyleri kontrol grubuna kıyasla %96 daha yüksek bulunmuştur ve PKOS'taki CRP artışının obeziteden bağımsız olduğu belirtilmiştir (27). PKOS grubunun metabolik sendrom varlığına ve normal kilolu veya fazla kilolu olma durumuna göre 4 alt gruba ayrılıp kontrol grubu ile kıyaslandığı, ergenlerde yapılan bir çalışmada; fazla kilolu olan PKOS'lularda normal kilolu PKOS grubuna göre CRP'nin metabolik sendrom olsun veya olmasın daha yüksek olduğu gösterilmiştir. Kontrol grubunda ise CRP düzeyi, sadece fazla kilolu ve metabolik sendromu olan PKOS'lu gruba göre düşük bulunmuştur. Aynı çalışmada PKOS veya metabolik sendromun, CRP artışında bağımsız faktör olmadığı, sadece VKİ için bağımsız bir etkinin gösterildiği vurgulanmıştır. Diğer sonuçlarla birlikte, visseral yağlanma ve insülin direnci ile komplike olmuş PKOS'lu ergenlerde, sistemik inflamasyonun arttığı sonucuna varmışlardır (28). Ergen ve genç erişkinlerde yapılan başka bir çalışmada, PKOS ve kontrol grupları karşılaştırılmış, gruplar arasında CRP değeri açısından istatistiksel olarak anlamlı fark saptanmamıştır. Ancak PKOS grubunda CRP ile VKİ arasında anlamlı bir pozitif korelasyon bulunmuştur (29). Çalışmamızda da CRP ile bel çevresi, bel/kalça oranı, sistolik kan basıncı ve diyastolik kan basıncı arasında anlamlı pozitif korelasyon olduğu görülmüştür. Ergen çalışmaları ve çalışmamızın verileri birlikte değerlendirildiğinde, ergen yaş grubunda CRP'nin tek başına PKOS nedeniyle artmayabileceği, ancak özellikle visseral yağlanmanın ve VKİ artışının CRP artışıyla paralel olduğu söylenebilir.

Çalışmanın Kısıtlılıkları

Bu çalışmanın bazı kısıtlılıkları bulunmaktadır. Çalışmanın örneklem büyüklüğünün sınırlı olması sonuçların genellenebilirliğini kısıtlamaktadır. Ayrıca örneklem büyüklüğü sınırlı olduğundan, hastalar VKİ'ye göre alt gruplara ayrılıp analiz yapılamamıştır. Bu çalışmada, yalnızca tanı anında ölçüm yapılmıştır. Bu nedenle, değişkenler arasındaki nedensel ilişkiyi doğrulamak mümkün değildir. Ayrıca hastalar bir kez tanı anında değerlendirildiğinden, PKOS'ta hastalık süresi ve yaş arttıkça ortaya çıkabileceğini düşündüğümüz oksidatif stres artışı görülmemiş olabilir. Bu nedenle ileride yapılacak boylamsal izlem çalışmaları değerli olacaktır. Oksidatif stres pek çok faktörden etkilenmektedir. Kronik hastalığı ve sigara kullanımı olan hastalar çalışmaya dahil edilmeyerek bu etki azaltılmaya çalışılsa da, diğer değişkenler kontrol edilememiştir. Hastaların tanı anında oral konstraseptif gibi herhangi bir tedavi almadan, değerlendirilmiş olması etiolojik ilişkinin kurulması açısından araştırmanın güçlü yönlerindendir.

Sonuç

Sonuç olarak çalışmamızda oksidatif stres parametreleri açısından, PKOS ve kontrol grubu arasında istatistiksel olarak anlamlı fark bulunmamıştır. Günümüzde var olan teknikleri kullanarak yapılan çalışmalarda, serumda ölçülebilen düzeyde oksidatif stres artışı daha çok erişkinlerde gösterildiğinden; oksidatif stres ve PKOS arasındaki ilişkinin yaş ve hastalık süresi arttıkça ve hastalık komorbiditeleri ortaya çıktıkça belirgin hale geldiğini düşünmekteyiz. Bu ilişkinin gösterilebilmesi için daha büyük örneklem ile yapılacak, uzun süreli boylamsal çalışmalara gereksinim vardır.

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Kaynaklar

1. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97:28-38.
2. Naz MSG, Tehrani FR, Majd HA, Ahmadi F, Ozgoli G, Fakari FR, et al. The prevalence of polycystic ovary syndrome in adolescents: a systematic review and meta-analysis. Int J Reprod Biomed. 2019;17:533-42.
3. Ibáñez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, et al. An International consortium update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. Horm Res Paediatr. 2017;88:371-95.
4. Bahreiny SS, Ahangarpour A, Saki N, Dabbagh MR, Ebrahimi R, Mahdizade AH, et al. Association of free radical product and polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Sci. 2024;31:1486-95.
5. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. Turk J Med Sci. 2020;50:1728-38.
6. Mengen E, Uçaktürk SA, Kocaay P, Kaymaz Ö, Neşelioğlu S, Erel Ö. The significance of thiol/disulfide homeostasis and ischemia-modified albumin levels in assessing oxidative stress in obese children and adolescents. J Clin Res Pediatr Endocrinol. 2020;12:45-54.
7. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326-32.
8. Gaze DC. Ischemia modified albumin: a novel biomarker for the detection of cardiac ischemia. Drug Metab Pharmacokinet. 2009;24:333-41.
9. Rudnicka E, Suchta K, Grymowicz M, Calik-Ksepka A, Smolarczyk K, Duszewska AM, et al. Chronic low grade inflammation in pathogenesis of PCOS. Int J Mol Sci. 2021;22:3789.
10. Fenkci V, Fenkci S, Yilmazer M, Serteser M. Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. Fertil Steril. 2003;80:123-7.
11. Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. Hum Reprod Update. 2013;19:268-88.
12. Demirel F, Bideci A, Cinaz P, Camurdan MO, Biberoğlu G, Yesilkaya E, et al. Serum leptin, oxidized low density lipoprotein and plasma asymmetric dimethylarginine levels and their relationship with dyslipidaemia in adolescent girls with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2007;67:129-34.
13. Fulghesu A, Magnini R, Portoghese E, Angioni S, Minerba L, Melis GB. Obesity-related lipid profile and altered insulin incretion in adolescents with polycystic ovary syndrome. J Adolesc Health. 2010;46:474-81.
14. Karadeniz M, Erdoğan M, Tamsel S, Zengi A, Alper GE, Cağlayan O, et al. Oxidative stress markers in young patients with polycystic ovary syndrome, the relationship between insulin resistances. Exp Clin Endocrinol Diabetes. 2008;116:231-5.
15. Witchel SF, Oberfield S, Rosenfield RL, Codner E, Bonny A, Ibáñez L, et al. The diagnosis of polycystic ovary syndrome during adolescence. Horm Res Paediatr. 2015.

16. Martin KA, Anderson RR, Chang RJ, Ehrmann DA, Lobo RA, Murad MH, et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103:1233-57.
17. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the androgen excess and polycystic ovary syndrome society. Hum Reprod Update. 2012;18:146-70.
18. Ibáñez L, de Zegher F. Adolescent PCOS: a postpubertal central obesity syndrome. Trends Mol Med. 2023;29:354-63.
19. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203:201.
20. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 2000;19:311-5.
21. Sen B, Gonultas S, Albayrak C, Temur S, Acar I, Ozkan BN, et al. Evaluation of oxidative stress and inflammation in patients with polycystic ovary syndrome. Obstet Gynecol Sci. 2024;67:414-20.
22. Laleli B, Timur B. Examination of oxidative stress level in adolescents with polycystic ovary syndrome by biochemical parameters. Gümüşhane Sağlık Bilimleri Dergisi. 2021;10:935-42.
23. Aydın GA, Turan Özsoy HG, Ankaralı H, Özgen G, Neşelioğlu S. The association of dynamic thiol-disulfide homeostasis and inflammatory markers in patients with polycystic ovary syndrome. Taiwan J Obstet Gynecol. 2020;59:79-84.
24. Siemers KM, Klein AK, Baack ML. Mitochondrial dysfunction in PCOS: insights into reproductive organ pathophysiology. Int J Mol Sci. 2023;24:13123.
25. Yildirim M, Turkyilmaz E, Neselioglu S, Alisik M, Avsar AF. Dynamic thiol-disulphide status in polycystic ovary syndrome and its association with the pathogenesis of the disease. Gynecol Obstet Invest. 2017;82:54-9.
26. Ozler S, Oztas E, Tokmak A, Ergin M, Isci E, Eren F, et al. The association of thiol/disulphide homeostasis and lipid accumulation index with cardiovascular risk factors in overweight adolescents with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2016;84:516-23.
27. Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. Fertil Steril. 2011;95:1048-58.
28. Khashchenko E, Vysokikh M, Uvarova E, Krechetova L, Vtorushina V, Ivanets T, et al. Activation of systemic inflammation and oxidative stress in adolescent girls with polycystic ovary syndrome in combination with metabolic disorders and excessive body weight. J Clin Med. 2020;9:1399.
29. Ganie MA, Hassan S, Nisar S, Shamas N, Rashid A, Ahmed I, et al. High-sensitivity C-reactive protein (hs-CRP) levels and its relationship with components of polycystic ovary syndrome in Indian adolescent women with polycystic ovary syndrome (PCOS). Gynecol Endocrinol. 2014;30:781-4.

ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Patients with Hemolytic Uremic Syndrome

Hemolitik Üremik Sendromlu Hastalarımızın Değerlendirilmesi

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Abstract

Introduction: This study investigated the relationship between age, gender, initial laboratory findings, treatment modalities, and prognosis in pediatric patients diagnosed with hemolytic uremic syndrome (HUS) at Necmettin Erbakan University Meram Medical Faculty Pediatric Nephrology Department.

Materials and Methods: A retrospective analysis was conducted on 30 patients under 18 years of age who presented to the outpatient clinic between 2009 and 2020. Patient data, including demographics, clinical presentation, prodromal period, laboratory values at presentation, treatment strategies, and follow-up outcomes, were extracted from medical records.

Results: The cohort comprised 17 females (56.7%) and 13 males (43.3%). Nineteen patients (63.3%) presented with typical HUS, while 11 (36.7%) had atypical HUS. The mean age at presentation was 3.63 ± 3.69 years. The mean duration between symptom onset and hospital admission was 6.33 ± 3.95 days. The most frequent presenting symptoms were diarrhea (63.4%), bloody diarrhea (26.7%), and gross hematuria (20%). Hypertension was observed in 73.3% of the patients. During the course of the disease, 10% developed chronic renal failure, and 6.6% experienced recurrence. Anuria occurred in 56.6% of the patients. All patients exhibited proteinuria, with 93.3% demonstrating nephrotic-range proteinuria. Hypoalbuminemia was observed in all patients with nephrotic-range proteinuria. Hematuria was universally present, with 20% exhibiting gross hematuria. Eculizumab was administered to 33.3% of the patients, with 13.3% receiving regular treatment. Persistent proteinuria was noted in 13.3% despite treatment, and these patients remain under clinical observation with stable medication. Dialysis was required in 60% of the cases, with peritoneal dialysis employed in 36.6% and hemodialysis in 23.3%. Fresh frozen plasma was administered in 53.3% of the cases, with a higher proportion in atypical HUS (91%) compared to typical HUS (36.8%).

Conclusion: HUS is a prevalent thrombotic microangiopathy in children. Initial laboratory parameters can provide valuable insights into disease progression. Prolonged hospitalization was associated with anuria exceeding one day and the need for dialysis. Among the key diagnostic laboratory markers, platelet count and urea levels normalized earliest. Eculizumab demonstrated efficacy in atypical HUS cases. No significant association was found between other treatment modalities and prognosis.

