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YAZIM KURALLARI

Klinik Psikiyatri Dergisi, Psikiyatri, Klinik Psikoloji, Psikofarmakoloji ve Nörolojinin psikiyatriyi ilgilendiren alanlarýnda yapýlan deneysel ve klinik araþtýrmalar, derlemeler, olgu sunumlarý, kýsa bildiriler ve editöre mektup türünden yazýlara yer vermektedir. Yýlda 4 kez yayýnlanan dergi, Türkçe ve Ýngilizce yazýlarý kabul etmektedir.

Gönderilen makaleler için; iletim, deðerlendirme, yayınlanma gibi hiçbir aşamada ücret talep edilmemektedir.

2016 sayýlarý itibari ile makalelere DOI numaralarý verilmektedir. Digital Object Identifier (DOI) sistemi digital ortamda yer alan içeriðe kolay eriþilebilmesini saðlayan bir sistemdir. DOI numarasý almýþ makaleler ile sistem, basili mecrada yayýnlanmasýna gerek kalmadan çevrimiçi yayýnlanmasý ile birlikte çalýþmalarýnýz arasýnda yer almasýný olanak sunmaktadýr. Bu durum akademisyenler için zaman açýsýndan avantaj saðlamaktadýr. DOI sistemi, ISO standardý olup International DOI Foundation tarafýndan idare edilmektedir. DOI Sisteminde yer alan dergimizde çalýþmalarý yayýnlanan yazarlar çalýþmalarýný ulusal ve uluslararasý bilim çevrelerinin hýzlý eriþimine sunmakta ve böylelikle yazýlarýnýn atýf potansiyelini artýrmaktadýrlar.

Dergimiz Journal Agent ara yüzü ile makale gönderimi ve takibi yapmaktadýr. Kullanýcýlar tarafýndan kolay ve hýzlý kulaným imkâný tanýyan makale takip sistemi ile çalýþmalarýnýz hýzlý bir þekilde deðerlendirilmektedir.

Yazıların değerlendirme süreci ve etik konular

Klinik Psikiyatri Dergisi makalelerin deðerlendirilmesinde baðýmsýz, tarafsýz, çift-kör hakem deðerlendirme raporlarýný temel alýnmaktadýr. Gönderilen makalelerin özgünlükleri, metodolojileri, tartýþýlan konunun önemi, Yayýn Kurulu üyeleri tarafýndan deðerlendirilir. Takiben, tarafsýz deðerlendirme sürecini saðlamak için her makale alanlarýnda uzman en az iki dýþ-baðýmsýz hakem tarafýndan deðerlendirilir. Bütün makalelerin karar verme süreçlerinde nihai karar yetkisi Editörler Kurulu'ndadýr.

Gözden geçirenler yazarların kimliğinden habersizdir ve yazarlar da gözden geçirenlerin kimliğinden habersizdirler.

Gönderilen yazýlar, isimleri gizli tutulan konuyla ilgili en az iki danýþma kurulu üyesince deðerlendirilir. Danýþma kurulunca deðerlendirmeleri tamamlanan yazýlar yayýn kurulunda görüþülür. Yayýn kurulu yazýyý yayýnlamaya, düzeltilmesi için geri göndermeye, düzelterek yayýnlamaya ya da yayýnlamamaya yetkilidir. Dergimizin editöryel ve yayýn süreçleri International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE) ve National Information Standards Organization (NISO) organizasyonlarýnýn kýlavuzlarýna uygun olarak biçimlendirilmiþtir.

Derginin editöryel ve yayýn süreçleri, Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice) ilkelerine uygun olarak yürütülmektedir.

Yayýn Kurulu, dergimize gönderilen çalýþmalar hakkýndaki intihal, atýf manipülasyonu ve veri sahteciliði iddia ve þüpheleri karþýsýnda COPE kurallarýna uygun olarak hareket edecektir. Bütün makalelerin benzerlik tespiti denetimi, iThenticate yazýlýmý aracýlýðýyla yapýlmaktadýr

Eðer makalede daha önce yayýnlanan makalelerden alýntý varsa, makalenin yazarý yayýn hakký sahibi ve yazarlarýndan yazýlý onay almak ve bunu makalesinde belirtmek zorundadýr. Alýnan onay belgesi makaleyle beraber editörlüðümüze gönderilmelidir. Hakemlerin, mükerrer yayýn, intihal vb gibi olasý araþtýrma ve yayýn etiði ihlalleri konusunda yorumda bulunmalarý beklenir..

Yazar olarak listelenen herkesin ICMJE tarafýndan önerilen yazarlýk ölçütlerini karþýlamasý gerekmektedir. ICMJE, yazarlarýn aþaðýdaki 4 ölçütün her birini karþýlamasýný verilerin toplanmasýna, analiz edilmesine ve yorumlanmasýna önemli katký saðlamýþ olmak;

2. Yazý taslaðýný hazýrlamýþ ya da önemli fikirsel içeriðin eleþtirel incelemelerini yapmýþ olmak;

3. Yazýnýn yayýndan önceki son halini gözden geçirmiþ ve onaylamýþ olmak;

4. Çalýþmanýn herhangi bir bölümünün geçerliliði ve doðruluðuna iliþkin sorularýn uygun þekilde soruþturulduðunun ve çözümlendiðinin garantisini vermek amacýyla çalýþmanýn her yönünden sorumlu olmayý kabul etmek.

Yazarlar bu dört kuralý karþýladýklarýna dair yazýlý onayý Yayýn Hakký Devir Formu'nda bildirmek durumundadýr. Dört kriterin hepsini karþýlamayan kiþilere makalenin baþlýk sayfasýnda teþekkür edilmelidir. Yayýn Kurulu'nun gönderilen bir makalede "armaðan yazarlýk" olduðundan þüphelenmesi durumunda söz konusu makale deðerlendirme yapýlmaksýzýn reddedilecektir.

Yazarlar, çalýþmalarýndaki doðrudan ya da ticari baðlantý, maddi destek gibi konularda tam olarak açýk olmalýdýrlar. Yazarlar bu türden bir iliþkileri varsa bunun nasýl bir iliþki olduðunu bildirmek, yoksa hiçbir iliþkileri olmadýðýný belirtmek zorundadýrlar. Dergimiz, WAME'in çýkar çatýþmasý tanýmýný benimsemektedir.

Yazýlarýn geliþ tarihleri ve kabul ediliþ tarihleri makalenin yayýnlandýðý sayýda belirtilir. Derginin internet sayfasýnda bütün makalelerin Türkçe ve Ýngilizce özet versiyonlarý ile gönderilen dildeki tam metin versiyonlarý bulunur. Ýçerik, yayýn sürecinin tamamlanmasýný takiben derginin internet sayfasýnda ücretsiz eriþime açýk hale getirilir. Eðer abone deðil iseler yazarlara, yazýlarýnýn yayýnlandýðý dergi gönderilmemektedir.

Dergimizde yayýnlanan yazýlarýn yayýn hakký ANP Özel Saðlýk Hizmetleri LTD ÞTÝ'ne aittir. Yazarlara telif ücreti ödenmemektedir.

Yayýnlanan yazýlarýn bilimsel ve hukuki sorumluluðu yazarlarýna aittir. Dergide yayýnlanan makalelerde ifade edilen görüþler ve fikirler Klinik Psikiyatri Dergisi, Editörler ve Yayýn Kurulu'nun deðil, yazar(lar)ýn bakýþ açýlarýný yansýtýr. Editörler, Yayýn Kurulu ve Yayýncý bu gibi durumlar için hiçbir sorumluluk ya da yükümlülük kabul etmemektedir.

Gönderilen yazýlarýn hemen iþleme konulabilmesi için belirtilen yazým kurallarýna tam olarak uygun olmasý gereklidir.

Yazım Kuralları

Dergide yayınlanmak üzere gönderilen yazıların uzmanlarca tarafsız deðerlendirmeye alınabilmesi için, yazarların kimliklerine iliþkin bilgilerin, yazının başında yer alacak ayrı bir sayfada bulunması gereklidir.

Yazılar, yazının daha önce bir dergide yayınlanmamış veya yayınlanmak üzere gönderilmemiş, olduğunu bildiren ve tüm yayın haklarının ANP Özel Sağlık Hizmetleri LTD ŞTİ'ne devredildiği belirtilen, yazarlarca imzalanmış bir üst yazı ile gönderilmelidir.

Yazılarınızı web anasayfamızda yer alan "online makale gönder" butonuna tıklayarak gönderebilirsiniz. Her türlü sorunuz için klinikpsikiyatri@gmail.com adresinden bize ulaşabilirsiniz.
İlk sayfada, makale başlığının altında, yazarların isim, soyadı, unvan, çalışma adresleri ve varsa e-mail adresleri belirtilmelidir. En sonda da yazışmaların yapılacağı sorumlu yazarın adres, telefon ve e-mail adresi yer almalıdır.

Araştırmalar, olgu sunumları ve derleme yazıları için Türkçe özet ve anahtar sözcükler ile İngilizce başlık, İngilizce özet ve İngilizce anahtar sözcükler bulunması zorunludur. Türkçe özet en az 150, en fazla 200, İngilizce özet en az 230, en fazla 250 sözcükten oluşmalıdır. Anahtar sözcükler Index Medicus'a göre seçilmeli, en az 3 en fazla 6 kelime olmalıdır. Araştırma yazılarında Türkçe ve İngilizce özetler, Amaç (Objectives), Yöntem (Method), Bulgular (Results), Sonuç (Conclusion)

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Kısaltmalar uluslararası kabul edilen şekilde olmalı, ilk kullanıldıkları yerde açık olarak yazılmalı ve parantez içinde kısaltılmış şekli gösterilmelidir. Özette kısaltmalara yer verilmemelidir. Yazılarda dipnot kullanılmamalı, açıklamalar yazı içinde verilmelidir.
Makaleler sadece www.klinikpsikiyatri.org adresinde yer alan derginin online makale yükleme ve değerlendirme sistemi üzerinden gönderilebilir. Diğer mecralardan gönderilen makaleler değerlendirilmeye alınmayacaktır.

MAKALE TÜRLERİ

Araştırma

Araştırma yazı kuralı sırasıyla Giriş, Gereç ve Yöntem, Bulgular, Tartışma ve Sonuç alt başlıklarından oluşmalıdır. Türkçe ve İngilizce özetler, Amaç (Objectives), Gereç ve Yöntem (Method), Bulgular (Results), Sonuç (Conclusion) şeklinde başlıklardan oluşmalıdır.

Makaleler, ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals ile uyumlu olarak hazırlanmalıdır. Araştırmalarda etik ilkelere uyulmalıdır. Etik Kurul kararları ve olgu onay formları yazılara eklenmeli, makalede etik ilkelere uyulduğu bir cümle ile belirtilmelidir.

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

Derleme ve Olgu Sunumu

Derleme ve olgu sunumu şeklindeki makalelerde de yukarıdaki ana yazım düzenine uyulmalı, özet sayfasından sonra yazının türüne uygun şekilde kaleme alınmalı, derlemelerde kaynak sayısı 50'yi üzerinde olmamalıdır. Derlemelerde, yazarlardan birinin konuyla ilgili 3 veya daha çok özgün araştırmasının yayımlanmış olması gereklidir. Derleme yazarlarının konu hakkındaki birikimi uluslararası literatüre yayın ve atıf sayısı olarak yansımış uzmanlar olması gerekir. Bu ölçütlere uyan yazarlar derleme yazısı yazmaları için Yayın Kurulunca davet edilebilir.

Olgu sunumlarının giriş ve tartışma kısımları kısa-öz olmalı, kaynak sayısı kısıtlı tutulmalıdır. Bu yazılar, "Giriş", "Olgu Sunumu" ve "Tartışma" alt başlıklarını içermelidir.

Kısa Bildiriler

Kısa bildiriler özet içermemeli, kısa-öz olmalı, kaynaklar sınırlı olmalıdır. Kısa Bildirim yazıları (başlık sayfası, kaynaklar, tablo, şekil/resim hariç) 2500 kelimeyi geçmemelidir.

Editöre Mektup

Editöre mektup bölümü, dergide daha önce yayınlanmış yazılara eleştiri getirmek, katkı sağlamak ya da orjinal bir çalışma olarak hazırlanmamış ve hazırlanamayacak bilgilerin iletilmesi amacıyla oluşturulduğundan kısa-öz olmalı, özet içermemeli, kaynakları sınırlı olmalıdır.

TABLO, ŞEKİL VE RESİMLER

Tablo, Şekil ve Resimler numaralandırılmalı ve metin içinde geçiş sırasına göre belirtilmelidir. Başlık veya alt yazıları ile birlikte her biri ayrı sayfada hazırlanarak yazıya eklenmelidir. Şekiller fotoğraf filmi alınabilecek kalitede gönderilmelidir. Şekil içindeki harf, numara ya da semboller net ve okunabilir olmalıdır.

Tablolar ana dosyaya eklenmeli, kaynak listesi sonrasında sunulmalı, ana metin içerisindeki geçiş sıralarına uygun olarak numaralandırılmadır. Tabloların üzerinde tanımlayıcı bir başlık yer almalı ve tablo içerisinde geçen kısaltmaların açılımları tablo altına tanımlanmalıdır. Tablolar Microsoft Office Word dosyası içinde "Tablo Ekle" komutu kullanılarak hazırlanmalı ve kolay okunabilir şekilde düzenlenmelidir. Tablolarda sunulan veriler ana metinde sunulan verilerin tekrarı olmamalı; ana metindeki verileri destekleyici nitelikte Resimler, grafikler ve fotoğraflar (TIFF ya da JPEG formatında) ayrı dosyalar halinde sisteme yüklenmelidir.

KAYNAKLAR

Atıf yapılırken en son ve en güncel yayınlar tercih edilmelidir. Atıf yapılan erken çevrimiçi makalelerin DOI numaraları mutlaka sağlanmalıdır. Kaynakların doğruluğundan yazarlar sorumludur. Dergi isimleri Index Medicus/Medline/PubMed'de yer alan dergi kısaltmaları ile uyumlu olarak kısaltılmalıdır. Kaynaklarda tüm yazar isimleri listelenmelidir. Ana metinde kaynaklara atıf yapılırken parantez içinde Arabik numaralar kullanılmalıdır.

Vancouver stilinde kaynak gösterimi yapılmalıdır. Dergi isimlerinin kısaltmaları, "NLM Katalog: NCBI Veri tabanlarında atıf yapılan dergilerde" (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals) kullanılan stilde olmalıdır. Dizine eklenmemiş dergilerin kısaltılması gerekir. Farklı yayın türleri için kaynak stilleri aşağıdaki örneklerde sunulmuştur:

Kaynak bir makale ise,

Boyce P, Parker G, Barnett B, Cooney M, Smith F. Personality as a vulnerability factor to depression. Br J Psychiatry 1991; 159:106-114.

Zinbarg RE, Barlow DH, Liebowitz M, Street L, Broadhead E, Katon W, Roy-Byrne P, Lepine J-P, Teherani M, Richards J, Brantley PJ, Kraemer H. The DSM-IV field trial for mixed anxiety-depression. Am J Psychiatry 1994; 151:1153-1162

Bir derginin ek sayısı ise; Beskow J. Depression and suicide. Pharmaco-psychiatry 1990; 23 (Suppl 1): 3.

Burrows GD, Norman TR, Judd FK, Marriott PF. Short-acting versus long-acting benzodiazepines: discontinuation effects in panic disorders. J Psychiatr Res 1990; 24 (suppl 2): 65-72.

Kaynak bir kitap ise; Beahrs JO. The Cultural Impact of Psychiatry: The Question of Regressive Effects, in American Psychiatry After World War II: 1944-1994. Edited by Menninger RW, Nemiah JC. Washington, DC, American Psychiatric Press, 2000, pp. 321-342.

Çeviri kitaptan alıntı ise; Saddock BJ, Saddock VA. Klinik Psikiyatri. Aydın H, Bozkurt A (Çeviri Ed.) 2. Baskı, Ankara: Güneş Kitabevi Ltd. Şti., 2005, 155-157.

Tezden alıntı ise| Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki İlişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Baskıdaki makaleler için| Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016; 24. doi: 10.5152/dir.2015.15323. [In press].

Kongre bildirileri için| Yumru M, Savas HA, Kalenderoglu A, Bulut M, Erel O, Celik H. Şizofrenli bozukluk alt tiplerinde oksidatif dengesizlik. 44. Ulusal Psikiyatri Kongresi Bildiri Kitabı 2008; 105.

İnternetten alıntılar için| World Health Organization. Depression. http://www.who.int/mediacentre/factsheets/fs369/en/. Erişim tarihi: Ağustos 22, 2016.

Kaynakların doğruluğundan yazarlar sorumludur. Doğrudan yararlanılmayan ya da başka kaynaklardan aktarılmış kaynaklar belirtilmemeli, basılmamış eserler ya da kişisel haberleşmeler kaynak gösterilmemelidir.

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Emerging Sources Citation Index (ESCI)(2017 yılından itibaren)
Scopus (2017 yılından itibaren)
DOAJ (2018 yılından itibaren)
EBSCO Academic Search Complete (2007 yılından itibaren)
EBSCO TOC Premier (2007 yılından itibaren)
Türkiye Atif Dizini (2000 yılından itibaren)
PsycINFO/ Psycological Abstracts (2004 yılından itibaren)
TÜBİTAK/ULAKBİM-Türk Tip Dizini (2000 yılından itibaren)
Google Scholar (1998 yılından itibaren)
Index Scholar (2007 yılından itibaren)
Akademik Dizin (2000 yılından itibaren)
Türk Medline (2000 yılından itibaren)
Türk Psikiyatri Dizini (1998 yilindan itibaren)
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Index Copernicus

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Sahibi ve Yazı İşleri Müdürü
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ANP Özel Sağlık Hizmetleri Ltd. Şti. Adına,
Dr. Mehmet Yumru
Kapak Resmi: Mehmet Emin Erşan

Bir bilimsel makalenin ölüm fermanı: Geri çekme

The death decree of a scientific paper: Retraction

Mehmet Yumru[1], Oguzhan Herdi[2]
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https://orcid.org/0000-0002-2117-7775-https://orcid.org/0000-0003-0101-2663

Bilimsel okuryazarlık, bilimsel makalelerin yayınlanma aşamasından sonra, ister bilimsel merak ister çalışmalarımızda atıf yapmak amacıyla olsun, ilgili makalelerin eleştirel gözle ve bilimsel bir şüphe ile yaklaşmayı gerektiriyor. Tüm dünyada giderek artan ticari yayıncılığın gözden kaçan önemli sonuçlarından birisi bilimsel makalelerin yayınlanma sürecinden sonraki aşamalarında yaşanan gelişmelerdir. Son yıllarda bilimsel dergiler tarafından giderek artan oranda bilimsel makalenin yayın ömrü sonlandırılmaktadır.

Bilimsel makalelerin ölüm fermanı anlamına gelen geri çekmenin birçok nedeni olabilmektedir. En çok bilinen nedenleri arasında intihal, sahte hakem değerlendirmesi, yanlış veriler, geçersiz varsayımlar, sahte sonuçlar, bilinçli çarpıtmalar gibi bilimsel sahtekarlıklar yer almaktadır. Ancak bazen teknik hatalar gibi bilimsel sahtekarlık içermeyen nedenler de yer almaktadır. Bilimsel sahtekarlığın son 10 yılda yapılan geri çekmelerin %60'ni oluşturduğu belirtilmektedir (1)

Bilimsel makalelerin geri çekilmesinin bilimciler arasında bilinir olması önem arz etmektedir. Maalesef geri çekme nedenleri bazen ilgili derginin internet sitesinde belirtilmemektedir ya da bilimsel makalenin geri çekme zamanına kadar geçen sürede çok sayıda okuma ya da atıf yapılmış olabilmektedir. Geri çekme nedenleri bilinmediği zaman diğer bilimciler orijinal bilimsel makalenin bulgularına atıf yaparak zaman, çaba ve fon harcayabilmektedir. Tüm bu nedenlerden dolayı geri çekmelerin izlenebilir olması amacıyla 2010 yılında Ivan Oransky ve Adam Marcus tarafından, bilimsel makalelerin geri çekilmesi hakkında veri sunan ve bilimde şeffaflığı artırmayı amaçlayan bir veri tabanı (http://retractiondatabase.org/) oluşturuldu (2).

Geri çekme izleme veri tabanı, geri çekmeleri ve düzeltmeleri, dergi, yazar, kurum, ülke, alan gibi birçok ölçüte göre tarama imkânı sunuyor. Veri tabanı şu anda bilinen en kapsamlı, en büyük geri çekme veri tabanı konumundadır. Veri tabanında 1970'li yıllara dayanan 20.000'e yakın geri çekilmiş makale ve konferans özeti listelenmektedir. Her bir bilimsel makalenin geri çekme nedenleri, künyesi ve ulaşılabilir uzantıları yer almaktadır (2). İlgili veri tabanı geri çekmelerin görünür olması açısından önemli bir boşluğu doldurmasına karşın, bu tür veri tabanlarının ticari yayıncılıkla ilişkili olmayan bağımsız kurum ya da kuruluşlarca oluşturulması gerekmektedir. Bu gelişmelere eş zamanlı olarak çok sayıda dergi editörüne ve yayıncısına danışmanlık yapan Yayın Etiği Komitesi (COPE), dergilerin geri çekme işlemlerini nasıl ele alması gerektiğine dair bir yönerge yayınlamıştır (3).

Dergiler tarafından geri çekilen bilimsel makale sayısı son 10 yılda 10 kat artmıştır. 1997 yılında sadece 44 dergi bir makaleyi geri çektiğini belirtirken, 2016'ya gelindiğinde bu sayı 488'e yükselmiştir. 2003 ve 2016 yılları arasında en az 100.000 bilimsel makale yayınlayan ülkeler arasında en yüksek geri çekilme oranlarına sahip ülkeler arasında birinci sırada İran yer alırken, Türkiye'nin 8. sırada yer aldığı görülmektedir (1). Geri çekme veri tabanının güncel verilerine göz attıldığında Türkiye kaynaklı 332 bilimsel makalenin geri çekme listesinde yer aldığı görülmektedir. "Türkiye" ve "psikiyatri" arama seçenekleri işaretlendiğinde ise 3 makale göze

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çarpmaktadır (4). 2000 yılında geri çekilen bilimsel makale sayısı 38 iken 2020 yılında bu rakam 2300'den fazla idi (5). Tüm bu verilere karşın geri çekilen bilimsel makaleler maalesef geri çekildikten sonra da okunmaya ve atıf yapılmaya devam etmektedir (6).

Geri çekmenin her zaman bilimsel sahtekarlık olmadığına dikkat çekmek önemlidir. Ancak bilimcilerin her zaman bir bilimsel makaleye atıf yapmadan önce geri çekme açısından bilimsel makaleleri gözden geçirmeleri önem arz etmektedir. Diğer önemli husular ise, geri çekme sayısının azaltılmasının amacıyla, sahte dergiler, ücretli yayıncılık gibi ticari yayıncılık anlayışının bir an önce sonlandırılması ve ayrıca editorial süreçlerin olması gerektiği şekilde titizlikle yürütülmesinin sağlanmasıdır.

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The death decree of a scientific paper: Retraction

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Scientific literacy requires approaching the relevant articles with a critical eye and scientific scepticism, whether for scientific curiosity or for citing our studies, after the publication of scientific articles. A crucial and missed consequence of increasing commercial publishing is the developments experienced in the post-publishing stages. In recent years, scientific journals have terminated the publication of an increasing number of scientific papers.

The retraction that means 'death decree' for scientific papers has several reasons. The foremost reasons are scientific frauds such as plagiarism, fake peer review, incorrect data, invalid hypotheses, false data, and deliberate distortions. However, the reasons which are not scientific frauds could sometimes occur, like technical mistakes. It is stated that scientific fraud accounts for 60% of retractions made in the last 10 years(1).

The retraction of a scientific paper must be got known by scientists. Unfortunately, the reasons for retraction are not stated on the web pages of the relevant journals or there may be a great number of readings or citations in the period until the time of the retraction of the scientific article. When the reasons for retraction are unknown, the other scientists may waste time, effort and funds citing the findings of the original scientific article. In 2010, a database presenting data about the retraction of a scientific paper and purposing to increase transparency in the scientific area was created by Ivan Oransky and Adam Marcus to traceability of retractions due to all the above-mentioned reasons (http://retractiondatabase.org/)(2).

The retraction tracking database provides screening opportunities for a great number of criteria, such as retraction, revision, journal, author, affiliation, country, and area. The database is currently the most comprehensive and largest retraction database known. Approximately 20000 retracted articles and conference abstracts dating back to the 1970s have been listed in the database. The retraction reason, tag and accessible extensions of each scientific article take place in the database (2). Although the relevant database has filled a gap in terms of visibility of retractions, this kind of database must be created by institutions or associations which are independent and do not touch with commercial publishing. In concert with these developments, The Committee on Publication Ethics (COPE) avising to a great number of journal editors and publishers issued an instruction regarding how the retraction process must be handled (3).

The number of retracted scientific papers by journals has increased 10 fold in the last 10 years. While only 44 journals declared a retraction of a scientific paper in 1997, the number increased to 488 in 2016. Among the countries where at least 100000 scientific articles were published between 2003-2016, Iran had first place in terms of the highest retraction rates, Turkey was 8th (1). When the current data of the retraction database is screened, it is observed that 322 scientific articles from Turkey take place in the list. In addition to this, when 'Turkey' and 'psychiatry' screening criteria are selected, 3 articles leap to the eye (4). While the number of the retracted scientific articles was 38 in 2000, the number was more than 2300 in 2020 (6). Despite all these data, the retracted articles keep being cited and read even after being retracted (6).

It is important to draw attention that retraction does not always occur due to scientific fraud. Nevertheless, screening a scientific article before citing it in terms of retraction has importance for

scientists. Other important issues are those, to decrease the number of retracted articles, fake journals, commercial publishing (publication fees etc.) must be immediately terminated and it must be ensured that editorial processes are carried out meticulously as they must be.

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Serum zonulin levels are correlated with symptom severity independent from body mass index and gender in children with attention deficit hyperactivity disorder

Dikkat eksikliği hiperaktivite bozukluğu olan çocuklarda serum zonulin seviyelerinin belirti şiddeti, vücut kitle indeksi ve cinsiyet ile ilişkisi

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SUMMARY

Objective: It has been recently emphasized that neurodevelopmental disorders such as schizophrenia, autism spectrum disorder and attention deficit hyperactivity disorder (ADHD) may be related to the gut-brain axis. Zonulin is a protein that changes the integrity of tight junctions between gastrointestinal mucosa cells. We aimed to investigate serum zonulin levels and its relationship with symptom severity in children with ADHD. **Method:** 21 ADHD patients and 19 controls were included. Zonulin levels were obtained from blood specimens. Clinical severity of the ADHD symptoms was evaluated by Conner's Parents Rating Scale-Revised/Long Form (CPRS-R/L) and Conner's Teacher Rating Scale-Revised/Long Form (CTRS-R/L) in ADHD group. **Results:** There was no significant difference between the groups in terms of age, gender and body mass index. Mean serum zonulin level of the ADHD group was 13.45±9.08 and 21.32± 19.96 in the control group. There was no significant difference between groups (t=1.99, p=0.51). Significant correlation was found (R=0.82, p<0.01) between serum zonulin levels and CTRS-R/L scores in the ADHD group. This correlation persisted when BMI and sex variables were controlled (R=0.85, p<0.01). **Discussion:** We have found significant correlation between ADHD symptom severity and serum zonulin levels, whereas there was no significant difference between children with ADHD and controls.

Key Words: Attention deficit, zonulin, children, intestinal, gut

ÖZET

Amaç: Şizofreni, otizm spektrum bozukluğu ve dikkat eksikliği hiperaktivite bozukluğu (DEHB) gibi nörogelişimsel bozuklukların bağırsak-beyin ekseniyle ilişkili olabileceği son zamanlarda vurgulanmıştır. Zonulin, gastrointestinal mukoza hücreleri arasındaki sıkı bağlantıların bütünlüğünü değiştiren bir proteindir. DEHB'li çocuklarda serum zonulin düzeylerini ve semptom şiddeti ile ilişkisini araştırmayı amaçladık. **Yöntem:** 21 DEHB hastası ve 19 kontrol dahil edildi. Zonulin seviyeleri kan örneklerinden elde edildi. DEHB belirtilerinin klinik şiddeti, Conners' Ebeveyn Derecelendirme Ölçeği-Gözden Geçirilmiş/Uzun Form (CPRS-R/L) ve Conners' Öğretmen Derecelendirme Ölçeği-Gözden Geçirilmiş/Uzun Form (CTRS-R/L) ile değerlendirildi. **Bulgular:** Gruplar arasında yaş, cinsiyet ve vücut kitle indeksi (VKİ) açısından anlamlı fark yoktu. DEHB grubunun ortalama serum zonulin düzeyi 13.45 ± 9.08 ve kontrol grubunda 21.32 ± 19.96 idi. Gruplar arasında anlamlı fark yoktu (t = 1.99, p = 0.51). DEHB grubunda serum zonulin düzeyleri ile CTRS-R / L skorları arasında anlamlı korelasyon (R = 0.82, p <0.01) bulundu. Bu korelasyon, VKİ ve cinsiyet değişkenleri kontrol edildiğinde de devam etti (R = 0.85, p <0.01). **Sonuç:** DEHB semptom şiddeti ile serum zonulin düzeyleri arasında anlamlı bir ilişki bulunmakla birlikte, DEHB olan çocuklar ve kontroller arasında anlamlı bir fark bulunamamıştır.

Anahtar Sözcükler: Dikkat eksikliği, zonulin, çocuk, bağırsak

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a condition that starts from early childhood and causes loss of function in various areas such as school, social environment, work and family life due to symptoms in the areas of inattention, impulsivity and hyperactivity. According to data obtained from different communities around the world, the prevalence of ADHD is approximately 5%(1). Twin studies show that ADHD has 70-80% heritability (2). In a study which was conducted in Turkey, the prevalence of ADHD was reported to be 12.4% (3). The contribution of many environmental factors such as alcohol and smoking during pregnancy, low birth weight, preterm birth, pesticides containing organophosphate, zinc and lead exposure on the etiology of ADHD has been examined until today. Despite this, studies have reported that those other than preterm birth may be affected by some unmeasurable familial confounding factors and their role in etiology has not been elucidated (4).

Although time management and information processing problems are frequently mentioned in the pathophysiology of ADHD, some changes in inflammatory mechanisms are thought to play a role in the formation of neuropsychiatric diseases such as schizophrenia, bipolar disorder, and post-traumatic stress disorder through pathways such as glial activation, neuronal damage, increase in oxidative stress, alteration of the neurotransmitter metabolism and the blood-brain barrier (5). There are some data indicating that the risk of ADHD increases in the presence of atopic immune disorders such as eczema, asthma, rheumatoid arthritis, type 1 diabetes and hypothyroidism, and evidence has been obtained from recent studies indicating that serum cytokine levels of individuals with ADHD are higher than the normal population (6).

It has become a frequently emphasized issue in recent research that the gut microbiota is important for the physiology and development of the host, and the deterioration of the microbiota has an effect on brain functions and behavior. It is known that the alteration of the intestinal flora for various reasons activates some pathways and causes the tight connections between cells to loosen, and that the loosened epithelium - that is, the "leaky gut", plays a role in the development of autoimmune diseases by increasing the antigen exposure of the organs (7). In recent years, it has been also reported in some cases that neurodevelopmental disorders may also occur through this mechanism (8). In addition to immune-mediated mechanisms, it is also suggested that some bacteria that grow excessively in microbiota facilitate the emergence of ADHD symptoms by increasing the production of neurotransmitters such as dopamine, serotonin and GABA. Although it is not known exactly whether these molecules can directly cross the blood brain barrier, it has been reported that the modified microbiota can contribute to neurotransmitter synthesis by causing an increase in peripheral tryptophan (9).

Zonulin, the precursor to haptoglobin (HP2), is a protein that causes changes in the integrity of tight junctions between gastrointestinal mucosa cells. Enteric bacteria and intestinal tissue exposed to gliadin increase zonulin secretion through chemokines (10,11). It has been reported that zonulin, which is higher in serum samples of celiac patients compared to healthy controls, is also associated with the etiology of neuropsychiatric disorders such as chronic inflammatory demyelinating polyneuropathy, multiple sclerosis (MS), and schizophrenia (12,13). There is a study in which increased serum zonulin levels were found in individuals with ADHD diagnosis compared to the control group (8). The number of studies examining the relationship between parameters related to intestinal permeability and ADHD in this age group is very limited.

In this study, we examined the intestinal permeability of individuals with ADHD who did not receive any medical treatment by determining their serum zonulin levels and we aimed to contribute to the literature by investigating the relationship between these levels and symptom severity.

METHOD

Study Sample

This study was conducted in Aksaray University Medical Faculty. Participants were recruited from the outpatient clinic of child and adolescent psychiatry. Children and adolescents within 8-12 years old who have diagnosed as ADHD and admitted to the clinic for the first time have been included in the patient group (n=21). Nine ADHD patients have ODD (oppositional defiant disorder) comorbidty. Newly diagnosed and psychotropic medication-naive patients were selected. Patient group have been compared with healthy controls (n=19) similar to the patient group in terms of age and sex. Exclusion criteria for the ADHD group were determined as major physical, allergic, endocrine or neurologic (such as epilepsy) diseases; those with body mass index (BMI) percentile ≥ 95%; those who use corticosteroids or any other drugs that affect the immune system in any time; and having an active infection within the past month. Those with comorbid depression, anxiety, mental retardation, autism spectrum disorder (ASD) and psychotic disorders were excluded from the study.

Control group was recruited from outpatient clinic for pediatric at the same hospital. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version-DSM-5 (K-SADS-PL-DSM-5) was used to screen healthy controls for psychiatric disorders by psychiatrist after physical examination by a pediatrician. The following exclusion criteria were implemented for control group: the existence of psychiatric disorders such as mental retardation, ASD, ADHD, schizophrenia, bipolar disorder, major depression, obsessive-compulsive disorder and anxiety disorders; major physical, allergic, endocrine or neurological diseases; those with body mass index (BMI) percentile ≥ 95%; those who use corticosteroids or any other drugs that affect the immunological system in any time and having an active infection within the past month. The control group consisted of healthy children and adolescents matched by age and sex who applied to the hospital for a routine checkup. The study was reviewed and approved by the Ethics Committee at Ankara City Training and Research Hospital Ethical Committee. The study's subjects, and parents of the subjects were briefed about the purpose of the study, and written consent was obtained from each of them.

Tools

Demographic and clinical information have been reported in a form prepared by researchers. BMI were calculated for each patient. Each patient underwent a detailed diagnostic evaluation by child and adolescent psychiatrist by using The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version-DSM-5 (K-SADS-PL-DSM-5) (15). Conners' Parents Rating Scale and Conners' Teacher Rating Scale were used during the diagnostic procedure.

Conners' Parents Rating Scale- Revised/Long Form (CPRS-R/L): CPRS-R/L consists subscales of cognitive problems/inattention, oppositionality, hyperactivity, anxiety-shyness, perfectionism, social problems, and psychosomatic symptoms. DSM-IV index, ADHD index, and Global Index according to DSM-IV diagnostic criteria are used for contribution. Parents are requested to answer items taking the last month into consideration. Each item is answered as one the following four choices: Not true at all (rarely), somewhat true (sometimes), quite true (mostly), and completely true (almost always) (16).

Conners' Teachers Rating Scale-Revised/Long Form (CTRS-R/L): CTRS-R/L includes 38 items, 6 subscales, and additionally 3 assistant scales based on the ADHD symptoms in DSM-IV: ADHD index, Conner's Global Index and DSM-IV Symptoms Index. Teachers are requested to evaluate children/adolescent's behaviors while taking the last one month into consideration. For each item, four answer choices: Not true at all (rarely), somewhat true (sometimes), quite true (mostly), and completely true (almost always) (17).

Biochemical Analysis

Venous blood specimens were collected between

8.00 and 10.30 a.m. after overnight fasting. The blood samples were centrifuged at 4000 rpm for 5 min at 4Co, and the separated serum was stored at -80Co until the time of the assay. Serum zonulin levels were measured using commercial enzyme-linked immunosorbent assay kits following the protocols of the manufacturers (Serum Zonulin Sunredbio, China; Cat No:201-12-5578; Lot: 202003). The results of the analysis were presented in ng/dl. Intra- and inter-assay coefficients of variation of zonulin kit was intra-assay CV <10%, inter-assay CV <10%.

Statistical Analysis

The statistical analysis was conducted using SPSS 23. Shapiro–Wilkinson test was used to determine the normality of the variable distribution. Relationships between dichotomous variables were assessed with the x^2 test. The scale scores and biochemical parameters of the patient and control group were compared using the Mann–Whitney U test according to the distribution properties. The correlation between serum zonulin levels and the psychological test scores was evaluated by the Spearman correlation coefficient. A value of p less than 0.05 (two-tailed) was considered statistically significant.

RESULTS

Twenty-one ADHD patients and nineteen healthy controls were included in this study. There was no significant difference in terms of sex (x^2=2.50, p=0.11). In the ADHD group, the mean age was 9.85 (SD=2.79) years and the control group's mean age was 8.72 (SD=3.27) years. There was no significant difference in terms of age between ADHD and control groups. (u=160,5, z=-1.05, p=0.29). The mean BMI was 21.79 in the patient group (SD=1.88) and 21.99 (SD=2.47) in the controls. There was no significant difference regarding mean BMI (u=190, z=-0.25, p=0.81). Demographic variables were presented in Table 1.

When we examined the relation of Conners' scores between the groups, CTRS total score (u=50.5, z=-4.03, p <0.001), CTRS ADHD index (u=63.5, z=-3.70, p <0.001), CPRS total score (u=0, z=-5,40, p <0.001), and CPRS ADHD index (u=9.0, z=-5.17, p <0.001) sub-scores were found to be statistically significant.

Table 1: Demographic and clinical characteristics of patients with ADHD and controls

	ADHD (n:21)	Controls (n:19)	*z/?2*	p
Age (years)	9.85 – 2.79	8.72 – 3.27	-1.05[a]	0.29
Sex				
Boy/girl	16/5	10/9	2.50[b]	0.11
BMI	21.79–1.88	21.99–2.47	0.25[a]	0.81

BMI: Body Mass Index; a: Mann-Whitney U test; [b]: Chi-square test

When compared, mean serum zonulin level in the ADHD group was 16.88 (SD=9.67) and 13,34 (SD=7.15) in the control group. There was no significant difference in terms of zonulin levels between groups (u=148, z=-1.39, p=0.16) (see Table 2 and Figure 1).

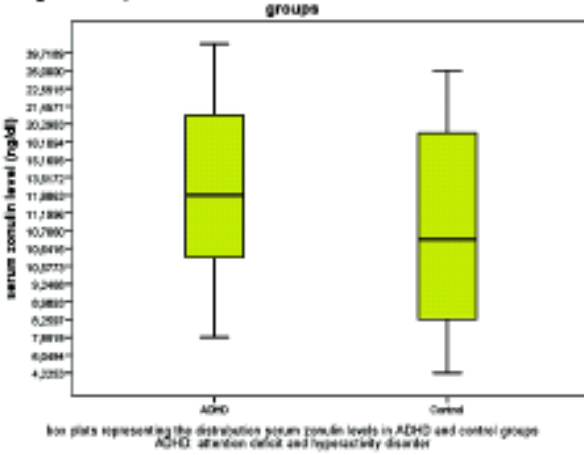
Table 2: Zonulin levels in ADHD and control groups

	ADHD	Control	u/z	p	Min/max value in ADHD group
Zonulin (ng/dl)	16.88 – 9.67	13.34 – 7.15	148/-1.39[a]	0,16	7.85/41.80

[a]: Mann-Whitney U test

When we examined the relationship between serum zonulin levels and CTRS total scores in the ADHD group, significant correlation was found (rs=0.905, p<0.01). Similar correlation existed with CPRS total score (rs=0.888, p<0.01) (Figure 2). There was no correlation between zonulin levels and total CTRS scores (rs= 0.214, p= 0.38) as well total CPRS scores (rs = -0.258, p = 0.28) in the control group.

Figure 1: comparision of serum zonulin levels between ADHD and control groups



box plots representing the distribution serum zonulin levels in ADHD and control groups
ADHD: attention deficit and hyperactivity disorder

Table 3. Correlation values of variables in ADHD group (n: 21)

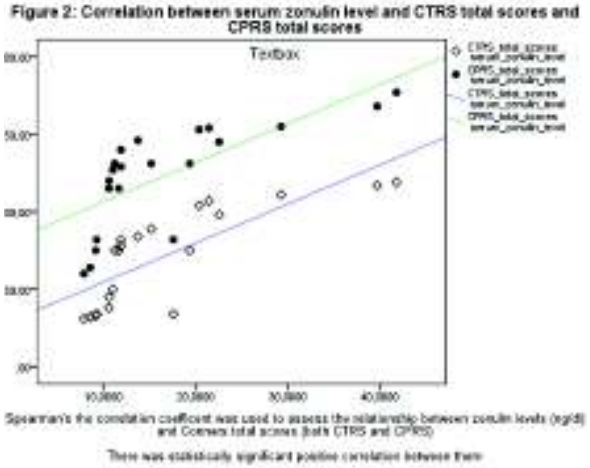
		1	2	3	4	5	6	7	8	9	10	11	12	13
1.	Serum zonulin levels (ng/dl)	1												
1.	CTRS total scores	.905[a], <.01[b]	1											
1.	CPRS total scores	.888[a], <.01[b]	.973[a], <.01[b]	1										
1.	CTRS. ADHD index subscale	.786[a], <.01[b]	.900[a], <.01[b]	.876[a], <.01[b]	1									
1.	CTRS. opposition subscale	.694[a], <.01[b]	.611[a], <.01[b]	.590[a], <.01[b]	.523[a], <.01[b]	1								
1.	CTRS. social problems subscale	.838[a], <.01[b]	.842[a], <.01[b]	.781[a], <.01[b]	.699[a], <.01[b]	.620[a], <.01[b]	1							
1.	CTRS. restlessness-impulsivity subscale	.794[a], <.01[b]	.912[a], <.01[b]	.898[a], <.01[b]	.923[a], <.01[b]	.512[a], =.01[b]	.651[a], <.01[b]	1						
1.	CTRS. emotional lability subscale	.599[a], <.01[b]	.606[a], <.01[b]	.584[a], <.01[b]	.923[a], <.01[b]	.533[a], =.01[b]	.753[a], <.01[b]	.451[a], <.05[b]	1					
1.	CPRS. ADHD index subscale	.630[a], <.01[b]	.726[a], <.01[b]	.792[a], <.01[b]	.717[a], <.01[b]	.277[a], =.22[b]	.615[a], <.01[b]	.608[a], <.01[b]	.370[a], =.09[b]	1				
1.	CPRS. opposition subscale	.625[a], <.01[b]	.758[a], <.01[b]	.727[a], <.01[b]	.786[a], <.01[b]	.257[a], =.26[b]	.556[a], <.01[b]	.829[a], <.01[b]	.383[a], =.08[b]	.484[a], <.05[b]	1			
1.	CPRS. social problems subscale	.506[a], <.05[b]	.598[a], <.01[b]	.627[a], <.01[b]	.535[a], =.01[b]	.234[a], =.30[b]	.455[a], <.05[b]	.597[a], <.01[b]	.500[a], <.05[b]	.431[a], =.05[b]	.370[a], =.09[b]	1		
1.	CPRS. restlessness-impulsivity subscale	.726[a], <.01[b]	.856[a], <.01[b]	.890[a], <.01[b]	.779[a], <.01[b]	.514[a], <.05[b]	.617[a], <.01[b]	.794[a], <.01[b]	.588[a], <.01[b]	.761[a], <.01[b]	.614[a], <.01[b]	.562[a], <.01[b]	1	
1.	CPRS. emotional lability subscale	.564[a], <.01[b]	.658[a], <.01[b]	.650[a], <.01[b]	.467[a], <.05[b]	.486[a], <.05[b]	.568[a], <.01[b]	.536[a], =.01[b]	.733[a], <.01[b]	.322[a], =.15[b]	.391[a], =.08[b]	.670[a], <.01[b]	.651[a], <.01[b]	1

CTRS: Conner's Teacher Rating Scale-Revised Long Form. CPRS: Conner's Teacher Rating Scale-Revised Long Form

[a] Spearman's rho correlation coefficient [b] p value (p value <0.05 is bolded)

The correlation between the CTRS-CPRS subscales and zonulin levels was also evaluated in the patient group. In the CTRS scale; opposition, social problems, ADHD index, restlessness-impulsivity and emotional lability subscales were positively correlated with zonulin levels. In the CPRS scale opposition, social problems, ADHD index, restlessness-impulsivity and emotional lability subscales were also positively correlated with zonulin levels (Table 3).

We evaluated whether BMI, age and sex variables had any effect on correlation by performing partial correlation analysis. In ADHD group, CTRS (r=0.756, p<0.01) and CPRS total scores (r=0.756, p<0.01), CTRS opposition (r=0.825, p<0.01), CTRS social problems (r=0.778, p<0.01), CTRS ADHD index (r=0.592, p=0.01), CTRS restlessness-impulsivity (r=0.586, p=0.01) and CTRS emotional lability (r=0.644, p<0.05) subscales was still found to be correlated after analysis. In CPRS, ADHD index(r=0.499, p<0.05), restlessness-impulsivity (r=0.553, p<0.05) and emotional lability subscales (r=0.728, p=0.01) were also found to be correlated.



We also evaluated the correlation between the CTRS and CPRS subscales and zonulin levels in the control group. The only positively correlated subscale was restlessness-impulsivity (rs = 0.501, p= 0.02) in the CTRS. On the other hand, there weren't any correlations regarding the CPRS subscales.

DISCUSSION

In this study, we investigated the serum zonulin levels among patients with ADHD and healthy controls. According to our results, there was no significant difference between patients diagnosed as ADHD and healthy controls in terms of serum zonulin levels. In addition, there was a significant correlation between CTRS/CPRS total scores and serum zonulin levels in patient group. Our study is

one of the few studies on this subject.

To our best knowledge, there are only two studies in the literature investigating serum zonulin levels in ADHD patients. Ozyurt et al. investigated serum zonulin levels in patients with ADHD and healthy controls. They found higher serum zonulin levels among children with ADHD and reported that these children have more impairment in social functioning compared to controls. Also, serum zonulin levels were found to be an independent predictor for hyperactivity and social deficit scores in regression analysis (8). In addition to this study, Aydogan Avsar et al. found significant differences between the study groups in terms of serum log-claudin-5 levels. However, according to this study there was no significant difference between the study groups in terms of serum zonulin levels. They suggested that the significant increase in serum claudin-5 levels could be evaluated as a mechanism of secondary compensation for increased blood-brain-barrier permeability and may be a marker for neuroinflammation. They mentioned some points while explaining lack of significance in serum zonulin levels such as excluding potential confounding factors such as obesity and methodological limitations (14). Therefore, in our study, we controlled BMI, age and gender variables, and yet we found that zonulin levels were still positively correlated with symptom severity.

According to our results, as the zonulin levels increased in the ADHD group, there was a more significant deterioration in opposition, social problems, restlessness-impulsivity and emotional lability sub-scores. These data were in parallel with the results found by Ozyurt et al., which can be summarized as increased zonulin levels might be related to impaired social functions (18).

Zonulin is a prehaptoglobulin which regulates intestinal permeability. Increase in zonulin levels which is induced by intestinal exposure to bacteria, gluten and gliadin could trigger opening of the paracellular pathway which is followed by an increase in intestinal permeability with the disengagement of the zonula occludens (ZO)-1 from the tight junctions. Impaired intestinal barrier permeability can lead to increased translocation of gut bacteria or of metabolic products such as lipopolysaccharide (LPS) and neuroactive peptides which could trigger an immune response that can lead to release of inflammatory cytokines and activation Inflammatory cytokines and the vagal system in turn can modulate the activity of the CNS (19). Several studies have been conducted to investigate the hypothesis that gastrointestinal permeability increased in patients with neurodevelopmental disorders and mental illnesses (20). In addition to ADHD, possible association between other psychiatric disorders and serum zonulin levels was investigated. Esnafoglu et al. found higher serum zonulin levels among patients diagnosed as autism spectrum disorders (21), Kilic et al. found higher serum zonulin levels in patients diagnosed as bipolar disorder (22) and Isik et al. also investigated serum zonulin levels among patients diagnosed as obsessive compulsive disorders and found no significant difference between patients and controls (23). As presented, there are studies investigating the association between psychiatric disorders and zonulin. Yet, studies about serum zonulin levels and ADHD are limited. We think that although a mechanic link in the gut–brain axis in ADHD has been proposed, there is still a lack of information about gut-brain axis role on ADHD etiology. In a recent review, it was suggested that there are several limitations on studies those investigating this association and little information is known whether alteration on microbiota and gut-brain axis contribute the etiology of ADHD or not. The reason we couldn't find any difference between groups may be because of this lack of association which was aforementioned by Aydogan Avsar et al (14). Another reason we didn't find any difference between groups could be the methodological limitations those mentioned by Ajamian et al. They suggest that although zonulin is a popular marker about disorders related with gut-brain axis, current commercial zonulin assays are not detecting the actual protein as prehaptoglobin-2. The researchers also recommended caution when considering serum zonulin levels as a marker of mucosal barrier integrity until assay methodology is improved (24). In a recent review, it was mentioned that studies investigating the association between ADHD and gut-brain axis have some limitations about methodological issues such as small sample sizes and standardization (25). Our sample size is

relatively small, and this could be a reason for this insignificance results between group.

Although we could not find a significant difference between patient and control groups in terms of serum zonulin levels, we found a significant correlation between serum zonulin levels and ADHD severity in patient group. In addition to this finding, when we controlled BMI and gender because of the confounding effect, positive correlation still persisted. Thus, we could suggest that serum zonulin levels does not differentiate patients with ADHD from healthy controls but could be used as a marker for determine ADHD severity. Higher serum zonulin levels could reflect increased intestinal permability (26) and this could result as more severe ADHD symptoms. If we could include more participants in our study, we think we would find some differences between the groups.

Our study has certain limitations. First, our sample size is relatively small. We did not standardize our patients' dietary habits, so dietary differences between patient and control groups could have influenced our results. This limitation is valid for most studies investigating gut-brain axis and autism spectrum disorder association. Finally, our study was cross-sectional and the patients were not followed up.

CONCLUSION

In conclusion, our study revealed the relationship between serum zonulin levels and symptom severity in patients with ADHD. The search for the use of biomarkers in psychiatric disorders continues, and studies with larger samples need to be repeated in order for zonulin to be a candidate in this regard.