Keywords
hemolytic uremic syndrome, acute renal failure, thrombocytopenia, eculizumab

Anahtar kelimeler
Hemolitik üremik sendrom, Akut böbrek yetmezliği, Trombositopeni, Eculizumab

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Öz

Giriş: Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi (NEÜMTF) Pediyatrik Nefroloji bilim dalında, Hemolitik Üremik Sendrom (HÜS) tanısı ile

izlenen olguların yaş, cinsiyet, başvuru anındaki laboratuvar bulguları, uygulanan tedavi ve prognoz ilişkisini belirlemeyi planladık.
Gereç ve Yöntem: Biz çalışmamızda polikliniğimizde 2009-2020 yılları arasında başvuran, 18 yaş altında 30 olguyu inceledik. Bu hastaların dosyalarını tarayarak yaş, cinsiyet başvuru, şikâyeti, başvuru yaşı, prodromal süre, başvuru laboratuvar değerleri, takiplerini tedavilerini ve tedavi prognoz ilişkisini inceledik. Dosyaların incelenmesinde, tanı ve takibi sırasındaki kayıt edilen bilgiler ve laboratuvar sonuçları dikkate alınarak veriler elde edilmiştir.
Bulgular: Çalışamaya katılan 30 olgunun 17'si kız (%56,7), 13'ü erkekti (%43,3). Olguların 19'u (%63,3) tipik HÜS, 11'i (%36,7) ise atipik HÜS olarak değerlendirildi. Olguların kliniğimize başvuru yaşı ortalaması 3,63±3,69 yıldı. Tüm olguların şikâyetlerinin başlama zamanı ile hastaneye başvuru zamanı arasındaki süre ortalama 6,33±3,95 gündür. Olgular en çok 19 (%63,4) ishal bu grubun içinde 8 (% 26,7) olgu kanlı ishal ve 6 (%20) olgu gros hematuri ile başvurmuştur. Olgularımızın 22 sinde (%73,3) hipertansiyon gelişti, 8 inde (%26,7) tansiyon normal aralıkta seyretti. Olguların 3'ünde (%10) seyir esnasında kronik böbrek yetmezliği gelişti. Ayrıca takipler esnasında 2 kardeş vakada (%6,6) nüks gelişti. Takipler sırasında 2 vaka (%6,6) exitus olmuştur. Takipler sırasında 17 hastada (%56,6) anüri gelişmiştir. Olguların hepsinde proteinüri mevcuttu ayrıca 28 olguda (%93,3) nefrotik düzeydeydi. Aynı olguların albümin düzeyleri azalmış olarak bulundu. Bununla birlikte tüm olgularda hematüri gözlendi. Bunun yanında 6 olguda (%20) gros hematüri gözlendi. Olgulardan 10'una (%33,3) Eculizumab tedavisi verildi. Dört vaka (%13,3) düzeli eculizumab almaktadır. Dört vakada (%13,3) proteinüri devam etmiş ilaçlı stabil klinik olarak takip edilmektedir. Olguların 18'i (%60) diyaliz almıştır. Bunun 11'i (%36,6) periton, 7'si (%23,3) hemodiyalizdir. Olguların 16'sına (%53,3) atipik HÜS'lerin %91'ine tipik HÜS'lerin %36,8'ine TDP verilmiştir.
Sonuç: HÜS, çocuklarda sık görülen bir trombotik mikroanjiyopati türüdür. Başvuru laboratuvar parametreleri, hastalığın seyri hakkında önemli ipuçları sağlayabilir. Bir günü aşan anüri ve diyaliz ihtiyacı, uzamış hastane yatışı ile ilişkilidirHastalık için tanı koydurucu laboratuvar değerleri olan hemoglobin trombosit üre kreatinin LDH içinde ilk normal değere ulaşan trombosit (8 gün) en son üre (23 gün) olarak bulunmuştur.. Eculizumab, atipik HÜS vakalarında etkinlik göstermiştir. Diğer tedavi yöntemleri ile prognoz arasında anlamlı bir ilişki bulunamamıştır.

Introduction

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TMA) characterized by the triad of acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. It represents a significant cause of acute kidney injury, particularly in developed countries (1,2). The most prevalent form of HUS in children (90%) is typical HUS, primarily associated with Shiga-toxin (Stx)-producing Escherichia coli (E. coli) infections. HUS is broadly classified into two categories: typical and atypical.

Recent advances in genetic analysis and heightened awareness have contributed to an increased recognition of atypical HUS cases. Atypical HUS is predominantly attributed to complement-related dysregulation, arising from inherited or acquired abnormalities in the complement system (3).

In the pediatric population, HUS can manifest with prolonged anuria and severe clinical presentations. Progression to chronic renal failure is observed in approximately 10% of cases. While supportive care remains the cornerstone of management, the advent of eculizumab, a monoclonal antibody targeting the complement system, has shown promising results, particularly in atypical HUS.

This study aimed to conduct a retrospective analysis of pediatric HUS patients managed at our clinic, with a focus on characterizing clinical and laboratory findings at presentation, evaluating administered treatments, and assessing the relationship between these treatments and patient outcomes.

Material and Methods

Study Design and Population

This retrospective cohort study included 30 patients diagnosed with HUS who were treated at the Pediatric Nephrology-Rheumatology clinic of Necmettin Erbakan University Meram Medical Faculty between January 2009 and May 2020.

Data Collection

Patient data were extracted from medical records. Variables of interest included demographics (age, gender), clinical presentation (age at symptom onset, initial symptoms, duration of anuria, presence of extra-renal manifestations), laboratory findings at presentation, treatment modalities, complications, and clinical outcomes.

Laboratory Analysis

Comprehensive laboratory evaluations were performed, including:

- Complete blood count (hemoglobin, leukocyte count, platelet count)
- Biochemical parameters (urea, creatinine, lactate dehydrogenase [LDH], C-reactive protein [CRP], complement components C3 and C4, ferritin, electrolytes [sodium, potassium, calcium], liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], lipid profile [triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL)], coagulation tests [prothrombin time (PT), activated partial thromboplastin time (aPTT)], albumin, total and direct bilirubin)
- Urinalysis
- Blood gas analysis

Laboratory values were assessed according to age-specific reference ranges. Leukopenia was defined as a total leukocyte count < 4000/mm³, leukocytosis as > 10,000/mm³, anemia as a hemoglobin value < 11.9 g/dL, and thrombocytopenia as a platelet count < 150,000/mm³.

Statistical Analysis

Statistical analyses were performed on the SPSS 25 software package (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Descriptive statistics were used to summarize patient characteristics. Kruskal-Wallis and Mann-Whitney U tests were employed to compare continuous variables between groups. Categorical data were analyzed via chi-square tests. Pearson correlation coefficients were calculated to assess relationships between variables. Statistical significance was set at $p<0.05$.

Ethical Considerations

This study was approved by the Necmettin Erbakan University Meram Medical Faculty Drug and Non-Medical Device Research Ethics Committee (date: 19.07.2020, approval number: 2020/2604).

Results

Demographics and Classification

Of the study population, 17 patients (56.7%) were female and 13 (43.3%) were male. Nineteen cases (63.3%) were classified as typical HUS, while 11 cases (36.7%) were diagnosed as atypical HUS. Among atypical cases, the gender distribution was nearly equal, with 5 males (45.4%) and 6 females (54.6%). Similarly, typical cases showed a balanced gender distribution with 9 males (47.3%) and 10 females (52.7%).

The mean age at presentation was 3.63 ± 3.69 years. The mean interval between symptom onset and hospital admission was 6.33 ± 3.95 days across all cases. Further analysis revealed that patients with typical HUS (diarrhea-positive) presented at a mean age of 3.12 ± 3.64 years, with a mean symptom duration of 7.37 ± 4.57 days before admission.

Clinical Manifestations

Analysis of presenting symptoms revealed that diarrhea was the predominant complaint, occurring in 19 cases (63.4%), followed by bloody diarrhea in 8 cases (26.7%), and gross hematuria in 6 cases (20%). Less frequent presenting symptoms included vomiting and periorbital edema. Detailed clinical manifestations are presented in Table 1.

The mean duration of hospitalization was 25.9 days (range: 2-71 days). Patients with typical HUS had shorter hospital stays (20.16 ± 10.95 days) compared to those with atypical HUS (32.83 ± 20.51 days).

Hypertension was observed in 22 patients (73.3%), while 8 patients (26.7%) maintained normal blood pressure throughout their clinical course. Chronic renal failure (CRF) developed in 3 cases (10%). Anuria occurred in 17 patients (56.6%), with duration ranging from 12 hours to 23 days (mean duration: 16.11 ± 10.42 days). Persistent proteinuria was observed in four patients (13.3%), who remained clinically stable on medication.

The majority of patients (24 cases, 80%) did not experience extrarenal complications. Among those with extra-renal involvement, one patient (3.3%) developed HUS secondary to acute lymphoblastic leukemia, and two patients (6.6%) presented with acute liver involvement. Single cases (3.3% each) of deep vein thrombosis (DVT), encephalopathy, and cholelithiasis were also documented.

Initial Laboratory Parameters

All patients demonstrated evidence of hemolysis on peripheral blood smear examination. At admission, the median (Q1-Q3) values for key laboratory parameters were as follows: platelet count 49,000/μL (25,000-73,400), hemoglobin 6.25 g/dL (5.65-6.83), blood urea

Table 1. General characteristics of the patients						
Gender	**N**	**%**	**Typical-atypicality**		**N**	**%**
Female	17	56.7	Typical		19	63.3
Male	13	43.3	Atypical		11	36.7
Total	30	100.0	Total		30	100.0
Complaint at presentation	**n**	**%**	**Complaint at presentation**		**N**	**%**
Diarrhea	19	63.4	Periorbital edema		1	3.3
Bloody diarrhea	8	26.7	Upper respiratory tract infection (URTI)		1	3.3
Gross hematuria	6	20.0				
Vomiting	3	10				
Variables	**N**	**Lowest value**	**Highest value**		**Mean**	**S**
Age at presentation (years)	30	0.75	16.75		3.63	3.69
Time of complaint (days)	30	3.00	19.00		6.33	3.96

151.50 mg/dL (122.50-211.504), serum creatinine 3.09 mg/dL (1.25-4.55), and lactate dehydrogenase (LDH) 2,014 U/L (1,159-2,615.50). A detailed comparison of the median values for typical and atypical HUS cases is presented in Table 2.

In typical HUS cases, the median values were hemoglobin 6.35 g/dL (4.80-9.50), platelets 48,500/µL (12,000-175,000), LDH 2,188 U/L (533-3,408), creatinine 3.32 mg/dL (0.43-9.90), and urea 156.50 mg/dL (33-284). For atypical HUS cases, the corresponding values were hemoglobin 5.70 g/dL (4.9-6.70), platelets 70,000/µL (24,900-84,000), LDH 1,558 U/L (751-3,115), creatinine 3.19 mg/dL (1.01-5.90), and urea 135.8 mg/dL (112-242).

Additional Laboratory Parameters

The median white blood cell count across all patients was 14,200/µL (4,000-10,000), with mean values of 8,165.63 ± 1,930.30/µL and 4,968.0 ± 1,823.49/µL for typical and atypical HUS, respectively. Other notable findings included elevated C-reactive protein (CRP) with a median of 13.45 mg/L (reference range: 0-5), and mildly elevated aspartate transaminase (AST) with a median of 64 U/L (reference range: 5-34). Significant elevations in alanine transaminase (ALT) were observed in two cases (6.6%). Ferritin levels were elevated with a median of 495.45 ng/mL (reference range: 14.5-290). Detailed comparative data are presented in Table 2.

Two siblings (6.6%) experienced disease recurrence during follow-up, with positive MCP mutation identified in both cases. Additionally, factor H heterozygous mutations were detected in three patients with atypical HUS.

While median C3 and C4 complement levels were within normal ranges for the cohort, two patients (6.6%) exhibited low C3 levels. ADAMTS13 activity was assessed in 15 patients (50% of the cohort), with all results within normal range (>10%). Values ranged from 43% to 109%. Complete blood parameters are detailed in Table 2.

Laboratory investigations revealed that 25 patients tested negative for antinuclear antibodies (ANA), and 16 tested negatives for anti-double-stranded DNA (anti-dsDNA) antibodies. All patients exhibited proteinuria, with 28 (93.3%) demonstrating nephrotic-range proteinuria accompanied by hypoalbuminemia. Hematuria was a universal finding, with gross hematuria observed in 6 cases. Urine cultures, performed in all cases, yielded positive results in 5 patients (16.7%): Proteus species (n=2), Klebsiella species (n=1), E. coli (n=1), and yeast (n=1). Five patients (16.6%) underwent diagnostic renal biopsies, which revealed mesangial cell proliferation in one patient and thrombotic microangiopathy in four.

Analysis of the time to normalization of key hematologic and biochemical parameters showed that platelet count recovered earliest (median: 8 days; IQR: 4-60 days), followed by creatinine (median: 16 days; IQR: 3-46 days), hemoglobin (median: 23 days; IQR: 5-103 days), and urea (median: 30 days; IQR: 7-125 days).

Patients requiring dialysis demonstrated significantly higher blood urea and serum creatinine levels at presentation compared to those who did not

Table 2. Blood test results of patients						
Values	**Platelet Count**	**Hemoglobin**		**Urea**	**Creatinine**	**LDH**
Median	49000	6.25		151.50	3.09	2014
Q1	25000	5.65		122.50	1.25	1159
Q3	73400	6.83		211.50	4.55	2615.50
Normal Values	150-400 10^3/uL	12.1-17.2 g/dL		16.6-48.5 g/dL	0.24-0.6mg/dL	135-214u/L
Values	**WBC**	**MCV**	**Iron**	**Iron Binding**	**Ferritin**	**INR**
Median	14200	75.75	91.00	210.50	495.45	1.06
Q1	8585	70.75	83.00	178.50	99.25	.97
Q3	18465	77.40	123.00	263.25	678.43	1.25
Normal Values	4-10 10^3/uL	82-99fL	50-170 µg/dL	70-310 µg/dL	14.5-290ng/mL	1-1.5
Values	**CRP**	**LDL**	**HDL**	**Cholesterol**	**TG**	**VLDL**
Median	13.45	90.00	29.70	192.00	308.50	42.00
Q1	4.45	66.18	19.55	160.00	198.00	26.40
Q3	55.75	110.25	44.90	227.50	492.25	61.75
Normal Values	0-5 mg/L	<100mg/dL	35-70mg/dL	0-200mg/dL	0-150mg/dL	0-30mg/dL
Values	**Sodium**	**Potassium**	**Calcium**	**Phosphorus**	**AST**	**ALT**
Median	133	4.25	8.40	5.64	64.00	32.00
Q1	130	3.72	8.00	4.80	46.00	19.75
Q3	136	5.10	9.00	7.21	104.00	85.50
Normal Values	135-145mmol/L	3.5-5.1 mmol/L	8.4-10mg/dL	2.3-4.7mg/dL	5-34 u/L	0-55u/L
Values	**Albumin**	**Urine Density**	**Micro Albumin**	**Fibrinogen**	**D-dimer**	**Sedimentation Rate**
Median	3.00	1012.00	50.00	338.50	6.29	17.50
Q1	2.60	1009.75	9.14	283.25	2.29	9.00
Q3	3.13	1014.25	193.0	385.50	10.85	41.25
Normal Values	3.5-5.2 g/dL	1015-1025	0-30 mg/g	200-400mg/dL	0-0.4mg/mL	0-20mm/h
Values	**Uric Acid**	**PH**	**PT**	**APTT**	**DBIL**	**IBIL**
Median	8.80	7.37	13.10	26.00	.32	.72
Q1	7.30	7.31	12.80	23.80	.18	.42
Q3	12.30	7.41	15.90	29.00	.44	1.23
Normal Values	2.6-6mg/dL	7.35-7.45	9.8-14 sec	25-40sec	0-0.30mg/dL	0.2-1.2mg/dL
Values	**CO2**	**HC03**	**C3**	**C4**	**ADAMTS-13**	**Protein in Urine/ Creatinine**
Median	29.00	17.00	1.22	0.16	90.50	8.95
Q1	20.00	11.60	1.01	0.11	66.75	5.00
Q3	33.00	19.60	1.39	0.24	107.25	16.25
Normal Values	35-45mmHg	21-27mmol/	0.9-1.8g/L	0.1-*.4g/L	-	-

require dialysis intervention. Comparative analysis of laboratory parameters between typical and atypical HUS cases revealed distinct patterns in specific hematological and coagulation markers. White blood cell counts were significantly elevated in typical HUS cases compared to atypical cases, while fibrinogen levels showed the opposite pattern, being considerably higher in atypical HUS cases. Detailed statistical

comparisons of all measured parameters are presented in Table 3. When patients were stratified based on the presence and duration of anuria (no anuria, anuria ≤ 1 day, anuria > 1 day), a significant difference in hospitalization duration emerged. Specifically, patients with anuria lasting longer than one day had significantly longer hospital stays compared to those without anuria or with anuria lasting one day or less ($p < 0.001$).

Table 3. Comparison of blood measurement values in typical and atypical disease presentations

Values	Typical (n)	Typical (Rank Mean)	Atypical (n)	Atypical (Rank Mean)	z	T
WBC count	19	18.47	11	10.36	-2.432	15
MCV	19	15.42	11	15.64	-65	949
Iron	7	4.92	5	7.30	-1.189	234
Iron Binding	6	6.67	4	3.75	-1.492	136
Ferritin	9	7.00	7	10.43	-1.429	153
INR	17	14.82	10	12.60	-705	481
PT	17	14.94	10	12.40	-804	421
APTT	10	14.18	10	13.70	-151	880
Fibrinogen	16	10.38	10	18.50	-2.636	8
D-DIMER	13	12.08	8	9.25	-1.014	311
SEDIMENTATION	19	14.87	11	16.59	-517	605
CRP	19	15.26	11	15.91	-194	846
LDL	4	4.00	4	4.00	-577	564
HDL	5	5.20	4	4.75	-245	806
Cholesterol	6	5.83	6	7.17	-641	522
TG	6	6.33	4	6.67	-160	873
VLDL	4	5.25	5	4.80	-245	806
DBIL	13	9.77	9	14.00	-1.504	133
IBIL	13	10.00	9	13.67	-1.038	193
Urine Density	19	16.76	11	13.32	-1.038	299
Microalbumin	17	13.82	10	14.30	-151	880
ADAMTS13	6	6.67	8	8.13	-646	518
Sodium	19	15.92	11	14.77	-346	729
Potassium	19	14.16	11	17.52	-1.100	271
Calcium	19	15.97	11	14.68	-388	698
Phosphorus	19	14.13	11	17.86	-1.119	263
Albumin	19	15.87	11	14.86	-303	762
AST	19	16.05	11	14.55	-452	651
ALT	19	16.45	11	14.45	-452	651
Uric Acid	19	15.21	11	11.95	-1.030	303
PH	19	12.37	11	9.63	-1.230	219
CO2	19	12.23	11	11.56	-227	821
HCO3	19	12.23	11	11.56	-226	821
C3	11	13.55	11	14.14	-427	669
C4	13	13.36	10	16.55	-986	324

Table 4. Relationship between dialysis type, medication use, final outcome and length of hospitalization

			Final Outcome				Total
			Death	Stable, No medication	Stable, medicated	Regular eculizumab	
Dialysis type	No dialysis	n	1	8	2	2	13
		%	7.7	61.5	15.4	15.4	100
	Peritoneal dialysis	n	-	7	2	1	10
		%	-	70	20	10	100
	Hemodialysis	n	1	4	1	1	7
		%	14.3	57.1	14.3	14.3	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
Antibiotic use	No antibiotics	n	-	3	1	-	4
		%	-	75	25	-	100
	Received antibiotics	n	2	16	4	4	26
		%	7.7	61.5	15.4	15.4	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
Eculizumab therapy	No eculizumab	n	1	15	4	-	20
		%	5	75	20	-	100
	Received eculizumab	n	1	4	1	4	10
		%	10	40	10	40	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
FFP therapy	No FFP	N	1	11	1	1	14
		%	7.1	78.6	7.1	7.1	100
	Received FFP	N	1	8	4	3	16
		%	6.3	50	25	18.8	100
	Total	N	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100
Steroid treatment	No steroids	n	-	4	-	2	6
		%	-	66.7	-	33.3	100
	Received steroids	n	2	15	5	2	24
		%	8.3	62.5	20.8	8.3	100
	Total	n	2	19	5	4	30
		%	6.7	63.3	16.7	13.3	100

		n	Duration of Hospitalization (day)			z	*P*
			Rank Mean	Median	CRI (%25-%75)		
Dialysis type	No dialysis	13	9.31	12.00	(8-21.30)	-2.181	.029
	Peritoneal dialysis	10	15.50	24	(18.75-32.50)		
	No dialysis	13	8.19	12	(8-21.30)	-2.383	.017
	Hemodialysis	7	14.79	30	(22-43)		
Gender	Female	17	16.71	24	(12-35)	-.861	.389
	Male	13	13.92	21	(10-31)		

Table 4. Continued

		Final Outcome				Total	
		Death	Stable, No medication	Stable, medicated	Regular eculizumab		
Antibiotic use	**No antibiotics**	4	8.13	10	3.50-21	-1.805	.071
	Received Antibiotics	26	16.63	22	12-40		
Eculizumab therapy	**No eculizumab**	20	13.40	21.50	(9-25.50)	-1.853	.064
	Received eculizumab	10	19.70	34.00	17.25-43.75		
FFP therapy	**No FFP**	14	10.11	12	8-22	-3.148	.002
	Received FFP	16	20.22	29	21.25-41.75		
Steroid treatment	**No Steroids**	6	9.00	11	6.50-21.75	-2.028	.043
	Received steroids	24	17.13	22	13-40		

Treatment and Prognosis

The study analyzed prognostic indicators using two primary outcome measures: duration of hospitalization and clinical outcome. Clinical outcomes were categorized into four groups: death, medication-free stable condition, maintenance eculizumab therapy, and stable condition with medication (defined as patients requiring ACE inhibitors for proteinuria management).

Of the total cohort, 18 patients (60%) required renal replacement therapy, with 11 patients (36.6%) receiving peritoneal dialysis and 7 patients (23.3%) receiving hemodialysis. The proportion of patients requiring dialysis was similar between typical (57.8%) and atypical (63.6%) HUS cases. However, both peritoneal and hemodialysis recipients experienced significantly longer hospitalizations compared to those who did not require dialysis ($p < 0.05$).

Eculizumab therapy was initiated in 33.3% (n=10) of patients, with four patients (13.3%), including two siblings, currently maintaining regular treatment schedules. While hospitalization duration showed no significant correlation with eculizumab administration ($p > 0.05$), patient outcomes demonstrated a statistically significant difference between treatment groups ($p < 0.01$).

Therapeutic plasma exchange (TPE) was performed in 53.3% (n=16) of cases, encompassing 91% of atypical HUS and 36.8% of typical HUS cases. Analysis revealed significantly longer hospitalization periods among patients who underwent TPE compared to those who did not. Corticosteroid therapy was administered to 80% (n=24) of patients. Statistical analysis demonstrated significantly higher mean hospitalization duration ranks among patients receiving steroid therapy compared to those who did not. Further details are provided in Table 4. Two patients (6.6%) died during the follow-up period.

Discussion

The cohort comprised 17 female (56.7%) and 13 male (43.3%) patients. The existing literature presents varying findings regarding sex distribution in HUS. For instance, Micheletti et al. (4), in a study of 22 patients, reported a female predominance with 14 (64%) female and 8 (36%) male cases. Similarly, Balgradean et al. (5), examining 32 patients, observed a comparable trend with 19 (59.3%) female and 13 (40.6%) male cases. These findings, along with those of the present study, suggest a potential, though not consistently demonstrated, female preponderance in pediatric HUS.

Analysis of HUS subtype classification in our cohort revealed 19 cases (63.3%) of typical HUS and 11 cases (36.7%) of atypical HUS. This distribution differs from earlier reports. Elliot et al. (6) and reported a significantly higher proportion of typical HUS (86%) and a correspondingly lower proportion of atypical HUS (14%). A similar pattern was observed by Bitzan et al. (7), who reported 92% typical HUS and 8% atypical HUS. The observed increase in the proportion of atypical HUS in the present study compared to these earlier reports may be attributable to advances in diagnostic capabilities, particularly in genetic testing. These advancements have facilitated the identification of genetic mutations and complement dysregulation associated with atypical HUS, leading to increased recognition and diagnosis of this subtype.