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Investigation of the effect of comorbid psychopathologies on glycemic control in children and adolescents with type 1 diabetes mellitus

Tip 1 diabetes mellituslu çocuk ve ergenlerde komorbid psikopatolojilerin glisemik kontrol üzerine etkisinin araştırılması

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SUMMARY

Objective: The presence of comorbid psychiatric conditions in chronic diseases makes the management of the disease difficult. Our study, we aimed to examine the relationship between psychiatric comorbid conditions and glycemic control in children and adolescents with Type 1 Diabetes. **Method:** In our study, depending on the number of patients, good and moderate controls were evaluated as a single group, and HbA1c levels of 8.5 and below were included in this group. Children for Depression Inventory (CDI), Screen for Child Anxiety-Related Emotional Disorders (SCARED), Turgay Child and Adolescent Behavioral Disorders Based on DSM-IV Screening and Evaluation Scale were applied. The case and parents were evaluated with K-SADS-PL.Among 778 diabetic patients who were followed up in the pediatric endocrinology clinic, 73 cases between the ages of 8 and 17 who were followed up regularly, who did not have any comorbidities and who accepted to participate in the study were evaluated psychiatrically. **Results:** Of the 73 cases included in the study, 29 were accepted as the patients with good glycemic control (HbA1c≤8.5 mg / dl), and 44 as with poor glycemic control (HbA1c> 8.5mg / dl). In cases with poor glycemic control, parents' education level and income level were significantly lower, while the rate of attention deficit and hyperactivity disorder, major depressive disorder, social anxiety disorder and psychopathology was significantly higher. **Discussion:** The findings of this study revealed that there are many factors affecting glycemic control and there is a strong relationship between glycemic control and psychopathologies.

Key Words: Type 1 diabetes mellitus, children, adolescents, adhd, psychiatric disorder

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ÖZET

Amaç: Kronik hastalıklarda eşlik eden psikiyatrik durumların varlığı, hastalığın yönetimini zorlaştırmaktadır. Çalışmamızda Tip 1 Diyabetli çocuk ve ergenlerde psikiyatrik eştanı durumları ile glisemik kontrol arasındaki ilişkiyi incelemeyi amaçladık. **Yöntem:** Çalışmamızda hasta sayısına bağlı olarak iyi ve orta kontroller tek grup olarak değerlendirildi, HbA1c düzeyi 8.5 ve altında olan olgular bu gruba dahil edildi. Çocuklar İçin Depresyon Ölçeği (ÇDÖ), Çocuklarda Anksiyete Tarama Ölçeği (ÇATÖ), Turgay Çocuk ve Ergen Davranış Bozuklukları DSM-IV'e Göre Tarama ve Değerlendirme Ölçeği uygulandı. Olgu ve ebeveynleri K-SADS-PL ile değerlendirildi. Çocuk endokrinoloji polikliniğinde takip edilen 778 diyabetik hastadan 8-17 yaşları arasında düzenli takipleri yapılan, ek hastalığı olmayan ve çalışmaya katılmayı kabul eden 73 olgu psikiyatrik olarak değerlendirildi. **Bulgular:** Çalışmaya alınan 73 olgunun 29'u glisemik kontrolü iyi (HbA1c≤8.5 mg/dl), 44'ü glisemik kontrolü kötü (HbA1c> 8.5mg/dl) olarak kabul edildi. Glisemik kontrolü zayıf olan olgularda anne-baba eğitim düzeyi ve gelir düzeyi anlamlı olarak daha düşük, dikkat eksikliği ve hiperaktivite bozukluğu, majör depresif bozukluk, sosyal anksiyete bozukluğu ve psikopatoloji oranları anlamlı olarak daha yüksekti. **Sonuç:** Bu çalışmanın bulguları, glisemik kontrolü etkileyen bir çok faktör olduğunu ve glisemik kontrol ve psikopatolojiler arasında güçlü bir ilişki olduğunu ortaya koymuştur.

Anahtar Sözcükler: Tip 1 diabetes mellitus, çocuklar, ergenler, DEHB, psikiyatrik bozukluk

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INTRODUCTION

Type 1 diabetes mellitus (DM) is an endocrinological disease associated with insufficient insulin secretion. Type 1 DM is one of the most frequently diagnosed chronic diseases in childhood. Its incidence and prevalence varies by country. The prevalence in a study published in 2017 were found to be 0.75 /1000 in Turkey (1). The annual incidence in our region has been determined as 7.2 / 10 thousand (2). Children and adolescents with type 1 DM are under risk in terms of psychiatric diseases due to the psychological burden brought by diabetes compared to the healthy population. Studies have found 2-3 times more psychiatric illnesses than the healthy population. It is known that depression, anxiety disorder, and attention deficit hyperactivity disorder (ADHD) are the most common psychiatric diagnoses (3).

Since cognitive and emotional abilities are not yet grown in children and adolescents, it is difficult to cope with diabetes on their own (4). When comorbid psychiatric diseases are added to the chronic disease manifestation, it becomes more difficult to manage diabetes. Short and long-term complications such as severe hypoglycemia attacks, hyperglycemia, obesity and microvascular disorders can be seen frequently in these cases. Patients with severe hypoglycemia attacks, obesity, or growth-developmental retardation may have internalizing symptoms (such as guilt, insecurity, avoidance of social environments, sadness, eating problems) due to social anxiety. This may lead to psychiatric disorders such as depressive disorder and anxiety disorder. In addition, it was found that disorders such as depressive and anxiety disorders were more common in patients with poor glycemic control and the presence of them has been found to be associated with glycemic control (4, 5).

Attention deficit and hyperactivity disorder is one of the most common neurodevelopmental disorders of childhood. This disease causes loss of function in academic and social areas in individuals (6). Among the basic symptoms of ADHD, there are symptoms related to the attention area such as inability to organize daily tasks and activities, forget fulness in daily activities, avoiding and delaying tasks, and inadequate organizational skills. (6). This situation makes it difficult to manage a chronic disease. Recent studies have shown that metabolic controls of type 1 DM cases diagnosed with ADHD are worse than those without ADHD (7, 8).There is no study in the literature examining good and bad glycemic control separately.

In this study, it was aimed to investigate the effect of comorbid psychopathologies on glycemic control in children and adolescents with type 1 DM. However, investigating the effect of other sociodemographic factors on glycemic control is another aim of the study.

METHOD

Participants

The cases participating in this study were selected from the cases with type 1 DM who were followed up in Gazi Yaşargil Training and Research Hospital Pediatric Endocrinology Unit. The inclusion criteria were determined as; the patient and her family agreed to participate in the study, had been diagnosed with Type 1 DM for at least one year and came for a check-up at least 4 times a year, the cases were between the ages of 8 and 17, the patient and the parent were literate, had no obstacle to filling the forms, the patient were using insulin injection method in the treatment. In the study, 778 patients with type 1 DM who were followed up in the pediatric endocrinology clinic were screened. Of the 79 cases who accepted to participate in the study and met the criteria, 5 were excluded from the study because they filled the forms incompletely and 1 case had mental retardation clinically. The study was completed with 73 cases.

The procedure

Approval was obtained from Diyarbakır Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee for the study (ethics committee decision dated 15.03.2020, numbered 474). After the study approval was obtained, the patients who

came to the Pediatric Endocrinology unit for control were referred to the child and adolescent psychiatry clinic. A brief preliminary interview was made to the cases meeting the criteria and evaluated. The patients and the parents (at least one parent or both) dealing with the patient during the clinical follow up of diabetes were assessed. Semi-structured psychiatric interviews and scales were used.

Measurements

Sociodemographic data form: The form which is prepared by the researchers contained sociodemographic data (age, gender, education level, socioeconomic level, parental age, education level, etc.) and clinical information about type 1 DM (HbA1c, annual number of hospitalizations, number of intensive care admissions, etc.).

Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS Lifetime Version) (K-SADS-PL): It is a semi-structured diagnostic interview developed to describe the past and present psychopathologies of children and adolescents according to DSM-4 diagnostic criteria (9). K-SADS-PL is administered through interviews with parents and the child, and is finally evaluated based on information from all sources. The final decision on diagnosis is based on the clinician's opinion. This interview is applied between the ages of 6-18. The Turkish version was adapted to DSM-5 (10).

Children for Depression Inventory-CDI: Adapted from Beck depression scale. The Turkish validity and reliability study of the form consisting of 27 questions was conducted. Each item evaluates the child's last two weeks. The answers given are scored between 0 and 2. The cut-off point of the form, which can be used between the ages of 6-17, was determined as 19. Maximum 54 points can be obtained from CDI, which is a self-report scale. The higher the scores obtained on the scale, the higher the severity of depression. (11,12)

Screen for Child Anxiety-Related Emotional Disorders (SCARED): It was developed by Birmaher et al. for screening childhood anxiety disorders. Turkish validity and reliability of the scale was made by Çakmakçı. It has parent and child forms. It is accepted that a score of 25 and above in SCARED, which consists of 41 items in total, is a warning for anxiety disorder. The scale also includes somatic-panic, generalized anxiety, separation anxiety, social anxiety, and school phobia subscales (13,14).

Turgay Screening and Evaluation Scale for Behavioral Disorders in Children and Adolescents Based on DSM IV: Screening and Evaluation Scale for Conduct Disorders in Children and Adolescents Based on DSM-IV was prepared by Atilla Turgay by considering DSM-IV diagnostic criteria. With this scale, ADHD, ODD (oppositional defiant disorder) and CD (behavioral disorder), which are disruptive behavioral disorders, are screened and evaluated. In this scale consisting of 41 questions in total, 9 questions are for attention deficit, 9 questions for hyperactivity, 8 questions for ODD and 15 questions for CD screening and evaluation. Each question may be answered as "no answer, a little, more and too much" (15, 16).

HbA1c (Glycosylated Hemoglobin): It is a marker that provides information about the glycemic index in the last 3 months, used in routine controls. It also predicts the risk of complications due to diabetes. Its normal range is stated to be 4.3-5.8%. For diabetic cases, below 7.5% are considered good control, 7.5-8.5% range as moderate control, and over 8.5% as poor glycemic control (17). In our study, depending on the number of patients, good and moderate controls were evaluated as a single group, and HbA1c levels of 8.5 and below were included in this group.

Statistical analysis

The data of the cases included in the study were recorded in the SPSS 22.0 program. In the normality test, it was determined that the data were suitable for normal distribution. In the study, independent sample t test was used for nominal data and chi-square test was used for categorical data. P value less than 0.05 was considered significant.

RESULTS

Of the 73 cases participating in the study, 29 were accepted as to have good glycemic control (HbA1c% ≤8.5 mg / dl), and 44 as with poor glycemic control (HbA1c%> 8.5mg / dl). The mean age of the cases was 13.5 (SD ± 2.4, min: 8.9 max: 17.8), 53.4% (n = 39) were female and 46.6% (n = 34) were male. Sociodemographic and clinical information of the cases are shown in Table 1.

While there was no psychiatric diagnosis according to K-SADS and scale scores in 37% of the cases (n = 27), at least one psychiatric diagnosis was found in 63% (n = 46). The most detected diagnosis proportionally in the cases is ADHD (28.7%). The distribution of psychiatric diagnoses of the cases by groups was shown in Table 2. ADHD, major depressive disorder (MDD) and social anxiety disorder (SAD) were significantly higher in patients with poor glycemic control.

Regardless of the glycemic status, those with and without psychopathology were evaluated in terms of age distribution. The mean age of those with psychopathology (n = 46) was 13.6 (SD ± 2.4), and the mean age of those without psychopathology (n = 27) was 13.3 (SD ± 2.41). No significant difference was found in terms of age distribution (independent sample t test p <0.05).

Table 1. The sociodemographic-clinical characteristics of the cases

	Good glycemic control (n=29)	Poor glycemic control (n=44)	P
Gender	Male: 48.3 % (n=14) Female:51.7 % (n=15)	Male: 43.2% (n=19) Female: 64.1 % (n=25)	0.474*
Age (year)	13.2 (SD 2.6)	13.7 (SD 2.3)	0.326**
HbA1c(%)	7.24 (SD 0.7)	10.8 (SD 1.5)	0.001*
Number of annual hospitalization	0.4 (SD 0.7)	1.9 (SD 1.2)	0.001*
Number of hospitalizationin ICU	0.4 (SD 0.6)	0.7 (SD 0.8)	0.037*
Maternal age (y l)	40.3 (SD 6.9)	40.7 (SD 6.8)	0.805**
Paternal age (y l)	44.3 (SD 7.2)	44.4 (SD 6.6)	0.942**
Maternal educational status	literate: 20.7% (n = 6) primary school graduate: 31% (n = 9) secondary school graduate: 6.9% (n = 2) high school graduate: 24.1% (n = 7) university graduate: 17.2% (n = 5)	literate: 50% (n = 22) primary school graduate: 36.4% (n = 16) secondary school graduate: 9.3% (n = 4) high school graduate: 2.3% (n = 1) university graduate: 2.3% (n = 1)	0.002*
Paternal educational status	literate: 0% (n = 0) primary school graduate: 27.6% (n = 8) secondary school graduate: 10.3% (n = 3) high school graduate: 20.7% (n = 6) university graduate: 41.4% (n = 12)	literate: 20.5% (n = 9) primary school graduate: 47.7% (n = 21) secondary school graduate: 6.8% (n = 3) high school graduate: 18.2% (n = 8) university graduate: 6.8% (n = 3)	0.001*
Income level (TL)	2300 TL and below: 27.6% (n = 8) 2300 TL and 5000 TL: 48.3% (n = 14) Over 5000 TL): 24.1% (n = 7)	2300 TL and below: 79.5% (n = 35) 2300 TL and 5000 TL: 18.2% (n = 8) Over 5000 TL: 2.3% (n = 1)	0.001*
School attendance	Yes: 96.6% (n = 28) None: 3.4% (n = 1)	Yes: 88.6% (n = 39) None: 11.4% (n = 5)	0.228*

Table explanation: SD: standard deviation, * chi-square test p <0.05, ** independent sample t test p <0.05

Table 2. Distribution of psychiatric diagnoses of the cases

		Good glycemic control	Poor glycemic control	Total	P
ADHD	Yes	10.3% (n=3)	40.9% (n=18)	21	0.007
	None	89.7% (n=26)	59.1% (n=26)	52	
ODD	Yes	3.4% (n=1)	9.1 % (n=4)	5	0.642
	None	96.6% (n=28)	90.9 % (n=40)	68	
adjustment disorder	Yes	6.9% (n=2)	13.6% (n=6)	8	0.465
	None	93.1 % (n=27)	86.4 % (n=38)	65	
MDD	Yes	0 % (n=0)	18.2 % (n=8)	8	0.019
	None	100% (n=29)	81.8 % (n=36)	65	
SAD	Yes	6.9% (n=2)	34.1% (n=15)	17	0.010
	None	93.1% (n=27)	65.9 % (n=29)	56	
OCD	Yes	3.4 % (n=1)	0 % (n=0)	1	0.397
	None	96.6% (n=28)	100% (n=44)	72	
GAD	Yes	3.4% (n=1)	11.4% (n=5)	6	0.392
	None	96.6% (n=28)	88.6% (n=39)	67	
STUTTERING	Yes	3.4% (n=1)	0% (n=0)	1	0.397
	None	96.6 % (n=28)	100% (n=44)	72	
ENURESIS	Yes	0 % (n=0)	4.5% (n=2)	2	0.514
	None	100% (n=29)	95.5% (n=42)	71	
Psychopathology	Yes	34.5% (n=10)	81.8% (n=36)	46	0.001
	None	65.5% (n=19)	18.2% (n=8)	27	

ADHD: Attention deficit and hyperactivity disorder, ODD: Oppositional defiant disorder, MDD: Major depressive disorder, SAD: Social anxiety disorder, OCD: Obsessive -compulsive disorder, GAD: Generalized Anxiety disorder
chi-square test p <0.05

DISCUSSION

In this study, cases with good and poor glycemic control followed with type 1 DM diagnosis were compared in terms of sociodemographic and clinical characteristics and comorbid psychiatric disorders. The two groups were determined according to their HbA1c levels. The annual number of hospitalizations and the number of intensive care hospitalizations of these two groups are also statistically significantly different. Groups that were statistically similar in terms of gender and age distribution were found to be significantly different in terms of maternal education level, father education level and income levels (p <0.005). As expected, in cases with poor glycemic control, maternal education level, father education level and income level were found to be significantly lower. These findings are consistent with previous studies. Parents have an

important role in the management of type 1 diabetes. In a study evaluating glycemic control and maternal education levels, a significant positive correlation was found between maternal education level and glycemic control. However, unlike our study, no significant relationship was found between income level and glycemic control in the same study (18). In a study comparing two different ethnic groups; a positive relationship was found between income level and glycemic index (19). In a study conducted in 2011, it was shown that most of the patients who reach the good glycemic index, which is their goals in diabetes treatment, have a high education level of their mothers (20). In a study examining the relationship between the education level of mothers and fathers, profession and metabolic control in Iran; it was found that high education level of both parents was positive for metabolic control. In addition, in this study, it was seen that the mother's having a job was also effective on metabolic control (21). In a study evaluating 259 children and their families in Jordan in 2019, low maternal education level and low income level were found to be associated with poor metabolic control (22). Studies emphasize that family factor is also important in type 1 DM, as well as medical and technical factors. In terms of school attendance, no significant difference was found between the two groups. In our study, both the subjects in the good glycemic control group (96.6%) and the patients in the poor glycemic control group (88.6%) were mostly attending school. No study comparing good glycemic control with poor glycemic control in terms of school dropout could not be found in the literature. However, in a study compared with healthy controls, it was found that the diabetic group had higher rates of absenteeism and school dropout (23). In a study conducted abroad, it was shown that it is associated with more absenteeism in patients with poor glycemic control (24).

In our study, the rate of psychiatric comorbidity was found to be statistically significantly higher in cases with poor glycemic control ($p < 0.05$). It is known that the frequency of psychiatric disorders in Type 1 DM cases is higher than the general population. In a long follow-up study conducted in Sweden, cases of type 1 diabetes and their healthy siblings were compared in terms of psychiatric comorbidity and suicide attempts. It has been shown that the frequency of psychiatric illness and suicide attempts is higher in cases followed up to the age of 18 after being diagnosed with type 1 diabetes (25). Various studies have shown that patients with type 1 diabetes have a higher rate of psychiatric comorbidity in patients with poor glycemic levels and high HbA1c levels (29, 20). Likewise, it is known that patients with psychiatric comorbidity also have poor metabolic outcomes. In other words, in children and adolescents with type 1 DM; there is a two-way relationship between comorbid psychopathologies and glycemic control. However, adolescence is known as the period in which psychiatric disorders are most common. In a study evaluating risk factors in terms of psychiatric disorders, the age range of 10-15 was given as the most risky age range (17). In our study, when the age distribution of those with and without psychopathology independent of glycemic status was examined, no significant difference was found between the two groups ($p > 0.05$). However, the age range in this study is similar to our study.

In our study, ADHD, MDD and SF were statistically significantly higher in patients with poor glycemic control than in patients with good glycemic control ($p < 0.05$). No significant difference was found for other psychopathologies. In a study conducted in our country, HbA1c levels were found to be associated with ADHD and MDD diagnoses. In this study in which 60 cases and their parents were evaluated, it was observed that ODD and conduct disorder diagnoses were also predictors for HbA1c (8). In our study, there was no patient with conduct disorder. There was no significant difference between the two groups for the diagnosis of ODD. Similar to the results of the study, it was found that ADHD and MDD diagnoses were higher in patients with poor glycemic levels. In a study conducted in our country with 75 patients with type 1 DM, the most common diagnosis was ADHD followed by MDD, anxiety disorder, and eating disorder (27). In a retrospective study with a large sample, 56722 pediatric diabetes cases were screened, and those with and without ADHD were compared. Poor glycemic control (high HbA1c, insulin level, body mass index, systolic blood pressure) was found in the diabetic patient group with ADHD (7). The most important reason for the poor prognosis of the glycemic index is poor

compliance with treatment (such as timely use of insulin, diet). These results support the hypothesis of our study, as attention problems, decision-making and organizational skills, and executive functions will be affected in ADHD and other psychiatric disorders. In a study comparing diabetic patients and healthy controls, 184 patients aged 6-14 years were evaluated. Anxiety and depression rates were found to be higher in diabetic patients than in the healthy group. In addition, poor treatment compliance and poor glycemic control were significantly higher in these cases (26). In a study in which 150 adolescents were evaluated, a positive relationship was found between high depression and anxiety levels and high HbA1c levels. However, anxiety disorders are not differentiated (28). Although there are many studies in the literature that examine the depression and anxiety levels of diabetic patients, there are a limited number of studies evaluating social anxiety and other anxiety disorders. In a study comparing adolescents with diabetes between the ages of 12-15 with healthy controls, social anxiety disorder was found to be significantly higher in the diabetic group (29). Similarly, in a study conducted in 2002, it was determined that social anxiety affects HbA1c levels (30). Patients who are afraid of hypoglycemia may reduce the insulin dose or postpone insulin injection or exhibit overnutrition due to social concerns. This may explain poor glycemic control in social phobic cases.

The limitations of the study were the small sample size and the recruitment of cases for six months. Studies with long follow-up and large samples are needed in this field.

CONCLUSION

As a result, there are many factors affecting glycemic control. The most important of these factors are the family factor and the psychiatric status of the case. In our study, we found that parental education level and income level were lower, whereas the rate of psychopathology (ADHD, MDD, SF) was significantly higher in cases with poor glycemic control. Therefore, in addition to routine metabolic monitoring of diabetes, psychiatric support and economic support opportunities for the family should be reviewed if psychiatric follow-up of the child and adolescent is necessary.

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Klozapin serum düzeylerinin cinsiyet, sigara içme ve belirti şiddeti ile ilişkisi

Klozapin serum düzeylerinin cinsiyet, sigara içme ve belirti şiddeti ile ilişkisi

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ÖZET

Amaç: İlaç metabolizmasına etkisi olan değişkenler olan cinsiyet ve sigara içme durumunun klozapin serum düzeyenlerine etkisini psikotik bozukluğu olan hastalarda incelenmeyi planladık. **Yöntem:** Toplum Ruh Sağlığı Merkezimizde (TRSM) şizofreni ve ilişkili psikotik bozukluklar tanıları olan hastaların dosyaları klozapin serum düzeyleri ve klinik özellikler açısından geriye dönük olarak incelendi. Klozapin düzeyi bakıldığı zamanki belirti şiddeti, Kısa Psikiyatrik Değerlendirme Ölçeği (KPDÖ), UKU Yan Etki Değerlendirme Ölçeği (UKU) ile; işlevsellik Kişisel ve Sosyal Performans Ölçeği (BSPÖ) ile değerlendirildi. Sigara içme durumu ve cinsiyete göre, günlük klozapin dozu, klozapin düzeyi, UKU, KPDÖ ve BSPÖ sonuçları karşılaştırıldı. **Bulgular:** Cinsiyete göre klozapin dozları, klozapin düzeyleri, KPDÖ, UKU ve BSPÖ puanları karşılaştırıldığında anlamlı farklılık saptanmadı. Erkeklerde sigara içme oranı kadınlardan daha yüksekti (p=0,008). Sigara içen hastaların ortalama klozapin dozlarının 310,0 ± 146,53 mg/gün, içmeyenlerin 360,0 ± 142,98 mg/gün olduğu (p>0,05) görüldü. Sigara içen hastaların klozapin düzeyleri (384,4 ± 226,80 ng/mL), içmeyenlerden (835,6 ± 444,95 ng/mL) daha düşüktü (p=0,003). Klozapin düzeylerinin içilen sigara miktarı ile negatif korelasyonu, günlük klozapin dozu ile pozitif korelasyonu olduğu saptandı. Klinik ölçek puanlarından sadece KPDÖ'nün aktivasyon alt ölçeği ile klozapin düzeyleri arasında korelasyon saptandı. **Sonuç:** Klozapin düzeylerinin sigara içen hastalarda terapötik dozun altında, içmeyenlerde ise güvenli dozun üstünde olması olasılığı dikkate alınmalıdır.

Anahtar Kelimeler: Klozapin, şizofreni, serum düzeyi, sigara, cinsiyet, tedaviye direnç

SUMMARY

Objective: We planned to analyze the variations in clozapine levels with regard to gender and smoking which are variables with effects on drug metabolism in patients with psychotic disorders. **Method:** The records of patients with the diagnosis of schizophrenia and related psychotic disorders, who were attending the Community Mental Health Center (CMHC) were investigated retrospectively for clozapine serum levels and clinical features. Symptom severity at the time of the clozapine level detection was evaluated by Brief Psychiatric Rating Scale (BPRS), UKU side effects rating scale (UKU) and Personal and Social Performance Scale (PSP). Clozapine daily dose, clozapine levels, and the scores of BPRS, UKU and PSP scales were compared according to smoking habits and gender. **Results:** There was no significant difference in clozapine dose, clozapine level and the scales of BPRS, UKU and PSP for the comparison of gender. Smoking was more frequent in males (p=0.008). Mean clozapine doses of the smoking patients were 318.1±154.72 mg/day and non-smoking patients were 360.0±142.98 mg/day (p>0.05). Clozapine levels of smoking patients (384.4±226.80 ng/mL) were lower than non-smoking patients (835.6±444.95 ng/mL) (p=0.003). The only clinical scale score which was correlated with the clozapine levels was the activation subscale of BPRS. **Conclusion:** The possibility of clozapine levels being lower than the therapeutic dose in smoking patients and higher than safety limits in non-smoking patients should be taken into consideration.

Key Words: Clozapine, schizophrenia, serum levels, smoking, gender, treatment resistance

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GİRİŞ

Şizofreni; bireylerin günlük yaşam faaliyetlerini, işeğitim ve sosyal hayatlarını olumsuz yönde etkileyen, yaşam boyu yaygınlığı %0,30-%0,66 olan süreğen ve ilerleyici bir psikiyatrik bozukluktur (1,2,3). Tedavisinde; semptomların ve hastaneye yatışların azaltılması gibi klinik olarak iyileşmenin yanında, kişiler arası ilişkilerin geliştirilmesi, sosyalleşme becerilerinin, hobilere ve çalışmaya olan ilginin arttırılması da hedeflenmektedir (4). Klozapinin günümüzde tedaviye dirençli şizofrenide kullanılması Dünya Sağlık Örgütü tarafından önerilmektedir ve prolaktin düzeylerini yükseltmemesi, tardiv diskinezi gibi hareket bozukluklarına çok daha az neden olması, psikotik belirtiler ile birlikte suisidal davranışları azaltmadaki etkinliği avantajlarıdır (5,6,7). Agranülositoz gibi nadir fakat ciddi yan etkilerinin görülebilmesi sebebiyle tedavide ilk sırada önerilmemekte ve izlemde hemogram kontrollerinin yapılması zorunlu tutulmaktadır (8,9).

Klozapinin yarı ömrü 12-16 saattir ve hepatik sitokrom p450 enzim sistemleriyle iki ana metaboliti olan klozapine-N-oksit ve norklozapine metabolize olur (10). Terapötik konsantrasyonlarda asıl olarak Cyp1A2 tarafından metabolize edilirken daha yüksek konsantrasyonlarda Cyp3A4 ile metabolize edilir (11). Kandaki düzeyi ise yaş, cinsiyet, sigara alışkanlığı, birlikte kullanılan ilaçlar, kilo gibi bireysel farklılıklara ve özellikle de metabolize olduğu Cyp450 enzimlerinin aktivitelerinin genetik değişkenlik göstermesine bağlı olarak verilen doza göre oldukça değişkenlik gösterir (12,13,14). Klozapinin farmakokinetiğindeki bu geniş bireysel farklılıklar, klozapin kullanımını optimize etmek ve ciddi yan etkilerden kaçınmak için plazma seviyelerini izlemenin olası faydalarına dikkat çekmiştir (15,16). Yapılan çalışmalarda etkinliğin kan düzeyi ile ilişkili olabileceği ileri sürülmüştür (17-21). Elde edilen verilere göre, yan etkiler açısından en güvenilir olan optimum terapötik serum düzeyi aralığının 350-600ng/mL olduğu düşünülmektedir (22) ve bu ikinci kuşak antipsikotikler arasında en dar terapötik aralıktır (23). Yan etki açısından güvenli düzey üst sınırı ise 1000ng/mL olarak bildirilmiştir (22). Hastaların yaklaşık %10'unda klozapin düzeyinin >1000ng/mL saptandığı bir çalışmada ise hastalarda belirgin bir yan etkinin gözlemlenmediği bildirilmiştir ve henüz bu konunun yeterince anlaşılmadığını söylemek mümkündür (23,24).

Bütün bu veriler ışığında, hastanemize bağlı olarak hizmet vermekte olan Toplum Ruh Sağlığı Merkezi (TRSM) bünyesinde klozapin düzeyi bakılmış hastaların tıbbi kayıtlarını gözden geçirerek, birincil olarak serum düzeylerinde cinsiyet ve sigara içme durumuna göre görülen farklılıkları incelemeyi, ikincil olarak da ölçeklerle kaydedilmiş olan klinik şiddet parametreleri ile klozapin düzeyi arasında ilişki var ise bunu ortaya çıkarmayı planladık. Ulkemizde klozapin serum duzeylerinin tetkiki henuz yayginlasmamistir ve bu konuda nadir sayida calisma bulunmaktadir.

YÖNTEM

Çalışmamızda klozapin serum düzeylerini etkileyebilecek değişkenlerin ilaç düzeyine ve dolaylı olarak da klinik duruma etkisinin incelenmesi planlandı. Çalışmada hipotezlerimiz; erkek hastalarda klozapin düzeylerinin daha düşük olacağı, sigara içen hastalarda klozapin düzeylerinin daha düşük olacağı ve klozapin düzeyleri daha düşük olan hastalarda psikotik belirti şiddetinin daha yüksek olacağıydı.

Olgu örneklemini, İstanbul Bağcılar Meydan Toplum Ruh Sağlığı Merkezi'nde 01.09.2019-01.09.2020 tarihleri arasındaki 1 yıllık dönemde, klozapin tedavisi ile takip edilmekte olan şizofreni ve ilişkili diğer psikotik bozukluklar tanılı hastaların oluşturması planlandı. Klozapin kullanan hastalardan klozapin düzeyi tetkik edilenlerin mevcut tedavi sırasında ilk tespit edilen ilaç düzeylerinin cinsiyet, sigara içme durumu ve diğer klinik özelliklere göre nasıl değiştiği retrospektif olarak incelendi. Araştırmayı yapabilmek için etik kurulundan onayı alındı. Çalışmaya katılma kriterlerine uyan hastaların tıbbi kayıtları incelendi. Tıbbi kayıtlarda eksik ya da şüpheli olan veri olması durumunda hastanın kendisi, bakım vereni ya da danışmanı ile görüşülerek kontrol edildi.

Çalışmaya katılma kriterleri, psikiyatri ünitemize bağlı TRSM'de takipli olmak, şizofreni spektrumu ve kapsamındaki diğer psikotik bozukluklar tanısı ile klozapin kullanıyor olmak ve klozapin düzeyinin uygun koşullarda tetkik edilmiş olmasıydı. Çalışmadan dışlama kriterleri, bipolar bozukluk tanısı ile klozapin kullanıyor olmak ve klozapin başlanmasından önce konulmuş olan epilepsi ya da diğer nörolojik komorbidite bulunmasıydı. Klozapin kullanımı sonrası EEG'de tespit edilmiş

biyoelektriksel aksama hali nedeni ile antiepileptik kullanmakta olan hastalar dışlanmadı.

İlacın kandaki kararlı durum konsantrasyonunun ölçülmesi amaçlandığı için kan örnekleri, sabah saatlerinde, ilk dozdan önce, son dozdan 12 saat sonra alınmıştı. Klozapin düzeyi bakıldığı sıradaki klinik durumun değerlendirilmesinde, klozapin düzeyi bakıldığı gün tıbbi dosyalara kaydedilmiş olan klinik ölçeklerden yararlanıldı. Klozapin düzeylerinin tespitinde yüksek performanslı likid kromatografi (high performance liquid chromatography- HPLC) yöntemi kullanıldı, sonuçlar ng/mL ünitesi ile verildi. Ülkemizde klozapin üretimi için lisansı olan iki farklı firma olmasına karşın, çalışmanın yapıldığı dönemde eczanelerde ulaşılabilir olarak klozapinin tek bir farmasötik markası bulunmaktaydı ve bütün hastalar, ülkemizde bu dönemde mevcut olan aynı firma tarafından üretilen bu molekülü kullanmaktaydı. Bunlara ek olarak, kararlı durum konsantrasyonuna ulaşılmasının sağlanmış olması için, son doz artışı ya da azaltılışından itibaren en az 4 hafta geçmiş olması da çalışmamızda klozapin düzeyi tetkikinden önce olmazsa olmaz bir şart olarak uygulanmıştır.

Veri Toplama Araçları

Sosyodemografik veri formu: Hastaların demografik bilgileri, hastalık öyküsü ve tedavi ile ile ilgili verilerin kaydedildiği, her TRSM başvurusunda kontrol edilen ve güncellenen formdur.

Kısa Psikiyatrik Değerlendirme Ölçeği (KPDÖ): Temel olarak psikotik belirti şiddetini paunlayan yarı yapılandırılmış bir ölçek olmasının yanında depresyon, anksiyete ve ajitasyon ile ilgili puanlamaya da imkân verir (25,26).18 maddeden oluşan ölçek 0-6 arasında puanlanarak kullanılmış olup, çalışmamızda toplam puan üzerinden değerlendirme yapılmıştır.

UKU (Udvalg for Kliniske Undersøgelser) Yan Etki Derecelendirme Ölçeği (UKU): Psikolojik, nörolojik, otonom sistem ve genel yan etkileri değerlendirilir. 48 maddeden oluşur. Her bir madde 4 seçenekli olup "0" yan etki olmadığını, "3" ise şiddetli olduğunu gösterir (27). Ülkemizde yapılan çalışmada değerlendiriciler arası güvenilirlik korelasyon katsayısının Türkçe çevirisi için 0,76 ($p<0,001$) olduğu bildirilmiştir (28).

Bireysel ve Sosyal Performans Ölçeği (BSPÖ): Şizofreni gibi ağır ruhsal bozukluklarda işlevselliğin global değerlendirilmesi için geliştirilmiş bir ölçek olup, Türkçe geçerlilik ve güvenilirlik çalışması şizofreni ve bipolar bozukluk tanılı hastalarda yapılmıştır (29, 30). Dört farklı alandaki işlevselliği değerlendirir: 1-sosyal açıdan yararlı aktiviteler, çalışma ve öğrenim görmek, 2-kişisel ve sosyal ilişkiler, 3-öz-bakım, 4- rahatsız edici ve agresif davranışlar. Sonuçta ise toplam puan üzerinden yorumlanır ve hasta ile ilgili genel bir izlenim sunar. Sosyal aktiviteler, çalışma ve öğrenim 0-100 arası puanlanır, 100 en iyi işlevsellik düzeyini gösterir, 71-100 arası hafif güçlükler, 31-70 arası değişen düzeydeki yetersizlikler, 0-30 arası ise yoğun destek ve gözlem gerektiren kötü işlevsellik olarak derecelendirilir.

İstatistiksel Analiz

Çalışma örnekleminin sosyodemografik ve klinik özellikleri tanımlayıcı istatistiklerle, normal dağılıma uygunluk SapiroWilk testi ile değerlendirildi. Normal dağılıma uyan sayısal veriler ortalama ve standart sapma ile, normal dağılıma uymayan veriler ise median ve IQR(interquartile range) ile incelendi. İkili grup karşılaştırmasında normal dağılım gösteren sayısal verilerde Student-t testi, normal dağılmayan verilerde Mann-Whitney U testi ve kategorik verilerde Kikare testi yapıldı. Sigara içme ve cinsiyet değişkenleri sabit değişken olarak alınarak, günlük klozapin dozu, klozapin serum düzeyi, UKU, KPDÖ, BSPÖ sonuçları Spearman'ın veya Pearson'ın bağıntı analizi ile analiz edildi.

BULGULAR

Çalışmamızın kaynaklandığı, hastanemize bağlı TRSM'de iki uçlu bozukluk, şizofreni ve bu iki bozukluğun spektrumu dahilinde bulunan tanıları olan 466 hasta takip edilmekteydi. Bu hastaların 197'si (%42,3) iki uçlu bozukluk, 171'i (%36,7) şizofreni açılımı kapsamında bulunan diğer psikotik bozukluklar, 85'i (%18,2) şizofreni, 13'ü (%2,8) ise şizoafektif bozukluk tanısı ile takip edilmekteydi.

Klozapin kullanan toplam 50 hasta bulunmaktaydı. Değerlendirilen hastalarda klozapin kullanım süresinin minimum 6 ay, maksimum 84 ay, ortalama 34,6 ± 16,77 ay olduğu görülmüştür. Bu hastalardan 20'si şizofreni tanısıyla, 23'ü diğer psikotik bozukluklar tanısıyla, 4'ü şizoafektif bozukluk tanısıyla, 3'ü ise iki uçlu bozukluk tanısıyla takip

edilmekteydi. Klozapin kullanan hastaların 35'inin klozapin düzeyi tetkik edilmişti. Klozapin düzeyi bakılmış olan 2 hasta psikotik bozukluk öncesinde konulmuş epilepsi tanısı bulunduğundan, 1 hasta ise iki uçlu bozukluk tanısı ile klozapin kullanmakta olduğundan dışlama kriterleri dolayısıyla çıkarıldıktan sonra, şizofreni ve diğer psikotik bozukluklar tanısı ile klozapin kullanmakta olan ve klozapin düzeyi tetkik edilmiş olan 32 hastanın kayıtları, analizimize temel oluşturdu.

Çalışmamızdaki hastaların ortalama hastalık başlangıç yaşı 23,8 ± 6,63; hastalık süresi 11,9 ±6,96 (yıl); yaşam boyu hastaneye yatış sayıları ise 5 ± 5,75 olarak saptandı. 4 hastanın (%12,5) son 6 ay içinde hospitalizasyonu olmuştu. Hastaların sosyodemografik ve klinik özellikleri ile klozapin düzeylerinin tetkik edilme nedenleri Tablo 1'de gösterilmiştir.

Hasta kayıtlarının geriye dönük incelenmesinden oluşan naturalistik çalışmamızda, hastalar klozapin dışında ilaçlar da kullanmaktaydılar. Buna göre valproik asit (n=12), paliperidon (n=7), sertralin (n=6), amitriptilin (n=6), aripiprazol (n=5), zuklopentiksol (n=5), haloperidol (n=4), biperiden (n=4), ketiyapin (n=3), lityum (n=3), risperidon (n=1), mirtazapin (n=1), modafinil (n=1), propranolol (n=1), lorazepam (n=1) kullanmakta olan hastalar mevcuttu.

Tablo 1. Klozapin Düzeyi Bakılan Şizofreni Spektrumundaki Hastaların Demografik ve Klinik Özellikleri

Demografik Özellikler (N=32)		**N**	**%**
Cinsiyet	Kadın	14	43.8
	Erkek	18	56.3
Medeni hal	Bekar	21	65.6
	Evli	6	18.8
	Boşanmış	3	9.4
	Dul	2	6.3
Eğitim	Yok	2	6.3
	Okuryazar	3	9.4
	İlkokul	19	59.4
	Lise	5	15.6
	Üniversite	3	9.4
Mesleki İşlevsellik	Çalışmıyor	28	87.5
	Çalışıyor	4	12.5
Klinik Özellikler		**Ortalama**	**Standart Sapma**
Yaş		35.7	9.10
Hastalık başlangıç yaşı		23.8	6.63
Hastalık süresi (yıl)		11.9	6.96
Yaşam boyu hastaneye yatış		5.0	5.75
Günlük tüketilen sigara adedi (sigara içenlerde)		27.36	16.22
Klozapin kullanımı sırasındaki olaylar		**N**	**%**
Son 6 ay içinde hastaneye yatış	Var	4	12.5
	Yok	28	87.5
Klozapin düzeyinin tetkik edilme nedeni	Tedaviye yetersiz yanıt	18	56.3
	Yan etkiler	4	12.5
	İlaç uyumu kontrolü	10	31.3

Cinsiyete göre yapılan karşılaştırmalarda ortalama klozapin dozları için kadınlar ve erkekler arasında anlamlı farklılık saptanmadı. Klozapin düzeyi ise kadınlarda 683,8 ± 454,92 mg/gün, erkeklerde 423,0 ± 230,00 mg/gün olarak saptandı, ortalama değerin kadınlarda daha yüksek olmasına karşın aradaki fark istatistiksel olarak anlamlı değildi. KPDÖ, UKU ve BSPÖ puanları için kadınlar ve erkekler arasında anlamlı fark saptanmadı. Sigara içen 22 hastanın 16'sı (%72,7) erkekti. Sigara içmeyen 10 hastanın 8'i (%80) kadındı. Kadın ve erkekler arasında sigara içme durumuna göre anlamlı farklılık vardı (p=0,008). Kadın ve erkekler arasındaki sigara içme durumuna göre karşılaştırma yapılırken günde 10 adetten az sigara kullanımı olan (günde 2 ve 5 adet sigara kullanan iki hasta) analizlerden çıkarıldığında da anlamlı farklılık vardı (p=0,004). Ayrıca kadın ve erkeklerde sigara içme durumu ve miktarı arasındaki farklar göz önüne alındığında sigaranın cinsiyet anlamında klozapin düzeyine etkisini değiştirebileceği düşünülmüş ancak kovaryasyon analizi için gerekli olan hata varyanslarının eşit dağılımı ilkesi sağlanamadığından (Levene testi p=0.041) ileri analizlerin yapılması mümkün olmamıştır. Cinsiyete göre karşılaştırmalar Tablo 2'te gösterilmiştir.

Sigara içmeye göre yapılan karşılaştırmalar, minimal yani günde 10 adetten az sigara kullanımı olan hastalar (günde 2 ve 5 adet sigara kullanan iki hasta), karıştırıcı rolü olabileceğinden analizden çıkarılarak yapıldı ve klozapin dozu sigara içen-

Tablo 2. Cinsiyete Göre Klozapin Dozu ve Klinik Özelliklerin Karşılaştırılması

		Kadın (N=14)	**Erkek (N=18)**		Z
		Ort. ± S.S.	Ort. ± S.S.		
Klozapin kullanım süresi (ay)		37.0 ± 19.61	32.7 ± 14.51	0.779*	-0.305
Klozapin günlük dozu (mg)		335.7 ± 163.42	327.7 ± 143.71	1.0*	0.020
Klozapin düzeyi		683.8 ± 454.92	423.0 ± 230.00	0.077*	-1.786
Belirti şiddeti (KPDÖ) toplam puanı		23.3 ± 11.42	19.7 ± 10.76	0.419*	-0.818
Yan etki (UKU) toplam puanı		10.0 ± 6.36	8.4 ± 3.41	0.587*	-0.581
İşlevsellik (BSPÖ) toplam puanı		55.0 ± 17.06	53.5 ± 17.14	0.750*	-0.324
Günlük Sigara Miktarı		11.2 ± 19.30	24.7 ± 15.72	**0,011***	-2.555
		N (%)	**N (%)**		
Sigara İçme	Var	6 (27.3)	16 (72.7)	**0,008#**	-
	Yok	8 (80.0)	2 (20.0)		

KPDÖ: Kısa Psikiyatrik Değerlendirme Ölçeği. BSPÖ: Bireysel ve Sosyal Performans Ölçeği. UKU: Udvalg for Kliniske Undersogelser Yan Etki Derecelendirme Ölçeği.
*: Mann – Whitney U Testi , Z: Standardize test istatistiği. #: Fisher's Exact Testi

Tablo 3. Sigara İçme Durumuna Göre Klozapin Dozu ve Klinik Özelliklerin Karşılaştırılması

	Sigara İçme		p	Z
	Var* (N=20)	Yok (N=10)		
	Ort. ± S.S.	Ort. ± S.S.		
Klozapin kullanım süresi (ay)	33.4 ± 15.37	37.7 ± 21.04	0.912	-0.110
Klozapin günlük dozu (mg/gün)	310.0 ± 146.53	360.0 ± 142.98	0.272	-1.098
Klozapin düzeyi (ng/mL)	384.4 ± 226.80	835.6 ± 444.95	**0,003**	**-2,838**
Belirti şiddeti (KPDÖ)	19.8 ± 10.39	21.7 ± 10.84	0.559	-0.617
Yan etki (UKU)	7.8 ± 4.64	9.9 ± 3.54	0.131	-1.523
İşlevsellik (BSPÖ)	54.1 ± 17.81	54.7 ± 16.58	0.914	-0.132

KPDÖ: Kısa Psikiyatrik Değerlendirme Ölçeği. BSPÖ: Bireysel ve Sosyal Performans Ölçeği

UKU: Udvalg for Kliniske Undersogelser Yan Etki Derecelendirme Ölçeği

p: Mann – Whitney U Testi anlamlılık değeri. Z: Standardize test istatistiği

*: Minimal (Günde 2'ye günde 5 adet) sigara kullanımı olan 2 hasta analizden çıkarılmıştır.

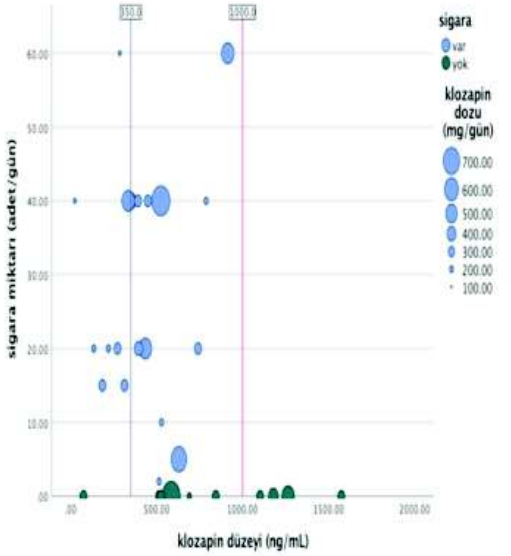
lerde 310,0 ± 146,53 mg/gün, içmeyenlerde 360,0 ± 142,98 mg/gün olarak saptandı, aradaki fark istatistiksel olarak anlamlı değildi (p>0,05). Klozapin düzeyi sigara içenlerde (384,4 ± 226,80) içmeyenlere göre (835,6 ± 444,95) anlamlı olarak daha düşüktü (p=0,003). Sigara içme durumunda göre KPDÖ, UKU ve BSPÖ puanları arasında anlamlı farklılık saptanmadı. Sigara içme durumuna göre olan karşılaştırmalar Tablo 3'te gösterilmiştir.

11 hastada klozapin düzeyinin önerilen terapötik düzeyin (350 ng/mL) altında, 4 hastada ise toksik sınırın (1000 ng/mL) üstünde olduğu saptandı. Klozapin düzeyi sigara içmeyen hastaların sadece birinde terapötik düzeyin altında çıkmıştır. Klozapin düzeyi 75 ng/mL çıkan bu hastanın düzey düşük çıktıktan sonra yapılan görüşmede düzenli ilaç kullanımında sorun olduğu tespit edilmiştir. Klozapin düzeyi toksik sınırın üstünde olan hastaların (4 hasta) hiçbirinin sigara kullanımı yoktur. Sigara kullanan 22 hastanın 10'unda klozapin düzeyinin terapötik sınırın altında olduğu görülmüştür. Saptanmış olan klozapin düzeyleri grafikte işaretli olarak Şekil 1'de gösterilmiştir.

İlaç düzeyi tetkik nedeni yetersiz yanıt olan 18 hastanın 7'sinde klozapin düzeyi terapötik düzeyin altındaydı, 3'ünde ise güvenli düzeyin üzerindeydi. İlaç düzeyi tetkik nedeni yan etki olan 4 hastanın hepsinde klozapin düzeyi terapötik sınırlar içindeydi. Tetkik nedeni ilaç uyumu kontrolü olan 10 hastanın 4'ünde klozapin düzeyi terapötik düzeyin altında, bir hastada ise güvenli düzeyin üzerindeydi.

Klozapin düzeyinin ve Sigara Kullanımının klinik

Şekil 1. Sigara içme miktarına göre klozapin düzeylerinin grafiği



Bir hastaya ait günlük sigara içme miktarı (y ekseni) ve klozapin düzeyine (x ekseni) göre konumlanmış olan her daire bir hastayı temsil etmektedir (Scatter Plot). Dairelerin çaplarının büyüklüğü günlük klozapin dozu ile orantılıdır. Klozapin düzeyi için terapötik düzeyin alt sınırı 350 ng/mL, toksik düzey sınırı 1000 ng/mL referans çizgileri ile işaretlenmiştir.

parametreler ile ilişkisi, sayısal dağılıma uygun olan Spearman korelasyon analizi ile incelendi ve klozapin düzeyi ile KPDÖ puanları, UKU puanları ya da BSPÖ puanları arasında anlamlı korelasyon saptanmadı (p>0,05). Klozapin düzeyi ve sigara kullanım miktarı ve arasında negatif yönde anlamlı ilişki saptandı (rho = -0,382; p = 0.03). Klozapin düzeyi ve klozapin dozu arasında pozitif yönde anlamlı ilişki saptandı (rho = 0,412; p = 0.01) Klozapin Dozu ve KPDÖ aktivasyon alt ölçeği arasında ise pozitif yönde anlamlı bir ilişki saptandı (rho = 0,412; p = 0.01). Korelasyon analizi sonuçları tablo 4'te gösterilmiştir.