In our study, the mean age at presentation is generally consistent with previous reports, although some variation exists. Micheletti et al. (4) reported a mean age at presentation of 44 ± 39 months (3.67 years), with an age range of 12 days to 13 years. Spizzirri et al. (8) found a lower mean age of 13.4 months (1.12 years), with a range of 3 to 48 months. Similarly, Girişgen and Yüksel (9) reported a mean age of 17 months (1.42 years) for diarrhea-positive HUS cases, with a range of 10 to 108 months. The observed differences in mean age at presentation across studies may be attributable to several factors, including variations in study populations, geographic location, and the prevalence of different HUS subtypes.

Alfandary et al. (10) reported a mean prodromal period of 4 days (range: 2-7 days) across all HUS patients. Studies focusing specifically on typical HUS have also reported shorter durations. Decluct et al. (11) found a mean of 5.5 days (range: 0-24 days), while Ninchoji et al. (12) reported a mean of 5 days (range: 3-18 days). The longer prodromal period observed in our study, particularly in typical HUS cases, may reflect differences in patient populations, the specific pathogens involved, or variations in data collection and reporting.

The most frequent presenting complaints in our cohort were diarrhea (36.7%), bloody diarrhea (26.7%), and gross hematuria (20%). These findings are partially consistent with previous reports, although some variations exist. Balgradean et al. (5) reported diarrhea and bloody diarrhea in 40% of cases each, gross hematuria in 15.63%, and a higher prevalence of vomiting (31%). Micheletti et al. (4) observed diarrhea in 60% of patients and bloody diarrhea in 40%, with vomiting present in 45% of cases.

Hypertension was observed in 52% of patients in the study by Spizziri et al. (8), while Alfandary et al. (10) reported hypertension in 44% and CRF in 11.8% of cases (8,10). In our study, the frequency of hypertension was reported to be higher compared to the literature, whereas the incidence of chronic renal failure (CRF) was found to be lower. The mortality rate in our study was 6.6%, compared to 9.3% reported by Alfandary et al (10).

Balgradean et al. (5) reported an anuria rate of 40.6%, similar to our study (5). Micheletti et al. (4) observed a higher incidence of anuria (90% in all patients, 84% in typical HUS patients), with a shorter mean duration of 8 ± 5 days.

The findings of our study show a trend of longer hospitalization for atypical HUS. This trend is also reflected by Micheletti et al. (4), who reported mean hospitalization durations of 18.5 ± 5 days for typical HUS and 38 ± 14 days for atypical HUS. In contrast, Jenssen et al. (13) reported shorter and similar mean hospitalization durations for both typical (15 days) and atypical HUS (16 days). The longer hospitalization durations observed in our atypical HUS patients, and to some extent in Micheletti's study, compared to Jenssen et al. (13), might reflect differences in disease management strategies or patient characteristics.

Gerber et al. (14) reported a 25% rate of neurologic involvement in typical HUS patients, while Ekinci et al. (15) reported 21.4%, both considerably higher than the 5% observed in our study. Encephalopathy was observed in only one patient (5%) with typical HUS, a rate lower than that reported in the literature.

Comparison of Laboratory Findings

Comparison with previous studies reveals some differences. Jenssen et al. (13) reported hemoglobin values of 6.5 g/dL (IQR: 5.8-7.5 g/dL) and 6.0 g/dL (IQR: 5.9-6.2 g/dL) in typical and atypical HUS, respectively, which are similar to our findings. However, their reported platelet counts (32,000/μL and 24,000/μL) were lower than those observed in our cohort. Micheletti et al. (4) reported higher hemoglobin levels (8.6 ± 2.3 g/dL for typical HUS and 7.1 ± 1.5 g/dL for atypical HUS) compared to our findings. Their platelet counts (66,100 ± 50,800/μL and 55,800 ± 39,400/μL) were also higher,

In our study, the median CRP level was 13.45 mg/L (range: 0-5), which was slightly elevated. This contrasts with the findings of Jenssen et al. (13), who reported mean CRP values of 67 mg/L (range: 19-138) in typical HUS and 29 mg/L (range: 15-161) in atypical HUS.

Our findings of frequent proteinuria and hematuria are consistent with those of Yüksel and Girişgen (9), who observed these urinary abnormalities in all cases of typical HUS. However, our observed rate of proteinuria was markedly higher than that reported by Jenssen et al. (13), who found proteinuria in 50% of typical HUS cases and 78% of atypical HUS cases.

In our study, platelet count normalized earliest, followed by creatinine, hemoglobin, and lastly, urea. These findings align with those of Yürük Yıldırım et al. (16), who reported that platelet count recovery preceded hemoglobin normalization in typical HUS. In their study, the mean time for platelet count to exceed 150,000/mm³ was 8.7 ± 8.3 days (range: 3-30 days), and anemia persisted for an average of 30 ± 19 days (range: 9-63 days). Such similarities suggest a consistent pattern of hematologic and biochemical recovery in typical HUS.

Micheletti et al. (4) reported no significant differences in LDH, creatinine, and WBC between typical and atypical HUS cases (4). Similarly, Al-Eisa and Al-Hajeri (17) documented comparable white blood cell counts, urea, and creatinine levels between the two groups. Contrary to the literature, in our cohort typical HUS cases demonstrated significantly elevated WBC compared to atypical cases, while fibrinogen levels were considerably higher in atypical HUS cases.

Treatment and Prognosis

Consistent with existing literature, dialysis was associated with significantly prolonged hospital stays. Micheletti et al. (4) found that 77% of their HUS cohort required dialysis, with similar rates in typical (70%) and atypical (88%) HUS. Zambrano et al. (18) reported a higher overall dialysis rate (78%), with peritoneal dialysis being the predominant modality (78% vs. 5% for hemodialysis) and identified dialysis as a poor prognostic factor for mortality and progression to chronic kidney disease, a finding that our study did not replicate. Our findings are broadly consistent with previous reports.

Our antibiotic utilization rate was higher than that reported by Jenssen et al. (13), who administered antibiotics to 61% of typical HUS patients and 44% of atypical HUS patients. The use of antibiotics in HUS, particularly typical HUS, remains a subject of debate while some studies have suggested a link between antibiotic use and the development or exacerbation of HUS, our findings, along with those of Freedman et al. (19), do not support this association.

The role of plasma therapy, including FFP, in typical HUS remains controversial. While recent studies, particularly following the 2011 entero-hemorrhagic Escherichia coli (EHEC) outbreak in Germany, have reported successful plasma exchange in adult patients, others have not demonstrated a clear benefit. In a large cohort study by Jenssen et al. (13), plasma infusion and exchange were performed in 16% and 8% of typical HUS patients, respectively. In contrast, eculizumab is the first-line treatment for atypical HUS, although plasma therapy, including FFP, is still considered an adjunct. Jenssen et al. (13) reported plasma infusion and exchange rates of 44% and 11%, respectively, in aHUS patients. In a domestic study by Besbas et al. (20), 22.6% of patients received plasma therapy alone.

In our study, steroid administration was associated with significantly prolonged hospital stays. The use of steroids as an immunosuppressive agent in HUS, particularly in atypical HUS cases with complement mutations (e.g., anti-complement factor H), has been suggested in the literature. Mittal et al. (21) reported a case of atypical HUS that responded to steroid therapy, although further research is needed to establish the efficacy and safety of steroids in the management of HUS. In our study, steroid administration was associated with significantly prolonged hospital stays.

Conclusion

In conclusion, in this retrospective study, we found that the basic findings such as age, gender, presenting complaint and laboratory tests at the time of presentation of HUS cases followed up in our clinic were consistent with the literature. There was an increase in the frequency of atypical HUS cases compared to literature. Laboratory findings at the time of presentation may be instructive in terms of the course of the disease. The duration of hospitalization was prolonged in patients with anuria lasting more than 1 day. Similarly, patients receiving dialysis had longer hospital stay. Hemoglobin platelet thrombocyte urea creatinine LDH, which are diagnostic laboratory values for the disease, were found to be the first to reach normal values (8 days) and the last to reach normal values (23 days). These findings provide information about the clinical course during the follow-up of the disease. Eculizumab treatment was found to be effective in atypical HUS cases. The effect of other treatments in terms of prognosis was examined and no significant difference was observed in terms of prognosis. Multicenter and prospective studies with a larger sample size are required for the relationship between auxiliary clinical and laboratory findings and treatment prognosis in HUS follow-up.

Ethics

Ethics Committee Approval: This study was approved by the Necmettin Erbakan University Meram Medical Faculty Drug and Non-Medical Device Research Ethics Committee (date: 19.07.2020, approval number: 2020/2604).

Footnotes

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

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References

1. Rosove MH. Thrombotic microangiopathies. Semin Arthritis Rheum. 2014;43:797-805.
2. Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int. 2001;60:831-46.
3. Geerdink LM, Westra D, van Wijk JA, Dorresteijn EM, Lilien MR, Davin JC, et al. Atypical hemolytic uremic syndrome in children: complement mutations and clinical characteristics. Pediatr Nephrol. 2012;27:1283-91.
4. Micheletti MV, Lavoratti G, Materassi M, Pela I. Hemolytic uremic syndrome: epidemiological and clinical features of a pediatric population in Tuscany. Kidney Blood Press Res. 2010;33:399-404.
5. Balgradean M, Croitoru A, Leibovitz E. An outbreak of hemolytic uremic syndrome in southern Romania during 2015-2016: epidemiologic, clinical, laboratory, microbiologic, therapeutic and outcome characteristics. Pediatr Neonatol. 2019;60:87-94.
6. Elliott EJ, Robins-Browne RM, O'Loughlin EV, Bennett-Wood V, Bourke J, Henning P, et al. Contributors to the Australian Paediatric Surveillance Unit. Nationwide study of haemolytic uraemic syndrome: clinical, microbiological, and epidemiological features. Arch Dis Child. 2001;85:125-31.
7. Bitzan M, Ludwig K, Klemt M, König H, Büren J, Müller-Wiefel DE. The role of Escherichia coli O 157 infections in the classical (enteropathic) haemolytic uraemic syndrome: results of a Central European, multicentre study. Epidemiol Infect. 1993;110:183-96.
8. Spizzirri FD, Rahman RC, Bibiloni N, Ruscasso JD, Amoreo OR. Childhood hemolytic uremic syndrome in Argentina: long-term follow-up and prognostic features. Pediatr Nephrol. 1997;11:156-60.
9. Girişgen İ, Yüksel S. Diyare ilişkili hemolitik üremik sendromlu çocuk hastalarımız; bölgesel sıklık artışı ve klinik sonuçları. Pamukkale Tıp Dergisi. 2019;12:485-95.
10. Alfandary H, Rinat C, Gurevich E, Eisenstein I, Goldberg O, Kropach N, et al. Hemolytic uremic syndrome: a contemporary pediatric experience. Nephron. 2020;144:109-17.
11. Decludt B, Bouvet P, Mariani-Kurkdjian P, Grimont F, Grimont PA, Hubert B, et al. Haemolytic uraemic syndrome and Shiga toxin-producing escherichia coli infection in children in France. The Société de Néphrologie Pédiatrique. Epidemiol Infect. 2000;124:215-20.
12. Ninchoji T, Nozu K, Nakanishi K, Horinouchi T, Fujimura J, Yamamura T, et al. Clinical characteristics and long-term outcome of diarrhea-associated hemolytic uremic syndrome: a single center experience. Clin Exp Nephrol. 2017;21:889-94.
13. Jenssen GR, Vold L, Hovland E, Bangstad HJ, Nygård K, Bjerre A. Clinical features, therapeutic interventions and long-term aspects of hemolytic-uremic syndrome in Norwegian children: a nationwide retrospective study from 1999-2008. BMC Infect Dis. 2016;16:285.
14. Gerber A, Karch H, Allerberger F, Verweyen HM, Zimmerhackl LB. Clinical course and the role of shiga toxin-producing escherichia coli infection in the hemolytic-uremic syndrome in pediatric patients, 1997-2000, in Germany and Austria: a prospective study. J Infect Dis. 2002;186:493-500.
15. Ekinci Z, Candan C, Alpay H, Canpolat N, Akyüz SG, Gündüz Z, et al. Hemolytic uremic syndrome outbreak in Turkey in 2011. Turk J Pediatr. 2013;55:246-52.
16. Yürük Yıldırım ZN, Yılmaz A, Yavaş Aksu B, Işık GS, Bilge I, Çıtak A, et al. Diyare öyküsü olan hemolitik üremik sendrom tanılı hastaların klinik özellikleri. İstanbul Tıp Fakültesi Dergisi. 2001;78:46-50.
17. Al-Eisa A, Al-Hajeri M. Hemolytic uremic syndrome in Kuwaiti Arab children. Pediatr Nephrol. 2001;16:1093-8.
18. Zambrano OP, Delucchi BA, Cavagnaro SF, Hevia JP, Rosati M, Lagos RE, et al. Síndrome hemolítico urémico en chile: presentación clínica, evolución y factores pronósticos [hemolytic-uremic syndrome in chile: clinical features, evolution and prognostic factors]. Rev Med Chil. 2008;136:1240-6.
19. Freedman SB, Eltorki M, Chui L, Xie J, Feng S, MacDonald J, et al. Province-wide review of pediatric shiga toxin-producing escherichia coli case management. J Pediatr. 2017;180:184-190. e1.
20. Besbas N, Gulhan B, Soylemezoglu O, Ozcakar ZB, Korkmaz E, Hayran M, et al. Turkish pediatric atypical hemolytic uremic syndrome registry: initial analysis of 146 patients. BMC Nephrol. 2017;18:6.
21. Mittal N, Hartemayer R, Jandeska S, Giordano L. Steroid Responsive Atypical Hemolytic Uremic Syndrome Triggered by Influenza B Infection. J Pediatr Hematol Oncol. 2019;41:e63-e67.