TARTIŞMA

Çoğunluğu sürekli bir işi olmayan, ilkokul mezunu olan, ortalama hastalık süresinin 11,9 yıl ve hastaneye yatış sayısının 5 olduğu çalışma örneklemimizde, sigara içen hastalarda ortalama klozapin düzeylerinin daha düşük olduğu ve terapötik doz altında klozapin düzeyinin sigara içen hastalarda daha sık olduğu sonucu önem arz etmektedir. Çalışmamızdaki sonuçlar, rutin klinik pratik sırasında gerekli olduğu takdirde klozapin düzeyi bakılmış olan hastaların sonuçlarıydı, buna göre klozapin düzeyinin tetkik edilme nedenleri de heterojendi. Tedaviye yetersiz yanıt (n=18) başlıca neden olmakla birlikte bunu ilaç uyumunun kontrol edilmesi (n=10) niyeti ile tetkik yapılan hastalar izlemekteydi, 4 hastada da yan etkiler

Tablo 4. Klozapin Düzeyi, Dozu, Kullanım Süresi ve Sigara Miktarı ile Klinik Ölçek Puanlarının Karşılaştırmasında Spearman (rho) Korelasyon Değerleri

		Sigara Miktarı	Klozapin Süresi	Klozapin Dozu	Klozapin Düzeyi
Sigara miktarı		1.000			
Klozapin kullanım süresi		-.006	1.000		
Klozapin dozu		-.091	.065	1.000	
Klozapin düzeyi		-,382*	-.023	,412*	1.000
Yan Etkiler (UKU)	Ruhsal	-.237	-.013	-.115	-.028
	Nörolojik	-.269	.078	.007	.308
	Otonomik	-.182	-.094	.212	.157
	Kilo artışı	.274	-.103	-.058	-.334
	Cinsel	-.084	.126	-.184	-.171
	Diğer	.302	-.259	.007	-.175
	Toplam	-.247	-.067	.072	.087
Belirti Şiddeti (KPDÖ)	Duygulanım	.310	-.002	.147	.047
	Pozitif belirtiler	-.239	-.096	.263	.192
	Negatif belirtiler	-.104	-.350	-.262	-.024
	Direnç	-.194	.008	.076	.185
	Aktivasyon	-.068	.069	,412*	.198
	Toplam	-.069	-.074	.146	.048
İşlevsellik (BSPÖ)		-.148	-.192	.088	.015

KPDÖ: Kısa Psikiyatrik Değerlendirme Ölçeği. BSPÖ: Bireysel ve Sosyal Performans Ölçeği. UKU: Udvalg for Kliniske Undersogelser Yan Etki Derecelendirme Ölçeği. *: tek yönlü anlamlılık p<0.05

nedeni ile klozapin düzeyinin tetkiki yapılmıştı. 11 hastada klozapin düzeyinin önerilen terapötik aralığın altında olduğu, 4 hastada ise güvenli aralığın üstünde olduğu saptanmıştı. Klozapin yeni başlandığında veya doz değişikliği yapılacağı zamanlarda rutin olarak kan düzeyinin bakılmasını öneren uzmanlar mevcuttur (22). Bunun dışında hastanın tedaviye uyumundan emin olunamaması, beklenilen klinik düzelmenin olmaması, sürdürüm tedavisi altında relaps olması, etkileşim olabileceği düşünülen farklı bir ilaç başlanılmış olması, yan etki gözlenmesi, hastanın farklı etnik kökenli olması, kilonun çok düşük veya çok yüksek olduğu durumlar, hastanın gebe veya emziren olması, akut veya kronik enfeksiyonların eşlik etmesi, emilimi etkileyecek sindirim sistemi hastalarının eşlik ettiği durumların olması, hastanın yaşlı (>65yaş) veya çocuk olması gibi özel durumlarda da kan düzeyinin ölçülmesi önerilmektedir (22). Çalışmamızda klozapin düzeyi tetkikinin, düzeyi terapötik aralığın dışında olan hastaların ilaç dozlarının düzenlenebilmesine imkân verdiği görülmektedir.

Analizlerimizde klozapin düzeyleri ile KPDÖ ile ölçülmüş olan pozitif veya negatif belirti şiddeti, Afektif belirtiler, direnç ve toplam belirti şiddeti arasında korelasyon saptamadık. KPDÖ'nün sadece aktivasyon alt ölçeği ile klozapin düzeyleri arasında pozitif korelasyon vardı. Klozapin düzeyi ile yan etki şiddeti (UKU) arasında da korelasyon yoktu, bu sonuç hem toplam puanlar için hem de UKU'nun alt ölçekleri için geçerliydi. Yazında klozapin düzeyleri ile etkinliği ve yan etkiler arasında anlamlı bir ilişki saptanamamış olan çalışmalar mevcuttur (20,31,32). Antipsikotiklerin kandaki düzeylerinin beyindeki konsantrasyonu ile korele olduğu gösterilmiş olsa da (27), kan-beyin bariyerini yalnızca serbest maddelerin geçebildiği ve klozapinin plazma proteinlerine bağlanma oranının %50-60 olması göz önüne alındığında, plazmadaki ilaç konsantrasyonu direkt olarak beyindeki konsantrasyonu yansıtmıyor olabilir (32). Serebrospinal sıvıda klozapin düzeyinin ölçüldüğü tek bir çalışma vardır ve bu çalışmada incelenen 9 hastanın serum klozapin düzeyi ile serebrospinal sıvıdaki düzeyi arasında korelasyon saptanmamıştır (32,33). Elde edilen çelişkili sonuçlar sebebiyle klozapin düzeyinin ölçülmesinin klinik anlamda kullanışlı ve gerekli olmadığını düşünen araştırmacılar vardır (34,35). Klozapin düzeyindeki %40 düşüşü, relaps olasılığında artış ile ilişkili bulan bir çalışmada relaps KPDÖ'nun psikoz itemlerinde 3 puan veya daha çok artış olarak tanımlanmıştır (36). Bu tür dizaynı olan çalışmalarda hastaların remisyon halindeki bazal ölçümlerinin olması, sonuçları yorumlamak için önem arz etmektedir: Ellison ve arkadaşları, akut alevlenme nedeni ile hospitalize edilen hastalarında klozapin düzeylerinin daha yüksek olduğunu tespit etmişlerdir, bu duruma, hospitalizasyon öncesindeki akut alevlenmenin başlangıç döneminde, tedavi amaçlı olarak klozapin düzeylerinin artırılmış olması ile açıklık getirmişlerdir (37). Bizim çalışmamız için de psikomotor aktivasyonu aşırı yüksek olan hastalarda, klinik durum nedeni ile klozapin dozlarının yüksek tutulması ve bu nedenle klozapin düzeyleri ile aktivasyon alt ölçeği arasında pozitif korelasyon saptanması, olası bir açıklamadır. Çalışmamızdaki hastaların remisyon halindeki klozapin düzeylerini rutin olarak ölçmemiş olduğumuzdan, klinik ölçek puanları ve klozapin düzeylerinin ilişkisini belirlemekte kısıtlılığımız mevcuttur. Hastalar remisyon halinde iken klozapin düzeylerinin ölçümü, gelecekteki akut alevlenme döneminde referans noktası olarak kullanılabileceğinden oldukça değerlidir (38).

Yanıt alınamayan hastalarda klozapin dozunu, klozapin düzeylerini tetkik etmeksizin gereğinden fazla artırmak, başta antikolinerjik yan etkilerde artış olmak üzere yarardan çok zarar ile sonuçlan-

abilir. Liu ve arkadaşları, 700 ng/mL'nin üzerindeki klozapin düzeylerinde yanıt oranının artmaya devam etmediğini bildirilmişlerdir (39). 500-600 mg/gün'ü geçen yüksek dozlarda epileptik nöbet riskinin arttığı bilinmektedir (40). Buna karşın istisnai durumlar ile karşılaşılabilmektedir: Klozapin düzeyinin 700 mg/gün dozu ile 357-986 ng/mL aralığında seyrettiği bir hastada, rutin kontrol sırasında tetkik edilen kan düzeyi 1192 ng/mL olarak saptandığı, fakat hastada herhangi bir toksisite belirtisi gözlenmediği, sonrasında klozapin dozu 50 mg azaltıldığında ise bunu hastaneye yatış ile sonuçlanan akut alevlenmenin izlediği bildirilmiştir (41). Remington ve arkadaşları, 1960-2011 arasındaki 70 makaleyi inceledikleri derlemelerinde, klozapin düzeyini terapötik üst eşik değerinin (iki farklı çalışmada 600 ve 838 ng/mL olarak bildirilmiş) daha üzerine çıkarmanın klinik yanıtta düzelmeye neden olmadığı ve klozapin düzeyinin, bizim çalışmamızda da olduğu gibi klinik yanıt ya da yan etkilerden çok klozapin dozu ile ilişkili olduğu sonucuna varmışlardır (40).

Klozapin düzeyinin tetkiki, klinik karar vermede arada kalınan durumlarda klinisyen için yol gösterici olabilir. Örneğin, bazı durumlarda hem hasta ısrarla ilaç dozunun azaltılmasını istemekte, hem de psikotik belirtiler halen belirgin biçimde varlığını sürdürmektedir. Böyle olgularda, klozapin düzeyi tetkiki ile terapötik düzeyin mevcut olduğu görüldüğünde, klozapin dışı ya da klozapine ek tedavi stratejilerine geçiş için yönlendirici olabilir, klozapin düzeyi terapötik düzeyin çok altında ise, hastanın yararı için dozun daha da artırılmasına ihtiyaç olduğu görülür ve bu durum ilaç düzeyi sonuçları da sunularak hasta ile tartışılabilir. Yetersiz yanıt ya da ilaç uyumu kontrolü nedeni ile yaptığımız ilaç düzeyi tetkiklerinde, terapötik aralığın altında düzeylere rastladığımız gibi, klozapin düzeyinin güvenli sınırın üzerinde olduğu hastaları da saptamış olmamız, klozapin düzeyi tetkikinin klinik uygulamada işe yararlığında dair bir göstergedir.

Çalışmamızda klozapin düzeylerinin kadın ve erkeklerde benzer olduğunu gördük. Her iki grupta da klozapin günlük dozları birbirine çok yakındı. Ortalama klozapin düzeyi ise kadınlarda 683,8 ng/mL erkeklerde 423,0 ng/mL olmasına karşın, aradaki fark istatistiksel anlamlılığa ulaşmadı ($p>0,05$). Klozapin serum düzeyi üzerinde cinsiyetin etkili olduğunu gösteren birçok çalışmada, doz ve kilo ayarlanmasından sonra bile kadınlarda daha yüksek düzeyler saptanmıştır (23,42-47). Bu durum, kadınlarda, klozapin klirensinin (48) ve cyp1A2 aktivitesinin daha düşük olması ile ilişkili olabilir (49,50,51). Vücuttaki yağ oranının ilaç plazma düzeyi üzerine etkisi de göz önünde bulundurulmalıdır. Daha yüksek yağ hacmi, daha yüksek dağılım hacmiyle ilişkilendirilebilir ve dolayısıyla kadınlarda klozapin yarılanma ömrü artmıştır (49,52). Bu, klozapinin tepe ve en düşük konsantrasyonları arasındaki farkı düşürür ve kadınlarda en düşük klozapin düzeyi erkeklere oranlara daha yüksek olurken, kararlı durum konsantrasyonlarının benzer seviyede olması ile sonuçlanabilir (49). Yapılan sistematik bir incelemeye göre kadınlar, erkeklerdeki klozapin kararlı durum konsantrasyonu/günlük doz oranının 0,84 üne sahip olma eğilimindedir (53). Fakat cinsiyet ve klozapin düzeyi arasında anlamlı bir ilişkinin saptanmadığı çalışmalar da mevcuttur (23,24,54-56). Ayrıca bazı çalışmalarda cyp1A2 aktivitesinin cinsiyetler arasındaki farklılığı doğrulanamamıştır (57). Kadınlarda ve erkeklerde klozapin dozlarının birbirine çok yakın olmasına karşın, cinsiyete göre klozapin düzeyleri arasında anlamlı fark saptamamış olmamıza, örneklemimizin yeterince büyük olmaması yol açmış olabilir. Buna ek olarak, klozapin düzeyi tetkik edilmiş olan kadınlarda sigara içme oranının erkeklerden daha düşük olması, cinsiyete dayalı farkı gölgeleyici rol oynamıştır.

Şizofreni tanılı hastalarda sigara içme oranının yüksek olduğu bilinmektedir (58). Bizim örneklemimizde de sigara içen hastalar çoğunluktaydı (%68,8) ve erkek hastaların %88,9'u sigara içmekte iken bu oran kadınlarda %42,9'du, aradaki fark istatistiksel olarak anlamlıydı ($p=0,005$). Sigara içen hastaların klozapin serum düzeylerinin daha düşük olduğunu gördüğümüz çalışmamızdaki 13 hastada klozapin düzeyi terapötik düzey olarak önerilen 350-600ng/mL aralığının altındaydı, bu hastaların 10'u sigara içen hastalardı. 4 hastada ise klozapin düzeyi güvenli üst sınır olan 1000ng/mL'nin üzerindeydi, bu hastaların arasında ise sigara içen yoktu. Sigara içme alışkanlıklarındaki bireysel farklılıklar ve sigaranın cyp1A2 enziminin potent bir indükleyicisi olması sigara tüketiminin klozapinin farmakokinetiği üzerine yapılan çalışmaların önemini arttırmıştır (59). Klozapinin kandaki düzeyinin, sigaradaki aro-

matik polisiklik hidrokarbonların cyp 1A2 enzimini indüklemesi yoluyla belirgin şekilde azaldığını gösteren birçok çalışma mevcuttur (23,60-70). Ayrıca sigaranın bırakılması sonrasında klozapin toksisitesi bildirilen vakalar da vardır ve hastanın sigarayı bırakmasından sonra da klozapin düzeyinin tetkik edilmesi önerilmektedir (66,71,72). Klozapin metabolizmasının maksimum indüksiyonu için günlük 7 ile 12 adet arasında sigara tüketiminin yeterli olabileceği düşünülmektedir (64). Sigaranın gastrointestinal sistemdeki nikotinik reseptörler aracılığıyla ilaç emilimini etkileyebileceğine yönelik varsayımlar olmakla birlikte (73,74), nikotin replasman tedavisinin kandaki klozapin düzeyini etkilemediğini gösteren çalışmalar da bulunmaktadır (61,62,69). Belirtmek gereklidir ki; çalışmamızda cinsiyete göre klozapin düzeyleri arasında anlamlı fark olmamasına karşın, erkeklerde ortalama klozapin düzeyini daha düşük saptamış olmamız ve sigara içenlerin arasında erkeklerin oranının daha yüksek olması, sigara içenlerde düşük bulduğumuz klozapin düzeylerinde, erkek cinsiyetin de katkısı olabileceğini düşündürmektedir.

Plazma klozapin düzeyi ve 'kandaki konsantrasyon/verilen doz' oranı hastaya özgü tedavi stratejilerini belirleme konusunda hekime yardımcı olabilir (75,76). Klozapin düzeyinin ölçülmesi başka hastalıkların eşlik ettiği, hepatik ve renal fonksiyonların bozulduğu durumlarda, gebelik, sigara bırakma gibi hallerde ve özellikle yüksek dozların (>600mg/gün) kullanıldığı durumlarda hastayı toksik etkilerden korumak ve tedavi sürecinin olumlu ilerlemesini sağlamak açısından avantaj sağlar (63,77-81). Enfeksiyon durumlarında klozapin düzeyinin ölçülmesinin önemi üzerinde durulmuş, artan sitokin salınımının p450 aktivitesini inhibe etmesi sonucunda, klozapinin kanda toksik düzeylere ulaşabildiği bildirilmiştir (81-83). Doz artırımında klozapin ile indüklenebilen epileptik nöbetleri önleme konusunda EEG ile birlikte yapılan düzey ölçümlerinin faydalı olabileceği önerilmiştir (77,84).

İlaç uyumunun kontrolü, tedaviye yetersiz yanıtın ardından tetkik nedenleri arasında sıklık olarak ikinci sıradaydı. Şizofreni tanılı hastalarda klozapin ile yapılan sürdürüm tedavisi sırasında, özellikle kötü ilaç uyumu başta olmak üzere, kandaki klozapin düzeyinin çeşitli sebeplerle %40'ı kadar (85) ya da 200-250 ng/mL'nin altına düşmesi (86,87) psikotik bulguların yinelemesi ile ilişkili bulunmuştur (88). Bununla ilgili olarak idame tedavi sırasında klozapin düzeyinin takip edilmesi tedavi uyumsuzluğu olan hastaların tespit edilmesinde (28,74), relapsların ve hastaneye yatışların öngörülerek önlemesinde faydalı olabilir (63,73,88). Çalışmamızdaki bir hastada tetkik sonrasında klozapin düzeyinin beklenenin çok altında (24,5 ng/mL) gelmesi üzerine yapılan yüzleştirmede, ilaç uyumunda ciddi sorun olduğu ve hastanın önerilenden farklı olarak kendi müdahalesi ile 50 mg/gün dozunda klozapin almakta olduğu anlaşılmıştır. Sigara kullanımı olmayan hastalardan sadece birinde klozapin düzeyinin terapötik düzeyin altında (75 ng/mL) olduğu saptanmış, bu hastanın da düzenli ilaç kullanımında sorun olduğu tetkik sonrası yapılan görüşmelerde anlaşılmıştır. Klozapin düzeyinin ölçülmesinin, tedavi uyumsuzluğu nedeni ile terapötik düzeyin sağlanamadığı hastaların klozapine yanıtsız olarak değerlendirilmesini (pseudo-direnç) önlemek ve tedaviye cevabı öngörmek gibi faydaları olabilir (28,89).

Çalışmamızdaki hastaların klozapin dışında ilaçlar da kullanmakta olması potansiyel bir karıştırıcı faktör olarak çalışmamızın bir kısıtlılığıdır. Çalışmamızdaki 12 hasta valproik asit kullanmaktadır. Valproik asit, epileptik nöbet profilaksisi amacı ile nöbet eşiğini yükseltilmesi ya da eşlik eden duygudurum belirtilerinin tedavisi amacı ile klozapin tedavisine eklenebilmektedir. Psikotik bozukluk başlangıcından önce epilepsi tanısı almış olmak çalışmamızın dışlama kriterlerindendir, fakat, klozapinin yüksek dozlara çıkıldığı bazı durumlarda tedaviye epileptik nöbet profilaksisi için valproik asit eklenmesi durumu, dışlama kriterlerimizden değildir. Yazında valproik asit kullanımının klozapin metabolizması üzerine etkilerine dair, ektisi olmadığı (86,90), hafif inhibisyon (32) ya da hafif indüksiyon (91-93) yaptığı gibi çalışma dizaynına göre değişiklikler gösteren sonuçlar mevcuttur. 151 hastanın verilerini içeren çalışmalarında Diaz ve arkadaşları, valproik asitin klozapin metabolizmasını indükleyici bir rolü olabileceği ve bu etkinin sigara kullanımını kontrol edildiğinde dahi klozapin düzeylerini düşürücü yönde etki yapabileceğini sonucunu saptamışlar ve valproik asitin klozapin metabolizması için sigara içmeyen hastalarda inhibitör, sigara içen hastalarda

ise indüktör rol yapıyor olabileceği yorumunu yapmışlardır (94). Sitokrom enzimleri üzerindeki bu göreceli ve karmaşık ektinin doz bağımlı olabileceği de öne sürülmüştür ve bu durum sadece valproik asit – klozapin etkileşimine özgü değildir: örneğin topiramat, düşük dozlarda valproat metabolizmasını indüklemekte, yüksek dozlarda ise inhibe edebilmektedir (95). Söz konusu ilaç etkileşimleri, ilgili hastalarda klozapin düzeylerinin tetkikinin öneminin altını çizmektedir. Klinik pratikte çoklu ilaç kullanımı, rehberler tarafından önerilmemesine karşın, monoterapi ile beklenen düzelmenin sağlanmadığı hastalar için nadir görülen bir uygulama değildir. Klozapin düzeyi ve psikotik belirti ya da yan etki puanları arasında ilişki saptamamış olmamızda, polifarmasinin etkisi söz konusu olabilir. Beden kitle endeksi ve enfeksiyonlar gibi faktörler de klozapin metabolizmasına etki edebilir ve bu değişkenlerin analiz edilmemiş olması kısıtlılıklardandır. Bu konu ile ilgili monoterapi alan ve homojen özellikleri olan hastaları değerlendiren çalışmalar, ya da daha büyük örneklemli ve karıştırıcı faktörlerin etkisinin daha etkin biçimde dışlanabildiği çalışmalar daha güçlü kanıtlar sunabilecektir.

Çalışmamız dahilindeki imkanlarımızın kısıtlılığı nedeniyle, klozapin düzeylerine ek olarak norklozapin düzeylerinin tetkiki gerçekleştirilememiştir. Norklozapin, klozapinin N-demetilasyonu sonucu oluşan aktif metabolitidir (96). Yazında fluvoksamin gibi ajanlar kullanılarak klozapinin norklozapine dönüşümünün azaltılması ve dolayısıyla klozapin/norklozapin oranının artırılması vasıtasıyla, sedasyon ve kilo alımı gibi yan etkilerin azaltılarak etkinliğin artırılabileceği öne sürülmüştür (97). Ülkemizden bir çalışmada, klozapinle tetiklenen obsesif-kompulsif belirtilerin görülmesinin genetik varyasyonlar gibi birçok değişken tarafından belirlendiği, fakat bir kez ortaya çıktığında, bu belirtilerin şiddetinin klozapin ve norklozapin düzeyleri ile ilişkili olduğu bildirilmiştir (98). Yan etkiler ile ilaç düzeyinin ilişkisi incelenirken de norklozapin düzeylerinin tetkiki fayda sağlayabilir: Yan etkiler ile klozapin düzeyleri arasında ilişki saptamayan bir çalışmada, baş dönmesi yan etkisi ile plazma norklozapin düzeyleri arasında anlamlı ilişki olduğu görülmüştür (99). Klozapin düzeyi ve klinik sonuçlarla ilişkisini belirlemeye yönelik gelecekteki araştırmalarda, norklozapin düzeyi ve klozapin/norklozapin oranının da analiz edilen parametereler arasında bulunması yararlı olacaktır (100).

Örneklem sayımızın kısıtlı olması, sigara içme durumu ve cinsiyetin etkisini ayrıştıracak analizler yapmamızı engellemiştir, bu nedenle daha büyük örneklemli çalışmalarla klozapin düzeyleri ile cinsiyet ve sigara içme arasındaki ilişkinin araştırılmasını önermekteyiz. Bununla birlikte küçük ölçekli ve retrospektif yapıdaki çalışmamız, ülkemizden klozapin düzeyleri ile ilgili nadir sistematik bildirimlerden biri olması yönü ile önem arz etmektedir.

SONUÇ

Güncel Birleşik Krallık rehberlerinde, klozapin kan düzeyini artırabilecek ilaç kullanımı ya da ağır enfeksiyon varlığında veya toksisite ya da yavaş metabolizasyon şüphesi var ise klozapin düzeylerinin tetkiki önerilmektedir (101). Bunlara ek olarak, sigarayı bırakan ya da elektronik sigaraya geçen hastalarda da klozapin düzeyi kontrolü yapılması tavsiye edilmektedir (101). Biz de ülkemizden veriler sunduğumuz çalışmamızın sonuçları ışığında, klozapin tedavisinde günlük hedef dozun hastanın cinsiyetine ve sigara içme durumuna göre farklı olarak belirlenmesinin klinik açıdan önemli olduğunu hatırlatmakta ve sigara kullanan hastalarda özellikle yetersiz yanıt varlığında, sigara kullanmayan hastalarda ise toksisiteden şüphelenildiğinde klozapin düzeyinin tetkik edilmesinde fayda olacağını belirtmekteyiz.

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Are the illness severity and treatment efficacy of the patients followed in the child psychiatry inpatient service during the pandemic period different from the ''normal'' period?

Pandemi döneminde çocuk psikiyatrisi yataklı servisinde izlenen hastaların hastalık şiddeti ve tedavi etkinliği "normal" dönemden farklı mı?

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SUMMARY

Objective: COVID-19 pandemic poses a serious threat to health systems and inpatient treatment units. With the increase in the size of the pandemic, it has become a difficult process to carry out routine treatment services. In this study we aimed to compare the clinical profile, illness severity and length of hospitalization of the patients who were hospitalized in the child psychiatry inpatient service during the normal and the pandemic period. **Method:** The patients who were treated in the child psychiatry inpatient service during the the pandemic period (n=19), and previously normal period (n=149) were compared in terms of clinical profile, illness severity and length of hospitalization. Psychiatric diagnoses were assessed using the K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version). The Clinical Global Impressions-Severity scale (CGI-S) was applied to all patients in both groups at hospitalization and discharge point. **Results:** We found that median level of CGI-S hospitalization scores in pandemic period was significantly higher than normal period. A significant negative correlation was found between CGI-S discharge scores and length of hospitalization during pandemic period. In addition, a significant difference was found between the groups in terms of the rate of anxiolytic drugs used. **Discussion:** Anxiety levels of people may increase in disasters such as pandemics, wars, earthquakes. During the pandemic period, patients with higher clinical severity of illness are treated in inpatient treatment units. In these cases, it is important to continue inpatient management without interruption, along with infection-preventive measures.

Key Words: Psychopathology, Mental health services, Child psychiatry, Pandemic

ÖZET

Amaç: COVID-19 pandemisi, sağlık sistemleri üzerinde ve yataklı servis tedavi birimleri üzerinde ciddi bir tehdit oluşturmaktadır. Pandeminin boyutunun artmasıyla birlikte rutin tedavi hizmetlerini yürütebilmek zorlu bir süreç haline gelmiştir. Bu çalışmada; çocuk psikiyatrisi yataklı servisinde salgın döneminde tedavi gören hastaların genel klinik profili, hastalık şiddetleri ve yatış süreleri ile pandemi öncesi dönemde tedavi gören hastaların karşılaştırılması amaçlanmıştır. **Yöntem:** Pandemi döneminde yataklı serviste tedavi gören 19 hasta ile daha önce yataklı servisimizde tedavi gören 149 hasta; hastalık şiddeti, klinik profil ve yatış süresi açısından karşılaştırılmıştır. Hastaların psikiyatrik değerlendirmesi için Okul Çağı Çocukları İçin Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-Şimdi ve Yaşam Boyu Şekli (K-SADS) kullanılmıştır. Hastaların yatış sırasında ve taburculuk sonrasındaki hastalık şiddetleri, Klinik Global İzlenim Ölçeği-Şiddet (KGİÖ-Ş) ile değerlendirilmiştir. **Bulgular:** Salgın döneminde yatan hastaların KGİÖ-Ş yatış puanlarının medyan değeri, pandemi öncesi döneme göre yatan hastalardan istatistiksel olarak anlamlı şekilde yüksek çıkmıştır. Salgın döneminde yatan hastaların yatış süresiyle taburculuk KGİÖ-Ş arasında negatif korelasyon ilişkisi saptanmıştır. Ayrıca, iki grup arasında anksiyolitik ilaç kullanım oranı açısından istatistiksel olarak anlamlı bir farklılık saptanmıştır. **Sonuç:** Salgın, afet, savaş gibi büyük toplum kesimlerini etkileyen olaylarda kişilerin kaygı düzeyleri artabilmektedir. Pandemi döneminde yataklı servis tedavi birimlerinde, daha yüksek klinik şiddete sahip hastalar tedavi görmektedir. Bu durumlarda, enfeksiyondan koruyucu önlemlerle beraber yataklı servis yönetimine ara vermeden devam etmek önemlidir.