REVIEW DERLEME

Current View of Hemorrhagic Fever with Renal Syndrome in Adults and Children: an Overview

Yetişkinlerde ve Çocuklarda Renal Sendromlu Hemorajik Ateşin Güncel Görünümü: Genel Bir Bakış

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Abstract

The review is devoted to hemorrhagic fever with renal syndrome (HFRS), analyzing studies on pathogenesis, etiology, diagnosis and treatment. The results of clinical features of the disease manifestation in children, as well as preventive measures aimed at reducing the disease in children are analyzed for the first time. The data on the available treatment of young patients were analyzed.

Öz

Bu derleme, patogenez, etiyoloji, tanı ve tedavi ile ilgili çalışmaları analiz ederek renal sendromlu hemorajik ateşe (HFRS) ayrılmıştır. Çocuklarda hastalık tezahürünün klinik özelliklerinin sonuçları ve çocuklarda hastalığı azaltmaya yönelik önleyici tedbirler ilk kez analiz edilmiştir. Genç hastaların mevcut tedavisine ilişkin veriler analiz edilmiştir.

Keywords
HFRS, children, diagnosis, treatment.

Anahtar kelimeler
HFRS, çocuklar, tanı, tedavi

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Introduction

Hemorrhagic fever with renal syndrome (HFRS) is a viral disease caused by the hantavirus genus, family Bunyaviridae. The disease is a zoonosis, and the field mouse (Apodemus agraricus) is considered to be a vector of viruses. It should be noted that there are studies proving that other mammals can also carry this infection (1). The virus is transmitted by biological secretions of the field mouse, namely saliva, feces and urine (2). The disease is not currently widespread on a territorial scale, but there is an annual increase in the number of cases, and this is due to the peculiarities of the infectious reservoir of HFRS (3).

Epidemiology

The increase and lack of decrease in the incidence of HFRS depends on the fact that rodents have the opportunity to be in close contact with humans. This is related to the diet of field mice, whose diet includes

the consumption of cereal plants, which causes them to enter human dwellings in search of food. After consumption, they leave their biological waste in the cereal tanks, thus human contact with rodent excretions occurs, which leads to human infection with Hantavirus (4). Mass field work has also become one of the variants of infection (5). In today's world, field and farm work is done by industrial organizations that use autonomous-specialized equipment, comb pared to years past, where manual labor of workers was previously used. The use of modern equipment, personal protective equipment, has reduced human contact with field mice and their biological secretions, which in turn has reduced the incidence of this pathology. Also, with the development of modern organization of health care and improvement of the quality of medical care, it became possible to better and competent diagnosis of HFRS in organizations where there is a risk of infection with this pathology, and also allowed better diagnosis of the pathology in conditions of civil medicine (6). One of the factors that has reduced the incidence of HFRS is the concentration of the population in cities, which allows people to move away from private homes, as rodents use human homes not only as a place to find food, but also as a warm and comfortable place to live. It should also be noted that at the moment there is supporting evidence that hantaviruses can be carried not only by rodents, but also by other mammals, including bats (7). There is statistical data confirming an increase in the incidence of HFRS in patients during the spring and fall seasons. It should be noted that the incidence of this pathology increases from year to year.

Virus Morphology

HFRS is a viral disease which is caused by a whole family of viruses, which includes such viruses as: Hantaan virus (HTNV), Amur virus (AMV), Seoul virus (SEOV), Dobrava virus (DOBV), Puumal virus (PUUV). An important feature is that these viruses are capable of causing disease of varying severity. There are studies demonstrating that with different species diversity of Bunyaviridae viruses, the disease has different degrees of severity (8). It should also be noted that the studies are not numerous and require further study and consideration. The viruses themselves are enveloped RNA-containing spherical viruses with a diameter of 80 to 120 nm and form a separate genus in the family Bunyaviridae (9). The genome consists of three single-stranded RNAs with a negative sense that share a common 3'-end sequence of genome segments. S (small), M (medium) and L (large) segments, encode nucleoprotein (N), envelope glycoproteins (Gn and Gc), and protein L or viral RNA-dependent RNA polymerase, respectively (10-12). The morphology of this virus allows it to tolerate high temperatures, thereby allowing the infection to persist in an aggressive environment. Despite this, the virus is easily killed when heated to 60 C ° for 30 minutes, exposed to UV irradiation and using organic solvents (13). This fact makes it possible to control the virus using specialized equipment, as well as to use personal protective equipment for humans, which in turn will reduce the risk of human exposure to infecting agents. In most cases, chemical agents are still used to kill rodents (14). These methods can help to limit the spread of the virus, but cannot eliminate it completely. It is very difficult to completely get rid of, or reduce the epidemiological zones, because anyway man will always be closely connected with nature, and regardless of the technological progress mankind will not be able to give up agricultural production, and completely get rid of interaction with animals, so this disease will exist and change, thus people will be interested in treatment for a long time. Based on existing studies, analyzing dangerous epidemiological areas, there are results in which the incidence remains high from year to year. It is important that in these areas' methods are used to control the virus, but the epidemiological zones are not reduced and the incidence is not reduced.

Pathogenesis is Associated with Changes in Hemodynamics

The pathogenesis of HFRS disease is not fully discovered, but there are already studies that have come close to deciphering this pathology. Hantavirus enters the human body through biological secretions of rodents, then the virus enters human cells through the respiratory and digestive systems, less often through the mucous membrane of the eyes (15,16). The damaging factor, namely inflammation, targets vascular endothelial cells, which in turn impairs their permeability, resulting in leakage from the bloodstream (17). There are studies that prove that the severity and the course of the disease depends on different associations of hantavirus RNA load (18). An

analysis of renal biopsies obtained from infected and uninfected patients was performed, concluding that intercellular contacts of the ZO-1 compound located in glomerular and tubointerstitial cells were impaired in infected patients. It is also important that the values of peptide reduction in cells correlate with the severity of clinical symptoms. Undoubtedly, the recovery of patients from hantavirus-induced HFRS, as well as other viral diseases, depends almost entirely on the immunological activity of the organism. Therefore, the pathogenesis is completely associated, with the action of the complement system, T-cell response, B-cells, and cytokine production, where everything and leads to the phenomenon of cytokine storm (19). This theory has already been supported by multiple studies describing those bioactive substances produced by macrophages, monocytes and lymphocytes in response to an inflammatory agent are involved in the regulation and activation of inflammation (20). There are studies demonstrating that during the febrile, hypotensive and oliguric period, serum concentrations of TNF-α, IL-6, IFN-γ, IL-8, IP-10 and RANTS are increased in the blood, and their levels are directly related to the severity of clinical symptoms. Thus, it was concluded that cytokines, namely TNF-α, IL-1 and IL-6, are mediators that lead to febrile syndrome, septic shock, as well as due to them increased production of acute phase proteins. There have been results highlighting that the cytokine IFN-β has the ability to act on endothelial cells, increasing the permeability of the vessel wall. IFN-β type I (IFN-β α/β) this cytokine is produced during viral infection, in proof there are studies that in vivo and in vitro showed that IFN-β is increased in serum (21). Another representative of cytokines is IFN-γ, the concentration of which also increases with the manifestation of the disease, so the dependence of the concentration, the manifestation of clinical symptoms, and the severity of the disease was investigated, resulting in a direct correlation of indicators (22). In the overall totality of the results obtained, a protective function of the immune system, represented by the cytokine storm, which is aimed at the elimination of the virus from the body, but at the same time is itself a manifestation of immunopathology, which also damages the body itself, is indeed observed. This defensive reaction leads to general clinical syndromes in the body: general toxic, hemodynamic disorders, acute renal failure, disseminated intravascular coagulation, abdominal (dyspeptic) syndrome and respiratory syndrome (23). Thus, when the immune response gets out of control, it leads to irreversible consequences in the body.

Clinic of the Disease

Infection of humans with the virus that causes HFRS occurs through inhalation of virus-containing aerosols released from rodent excretions, such as urine, feces, and saliva. In this way, the virus is transmitted by airborne droplets and spreads in the body. Infection and the disease process are divided into clinical periods: incubation, febrile, hypotensive shock, oliguric, polyuric, and recuperative periods. The incubation period may take 1-5 weeks. The next period is febrile, which lasts 3 to 5 days, manifesting itself by clinical symptoms such as fever, chills, thirst, cough, muscle and joint pain, which are not characteristic of a particular disease, so in practice these symptoms are usually written off as acute respiratory diseases (ARI). The key moment comes when the manifestation of hemorrhagic syndrome is determined, which in turn is represented by a petechial rash. All the listed manifestations vary and there is no clear gradation. Further, the course of the disease progresses to hypotensive shock, it lasts from several hours to several days. This period is very important in treatment, as it requires special attention and monitoring the dynamics of blood pressure, as it can rapidly fall to low values, which in turn aggravates the patient, as low blood pressure in combination with inflammatory renal damage closes in a pathological circle, which leads to deep kidney damage. The oliguric period (3 to 7 days), is, according to numerous studies, the most fatal, as patients die predominantly during this period (24). It is essential that all pathological manifestations reach their maximum, namely, general toxic manifestations, hemodynamic disorders, renal failure, etc in this period. Then there comes a period that leads to the resolution of the disease is polyuric (1-2 weeks). Here the pain disappears, sleep and appetite normalize, and diuresis resumes. All this is aimed to improve the patient's condition. And the final distinguished period is the period of recuperation (3-6 months), as pathological processes subside, laboratory parameters such as creatinine and urea are normalized. It is important to understand that acute condition caused by HFRS can lead to the development of non-cardiogenic pulmonary

edema, pathological development is directed towards ARDS, which closes with the death of the patient. The time and transition from one stage to another, depends not only on different hantavirus serotypes, but also depends on compensatory and individual body characteristics. Currently, there are no existing methods that can predict the exact stage and guarantee the transition from one to another, so there is a need for a more accurate differential diagnosis of the disease, and an increase in the speed of obtaining test results. A study was conducted to analysis the medical histories of children with HFRS and compare symptoms in children with adults to identify the characteristics of the disease. The result was similarity of symptoms with adult patients (25).