Anahtar Sözcükler: Psikopatoloji, Ruh sağlığı hizmetleri, Çocuk psikiyatrisi, Pandemi

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INTRODUCTION

Pandemics remain a threat to human health and healthcare management. The new Coronavirus hazard, which started in December 2019 and whose impact gradually increased in the first months of 2020, has been named COVID-19 by the World Health Organization and later declared as a global epidemic or pandemic in March 2020 (1). According to the analysis of the Chinese Center for Disease Control and Prevention on 44,500 patients, 87% of the patients are between 30 and 79 years old (2). In Italy, where the pandemic was most affected in Europe, the average age of those who lost their lives was 81, and more than two-thirds of these patients had comorbid conditions such as cardiovascular diseases, diabetes mellitus, or cancer (3). Although it has been stated that the incidence of symptomatic infection in childhood is very low and it is usually passed as a mild infection, cases with a severe infection have also been reported (4).

So far, over 3 million cases have been reported globally and are continuing to be reported on all continents except Antarctica. The vast majority of cases occur in family or business areas, and social organizations where close contact is common (5). Together with its high spreading rate, it creates a burden on all small or large-scale health institutions of the countries. Especially, in long-term care centers, cargo ships, and hospitals, where many people work and personal protective equipment is not used properly, secondary infections can occur (6). In all departments where inpatient treatment is given, it is necessary to take measures to prevent the spread of the pandemic and to make changes in functioning in order to continue the treatment of patients.

In the psychiatric inpatient services, besides the medication applied for psychopathology, milieu therapy, group activities, and social activities are of great importance. Among the precautions to be taken to prevent the spread of the outbreak, there are studies stating that such activities should be canceled and attention should be paid to social isolation rules, in psychiatric clinics (10). There are a few studies on the anxiety problems caused by Covid-19 outbreak in the literature; its effect on psychiatry and its impact on the management of patients in need of treatment in the field of mental health (11,12). In a study conducted in Germany to investigate the mental health burden of the society during the Covid-19 pandemic, it was shown that the prevalence of generalized anxiety symptoms and depression symptoms increased (13). But acute medical concerns and quarantine measures related to COVID-19 are causing delays in patients seeking psychiatric care (14).

The first case of COVID-19 in Turkey was announced by the Ministry of Health on March 11, 2020. Ege University Medical Faculty Hospital, to which we are affiliated as the Department of Child & Adolescent Psychiatry, has been declared a pandemic hospital with the published circular (15). Our clinic has been the only operating inpatient service during Mar 2020 – May 2020 among child psychiatry inpatient services located in the Aegean region. Furthermore, it has been the only university hospital that works as a child and adolescent psychiatry inpatient service during the pandemic in the country. In this period, in addition to the service functioning which has been revised suitable for the pandemic hospital, it was purposed to continue the treatment of inpatient child and adolescent patients. It has been observed that there is a need to compare patient characteristics in child and adolescent psychiatric services with the profiles of patients hospitalized during the pandemic.

In this study, the primary objective is to compare illness severity and length of stay between the normal period and the pandemic period. Secondary, to examine to clinic profile and family psychopathologies of patients. Thirdly, to evaluate the contribution of hospitalization treatment on recovery.

METHOD

Inpatient Service Functioning During The Covid-19 Pandemic

Ege University Faculty of Medicine Child and Adolescent Psychiatry Inpatient Service is a clinic with a capacity of 9 beds where children and adolescents aged under 18 years old are monitored and treated. Patients diagnosed except with substance

use disorder are hospitalized together with a mother or female companion. After the announcement of Ege University Medical Faculty Hospital as a pandemic hospital, some changes have been made in the functioning of the inpatient service. Due to the fact that our university has been declared a pandemic hospital and switched to a rotational work program, it has been planned to discharge patients who are worried about the pandemic environment or have no longer indication for hospitalization, considering that quarantine at home would be a better option for them. Inpatient treatment has been continued for patients whose discharge is not suitable. The double patient rooms in our service have been converted into single rooms, and the maximum number has been set as 5 for followed-up inpatients during this period (16).

Sample

Before the pandemic period between March 2013 and September 2014, 149 patients who have been hospitalized and discharged at the Ege University Child and Adolescent Psychiatry Inpatient Service, and 19 patients who were treated and discharged from our service in the period before June 2020 (March 2020-May 2020) when the inpatient service was temporarily suspended have been evaluated. The patient files were reviewed retrospectively and the data including demographic and clinical variables planned to be presented in this study were recorded in the forms created by the authors.

Study Design and Procedure

The information about the cases were evaluated using the data form created by the authors, in terms of age, gender, length of stay, diagnosis, medications, and Clinical Global Impression Scale-Severity (CGI-S) scores of hospitalization and discharge. The diagnoses of the cases were made by structured clinical interview. Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; K-SADS have been used for patients with suitable ages (17,18).

Materials

Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): This diagnostic tool is a semi-structured interview form developed by Kaufmann et al. (17) in 1997 and used to detect psychopathologies in children and adolescents according to DSM-IV-TR criteria. The validity and reliability study into the Turkish version was performed in 2004 (18). K-SADS-PL has been performed to all patients over 6 years old in the service.

The Clinical Global Impressions-Severity scale (CGI-S): The CGI-S represents a subjective judgment of illness severity at a specific point. It is rated on a seven-point Likert-type scale ranging from 1 (normal, not ill at all) to 7 (extremely ill). It is based on the clinician's assessment and it is used to designate the global severity of illness at a given point in time (19). This form has been applied to all patients in the service at hospitalization and discharge.

Statistical Analysis

The resulting data have been transferred to SPSS (The Statistical Package for Social Sciences) 22.0 database and performed using SPSS 22.0 program. Quantitative variables have been evaluated by the Kolmogorov-Smirnov test in terms of appropriateness for normal distribution. If normally distributed, the groups have been compared with two independent sample t-tests while they have been evaluated by the Mann Whitney-U test if not. Descriptive statistics of quantitative variables have been shown as the mean ± standard deviation and descriptive statistics of these variables were expressed as a frequency (%). Also, statistics of quantitative variables have been shown as the median (25th-75th percentile) if not normally distributed. A p-value of less than 0.05 was considered statistically significant. A comparison of categorical variables has been checked using chi-square analysis. The relationship between quantitative variables has been studied by Spearman and Pearson correlation analysis.

RESULTS

Descriptive Characteristics

Of the cases who received inpatient treatment before the pandemic period in the Ege University Child and Adolescent Psychiatry Inpatıent Service, 55 (36.9%) of them were boys and 94 (63.1%) were girls. The mean age of the girls and boys were 14.54 ± 2.88 and 13.62 ± 2.78 years, respectively. The gender distribution of 19 patients treated during pandemic was 63.2% girls and 36.8% boys; and the mean age of the girls and the boys are 14.57 ± 3.50 and 14.66 ± 2.83 years. There was no significant difference in terms of gender and age between the groups (p>0.05). In the normal period, of the inpatients 24.2% (n=36) did not attend to school, 36.9% (n=55) high school, 2.0% (n=3) open high school, 23.5% secondary school, 8.1% (n=12) primary school, and 2.7% (n=4) were special education students. During pandemic, 21.1% (n=4) of the inpatients did not attend school, while 42.1% (n=8) high school, 15.8% (n=3) secondary school, 5.3% (n=1) primary school, 10.5% (n=2) open high school and 5.3% (n=1) were special education students. In terms of the parental psychopathology of the cases; 24.2% (n=36) of the mothers and 7.4% (n=11) of the fathers had psychopathology in the normal period. During the pandemic period, the rates were 31.6% (n=6) and 21.1% (n=4), respectively. The difference of the presence of mother and father psychopathology was significant between the groups (p <0.05). The suicide attempt was 28.9% (n=43) during the normal period and 21% (4) during the pandemic period. Before the pandemic 36% (n=34) of girls and 16% (n=9) of boys attempted suicide among the inpatient group. During the pandemic these rates were 16% (n=2) of girls and 28% (n=2) of boys. No significant difference was found between the groups in terms of suicide attempt. Sociodemographic and clinical data of patients are presented in the Table 1.

Table 1. Comparison of sociodemographic and clinical data of patients between the two groups

Categories	Normal Period	Pandemic Period	Test
Gender n (%)	Girl: 94 (63.1) Boy: 55 (36.9)	Girl: 12 (63.2) Boy: 7 (36.8)	ns
Age Average mean–sd	Girl: 14.5 (±2,88) Boy: 13.6(±2,78)	Girl: 14.66 (±2,53) Boy 14.57(±3,50)	ns
Education Level n(%)	Did not attend school 36 (24.2) Special education 4 (2.7) Primary school 12 (8.1) Secondary school 35 (23.5) High school 55 (36.9) Open high school 3 (2.0)	Did not attend school 4 (21.1) Special education 1 (5.3) Primary school 1 (5.3) Secondary school 3 (15.8) High school 8 (42.1) Open high school 2 (10.5)	ns
Mother Psychopathology n(%)	36 (24.2)	6 (31.6)	χ2: 12.034 df: 2 **p<0.05**
Father Psychopathology n(%)	11 (7.4)	4 (21.1)	χ2: 14.150 df: 2 **p<0.05**
Suicide Attempt n (%)	43 (28.9) Girl: 34 (36) Boy: 9 (16)	4 (21.1) Girl: 2 (16) Boy: 2 (28)	ns

χ2 : Chi-square test; ns: Statistically non-significant

We examined the psychiatric diagnoses distributions. The most common diagnosis in both groups is mood disorders. Diagnosis rates before the pandemic were 57.7% (n=86) mood disorders (45.0% [n=67] major depressive disorder, 6.0% [n=9] bipolar disorder, 6.7% [n=10]) mood disorder not otherwise specified); 10.7% (n=16) attention deficit hyperactivity disorder (ADHD); 8.1% (n=12) schizophrenia and other psychotic disorders; 6.1% (n=9) autism spectrum disorder; 3.4% (n=5) conversion disorder; 4.7% (n=7) obsessive-compulsive disorder; 2.7% (n=4) conduct disorder; 1.3% (n=2) eating disorders. In pandemic period, 42.1% (n=8) mood disorders (31.6% [n=6] bipolar disorder, 10.5% [n=2] major depressive disorder); 21.1% (n=4) schizophrenia and other psychotic disorders; 15.8% (n=3) eating disorders; 10.5% (n=2) attention deficit hyperactivity disorder (ADHD); 10.5% (n=2) autism spectrum disorder were found. While the comorbid disorders during the normal period were 14.8% (n=22) conduct disorder, 13.4% (n=20) ADHD, 5.4% (n=8) intellectual disability, and 2.7% (n=4) major depressive disorder; during pandemic period the rates were 21.1% (n=4) ADHD, 15.8% (n=3) conduct disorder, 10.5% (n=2) intellectual disability, 10.5% (n=2) social anxiety disorder, 10.5% (n=2) obsessive-compulsive disorder and 5.3% (n=1) major depressive disorder (Table 2).

The psychotropic medication has been used in all patients undergoing inpatient treatment in both periods. The most commonly used psychopharma-

Table 2. Diagnostic rates of the both periods

Primary Diagnoses n (%)	Normal Period	Pandemic Period
Mood disorders	BPD: 9 (6) MDD:67 (45) MD-NOS:10(6.7)	BPD: 6 (31.6) MDD: 2 (10.5)
Psychotic disorders	12 (8.1)	4 (21.1)
Autism spectrum disorders	9 (6.1)	2 (10.5)
Eating disorders	2 (1.3)	3 (15.8)
Attention-deficit/hyperactivity disorder	16 (10.7)	2 (10.5)
Obsessive-compulsive disorder	7 (4.7)	
Conduct disorder	4 (2.7)	
Conversion disorder	5 (3.4)	
Comorbid Diagnoses n (%)		
Attention-deficit/hyperactivity disorder	20 (13.4)	4(21.1)
Conduct disorder	22 (14.8)	3 (15.8)
Intellectual disability	8 (5.4)	2 (10.5)
Major depressive disorder	4 (2.7)	1 (5.3)
Obsessive-compulsive disorder		2 (10.5)
Social anxiety disorder		2 (10.5)

Note. BPD: Bipolar Disorder; MDD: Major Depressive Disorder; MD-NOS: Mood disorder not otherwise specified

cological agent group is antipsychotics. The frequency of psychopharmacological agents in inpatient service in the normal period was 91.6% (n=99) antipsychotics, 65.7% (n=71) antidepressants, 16.6% (n=18) stimulants, 13.8% (n=15) mood stabilizers and 12.9% (n=14) anxiolytics. During the pandemic period 100% (n=19) antipsychotics, 73.6% (n=14) anxiolytics, 63.3% (n=12) antidepressants, 21.1% (n=4) stimulants and 15.9% (n=3) mood stabilizers were used for treatment. It was observed that aripiprazole was the most used antipsychotic in the normal period with 51.8% (n=56). Whereas, risperidone was commonly used (68.4%, n=13) in the pandemic group. Compared to the normal period, the use of olanzapine during the pandemic has increased significantly (x^2 = 13.596; df = 1; p < 0.001). In the antidepressant group, sertraline and escitalopram were most frequently used in both periods. Lastly, anxiolytics use in the pandemic group was significantly higher (x^2 = 34.744; df = 1; p < 0.001; Table 3).

Comparison the Length of Stay and CGI-S Scores

The median level of the length of stay in the normal period was 21 (10 - 36) days and in the pandemic group was 23 (8 – 38.75). On the other hand, 149 patients before the pandemic and 19 patients during the pandemic period have been evaluated for CGI-S during hospitalization. The median CGI-S

Table 3. Groups of psychopharmacological agents used in patients who were in the normal period and during the pandemic period

Categories n (%)	Normal Period	Pandemic Period	Test	
Antipsychotics	99(91.6)	19 (100)	ns	
Risperidone	54 (50)	13 (68.4)		
Aripipirazole	56 (51.8)	8 (42.1)		
Olanzapine	20 (18.5)	9(47.4)	$\chi2$= 13.596	df = 1
Antidepressants	71 (65.7)	11 (64.7)	ns	
Sertraline	34 (31.5)	6 (31.6)		
Escitalopram	21 (19.4)	6 (31.6)		
Citalopram	10 (9.2)	2 (10.5)		
Stimulants	18 (16.6)	4 (21.1)	ns	
Mood stabilisers	15 (13.8)	3 (15.9)	ns	
Anxiolytics	14 (12.9)	14 (73.6)	$\chi2$ = 34.744	df = 1

$\chi2$: Chi-square test; ns: Statistically non-significant

score was 5 (4 - 6) and 6 (5 - 7) during the hospitalization, and during the discharge was 3 (2 - 4) and 3 (3 – 4) in normal and pandemic group respectively. The comparison of CGI-S scores during the hospitalization and discharge was significantly different in both group (p<0.001). We have also investigated the relationship between median score of CGI-S during hospitalization/discharge and length of stay. There is no significant difference in CGI-S scores of discharge. However, the CGI-S scores of hospitalization in the pandemic period was signifi-

Table 4. Comparison of the CGI-S scores and length of stay between the both periods

	Normal Period			Pandemic Period			Z score*	p value
	N	Mean	SD	N	Mean	SD		
CGI-S hospitalization	149	4,91	0,95	19	6,00	0,88	-4,224	**<0,001**
CGI-S discharge	149	3,10	0,97	14	3,35	0,63	-1,255	=0,210
Length of stay	149	24,4	16,5	14	26,4	19,1	-0,302	=0,763

*, Mann-Whitney Test; CGI-S: Clinical Global Impression-Severity

cantly higher than the normal period (p<0.001). No significant difference was found between the two groups in terms of length of stay (Table 4).

Correlation Between CGI-S Scores of Discharge and Length of Stay

When we have examined the correlation between CGI-S discharge scores and length of stay in both

Table 5. Correlation between CGI-S scores of discharge and length of stay

	Normal Period		Pandemic Period	
	r (correlation coefficient)	P (Spearman S rho)	r (correlation coefficient)	P (Spearman S rho)
Correlation analysis between CGI -S scores of discharge and length of stay	-0,071	0,390	-0,622	**<0,005**

CGI-S: Clinical Global Impression-Severity

groups, a significant negative correlation was detected in the pandemic period. It was observed that the CGI-S discharge scores decreased as the length of stay increased (Table 5).

DISCUSSION

In this study; we compared the severity of illness and hospitalization duration of the inpatient child and adolescent psychiatry cases between the normal period and pandemic period. Nineteen patients who have received treatment in inpatient service between March 2020 and May 2020 and 149 patients who were treated in inpatient service before the pandemic were compared. Additionally, the clinical profile of inpatients treated during the pandemic in the psychiatry service were presented.

In our study, a significant difference was found between the CGI-S hospitalization scores between the periods. The CGI-S hospitalization scores of the inpatients during the pandemic was significantly higher than the normal period. Patients were not accepted to the inpatient clinic except in emergency situations due to the pandemic hospital regulations. Therefore, children who were at high risk of self-destructive behavior and environmentally destructive behavior were hospitalized in the pandemic period. Besides that, being one of the three child & adolescent inpatient clinics in Turkey and the only university hospital which was open during the pandemic can explain the higher CGI-S scores. For this reason, the severity of illness stands out as a result of this study rather than variables such as gender and age.

There is a significant difference between the CGI-S hospitalization and discharge scores in both periods. This may indicate that patients benefit from inpatient service treatment in both periods. In addition, when we have examined the relationship between the hospitalization duration and the CGI-S scores of discharge, it was observed as the hospitalization duration increased, the CGI-S scores of discharge decreased. This can be considered as an effective continuation of the treatment processes during the pandemic period contributes to the recovery.

In both periods, girls were similarly dominant and there was no significant difference between the mean age. Studies show that girls are treated in psychiatric services more than boys during adolescence (20,21). A higher rate of psychiatric problems has been detected in mothers of patients than fathers. In relation, a recent study in 2019 has found that the maternal psychopathology of children and adolescent patients in inpatient service is greater than father psychopathology (22). The higher prevalence of psychopathology in the mother in our inpatient service may have been due to the fact that the psychopathological findings were noticed by the treatment team. Also, mothers of cases referred to adult psychiatry clinic within the hospitalization period.

No significant difference was found in terms of suicide attempt in the present study between the periods. When we search the literature, a study published in 2019 reports that up to 5-11% of boys and up to 29% of girls in adolescents treated in the inpatient clinic had attempted suicide history (23). In our study, the rate of suicide attempts in boys was higher than in girls during the pandemic period. This can be due to the limited number of cases and severely ill patient hospitalization during that period.

Mood disorders were the most common primary diagnosis in cases. Then, psychotic disorders and eating disorders follow. The most common accompanying diagnoses were the conduct disorder and attention deficit hyperactivity disorder. Consistent with our findings, there are similar rates with regards to diagnosis frequency in the studies (24,25). Although the rate of eating disorders is higher in our study than other studies, this may depend on the limited number of cases admitted for hospitalization during the pandemic process. At the same time, the fact that eating disorders are a group of diseases requiring multidisciplinary treatment, that our clinic has come forward in terms of many clinical studies and scientific experiences in eating disorders spectrum patients and that it is in a university hospital, so more patient referral from other units for the treatment of eating disorders may explain this result (26,27).

According to our study, antipsychotics and antidepressants were the most commonly used psychopharmacological agent groups in the treatment. Some of the studies indicate that they are the most common group in child psychiatry clinics (28,29). The cause of the more frequent choice of Olanzapine in the pandemic period may be in consequence of higher illness severity and the need for a combined medication, and rapid sedation. Especially in patients who were hospitalized during the early outbreak, we found that anxiolytics were used up to 70% of cases. This may have been caused by the treatment of patients with high illness severity compared to the previous period. Also, the high level of anxiety seen during epidemic periods may be another reason. In one study, anxiety levels in college students during the Covid-19 pandemic period is reported to be around 26% (30). Additionally, studies investigating the impact of fear and anxiety caused by epidemic periods on anxiety levels have been also included in the literature (31,32). In a study aiming to prospectively investigate the effect of the COVID-19 pandemic on adolescent anxiety, depressive symptoms and changes in life satisfaction; an increase in depressive symptoms, anxiety and a decrease in life satisfaction were found (33).

The main focus of our study is to compare the patient profile between both periods and to assess the illness severity. This study may have an original place in the literature in terms of comparing patient profile and disorder data from a periodic standpoint. While many psychiatric inpatient services were closed during the pandemic period, our department was one of the rare services where inpatient treatment continued. Therefore, we think that this study may be a guide to the studies to be carried out later.

Some limitations are important to note. Firstly, it has been done during the two-month stage of the pandemic period. For this reason, there has been a restriction in the number of cases. The limited number of hospitalizations during the pandemic period and the priority given to patients with high severity of illness in our inpatient service may explain the difference in CGI-S scores between the groups. Besides that, patients with different diagnoses are treated in our inpatient service. This can make it difficult to assess what may have been affected by the change in illness severity during hospitalization and discharge. This study has been conducted in a child and adolescent psychiatric clinic and is a cross-sectional study. Cross-sectional studies may only indicate psychiatric conditions over a certain time period and do not represent all clinical samples.

CONCLUSION

In this study, clinical characteristics of the cases treated in the child and adolescent psychiatry inpatient service were compared between the normal period and the pandemic period. We found that patients with higher illness severity during the pandemic period were hospitalized, and patients benefited from inpatient treatment in both periods. In addition, we found that mood disorder was the most common diagnosis in both periods and psychiatric problems was found more frequently in the mothers of the patients than in their fathers.

The continuation of the psychiatric inpatient treatment services with infectious prevention measures in the field of child and adolescent during pandemic times has an important place. Clinical severity and profile of patients who are hospitalized during the pandemic may vary compared to normal period. In these cases, it is essential to provide therapeutic and preventive health services. Because the studies about the effect of the pandemic on the child and adolescent psychiatry inpatient services is limited, we believe that this study will be a premise and be supported by studies including a broad sample and a longer follow-up.

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Ethical statement: The study was initiated with the approval of the Ege University Ethical Committee of Clinical Research (decision no: 20-5T/55).

Informed consent: Written informed consent for this study was obtained from patients and parents.

Author contributions: SK: Idea, Review, Draft Preparation BO: Idea, Review. ND: Literature Review,

Draft Preparation, Data Collection&Analyzing. IB: Literature Review, Draft Preparation, Data Collection. TB: Supervision.

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Comparison of emergency department and psychiatry physicians' views on decision-making capacity cases in the grey zone

Gri bölgedeki karar verme kapasitesi vakalarına ilişkin acil servis ve psikiyatri hekimlerinin görüşlerinin karşılaştırılması

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SUMMARY

Objective: The aim of this study is to demonstrate the level of reconciliation between different medical branches, decision-making processes over the same facts, both among themselves and with others. **Method:** An online survey was created with three cases and six questions in the grey area related to the decision-making capacity (DMC) situations. Surveys were sent to participants through their e-mails registered in hospital systems. A total of 165 physicians participated in the study. The first scenario concerned an unstable patient with gastrointestinal bleeding and major depression requesting discharge despite medical advice. The second scenario included the discharge request of a patient who was on the border of pulmonary insufficiency with a severe asthma attack. The final scenario was about a homeless person with chest pain that occurred at the time of alcohol withdrawal, demanding discharge, at a point where a heart attack wasn't excluded. **Results:** 54% of psychiatry specialists, 77% of psychiatry residents, 82% of emergency medicine specialists and 76% of emergency medicine residents stated that DMC was intact for scenario 1. For scenario 2, these rates were determined as %88, %90, %76, %71 while for scenario 3 they were %44, %35, %44 and 47%, respectively. Among the psychiatrists and residents, a statistically significant difference was found between the two groups only in scenario 1. **Discussion:** : Consistent with the literature, it was observed that the interrater agreement of DMC decisions between different medical branches was low. Differences can be explained by different experience years, educational differences, evaluating basic decision-making competencies with different degrees of importance and differences in malpractice concerns.