Markers in the Diagnosis of HFRS

In scientific studies related to HFRS disease, a lot of data was obtained, namely, a new feature of more in-depth pathogenesis was revealed, as a precursor of natriuretic hormone called NTproBNP peptide was identified (26). It was possible to achieve the detection of NTproBNP peptide in the blood, thus it became possible to focus on the concentration of this peptide and analyze the degree of damage to the body, as well as to use as a diagnostic marker in the disease of HFRS (27). In essence, this peptide has become a marker that can now be used in the diagnosis of the disease and used to analyze the disease. This peptide is released in response to renal and cardiac damage. This peptide is known to be elevated during all periods of HFRS disease, but its maximum serum concentration is reached during the oliguric period. This is due to the fact that NTproBNP peptide is produced by heart cells in order to reduce the hemodynamic load on the heart (28,29). This may be due to the fact that during the disease of HFRS in conjunction with pathological syndromes, there is hemorrhage in the right atrial auricle, which provokes receptors for the production of the peptide. It should be noted that the manifestation of renal pathology also leads to retention of NTproBNP peptide, which increases its concentration in the blood as its excretion from the body is impaired. (30). Thus, the manifestation of cardiorenal syndrome type 3 leads to an increase in serum peptide concentration. Currently, studies have been carried out investigating the effect of clotting system and folate cycle gene polymorphism on echocardiographic parameters in HFRS (31). The F7:10976 G/A gene polymorphism is known to decrease gene expression, resulting in lower levels of factor VII, which is used as a marker of thrombosis formation and myocardial infarction. Thus, it was revealed that allele a of F7:10976 G/A gene was detected more often in patients with developed signs of thromboendocarditis, and genotype G/G of FGB: -455G/A gene was often detected in myocardial longitudinal peak strain disorder. Thus, it is possible to distinguish and diagnose each period, as well as to analyze and speak about the patient's prognosis. Due to competent analysis and identification of patterns, a new marker of HFRS, which is a biological component of the body (peptide), has been identified, which allows to diagnose the disease without using external substances for diagnosis without infusion. Therefore, this fact may allow improving the quality and speed of diagnosis of HFRS. Despite already having disease markers that were detected at different periods of the disease, they can fall out of the cycle and also overlap with each other, which in turn certainly blurs the clinical picture. These features are important when choosing the right treatment tactics.

Diagnosis of HFRS with an Emphasis on Instrumental Methods of Investigation

The most important thing in the practice of any clinician is an early diagnosis, because it is early diagnosis that will solve the patient's problem with lower consequences, namely damage to organs and systems, and increase the likelihood of complete recovery. Therefore, it is very important to identify the patient as early as possible and begin specialized treatment of the patient. It is known that everything is not limited to one method, there are also used laboratory methods (biochemical, serological), electrocardiography (ECG), chest radiography in direct projection, renal ultrasound, and determination of oxygen saturation (SpO_2) using pulse oximeter (32-35). Further, it is necessary to expand on the above studies. The use of the biochemical blood test is more general, and indicates general inflammation despite the fact that the spectrum is much broader compared to the general blood test, clear detection of the virus is not detected. Therefore, in such a case, a serological method of investigation is further used, which in turn allows definitive confirmation and

identification of the virus that causes HFRS (36). Discoveries in the field of HFRS diagnosis do not stand still, so there is a development of this direction and research in this area. A patent has been received for a method that makes it possible to increase the accuracy, speed and quality of HFRS diagnosis at early stages (RU Patent 2735810). This invention allows to carry out a diagnosis of HFRS, using the results of research, which are based on syndromes, such as fever, hemorrhagic syndrome, urinary syndrome and using ultrasound elastometry method allows to make an accurate diagnosis quickly, namely by determining the stiffness of the renal parenchyma when the stiffness value is below 16 kPa, and if the patient has the syndromes listed above, then the patient can be diagnosed with hemorrhagic fever with renal syndrome. And if the stiffness is above 16 kPa, then the diagnosis cannot be HFRS. The presented method development bears unique properties, namely that the method is very cheap and easy to use, as it does not use expensive equipment. This method makes it possible to increase the speed of diagnosis, as well as to use it in hospitals that are less financed and thus have less equipment. Therefore, this method is already recognized and used in practice.

Treatment

HFRS carries many features that need to be considered in the treatment of this disease. The following treatments and studies were conducted on adult patients. There are many drugs that can be used in treatment, namely, including IFN-α, steroids, and cyclophosphamide, they have been shown to be effective in improving the condition of patients (37,38). It is also important to understand that special attention needs to be given to the patient by equalizing the water-salt balance, as due to the implications of the clinic, this is the primary goal in stabilizing the patient during the disease (39). One of the antiviral drugs ribavirin (1-beta-D-ribofuranosi-11,2,4-triazole-3-carboxamide) was used in the treatment of patients, and it was found that for the best effectiveness of the drug it is necessary to start treatment as early as possible, this allows achieving a rapid recovery, but also an important feature that with its use the mortality of patients was higher (40). New monoclonal antibodies (MAbs), which have shown good results in trials, are a hope to improve the effectiveness of HFRS therapy (41). An important problem is that there is no specific treatment for children, so the treatment of patients is only symptomatic.

Prevention

HFRS is a very common pathology, thus it remains a current problem in epidemiology. As we already know, the way of infection is practically figured out. At the moment we know how to fight it, namely to use individual means of protection, to protect one's home from rodents to use poisonous substances (42-44). All this is used by the population and it is also important to carry out sanitary-educational measures for the population, which allowed to increase the safety of the population in epidemiological foci. These measures already exist and in most cases are used, but the infection of the population still occurs, so they are not the key to solve the problem. Therefore, all hope of preventing HFRS should be directed to vaccination of the population, which would allow to receive protection properly. In connection with this, a Hantavax vaccine was developed in China (Korea Green Cross, Seoul, Korea), which was based on dead Hantavirus DNA, this was derived from the brain of infected rodents, but its effectiveness tended to zero over time, and eventually became completely useless (45-47).

Conclusion

As a result, HFRS remains and will continue to be an urgent problem for which a lot of effort will have to be put into finding a solution, also the pathogenesis of the disease will have to be fully studied, and new methods of individual protection, chemical substances, with higher effectiveness and greater humanity to the reservoirs of the virus will have to be invented. This would help reduce transmission in humans and would have a major impact on reducing the incidence of the disease. The development of new drugs would produce more effective results, thereby improving the therapy for HFRS disease. Creation of a working vaccine would lead to the development of general immunity in the population, could lead to a complete victory over the problem. Therefore, it is necessary to work together with the entire scientific community to achieve these results in the future.

Ethics

Footnotes

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

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References

1. Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2019;21:e6-16.
2. Riquelme R. Hantavirus. Semin Respir Crit Care Med. 2021;42:822-7.
3. Jiang H, Zheng X, Wang L, Du H, Wang P, Bai X. Hantavirus infection: a global zoonotic challenge. Virol Sin. 2017;32:32-43.
4. Tian H, Stenseth NC. The ecological dynamics of hantavirus diseases: from environmental variability to disease prevention largely based on data from China. PLoS Negl Trop Dis. 2019;13:e0006901.
5. Amaral CD, Costa GB, de Souza WM, Alves PA, Borges IA, Tolardo AL, et al. Silent orthohantavirus circulation among humans and small mammals from central minas gerais, Brazil. Ecohealth. 2018;15:577-89.
6. Zhang R, Mao Z, Yang J, Liu S, Liu Y, Qin S, et al. The changing epidemiology of hemorrhagic fever with renal syndrome in Southeastern China during 1963-2020: a retrospective analysis of surveillance data. PLoS Negl Trop Dis. 2021;15:e0009673.
7. Sabino-Santos G Jr, Maia FGM, Martins RB, Gagliardi TB, Souza WM, Muylaert RL, et al. Natural infection of neotropical bats with hantavirus in Brazil. Sci Rep. 2018;8:9018.
8. Tariq M, Kim DM. Hemorrhagic fever with renal syndrome: literature review, epidemiology, clinical picture and pathogenesis. Infect Chemother. 2022;54:1-19.
9. Gu SH, Kumar M, Sikorska B, Hejduk J, Markowski J, Markowski M, et al. Isolation and partial characterization of a highly divergent lineage of hantavirus from the European mole (Talpa europaea). Sci Rep. 2016;6:21119.
10. Wang N, Yin JX, Zhang Y, Wu L, Li WH, Luo YY, et al. Genetic evolution analysis and host characteristics of hantavirus in yunnan province, china. Int J Environ Res Public Health. 2022;19:13433.
11. Singh S, Numan A, Sharma D, Shukla R, Alexander A, Jain GK, et al. Epidemiology, virology and clinical aspects of hantavirus infections: an overview. Int J Environ Health Res. 2022;32:1815-26.
12. Serris A, Stass R, Bignon EA, Muena NA, Manuguerra JC, Jangra RK, et al. The hantavirus surface glycoprotein lattice and its fusion control mechanism. Cell. 2020;183:442-56.
13. Kallio ER, Klingström J, Gustafsson E, Manni T, Vaheri A, Henttonen H, et al. Prolonged survival of puumala hantavirus outside the host: evidence for indirect transmission via the environment. J Gen Virol. 2006;87:2127-34.
14. Dheerasekara K, Sumathipala S, Muthugala R. Hantavirus infections-treatment and prevention. Curr Treat Options Infect Dis. 2020;12:410-21.
15. Torriani G, Mayor J, Zimmer G, Kunz S, Rothenberger S, Engler O. Macropinocytosis contributes to hantavirus entry into human airway epithelial cells. Virology. 2019;531:57-68.
16. Lim SC, Lee YM, Kim CM, Yun NR, Kim DM. Acute appendicitis associated with hantaan virus infection. Am J Trop Med Hyg. 2021;105:801-6.
17. Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. Front Cell Infect Microbiol. 2016;6:1.
18. Lu S, Zhu N, Guo W, Wang X, Li K, Yan J, et al. RNA-Seq Revealed a Circular RNA-microRNA-mRNA regulatory network in hantaan virus infection. Front Cell Infect Microbiol. 2020;10:97.
19. Garanina E, Martynova E, Davidyuk Y, Kabwe E, Ivanov K, Titova A, et al. Cytokine storm combined with humoral immune response defect in fatal hemorrhagic fever with renal syndrome case, tatarstan, Russia. Viruses. 2019;11:601.
20. Vangeti S, Strandin T, Liu S, Tauriainen J, Räisänen-Sokolowski A, Cabrera L, et al. Monocyte subset redistribution from blood to kidneys in patients with Puumala virus caused hemorrhagic fever with renal syndrome. PLoS Pathog. 2021;17:e1009400.
21. Jiang H, Wang PZ, Zhang Y, Xu Z, Sun L, Wang LM, et al. Hantaan virus induces toll-like receptor 4 expression, leading to enhanced production of beta interferon, interleukin-6 and tumor necrosis factor-alpha. Virology. 2008;380:52-9.
22. Khaiboullina SF, Martynova EV, Khamidullina ZL, Lapteva EV, Nikolaeva IV, Anokhin VV, et al. Upregulation of IFN-γ and IL-12 is associated with a milder form of hantavirus hemorrhagic fever with renal syndrome. Eur J Clin Microbiol Infect Dis. 2014;33:2149-56.
23. Borodina ZI, Tsarenko OY, Monakhov KM, Bagautdinova LI. Hemorrhagic fever with renal syndrome: the challenge of our time. The Russian Archives of Internal Medicine. 2019;9:419-27.
24. Wang WJ, Zhao J, Yang JS, Liang MM, Ni MY, Yang JH. Clinical analysis of patients with acute pancreatitis complicated with hemorrhagic fever with renal syndrome and acute biliary pancreatitis. Medicine (Baltimore). 2020;99:e18916.
25. Echterdiek F, Kitterer D, Alscher MD, Schwenger V, Ruckenbrod B, Bald M, et al. Clinical course of hantavirus-induced nephropathia epidemica in children compared to adults in Germany-analysis of 317 patients. Pediatr Nephrol. 2019;34:1247-52.
26. Manakhov KM, Bagautdinova LI, Malinin OV, Dudarev MV, Sarksyan DS, Ivanov VG, et al. Dynamics of n-terminal fragment of the brain natriuretic peptide precursor serum concentration in patients with hemorrhagic fever with renal syndrome. Bashkortostan medical journal. 2021;16:5-11.
27. Rajaniemi SM, Hautala N, Sironen T, Vainio O, Vapalahti O, Vaheri A, et al. Plasma B-type natriuretic peptide (BNP) in acute puumala hantavirus infection. Ann Med. 2014;46:38-43.
28. Rasmuson J, Lindqvist P, Sörensen K, Hedström M, Blomberg A, Ahlm C. Cardiopulmonary involvement in puumala hantavirus infection. BMC Infect Dis. 2013;13:501.
29. Fan J, Ma J, Xia N, Sun L, Li B, Liu H. Clinical value of combined detection of CK-MB, MYO, cTnI and Plasma NT-proBNP in diagnosis of acute myocardial infarction. Clin Lab. 2017;63:427-33.

30. Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, Ali U, Hill SA, et al. BNP and NT-proBNP as prognostic markers in persons with acute decompensated heart failure: a systematic review. Heart Fail Rev. 2014;19:453-70.
31. Manakhov KM, Sarksyan DS, Dudarev MV, Chernobrovkina M, Pribytkova PY, Filimonova SV. Gene polymorphism in blood coagulation system and folate cycle affecting heart condition in patients with hemorrhagic fever and renal syndrome. Russian Journal of Infection and Immunity. 2022;12:347-56.
32. Lebecque O, Falticeanu A, Mulquin N, Dupont M. Abdominal CT findings in Puumala hantavirus-infected patients. Abdom Radiol (NY). 2022;47:2552-9.
33. Teng AY, Che TL, Zhang AR, Zhang YY, Xu Q, Wang T, et al. Mapping the viruses belonging to the order Bunyavirales in China. Infect Dis Poverty. 2022;11:81.
34. Prince HE, Lieberman JM. Impact of the Yosemite hantavirus outbreak on hantavirus antibody testing at a national reference laboratory. Clin Vaccine Immunol. 2013;20:1213-6.
35. Galieva GA, Mirsaeva GK, Fazlyeva RM. Comparative study of myocardial damage in hantavirus and new coronavirus infection. Meditsinskiy Sovet. 2023;17:44-50.
36. Chau R, Bhatt N, Manhiça I, Cândido S, de Deus N, Guiliche O, et al. First serological evidence of hantavirus among febrile patients in Mozambique. Int J Infect Dis. 2017;61:51-5.
37. Brocato RL, Hooper JW. Progress on the Prevention and Treatment of Hantavirus Disease. Viruses. 2019;11:610.
38. Mittler E, Dieterle ME, Kleinfelter LM, Slough MM, Chandran K, Jangra RK. Hantavirus entry: perspectives and recent advances. Adv Virus Res. 2019;104:185-224.
39. Zhang D, Wang X, Lv J, Dong Y. Treatment of a patient with severe hemorrhagic fever accompanied by infection with methicillinresistant staphylococcus aureus, acinetobacter baumannii, aspergillus and mucor: a case report. Int J Clin Pharmacol Ther. 2015;53:1028-34.
40. Szabó R. Antiviral therapy and prevention against hantavirus infections. Acta Virol. 2017;61:3-12.
41. Duehr J, McMahon M, Williamson B, Amanat F, Durbin A, Hawman DW, et al. Neutralizing monoclonal antibodies against the gn and the gc of the andes virus glycoprotein spike complex protect from virus challenge in a preclinical hamster model. mBio. 2020;11:e00028-20.
42. Hansen A, Cameron S, Liu Q, Sun Y, Weinstein P, Williams C, et al. Transmission of haemorrhagic fever with renal syndrome in china and the role of climate factors: a review. Int J Infect Dis. 2015;33:212-8.
43. Rubio AV, Fredes F, Simonetti JA. Exotic pinus radiata plantations do not increase andes hantavirus prevalence in rodents. Ecohealth. 2019;16:659-70.
44. Tosa N, Ishida T, Yoshimatsu K, Hayashimoto N, Shiokawa K, Takakura A, et al. Simultaneous serodetection of major rat infectious pathogens by a multiplex immunochromatographic assay. Exp Anim. 2021;70:161-8.
45. Song JY, Jeong HW, Yun JW, Lee J, Woo HJ, Bae JY, et al. Immunogenicity and safety of a modified three-dose priming and booster schedule for the Hantaan virus vaccine (Hantavax): a multi-center phase III clinical trial in healthy adults. Vaccine. 2020;38:8016-23.
46. Khan A, Shin OS, Na J, Kim JK, Seong RK, Park MS, et al. A systems vaccinology approach reveals the mechanisms of immunogenic responses to hantavax vaccination in humans. Sci Rep. 2019;9:4760.
47. Bae JM. Introduction of vaccinomics to develop personalized vaccines in light of changes in the usage of hantaan virus vaccine (Hantavax®) in Korea. J Prev Med Public Health. 2019;52:277-80.

CASE REPORT OLGU SUNUMU

Transition from Orthorexic Eating Behavior to Anorexia Nervosa and the Role of Chronic Illness

Olgu Sunumu: Ortoreksik Yeme Davranışından Anoreksiya Nervozaya Geçiş ve Kronik Hastalığın Rolü

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Abstract

We present a case of a 15-year-old female with severe malnutrition (BMI =11.25 m^2/kg) caused by avoiding high-carbohydrate foods after being misdiagnosed with Type 1 Diabetes Mellitus and later diagnosed with Maturity Onset Diabetes of the Young (MODY) type 2, which led to anorexia nervosa (AN) subsequently. The report aims to examine the possible transitions between different types of disordered eating and eating disorders (EDs) and to stress the importance of further counseling for patients with chronic illnesses, particularly in cases where daily dietary habits could be significantly impacted.

Öz

Bu yazıda, gençlerde görülen erişkin tipi diyabet (MODY) tip 2 tanısı yerine konulması yanlışlıkla Tip 1 Diabetes Mellitus tanısı konulan sonrasında yüksek karbonhidratlı gıdalardan kaçınma nedeniyle ciddi beslenme bozukluğu (BMI=11,25 m^2/kg) yaşayan ve Anoreksiya Nervoza (AN) ile sonuçlanan 15 yaşında bir kız olgu sunulmuştur. Rapor, farklı düzensiz yeme türleri ve yeme bozuklukları (YB) arasındaki olası geçişleri incelemeyi ve özellikle günlük beslenme alışkanlıklarının önemli ölçüde etkilenebileceği durumlarda, kronik hastalığı olan hastalara daha fazla danışmanlık verilmesinin önemini vurgulamayı amaçlamaktadır.

Keywords
Adolescent, case report, disordered eating, maturity onset diabetes of the young, anorexia nervosa

Anahtar kelimeler
Ergen, vaka sunumu, bozulmuş yeme, gençlerde görülen erişkin tipi diyabet, anoreksiya nervoza

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Introduction

Chronic diseases like diabetes mellitus (DM) demand profound adjustments in one's lifestyle, particularly regarding daily dietary choices (1). Beyond the physical transition, there is a pressing need for emotional, psychological, and social adaptability, and without the proper emotional scaffolding, this emotional weight may be overwhelming (2). The diagnosis of DM can be distressing and lead to a sense of loss of control over one's body, driving some individuals towards behaviors that provide a sense of control. Individuals with DM, especially Type 1 DM, must pay close attention to their diet, carbohydrate counting, and meal planning to manage their blood sugar (3,4). This focus on food could potentially highlight or exacerbate underlying eating disorders

(EDs) or disordered eating behaviors DEBs (5). On the other hand, during adolescence, a period marked by profound transformations and increased body image anxieties, individuals diagnosed with Type 1 DM face a heightened susceptibility to developing eating disorders (6).

Given the focus on diet and health, some individuals with DM might become overly preoccupied with eating only "clean" or "healthy" foods, leading to orthorexic behaviors (7). Orthorexic behaviors refer to tendencies that align with an excessive focus on eating "healthy" or "clean" foods and avoiding those perceived as "unhealthy". They might be occasional or temporary and can be part of a broader interest in health without significantly impacting daily life. On the other hand, orthorexia, often termed orthorexia nervosa (ON), is an extreme and pathological extension of these behaviors (8,9). It denotes a chronic and pervasive obsession with dietary purity, where one's dietary rules become increasingly rigid. ON can lead to significant interference in daily life, including social isolation, emotional distress, and potential health complications (10,11). In short, while orthorexic behaviors highlight an unhealthy emphasis on "clean" eating, ON engulfs one's identity and self-worth in the pursuit of a "pure" diet. ON is not formally recognized as a distinct eating disorder diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (12). The difference between ON and other EDs is the motivation behind the restrictive behavior. While anorexia nervosa (AN) or bulimia nervosa (BN) focuses on the quantity of food and weight control, ON is about the quality of food and its perceived health benefits or potential harms (13,14). On the other hand, orthorexic behaviors can transition into or coexist with AN, though they are distinct conditions with different primary motivations (14). Both ON and AN may have underlying vulnerabilities like a need for control, perfectionism, or anxiety (13,15). While orthorexic behaviors initially stem from a concern about the purity or healthfulness of food over time, this focus can evolve, transitioning from an emphasis on food quality to its quantity and shifting from health considerations to concerns about weight and body shape (16).

We present a 15-year-old female who, influenced by family members' traumatic diabetes complications, avoided high-carbohydrate foods, leading to AN. The goal is to enhance disordered eating, facilitating early detection of EDs in patients with chronic conditions.

Case Report

The patient is a fifteen-year-old female admitted to an adolescent medicine service with malnutrition (body mass index of 11.25 m^2/kg, SDS; 8.03, weight for height; 57.65%). It was learned that during routine blood assessments at the age of 12, hyperglycemia was identified, accompanied by an HbA1c value at the upper threshold, leading to a provisional diagnosis of Type 1 DM in the honeymoon phase. Following this diagnosis, she was prescribed a dietary regimen under the guidance of a clinical dietitian to maintain optimal blood glucose levels. After adhering to a stringent DM dietary regimen for one year, she experienced a weight loss of 6 kg over ten months. Since there was no need for insulin treatment during follow-ups, at the age of 13, the patient had a genetic test that revealed a heterozygous mutation in the glucokinase gene (GCK), confirming a diagnosis of Maturity Onset Diabetes of the Young type 2 (MODY2). She was informed that strict dietary adherence was unnecessary. However, after a noticeable decline in her interest in food and eating patterns, she sought evaluation at another medical facility, where she was diagnosed with AN. As a result, a therapeutic regimen of fluoxetine (1x20 mg/day) and aripiprazole (1x5 mg/day) was prescribed. Figure 1 illustrates the patient's weight changes and diagnoses over time.

In the preceding six months, she has been administered levothyroxine (LT4) at a dosage of 25 mcg/day, with the last administration occurring two days prior. It was learned that this therapeutic intervention was in response to a diagnosis of euthyroid sick syndrome (ESS), which was evident from the diminished serum concentrations of triiodothyronine (T3) and thyroxine (T4), notwithstanding the preservation of thyroid-stimulating hormone (TSH) levels. She was premenarchal, and her family history revealed that her grandmother and aunt were diagnosed with type 2 DM and experienced vascular complications. The records indicate that the patient resided in an alternate city and visited our locality for vacation. During her stay, she sought a consultation at the adolescent health department of our institution for routine monitoring.

Upon initial examination, the patient appeared extremely malnourished. Hair presentation was thin and desiccated, and while the skin was parched, lanugo was observed on both the facial and dorsal regions. She had acrocyanosis and was not hypothermic. Her heart rate was elevated at 130-140 beats/min, and her blood pressure measurements bordered on hypotension. She experienced no prior episodes of dizziness or syncope. During the consultation, the patient revealed that although she initially had no concerns about body size, shape, or weight when her condition began, the background of having family members suffering major complications of diabetes and subsequent weight loss as an achievement for her occasionally triggered fixations on these factors, leading to mixed feelings about her body weight. She did not report any obsessive-compulsive behaviors in other areas of her life.