Key Words: Decision-making capacity, grey area, competency evaluation

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ÖZET

Amaç: Bu çalışmanın amacı, farklı meslek gruplarından değerlendiricilerin, aynı olgular üzerinden karar verme süreçlerinin hem kendi aralarında hem de diğerleriyle olan uzlaşma düzeyini ortaya koymaktır. **Yöntem:** Karar verme kapasitesi (KVK) ile ilgili gri alanda üç vaka ve altı soru ile çevrimiçi bir anket oluşturulmuştur. Anketler, katılımcılara e-posta adresleri üzerinden gönderilmiştir. Çalışmaya toplam 165 hekim katılmıştır. Senaryolardan birincisi, anstabil gastrointestinal kanaması ve majör depresyonu olan bir hastanın tıbbi önerilere karşın, taburcu olma talebiyle ilgiliydi. İkinci senaryo, ciddi astım atağı ile pulmoner yetmezlik sınırında olan hastanın taburculuk talebini içermekteydi. Son senaryo ise evsiz bir bireyin alkol yoksunluğu belirtilerinin olduğu anda ortaya çıkan göğüs ağrısının kalp krizi dışlanmadan taburculuk talebi hakkındaydı. **Bulgular:** Psikiyatri uzmanlarının %54'ü, psikiyatri araştırma görevlilerinin %77'si, acil tıp uzmanlarının %82'si ve acil tıp araştırma görevlilerinin %76'sı senaryo 1 için KVK'nin korunduğunu belirtmiştir. Senaryo 2 için bu oranlar %88, %90, %76, %71 iken senaryo 3 için sırasıyla %44, %35, %44 ve %47 olarak bulunmuştur. Psikiyatristler ve araştırma görevlileri arasında sadece senaryo 1'de iki grup arasında istatistiksel olarak anlamlı bir fark bulunmuştur. **Sonuç:** Literatürle uyumlu olarak, önemli sayıda vakada farklı tıp dalları arasında KVK kararlarının tutarlılığının düşük olduğu gözlendi. Farklılıklar, farklı deneyim yılı, eğitim farklılıkları, temel karar verme yetkinliklerinin farklı önem dereceleriyle değerlendirilmesi ve malpraktis kaygılarındaki farklılıklar ile açıklanabilir.

Anahtar Sözcükler: Karar verme kapasitesi, gri alan, yeterlilik değerlendirmesi

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INTRODUCTION

Decision-making capacity (DMC) is defined as "the minimum conditions required for individuals to have the ability to make decisions about themselves" (1). It is also defined as the cognitive potential that an individual can use to make rational decisions includes the processes of understanding, evaluating, making decisions, and expressing decisions (2). Understanding the medical condition and treatment alternatives, being able to make rational decisions in favor of or against treatment, understanding the personal consequences associated with a particular treatment choice, and deciding on a treatment option are the four main areas evaluated when examining the DMC (3). Although psychiatrists are often consulted, every physician can evaluate DMC and encounter situations that need to be evaluated.

Situations in which DMC assessment is requested are often seen by physicians as time consuming and complex (4). The most common condition in which DMC assessment is requested is when the patient refuses treatment. It was reported that 3% to 25% of psychiatric consultations were associated with DMC assessment and approximately 25% of these patients are found to have impaired DMC (4). Several factors make DMC assessments even more difficult, such as DMC is not a global structure, the person's diagnosis may influence the DMC decision, cognitive impairment does not directly determine DMC and DMC is not a static entity (2). It was reported that especially the "grey area" DMC cases are found to be most challenging. Seyfried et al. define "grey area" as "cases of marginal capacity" or "cases between obvious capacity and obvious incapacity" (5). Many studies have shown that the interrater agreement of DMC assessment between clinicians is quite low, especially in assessments without any assessment tool (3,5,6).

In studies where patient scenarios in different medical contexts are evaluated by different fields, there are significant differences between physicians and different professions in decisions regarding DMC. In a study conducted among psychology students, it was determined that physicians attribute the most importance to the principle of "do no harm" as the basic framework in the decision-making process (7), another study found that clinicians' individual value judgments could influence DMC decisions. (8). In a study conducted in 2016 by Armontrout et al., it was found that there were significant differences between DMC assessments of forensic psychiatrists, lawyers and consultation-liaison psychiatrists (9). In particular, the study found that consultation psychiatrists considered patients' DMC to be impaired at a lower rate than forensic psychiatrists and lawyers (9) .

Although DMC is evaluated under elective conditions and often by psychiatrists with consultation, it may also need to be evaluated by physicians other than psychiatry and in emergency room conditions where rapid decision-making can be vital. Although studies on DMC assessments have often been conducted among psychiatrists to date, there are no studies on DMC decisions of emergency department physicians on this issue. The aim of this study is to demonstrate the level of reconciliation between evaluators from different professional groups, decision-making processes over the same facts, both among themselves and with others. In previous studies, there is no data regarding the DMC decisions of psychiatry and emergency department residents. In this study, we also aimed to compare views on DMC regarding grey area cases of residents, who frequently encounter situations where DMC assessment is required. In this way, we aimed to evaluate the role of experience and training background in DMC assessments. In light of the literature data, it was hypothesized that the DMC interrater agreement between emergency doctors and psychiatrists on different scenarios was low. It was also hypothesized that, taken the previous literature data into consideration, interrater agreement between specialists and residents was also low on all three scenarios.

METHOD

The used measurement tools and pattern in this study are taken from a previous study on this issue by Armontrout et al. (9). Three cases and six questions in the grey area related to the DMC situation prepared by the authors two of whom are senior consultant and forensic psychiatrists with extensive

experience in DMC, were translated into Turkish with the permission of the authors.

Sociodemographic data, case vignetttes and DMC assessment questions were sent to the participants via Google Forms, an online survey tool. Unlike the study of Armontrout et al., all evaluators were not only selected from the field of psychiatry, but also emergency medicine physicians were also included in the study. Psychiatry specialists and residents, as well as emergency medicine specialists and residents were included in the study.

The first scenario concerned an unstable patient with gastrointestinal bleeding and major depression requesting discharge despite medical advice. The second scenario included the discharge request of the patient who was on the border of pulmonary insufficiency with a severe asthma attack. The final scenario was about a homeless person with chest pain that occurred at the time of alcohol withdrawal, demanding discharge, at a point where a heart attack wasn't excluded.

Surveys were sent to participants through their e-mails registered in hospital systems or through the e-mail groups they were involved in. The survey was sent to a closed mail group where all members consisted of Turkish psychiatrists, and another closed hospital mail group where the members consisted of emergency doctors. Inclusion criteria were acceptance to the participation, being a psychiatry or emergency physician, and having at least 1 year experience in the current medical profession. Those who were not fitting to these criteria were excluded from the study. At the beginning of the questionnaire, participants were sent a brief explanation about the study and participation requirements, and the survey responses were collected on a voluntary basis. 165 people who met the criteria and filled out the questionnaire were included in the study. Participants were asked whether the cases in the scenarios specified had DMC, and their self-confidence in their decisions was assessed with a 5-point Likert-type scale. Raters were asked whether the patient's DMC is intact in a dichotomized choiced model, whereas self-confidence level were rated on a 1-5 scale. The study was approved by the Osmangazi University Clinical Research Ethics Committee on April 18, 2017, with a decision number 117.

IBM SPSS Statistics 21.0 (IBM Corp Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used in the application of the analyzes. Continuous data are given as mean ± standard deviation. Categorical data is given as percentage (%). The Shapiro Wilk test was used to investigate the suitability of data for normal distribution. In comparison of groups that do not conform to normal distribution, Mann-Whitney U test was used for cases with two groups and Kruskal-Wallis H test was used for cases with three or more groups. Pearson Chi-Square analysis was used in the analysis of the created cross-tables. $p<0.05$ value was accepted as the criterion for statistical significance.

RESULTS

The survey was filled 170 times. 5 participants did not agree to participate in the study at the stage where the purpose of the study and informed consent were presented, and 165 people constituted the total sample of the study. The distribution of the sample by occupational groups is as follows:

Psychiatry specialist 79 (47.9%), psychiatry resident 31 (18.8%), emergency medicine specialist 34 (20.6%), emergency medicine resident 21 (12.7%). The age of the participants was between 25 and 60 years and the mean age was 34.63 (±7.04). Of the 165 respondents who completed the survey, the number of people who had special training on DMC was 4 (2.4%). The mean experience of the 4 people who had training was 9.33 years (±9.45). Data on the number of patients seen by psychiatrists and emergency physicians are presented in Table 1.

When the DMC decisions of psychiatrists, emergency medicine specialists and residents were examined, 42 (54%) psychiatry specialist, 24 (77%) psychiatry resident, 28 (82%) emergency medicine specialist and 16 (76%) emergency medicine resident stated that DMC was intact for scenario 1. For scenario 2, these rates were determined as 70 (%88), 28 (%90), 26 (%76), 15 (%71) while for sce-

Table 1. Data on the number of patients evaluated by psychiatrists and emergency physicians

	Psychiatrist (n = 110)	Emergency medicine physician (n = 55)
Years of experience (mean, – SD)	9.05 (–6.73)	7.22 (–4.93)
Number of patients evaluated per week (mean, – SD)	124.79 (–97.80)	413,55 (–:364,72)
Number of forensic cases evaluated per week (mean, – SD)	8.01 (–16.83)	43.11 (–57.50)
Number of consultations evaluated per week (mean, – SD)	8.97 (–11.08)	-

SD: standard deviation

nario 3 they were 34 (%44), 11 (%35), 15 (%44) and 10 (47%), respectively. Among the psychiatrists and residents, a statistically significant difference was found between the two groups only in scenario 1 (p=0.045, x2= 4.023). No significant differences were found in the other two scenarios (p>0.05, p>0.05).

When the degree of self-confidence was examined among psychiatrists and residents in scenario 1, it was found to be 3.06 (± 1.09) for psychiatrists and 2.19 (± 0.91) for psychiatry residents (p = 0.000, Z = -3.724.). No significant differences were found in terms of self-confidence rates for the other 2 scenarios (p>0.05, p>0.05).

Information about participants' assessment of DMC, confidence rates and statistical data are presented in Table 2. The mean self-confidence of participants in DMC decisions is presented in Table 3.

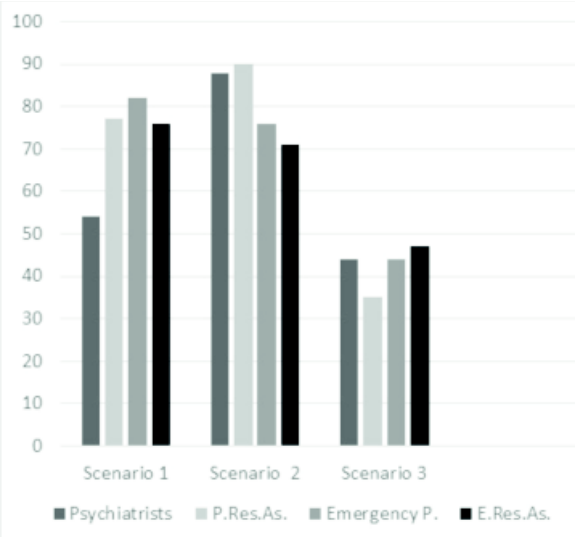

Figure 1. Percentages of participants stating that DMC is intact in the scenarios

Table 2. Assessment of participants' decision-making capacity and self-confidence rates

	Psychiatrist (n = 110)	Emergency medicine physician (n = 55)	x^{2}*	Z**	p
For Scenario 1, DMC intact (n, %)	67 (%60,9)	44 (%80)	5.234		**0.02**
For Scenario 2, DMC intact (n, %)	98 (%89,1)	41 (%74,5)	4.800		**0.028**
For Scenario 3, DMC intact (n, %)	46 (%42)	25 (%45)	0.053		0.818
Mean self-confidence for Scenario 1 (Mean, –SD)	2,82 (–1,11)	3,09 (–1,27)		- 1.453	0.146
Mean self-confidence for scenario 2 (Mean, –SD)	3,14 (–1.25)	3,69 (–1,28)		- 2.742	**0.006**
Mean self-confidence for scenario 3 (Mean, –SD)	2,94 (–1.16)	3,26 (–1.390)		- 1.809	0.070

* Chi-square test. ** Mann Whitney-U test. SD: standard deviation

DISCUSSION

In this study on the DMC about the grey zones, a statistically significant difference was found between the emergency medicine physicians and psychiatrists regarding the DMCs of the first case that has major depression who requests discharge while having gastrointestinal bleeding and the second case regarding an asthma attack, requesting discharge. Between psychiatry physicians, a significant difference was found between the specialists and residents' DMC decisions in the first case. Consistent with the literature, we observed that the interrater agreement of DMC decisions between different medical branches was low in a significant number of cases.

It has been asserted that one of the most important difficulties in DMC assessment is the inadequacy of formal education on this issue (9). In the literature, it was stated that psychiatrists who didn't have psychosomatic medicine training had a mean of 1.5 courses on DMC, while those who completed the training had a mean of 3.0 courses (4). As for psychiatric training in Turkey, there is no specific training in terms of "Requirements and Minimum Standards in Training for Psychiatric Specialty" set by the Psychiatric Association of Turkey and in the

Table 3. Participants ' mean self-confidence about DMC decisions

	Psychiatrist (mean, –SD)	Emergency medicine physician (mean, –SD)	p
Mean self-confidence for scenario 1			
DMC intact	2,75 (–1.02)	3,25 (–1.37)	>0.05
DMC impaired	2,93 (–1.24)	3,00 (–1.26)	>0.05
Mean self-confidence for scenario 2			
DMC intact	3,18 (–1,23)	3,90 (–1,09)	**0.006**
DMC impaired	2,75 (–1,42)	3 (–1,03)	>0.05
Mean self-confidence for scenario 3 (Mean, –SD)			
	2,94 (–1,19)	3,17 (–1,36)	>0.05
DMC intact	2,93 (–1,14)	3,38 (–1,43)	>0.05
DMC impaired			

qualification conditions of the Emergency Medicine Association of Turkey (10, 11). As in other countries, this causes difficulties in the practice of DMC assessment in Turkey. The difference between psychiatry specialists and residents in the assessment of DMC in the first case with depression may be related to this lack of education. Psychiatry residents, compared to specialists, considered that DMC was intact in the first case at a higher rate, but their self-confidence scores were significantly lower. This can be explained by less knowledge and experience of residents on the effects of depressive disorders on DMC. Affective disorders can be accompanied by cognitive losses, despite the presence of apparently preserved cognitive functions (12). Depressive disorders can significantly affect DMC, especially impairing the ability to 'appreciate' from 4 basic consent skills (13). A similar result was also found in the study by Armontrout et al., where the same scenarios were evaluated by different professions and the rate of psychiatrists who stated that DMC was intact in the first case was found to be significantly lower than lawyers (9). The reason why more emergency physicians think that DMC is intact in the first case than psychiatrists may be due to the fact that they encounter fewer depressive patients than psychiatrists in their professional practices and their lack of experience and knowledge about the relationship between depressive disorders and cognition could be the cause of this difference. This indicates the importance of knowledge and experience regarding the cognitive effects of mental illness as well as forensic knowledge in DMC assessments.

In the second scenario, there is a statistically significant difference between both emergency medicine physicians and psychiatrists in terms of self-confidence scores and DMC decisions. In this case, with a high rate of self-confidence, emergency physicians more often thought that DMC is impaired. DMC is traditionally evaluated with four basic consent abilities: ability 'to understand', to reason', to appreciate' and to choose' (2,14,15). Differences in DMC decisions between different professional areas may be the result of evaluating these four basic competencies with different degrees of weight and importance. The reason why emergency physicians often think that DMC is impaired in the second case may be because they have more experience on medical complications and life-threatening situations are more alerting for them. Psychiatrists, on the other hand, may have interpreted the case as DMC-intact, because the patient has the ability to plan ahead for his/her own medical care and there is no history of a psychiatric disorder. In our study, it has not been assessed which basic consent abilities are emphasized by different branches in DMC assessment and this area could be enlightened with further studies on this matter.

Compared to the literature data, we found that the percentage of psychiatry residents who considered DMC as intact was significantly higher and for the first two cases it was higher than psychiatry specialists (9). Differences in health law between countries and doctors' malpractice concerns may be playing a role in this difference. This conservative attitude, which gives importance to the autonomy of the patients rather than their prognosis, seems compatible with the fact that a high rate of health lawyers believe that DMC is intact compared to other professions in the Armontrout et al.'s study (9). Therefore, in addition to patient well-being, legal regulations may play a role in physicians' DMC decisions. Significant steps can be taken to reduce uncertainty with clear legal arrangements to be made on medical decisions of cases in the grey area, and with the inclusion of these regulations in medical education.

Competence and DMC are two related concepts that sometimes referred reciprocally. Appelbaum and Gutheil define competence as "a threshold requirement for persons to retain the power to make decisions for themselves" (1). It is helpful to consider this notion as two related sub-concepts, e.g general competence and specific competence. General competence is defined as the ability to be able to handle person's vocations in a proper way, whereas specific competence is defined as the ability to execute a particular act (1). Thus, its evaluation comprises of these abilities: communication of a choice, factual understanding of the issues, appreciation of the situation and its consequences and rational manipulation of information (1). The concept of decision-making capacity used in our study can be considered as specific competence. Many studies about specific competence state that

the 'MacArthur competence assessment tool' (MacCAT) is useful and has high sensitivity and specificity (16-18). It is a helpful tool to determine the patient's DMC in a clinical setting, which takes about 15-20 minutes to apply. Various newly developed forms of MacCAT measures person's ability to "understand, reasoning, appreciation and expression of a choice" (18). In addition, it was stated that the " Mental Competence Evaluation form" developed by Can et al in 2006 can be used for specific consent evaluations. In this form, decision making, rationality of the results, reasoning and knowing are evaluated, and the Cronbach Alpha value of the scale was determined as 0.98 (19). Considering the low consensus of physicians on the DMC decision both in our study and in the literature, using such a structured tool in DMC assessments may help to overcome the uncertainties in the grey area.

Our study has several limitations. The major limitation of the study is the sample size. With larger samples and including participants from different institutions, data regarding the impact of education on DMC decisions can be evaluated with greater precision. Online survey-based design of the study may not be representing the real world decisions of the physicians and the findings should be evaluated with this regard. Compared to previous studies in this issue, the stronger aspects of our study are that our study is the first on DMC evaluations of physicians in Turkey and that emergency physicians who may need to perform rapid DMC evaluations were also included in the study. Also, larger sample size compared to the previous study in the field is another strong aspect of this study. In future studies, by including physicians with different medical branches, more detailed data could be obtained. It may also be helpful to consider these results in more detail with larger samples, and to compare these results with distinct training backgrounds, e.g compare differences between different countries, to further determine the validity and generalizability of results.

As stated in previous studies, training background seems to influence the physicians' decisions and their self-confidence levels, with better-trained physicians being more self-confident (9). Thus, we suggest that in both emergency department and psychiatry resident training, it is essential to include DMC and competency evaluation training with an emphasis on structured assessment tools and interviews, such as MacCAT.

CONCLUSION

In conclusion, the assessment of DMC is an assessment made at the intersection of medical service providers principles of respecting patients' autonomy and providing benefit. The fact that both principles are indispensable makes this assessment special. Although the assessment criteria established to date shed some light on the clinician, the assessment of cases in the grey area is a more challenging process. Identifying the cause of the differences in this area will provide benefits on the advancement of medical services.

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The comparison of application profile to child psychiatry outpatient clinic before and during the COVID-19 pandemic and the effect of the pandemic on emotional-behavioral problems in children

COVID-19 pandemisi öncesi ve sırasında çocuk psikiyatrisi polikliniğine başvuru profilinin karşılaştırılması ve pandeminin çocuklarda duygusal-davranışsal sorunlar üzerine etkisi

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SUMMARY

Objective: This study aimed to investigate the effects of the COVID-19 pandemic and the measures taken in our country on application profile to the child psychiatry clinic. **Method:** In our study, the file data of the cases aged 0-18 years who applied to our clinic for the first time during the pandemic period (between 1st of April and 1st of august 2020) were retrospectively scanned, and they were compared with the file data of cases applying for the first time between the same dates of the previous year. As part of the evaluation, the data of the Strengths and Difficulties Questionnaire (SDQ) Parent form, which was filled out by the parents of all children between the ages of 6 and 16 who applied to our clinic for the first time, were also analyzed. **Results:** The data of 707 children and teenagers were examined in our study. It was found that the application rate of school-aged children decreased significantly during the pandemic period ($p < 0.05$). The rate of Anxiety Disorders (13.2%) showed a significant increase in the cases applied during the pandemic ($p < 0.05$). The total difficulty score of SDQ was found to be significantly higher in cases with the application at the time of pandemic compared to cases that applied at the same time of the previous year. The total difficulty scores of SDQ were respectively 15.98 ± 5.63, 13.87 ± 6.64 ($p < 0.05$). **Discussion:** : Our findings have shown that the pandemic and the measures taken for it are the reasons for changes in the practice of child psychiatry clinics.

Key Words: Child psychiatry, clinic, COVID 19, pandemic, mental health

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ÖZET

Amaç: Bu çalışmada, COVİD-19 pandemisi ve ülkemizde uygulanan tedbirlerin bir çocuk psikiyatrisi kliniğine başvuru profili üzerine etkisini araştırılması amaçlanmıştır. **Yöntem:** Çalışmamızda, pandemi dönemine denk gelen (01 Nisan-01 Ağustos 2020) tarihlerde kliniğimize ilk kez başvuran 0-18 yaş arası olguların dosya verileri geriye dönük olarak taranmış, bir önceki yılın aynı tarihleri arasında ilk kez başvuran olguların dosya verileri ile karşılaştırılmıştır. Değerlendirmenin bir parçası olarak kliniğimizde 6-16 yaş arası ilk kez başvuran tüm çocukların ebeveynlerine doldurtulan Güçler Güçlükler Anketi (GGA) Anne Baba formu verileri de analiz edilmiştir. **Bulgular:** Çalışmamızda 707 çocuk ve ergenin verileri incelenmiştir. Okul çağı çocuklarının başvuru oranının pandemi döneminde anlamlı olarak azaldığı saptanmıştır ($p<0.05$). Yine pandemi sırasında başvuran olgularda Kaygı Bozuklukları (%13.2) oranı anlamlı artış göstermiştir ($p<0.05$). GGA toplam güçlük puanı pandemi döneminde başvuran olgularda bir önceki yılın aynı tarihlerinde başvuran olgulara göre anlamlı düzeyde daha yüksek saptanmıştır. GGA toplam güçlük puanları sırasıyla 15.98±5.63, 13.87±6.64 idi ($p<0.05$). **Sonuç:** Bulgularımız pandemi ve alınan önlemlerin çocuk psikiyatrisi klinik pratiğinde değişikliklere neden olduğunu göstermiştir.

Anahtar Sözcükler: Çocuk psikiyatrisi, klinik, COVID 19, pandemi, ruh sağlığı

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a newly discovered ribonucleic acid coronavirus isolated from patients with unexplained pneumonia in Wuhan, China, in December 2019(1). The COVID-19, spreading rapidly to other parts of the world, has been declared a pandemic by the World Health Organization (WHO) on 11th ofMarch, 2020(2). Therefore, many countries have implemented various measures like quarantine practices, banning collective events, staying at home, working as much as possible from home to slow down the spread of the virus(3). The measures restricting human movement have been taken to fight the COVID-19 after the first case in Turkey on the 11th of March, 2020. Some of these measures are suspension on face-to-face education and imposing lockdown to under the age of 20(4). Because of these decisions, children stay at home for a long time, their physical activities have been reduced, and social communication with their classmates and teachers has been restricted. It has been stated that the COVID-19 pandemic causes an increase in the frequency of symptoms such as anxiety, depression, post-traumatic stress disorder, insomnia, anger, and disappointment in the literature(5,6). For instance, the prevalence of depression and anxiety during the pandemic period was found to be 43.7% and 37.4% in a study of 8079 teenagers between the ages of 12 and 18(7). However, it is clear that more studies are needed for children's emotional and behavioral responses to rarely seen events like pandemics.

This study aims to investigate patients who applied to our clinic for the first time between 1st of April and 1st of August 2020 in terms of age, gender, diagnosis, comorbidity, and used medicine by comparing them with the same dates of 2019 and to analyze the effect of the COVID-19 pandemic on the application profile to a child psychiatry clinic.

METHOD

Participants and Procedure

The files of 707 cases aged between 0 and 18 who applied to our clinic for the first time between 1st of April and 1st of August, 2019 and the data from the year 2020 were scanned retrospectively in terms of age, gender, diagnosis, comorbidity, and the medicine used. Cases with missing file information and/or not completing the evaluation process were excluded from the study.

DSM-5 diagnostic system was used to evaluate the cases who applied to our clinic for the first time. Diagnosis was supported by psychometric tools required contrary to the psychiatric examination in the evaluation made. The Strengths and Difficulties Questionnaire (SDQ) Parent form was routinely filled by parents of all children aged between 6 and 16 who applied to our clinic for the first time as a part of the evaluation. On the other hand, in the cases under the age of 6, a standard questionnaire was not used in the evaluation due to the differences in approaches of the child and adolescent psychiatrists working in our clinic. The ages, genders, psychiatric diagnoses, comorbidities, and medicine of each case were recorded.

In our study, the term "before the pandemic" was used for the dates between 1st of April and 1st of August 2019 and "the pandemic period" for the dates between 1st of April and 1st of August 2020.

Data Collection Tools

Strengths and Difficulties Questionnaire (SDQ):It is a questionnaire developed to screen mental problems in children and young agers. This questionnaire also has a parent form and a teacher form for ages between 4 and 16, and a teenager form for ages between 11 and 16 that they fill out by themselves. This questionnaire also has both hand-signed and computer-filled versions. SDQ includes 25 questions examining the behavioral characteristics, which are positive and negative. These questions are grouped under five subtitles. These titles are conduct problems, inattention and hyperactivity, emotional problems, peer problems, and prosocial behavior. The sum of the first four titles gives the "total difficulty score" when each title is evaluated within itself. High scores in prosocial behavior reflect the strong ways of the individual in the social area as well as high scores in the other four areas (conduct problems, attention deficit, and hyperactivity, emotional problems, peer problems)

reflect the intension of the problem areas. Besides, the impact score determining the level of individual exposure to mental difficulties can be calculated from the scale. Higher impact scores indicate that mental difficulties affect the individual more (8). Turkish validity and reliability were done by Güvenir et al. (9).