The patient was admitted for comprehensive assessment and therapeutic intervention. She had tachycardic values, and weight gain could not be achieved despite the calorie increase. Laboratory evaluations, comprising a complete blood count, hepatic and renal function tests, and serum biochemistry, all yielded results within the normal range. Electrocardiogram and echocardiogram evaluations were normal. Results from thyroid function tests were within normal ranges. The anti-thyroid peroxidase antibodies (AntiTPO) and thyroglobulin antibodies (TgAb) were negative. Anti-transglutaminase antibodies were negative. Fasting and postprandial blood glucose concentrations ranged between 75 and 115 mg/dl, with the HbA1C level at 5.9%. During the patient's hospitalization, daily caloric intake was regulated. Given that a MODY2 diagnosis does not carry the same risk of complications as Type 1 or Type 2 DM, there was no blood glucose monitoring, and her diet did not incorporate techniques like carbohydrate counting to mitigate hypo- or hyperglycemia. She did not want to eat certain foods that contained carbohydrates and was angry when presented with them in the early stages of the stay. Thorough guidance and counseling were offered on both MODY2 and issues related to disordered eating, encompassing eating disorders. Based on the decision to monitor thyroid tests during a follow-up, LT4 treatment was discontinued. On the fifteenth day, weight gain was commenced once the patient's pulse readings stabilized within the normal parameters. Following a 1-kilogram weight increment observed over a one-week hospitalization period, the patient was discharged with a structured daily monitoring regimen. This weight trajectory was sustained during subsequent outpatient evaluations. Subsequent thyroid function tests were within normal limits. The patient expressed an improved mood with the weight gain, although she preferred her body weight to remain below 40 kilograms. After seven weeks post-discharge,

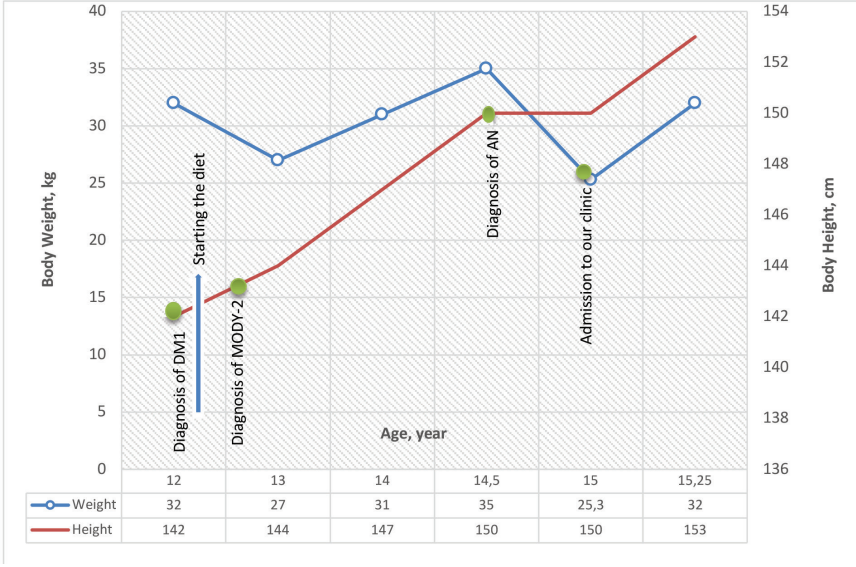

Figure 1. The follow-up of the patient's anthropometrics

the patient's weight has reached 33 kilograms, and she remains under consistent monitoring with an aripiprazole and fluoxetine regimen. Concurrently, there is notable progress in her physical and emotional well-being.

Discussion

Maturity Onset Diabetes of the Young Type 2 (MODY2) results from mutations in the glucokinase (*GCK*) gene and is a subtype of monogenic diabetes (17). This variant typically manifests as mild, non-progressive hyperglycemia, often detected in childhood or adolescence without the usual high blood sugar symptoms (18). Diagnosed through genetic testing, its presence hints at a hereditary pattern, with blood glucose levels often resting between 100 mg/dL (5.5 mmol/L) and 144 mg/dL (8.0 mmol/L). While lifestyle modifications usually manage MODY2, insulin or other diabetes medications are generally not required. Due to its mild nature, MODY2 carries a lower risk of diabetes-related complications than typical type 1 or 2 diabetes (17). Proper diagnosis is crucial to ensure appropriate care and prevent unnecessary treatments. Awareness of MODY2 is important because its management and prognosis can differ significantly from the more common type 1 or type 2 diabetes. Specific disordered eating habits have not been directly linked to MODY2 in the scientific literature in the same way they have been associated with type 1 or type 2 diabetes mellitus (19,20). However, introducing dietary implications or required changes from such diagnoses can be overwhelming, potentially leading to anxiety about food choices and avoiding specific foods. As for our case, the records indicate that following the honeymoon stage of type 1 DM diagnosis, the patient commenced a dietary regimen under the supervision of a registered dietitian. Due to a delayed diagnosis of GCK-MODY, unnecessary dietary interventions, and a familial antecedent of Type 2 DM with concomitant severe complications, the case developed orthorexic behaviors. There has not been specific literature directly linking orthorexic behaviors with MODY. Orthorexic tendencies often begin with a genuine intent to eat healthily, emphasizing organic or "clean" foods. Over time, this preference can intensify into strict rules, with more foods labeled "unhealthy" and eliminated (8). As this behavior becomes rigid, emotional responses intensify; eating "pure" foods may bring feelings of virtue, while deviations cause guilt. Eventually, these behaviors may dominate daily life, leading to avoiding social situations involving food, nutritional deficiencies from a narrowing list of "acceptable" foods, and significant distress (13).

On the other hand, prolonged restriction in any context about foods may lead to psychological changes. Over time, our case might have derived satisfaction from this condition's pronounced and reinforcing effects. Orthorexic behaviors, driven by an obsession with "pure" or "healthy" food, can potentially evolve into AN, characterized by a fear of weight gain and a distorted body image. Shared underlying traits like a need for control or perfectionism can predispose individuals to both disorders (13). Over time, dietary restrictions associated with orthorexia can lead to significant weight loss, and the resulting body changes might shift concerns to weight and shape, hallmarks of AN. Additionally, societal pressures emphasizing thinness or considering weight loss as success may exacerbate this transition. While there is potential for progression from orthorexic behaviors to anorexia, it is not universal (21).

Another feature that needs to be emphasized in our case is initiating levothyroxine (LT4) treatment because of euthyroid sick syndrome (ESS) due to weight loss (22). It is characterized by low circulating triiodothyronine (T3) levels, increased reverse T3, and normal or low levels of thyroxine (T4). Serum thyroid-stimulating hormone (TSH) may be low, normal, or slightly elevated. These alterations are considered adaptive and beneficial during acute illness but might contribute to prolonged illness in chronic conditions. While the ESS is the most common thyroid alteration in that situation, primary hypothyroidism can also be seen, although it is less common in this context. It is important to note that the symptoms of hypothyroidism, including fatigue, cold intolerance, dry skin, and constipation, may be similar to those of AN (23). The reason for the development of primary hypothyroidism in individuals with AN is not entirely clear. It might be linked to extreme nutritional deficiencies or autoimmune processes. Some studies suggest a higher prevalence of autoimmune disorders in AN, which might predispose to autoimmune thyroid diseases, such as Hashimoto's thyroiditis (24). Our patient was evaluated in this respect, and antithyroid

antibodies were negative. However, selenium and iodine levels could not be evaluated. Notably, most of these thyroid abnormalities resolve as the patient gains weight and recovers from AN (22). Given that many people with AN have an impaired physiological state, starting with a lower dose and increasing it gradually may be prudent. The patient in this report was initially prescribed LT4 to manage ESS resulting from AN. However, due to tachycardic episodes and an inability to achieve adequate weight gain, the LT4 treatment was discontinued. After discontinuing LT4, tachycardia typically improves within days to a few weeks. This timeline can vary based on factors such as the drug's half-life, previous dose, individual metabolism, coexisting medical conditions, and concurrent medications. Upon follow-up, tachycardic values showed improvement, and appropriate weight gain was noted. Concurrently, thyroid functions remained within normal limits.

Conclusion

Addressing chronic conditions requires an understanding that challenges are not limited to the physiological realm. There is a deep-seated symbiosis between the psyche and the body, especially when managing diseases that permeate daily life and self-worth. Putting much emphasis on dietary shifting may lead to high-risk thoughts arising in an obsessive focus on foods. Extending psychological counseling can alleviate mental burdens and pave the way for holistic well-being and adept disease management.

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Footnotes

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References

1. Awuchi CG, Echeta CK, Igwe VS. Diabetes and the nutrition and diets for its prevention and treatment: a systematic review and dietetic perspective. Health Sciences Research. 2020;6:5-19.
2. Weinger K, Lee J. Psychosocial and psychiatric challenges of diabetes mellitus. Nurs Clin North Am. 2006;41:667-80.
3. H Ibrahim SM, Shahat EA, Amer LA, Aljohani AK. The impact of using carbohydrate counting on managing diabetic patients: a review. Cureus. 2023;15:e48998.
4. Sami W, Ansari T, Butt NS, Hamid MRA. Effect of diet on type 2 diabetes mellitus: a review. Int J Health Sci (Qassim). 2017;11:65-71.
5. Dziewa M, Bańka B, Herbet M, Piątkowska-Chmiel I. Eating disorders and diabetes: facing the dual challenge. Nutrients. 2023;15:3955.
6. Young V, Eiser C, Johnson B, Brierley S, Epton T, Elliott J, Heller S. Eating problems in adolescents with type 1 diabetes: a systematic review with meta-analysis. Diabet Med. 2013;30:189-98.
7. Grammatikopoulou MG, Gkiouras K, Polychronidou G, Kaparounaki C, Gkouskou KK, Magkos F, et al. Obsessed with healthy eating: a systematic review of observational studies assessing orthorexia nervosa in patients with diabetes Mellitus. Nutrients. 2021;13:3823.
8. Moroze RM, Dunn TM, Craig Holland J, Yager J, Weintraub P. Microthinking about micronutrients: a case of transition from obsessions about healthy eating to near-fatal "orthorexia nervosa" and proposed diagnostic criteria. Psychosomatics. 2015;56:397-403.
9. Dunn TM, Bratman S. On orthorexia nervosa: a review of the literature and proposed diagnostic criteria. Eat Behav. 2016;21:11-7.
10. Strahler J. The dark side of healthy eating: links between orthorexic eating and mental health. Nutrients. 2020;12:3662.
11. Park SW, Kim JY, Go GJ, Jeon ES, Pyo HJ, Kwon YJ. Orthorexia nervosa with hyponatremia, subcutaneous emphysema, pneumomediastimum, pneumothorax, and pancytopenia. Electrolyte Blood Press. 2011;9:32-7.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; American Psychiatric Association: Washinton, DC, USA, 2013.
13. Cena H, Barthels F, Cuzzolaro M, Bratman S, Brytek-Matera A, Dunn T, et al. Definition and diagnostic criteria for orthorexia nervosa: a narrative review of the literature. Eat Weight Disord. 2019;24:209-46.
14. Koven NS, Abry AW. The clinical basis of orthorexia nervosa: emerging perspectives. Neuropsychiatr Dis Treat. 2015;11:385-94.
15. Fidan T, Ertekin V, Işikay S, Kirpinar I. Prevalence of orthorexia among medical students in Erzurum, Turkey. Compr Psychiatry. 2010;51:49-54.
16. Horovitz O, Argyrides M. Orthorexia and orthorexia nervosa: a comprehensive examination of prevalence, risk factors, diagnosis, and treatment. Nutrients. 2023;15:3851.
17. Bishay RH, Greenfield JR. A review of maturity onset diabetes of the young (MODY) and challenges in the management of glucokinase-MODY. Medical journal of Australia. 2016;205:480-5.
18. Giuffrida FM, Reis AF. Genetic and clinical characteristics of maturity-onset diabetes of the young. Diabetes Obes Metab. 2005;7:318-26.
19. Toni G, Berioli MG, Cerquiglini L, Ceccarini G, Grohmann U, Principi N, Esposito S. Eating disorders and disordered eating symptoms in adolescents with type 1 diabetes. Nutrients. 2017;9:906.
20. Mateo K, Greenberg B, Valenzuela J. Disordered eating behaviors and eating disorders in youth with type 2 diabetes: a systematic review. Diabetes Spectr. 2022;37:342-8.

21. Atchison AE, Zickgraf HF. Orthorexia nervosa and eating disorder behaviors: a systematic review of the literature. Appetite. 2022;177:106134.
22. Mehler PS, Brown C. Anorexia nervosa - medical complications. J Eat Disord. 2015;3:11.
23. Pehlivantürk Kızılkan M, Kanbur N, Akgül S, Alikaşifoğlu A. An adolescent boy with comorbid anorexia nervosa and hashimoto thyroiditis. J Clin Res Pediatr Endocrinol. 2016;8:92-5.
24. Raevuori A, Haukka J, Vaarala O, Suvisaari JM, Gissler M, Grainger M, et al. The increased risk for autoimmune diseases in patients with eating disorders. PLoS One. 2014;9:e104845.

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The mistake has been made inadvertently by the author.

The missing author name **Bahadır Dede** and missing author hor position (author position **3**) have been corrected as follows.

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