Statistical Analysis

The data obtained from the research were evaluated by using IBM SPSS statistics software version 25.0. The variables obtained with measurement were identified as mean ± standard deviation and categorical variables as percentages and numbers. Chi-square analysis was used in the comparison of categorical variables. The Kolmogorov-Smirnov test was used to evaluate whether the numerical variables were normally distributed. The student's t-test was used for normally distributed results, and the Mann-Whitney U test was used for results that did not show normal distribution in comparing scale scores between groups. Correlations were calculated by Spearman rank correlation analysis, and $p < 0.05$ was accepted as the statistical significance limit.

RESULTS

Four hundred seventy-three of the cases applied before the pandemic and 234 during the pandemic period included in the study. No statistically significant difference was found in comparing the cases applied before and during the pandemic period according to their age (U= 51344.5, p= 0.118) and gender ($x^2 = 0.003$, $p = 0.957$). However, statistical significance was found in the comparison of childhood periods. According to this result, it was observed that the application rate of children in pre-school period ($x^2= 6.036$, $p = 0.014$) and adolescence ($x^2= 27.219$, $p < 0.001$) increased significantly during the pandemic period. It was determined that the application rate of children in school-age ($x^2= 45.205$, $p < 0.001$) decreased significantly during the pandemic period.

SDQ Parent form was filled by parents of all children between the ages of 6 and 16 applying for the first time in our clinic as part of the evaluation. There was no statistical significance between the groups related to whether the parent filling out the questionnaire was a mother or father. The statistical evaluation of the parents' education levels who filled out the questionnaire was also made in the study. According to this, it was seen that only the application rate of parents at the primary education level increased significantly during the pandemic period ($x^2=6.335$, $p=0.012$). The general characteristics of the participants are given in Table 1.

The diagnosis distributions were evaluated according to DSM-5 in our study. The three most common diagnoses made in pre-pandemic cases were respectively Attention Deficit Hyperactivity Disorder (ADHD) with a rate of 26.0%, Specific Learning Disorder (SLD) with a rate of 13.7%, and Intellectual Disabilities (ID)with a rate of 10.4%. In cases applied during the pandemic period, the three most common diagnoses were respectively Anxiety Disorders (13.2%), ADHD (12.8%), and Communication Disorders (10.3%). The application rates of ADHD ($x^2=16.046$, $p<0.001$) and SLD ($x^2=25.737$, $p <0.001$) cases were found to be decreased significantly in the pandemic period compared to the pre-pandemic period.While the diagnosis of Anxiety Disorders ($x^2=3.978$, $p= 0.046$), Obsessive-Compulsive Disorders and Related Disorders ($x^2=18.150$, $p <0.001$), Disruptive, Impulse Control and Conduct Disorders ($x^2 =11.978$, $p = 0.001$) increased signi-

Table 1: General characteristics of the participants according to the application periods.

		Application Periods			
		Before the pandemic N(%)	During the pandemic N(%)	Statistics (U/ x^2)	*p*
Age		8.29 (–3.84)	9.31 (–5.15)	51344,5	0.118[a]
Gender	Female	187 (39.5)	93 (39.7)	0.003	0.957[b]
	Male	286 (60.5)	141 (60.3)		
Period	Pre-school	131 (27.7)	86 (36.8)	6,036	0.014[b]
	School age	258 (54.5)	65 (27.8)	45,205	<0.001[b]
	Adolescence	84 (17.8)	83 (35.5)	27,219	<0.001[b]
Parents filling out SDQ*	Mother	272 (83.4)	95 (81.2)	0.304	0.582[b]
	Father	54 (16.6)	22 (18.8)		
Education level of Parents filling out SDQ *	Primary school	162 (49.7)	74 (63.2)	6.335	**0.012[b]**
	High school	108 (33.1)	31 (26.5)	1.759	0.185[b]
	University	56 (17.2)	12 (10.3)	3.174	0.105[b]

*Includes only 6-16 age group
[a]Mann-Whitney U
[b]Pearson ki kare

ficantly during the pandemic period (Table 2).

Considering our findings, it was determined that anxiety disorders showed a significant increase in cases who applied during the pandemic period. Therefore, statistical analyses for anxiety disorders were also done. In the cases applying before the pandemic, Separation Anxiety Disorder (SAD) rate was %12.5 (n=5), Selective Mutism(SM) rate was %7.5 (n=3), Social Anxiety (SA) was %30.0 (n=12), Panic Disorder (PD) rate was % 12.5 (n=5), Specific Phobia (SP) rate was %12.5 (n=5) and Generalized Anxiety Disorder (GAD) rate was %25.0 (n=10) in the anxiety disorders. On the other hand, these rates were respectively 9.7% (n = 3), 19.4% (n = 6), 6.5% (n = 2), 16.1% (n = 5) and 48.4% (n = 15) for SAD, SA, PD, SP and GAD in the cases who applied during the pandemic period. In comparing groups for anxiety disorders, statistical significance was found only for GAD (x^2= 4.187, p= 0.041). Accordingly, getting a GAD diagnosis increased significantly during the pandemic period.

153 (21.6%) of 707 cases in our study did not get any diagnosis according to DSM-5. These cases form up 19.5% (n= 92) of the cases applied before the pandemic and 26.1% (n=61) of the cases applied during the pandemic period. In the statistical comparison completed, it was specified that the rate of not having any diagnosis according to DSM-5 increased significantly during the pandemic period (x^2=4.043, p=0.044).

The analyses of diagnosis distributions were revised by means of including only school-age children in order to understand the reasons for the significant decrease in the application rate of school-age children. Thereafter, ADHD (n = 89, 34.5%), SLD (n = 65, 25.2%), ID (n = 22, 8.5%), Communication Disorders (n = 19, 7.4%) and Anxiety Disorders in cases applyingbefore the pandemic (n = 16, 6.2%) were the most common diagnoses made. Different from this, in the cases applying during the pandemic period, the rate of these diagnoses was 26.2% (n =17) for ADHD, 6.2% for SLD (n=4), 7.7% for ID (n=5), 3.1% for Communication Disorders (n =2), and 18.5% (n=12) for Anxiety Disorders. Significance was found only for SLD (x^2=11.204, p =0.001) and Anxiety Disorders (x^2=9.857, p= 0.002) in the comparison of diagnosis distributions between groups.

Statistical evaluations were made regarding the presence of psychiatric comorbidities in the cases. At least one psychiatric comorbidity was found in 13.1% (n = 62) of the cases applied before the pandemic and 16.7% (n=39) of the cases that applied during the pandemic. No significance was found in the statistical comparison made about this context (x^2=1.619, p = 0.203).The most common comorbidities were SLD with a rate of 3.0% (n=14) in cases applying before the pandemic and Sleep-Wake Disorders with a rate of 6.0% (n=14) in cases applying during the pandemic period.

It was also evaluated whether there is a difference in psychotropic usage preferences between the groups in this study. The most preferred medicine before the pandemic was psychostimulants (15.9%) and atomoxetine (6.3%), considering the distribution of psychotropic usage by application periods. It was determined that Selective Serotonin Reuptake Inhibitors (SSRIs) with a rate of 21.4% and atypical antipsychotics with a rate of 8.1% were preferred more during the pandemic period. It was found in the statistical comparison that the usage of psychostimulants (x^2=9.134, p=0.003) and ato-

Table 2:Diagnostic distribution of cases applying before and during the pandemic period

Diagnosis	Before the pandemic N (%)	During the pandemic N (%)	Statistics (x^2)	p^a
AttentionDeficitHyperactivityDisorder	123(26.0)	30(12.8)	16.046	**<0.001**
Specific Learning Disorder	65(13.7)	4(1.7)	25.737	**<0.001**
IntellectualDisabilities	49 (10.4)	16 (6.8)	2.326	0.127
CommunicationDisorders	47(9.9)	24(10.3)	0.018	0.894
AnxietyDisorders	40 (8.5)	31 (13.2)	3.978	**0.046**
DepressiveDisorders	19 (4.0)	13 (5.6)	0.858	0.354
AutismSpectrumDisorder	14(3.0)	12(5.1)	2.078	0.149
TicDisorders	6(1.3)	6(2.6)	1.575	0.209
Obsessive-CompulsiveandRelatedDisorder	5 (1.1)	16 (6.8)	18.150	**<0.001**
Disruptive, Impulse-Control, andConductDisorder	2 (0.4)	9 (3.8)	11.978	**0.001**
TraumaandStressorRelatedDisorders	2 (0.4)	2 (0.9)	0.519	0.471
EliminationDisorders	4 (0.8)	2 (0.9)	0.000	0.990
SomaticSymptomandRelatedDisorder	1 (0.2)	2 (0.9)	1.533	0.216
Sleep-Wake Disorders	3 (0.6)	3 (1.3)	0.781	0.377
FeedingandEatingDisorder	0 (0.0)	1 (0.4)	2.024	0.155
GenderDysphori	0 (0.0)	1 (0.4)	2.024	0.155
BipolarandRelatedDisorders	0 (0.0)	1 (0.4)	2.024	0.155
SchizophreniaSpectrumandOtherPsychoticDisorders	1 (0.2)	0 (0.0)	0.495	0.482

[a]Pearson ki kare

moxetine (x^2=9.009, p=0.003) decreased significantly while the usage of SSRI (x^2=18.083, p <0.001) increased significantly during the pandemic period (Table 3).

Table 3: Distribution of medicine usage in cases applying before and during the pandemic period

Psychotropic	Before the pandemic N (%)	During the pandemic N (%)	Statistics (x^2)	p^a
Psychostimulants	75 (15.9)	18 (7.7)	9.134	**0.003**
Atomoxetine	30 (6.3)	3 (1.3)	9.009	**0.003**
Atypical antipsychotics	26 (5.5)	19 (8.1)	1.807	0.179
Selective Serotonin Reuptake Inhibitors	46 (9.7)	50 (21.4)	18.083	**<0.001**
No psychotropic	280 (59.2)	133 (56.8)	0.359	0.549
Other (Tricyclicantidepressants, benzodiazepines, etc.)	16 (3.4)	11 (4.7)		

[a]*Pearson ki kare*

Statistical Evaluation Results of Strengths and Difficulties Questionnaire (SDQ) Parent form

Strengths and Difficulties Questionnaire (SDQ) Parent form was filled out by 443 parents having children between the age of 6 and 16. The significant difference was found between the average scores of the questionnaire such as emotional problems (U= 15671.0, p=0.004), peer problems (U= 15396.0, p=0.002),internalizing (U=14568.0, P <0.001) and total difficulty (U=14962.0, p= 0.001) and impact (U=15965.5, p=0.008) scorescompared to application periods (Table 4). When the same comparison was made separately according to genders, emotional problems (U=2517.5, p <0.001), conduct problems (U=2885.0, p= 0.013),externalizing (U=2774.5, p=0.006), internalizing (U=2517.0, p <0.001), total difficulty (U = 2378.0, p<0.001), and impact (U=2860.0, p= 0.011) scores were significantly different in female gender.In the comparison made for male gender on the other side, statistical significance was found only in peer problems (U = 4687.0, p = 0.015) (Table 5).

Table 4: Comparison of mean SDQscores in cases aged between 6 and 16 years old applying before and during the pandemic period

	All Group			
SDQ	Before the pandemic Avg (SD)	During the pandemic Avg (SD)	Statistics (U)	p[a]
Conductproblemsscore	2.36 (–1.82)	2.64(–1.80)	17180.0	0.105
Hyperactivityscore	5.07(–2.78)	5.44(–2.68)	17827.0	0.292
Emotionalproblemsscore	3.49(–2.44)	4.35(–2.70)	15671.0	**0.004**
Peer problemsscore	2.98(–2.07)	3.56(–1.76)	15396.0	**0.002**
Prosocialscore	7.24(–2.35)	7.05(–2.29)	17892.5	0.316
Externalisingscore	7.43(–4.05)	8.09(–3.83)	17187.0	0.112
Internalisingscore	6.48(–3.92)	7.90(–3.61)	14568.0	**<0.001**
Total difficultiesscore	13.87(–6.64)	15.98(–5.63)	14962.0	**0.001**
Impactscore	2.69(–2.73)	3.38(–2.82)	15965.5	**0.008**

[a]*Mann-Whitney U*

Table 5: Comparison of the mean SDQ scores of cases aged 6 -16 years, who applied before and during the pandemic, according to gender

	Female				Male			
SDQ	Before the pandemic Avg (SD)	During the pandemic Avg (SD)	Statistics (U)	p[a]	Before the pandemic Avg (SD)	During the pandemic Avg (SD)	Statistics (U)	p[a]
Conductproblemsscore	2.02 (–1.56)	2.66(–1.61)	2885.0	**0.013**	2.59 (–1.96)	2.62(–1.97)	5828.5	0.906
Hyperactivityscore	4.28(–2.77)	5.07(–2.26)	3061.5	0.052	5.62(–2.65)	5.79(–2.99)	5747.5	0.780
Emotionalproblemsscore	3.65(–2.59)	5.34(–3.01)	2517.5	**<0.001**	3.38(–2.32)	3.44(–1.99)	5657.5	0.644
Peer problemsscore	3.03(–2.05)	3.55(–1.82)	3060.5	0.050	2.94(–2.09)	3.56(–1.72)	4687.0	**0.015**
Prosocialscore	7.14(–2.37)	7.20(–2.55)	3595.5	0.705	7.31(–2.34)	6.92(–2.03)	5006.0	0.075
Externalisingscore	6.30(–3.84)	7.80(–3.12)	2774.5	**0.006**	8.21(–4.03)	8.36(–4.40)	5805.5	0.870
Internalisingscore	6.68(–4.03)	8.88(–3.91)	2517.0	**<0.001**	6.34(–3.83)	7.00(–3.08)	5031.0	0.086
Total difficultiesscore	12.94(–6.21)	16.66(–5.41)	2378.0	**<0.001**	14.50(–6.86)	15.36(–5.80)	5282.0	0.226
Impactscore	2.58(–2.72)	3.57(–2.78)	2860.0	**0.011**	2.76(–2.75)	3.21(–2.86)	5296.0	0.236

[a]*Mann-Whitney U*

Again, statistical significance was found for emotional problems (U=1059.0, p<0.001) and internalizing scores (U=1230.0, p=0.009) in comparison of the SDQ scores of the patients applying during the pandemic period. On this basis, girls' emotional problems and internalization scores were significantly higher than boys.

The relationship between the parents' education levels completing the SDQ and the total difficulty score was evaluated using Spearman rank-order correlation analysis. According to the results of this evaluation, it has been determined that there was a negative correlation between education level and SDQ total difficulty score in both the patients applying before the pandemic (Spearman'srho = -0.132, p=0.017) and during the pandemic period (Spearman'srho =-0.284, p=0.002).

DISCUSSION

The pandemic process is a social crisis process. A child's reaction to the crisis is closely related to the child's developmental stage and the socioeconomic and cultural characteristics of the family. It has been reported in various publications that crises negatively affect children's mental well-being (5,10,11). Although children are not fully aware of the effects of the COVID 19 pandemic, they experience more fear, uncertainty, social and physical isolation, and interruption of school life.

Therefore, it is extremely important to understand their reactions to identify and fulfill their needs (12). Even though studies researching the effects of the pandemic on children and adolescents have increased in the literature, limited studies are reporting how this is reflected in clinical practice. In this context, the effects of the COVID-19 pandemic and the measures taken in our country on the clinical practice of child psychiatry were evaluated in our study.

The dates between 1st of April and 1st of August 2020 forming the data of our study is when COVID-19 infection level began to increase dramatically in Turkey. Face-to-face education was suspended on the 16th of March, 2020, and lockdown to under the age of 20 was announced on the 4th of April, 2020, within the scope of restrictive measures taken by the Government of Turkey (4). These decisions also mean that children are forced to stay at home, and as a result of this, their physical activity and social communication are restricted. The first findings of this study indicate that the pandemic and the measures taken have an effect on the education level of the parents and the application profile of the childhood period. According to these results, it was seen that parents with low education levels who applied significantly more during the pandemic period. As the education level increases, the knowledge and skill levels of the parents about the protection measures for themselves and their children from COVID-19 may increase. In a review working on COVID-19 and its effects on mental health, low education level was mentioned as a risk(13). A negative correlation was also found between the education level of parents and SDQ total difficulty scores in our study. This finding makes think about the lower the parents' education level, the higher the risk of mental health problems in children.

When we consider the application profile in the childhood period, the rates of children in the preschool and adolescent period who applied during the pandemic period increased significantly compared to the same dates of the previous year. It was observed that there was a significant decrease in school-age children in this respect. The negative effects of the COVID-19 pandemic on the mental health of children and teenagers have been shown (5). For this reason, it is difficult to interpret the findings about the significant decrease in the application rate of school-aged children as they are not affected by the pandemic. The decrease was detected in cases affecting academic skills, especially ADHD, SLD, and ID negatively, noticed and guided by school counselors and/or classroom teachers in the analyses including only school-aged children and made to understand the reasons for the decrease in the application rate of school-aged children. Although this decrease does not reach the significance level for ADHD and ID, it is significant for SLD.

Our study examined the effect of the pandemic and the measures taken on the distribution of diagnosis. In this case, the three most common diagnoses made in cases applying before the pandemic were respectively ADHD, SLD, and ID. A significant decrease was found in the rate of ADHD and SLD diagnosis during the pandemic period. This finding may be related to the suspension of face-to-face education in schools since teachers play an important role in noticing and guiding these children. In this respect, the suspension of face-to-face education may have made the diagnosis of ADHD and SLD difficult.

Additionally, these two diseases are also known to impair school functionality substantially and bring additional stress load to children with these diagnoses. Several studies have reported well-being for ADHD patients during the pandemic process (14,15).In one of these studies, parents have stated that their children with ADHD were better or the disease was progressing stably. It was stated in the same study that parents were better aware of the inattention and other problems of a child due to ADHD. Besides, the reduction of school-related anxiety and the ability to stretch according to the rhythm of a child were emphasized as other positive reflections of the process (14). According to parent reports, it was found in another study that children with ADHD improve their mood and behaviour after schools were closed (15).

Anxiety disorders' diagnosis was significantly higher than the same dates of the previous year during the pandemic period. The significant increase was

found only in the diagnosis of GAD among anxiety disorders during the pandemic period. Though there is an increasing tendency in diagnosing Depressive Disorders during the pandemic, it has not reached this level of significance. It was found that children showed high rates of anxiety, depression, and post-traumatic stress disorder symptoms in a review working towards COVID-19 (5). In a study in which the anxiety levels of 289 Brazilian children aged 6 and 12 years were measured during the pandemic, their anxiety prevalence was found as 21.8% (16). Eight thousand seventy-nine participants aged 12 and 18 years were recruited in a study investigating the prevalence of depression and anxiety among Chinese teenagers during the COVID-19 pandemic; moreover, the frequency of anxiety was reported as 37.4%, and the frequency of depression and comorbid anxiety as 31.3% (7). It was also stated that the risk for GAD was higher in this period (17).

Another diagnosis in which a significant increase was observed during the pandemic period in our study was Obsessive-Compulsive Disorder and Related Disorders. It is important to pay proper attention to certain psychiatric situations that may begin or become intensified by a disaster. Obsessive-Compulsive and Related Disorders may be one of these psychiatric circumstances because the derogation of the COVID-19 outbreak can affect individuals living with Obsessive-Compulsive Disorder (OCD). Anxiety about the virus may be the cause to increase of their transmission fear and further trigger compulsive behavior in some individuals having OCD. Studies have reported that the mood of children and teenagers due to fear during the COVID-19 pandemic is largely tended to disorders related to anxiety and stress, including OCD (18).

Our study shows that the differentiation in the diagnosis profile also affects the medicine usage preferences. Accordingly, the use of SSRIs increased significantly during the pandemic period. A significant increase in the diagnose of Anxiety Disorders and Obsessive-Compulsive and Related Disorders during the pandemic period, again an increase in the diagnosis of depressive disorders may explain the increase in SSRI usage, although it did not reach the level of significance in this diagnosis.

One of the exciting findings of this study is an increase in the rate of cases not diagnosed due to DSM-5 during the pandemic period. This finding may be related to reports of children and teenagers, such as less well-being due to the pandemic even though they did not receive any psychiatric diagnosis. Studies show that children at all developmental stages are at high risk during this process (7,19-27). In addition to this, causes such as job loss of parents, loss of income, increased caregiving burden, or their infection can adversely affect both parents and children's mental health (28). This may make it difficult for parents to manage mental problems appearing in children and teenagers.

The SDQ Parent form was routinely used as a part of the evaluation in cases aged 6 and 16 years applying to our clinic for the first time. Significant results were found in comparing the questionnaire scores in cases between the ages of 6 and 16 as to the application period. A significant increase was found in the emotional problems, peer problems, internalizing, and total difficulty and impact scores of the questionnaire in cases that applied during the pandemic. These findings regarding the SDQ data can be explained by the effect of the pandemic on children. Furthermore, the significant increase in SDQ impact score makes us think that mental difficulties occurring during the pandemic affect children more. This finding supports the literature reporting the negative effects of the pandemic in the pediatric population (5,6).

SDQ scores were also evaluated in terms of gender. Therefore, there were significant increases in emotional problems, conduct problems, externalizing, internalizing, total difficulty, and impact scores in female cases that applied during the pandemic compared to those applying before the pandemic. On the other hand, for the male gender, a statistically significant increase was found only in peer problems. Moreover, it was observed that the emotional problems and internalizing scores of the female gender were significantly higher than the male gender compared to the mean SDQ scores of the cases applied during the pandemic period.

These findings suggest that the COVID-19 pandemic may have different effects on the genders. Studies show that girls are more likely to exhibit anxiety and depressive symptoms during the pandemic (7,21).

Limitations

Our study has a retrospective design is a substantial limitation. In addition to this, it is a single-center study, and data collection within a relatively narrow time frame that does not only cover the early period of the pandemic is among the other limitations. In spite of these limitations in our study, the strengths of our study are that it compares with the characteristics of patients who applied in the pre-pandemic period and presents data on a commonly used measurement tool in the evaluation of emotional-behavioral problems in children.

CONCLUSION

The findings of the present study indicate that important findings like age, gender, diagnosis distributions, emotional and behavioral problems could be a guide about what waits for specialists working in the field of child and adolescent psychiatry clinics in as much as managing the applications of mental health is a critical problem in a pandemic scenario. Especially, it was determined that there was a significant decrease in the diagnosis rates of ADHD and SLD. Considering the role of teachers in recognizing and guiding these children, this situation may be related to the closure of schools, which was one of the measures taken during the pandemic period. Determination of a significant increase in the diagnosis of Anxiety Disorders is among our other note-worthy findings. In addition, SDQ data show that the female gender is more affected.

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Availability of Data andMaterial

Thedata sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

Ferhat Yaylaci designed the study, wrote the protocol, and conducted the survey. Baris Guller performed statistical analysis, and wrote the first draft of the manuscript. All the authors read and approved the submitted version of the manuscript.

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Mediterranean diet habits and their effects on symptomatology among children and adolescents with attention deficit hyperactivity disorder

Dikkat eksikliği ve hiperaktivite bozukluğu tanılı çocuk ve ergenlerde Akdeniz diyeti alışkanlıkları ve semptomlar üzerine etkileri

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SUMMARY

Objective: Attention deficit hyperactivity disorder (ADHD); is a common neurodevelopmental disorder with multifactorial etiology. Despite the dominant role of the genetic factors; environmental factors such as diet related features may have effect on ADHD diagnosis and symptomatology. In our study we aimed to compare Mediterranean diet (MD) habits of ADHD group with healthy controls and explore the effect of MD on ADHD symptom severity. **Method:** All participants were evaluated with semi-structured psychiatric interviews and total of 113 individuals with ADHD and 120 healthy controls were included. Socioeconomic and clinical features of both groups were examined. Adherence to MD was evaluated with Mediterranean Diet Quality Index (KIDMED) and ADHD symptomatology was evaluated with Turgay scale. **Results:** ADHD group had lower KIDMED scores and worse adherence to MD compared to healthy controls. "Medium adherence" to MD increased the risk of ADHD diagnosis two-folds and "low adherence" to MD increased the risk of ADHD diagnosis five-folds compared to "good adherence". Total KIDMED scores and MD adherence levels were negatively correlated with inattention symptoms. **Discussion:** Adherence to a healthy diet (MD) seems to be related to lesser inattention problems in addition to lower rates of ADHD diagnosis and this indicates the importance of a "healthy diet" not only in the occurrence of ADHD, but also in the clinical symptomatology. certain dietary habits may play a role in both ADHD development and clinical appearance; but further evaluation is needed to shed light on causality and to determine if dietary manipulation could ameliorate ADHD symptoms.

Key Words: Mediterranean diet, attention deficit hyperactivity disorder, symptomatology

ÖZET

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB), multifaktöriyel etiyolojiye sahip sık görülen nörogelişimsel bir hastalıktır. Genetik etmenlerin baskın rolüne rağmen; diyetle ilişkili özellikler gibi bazı çevresel etmenler de DEHB tanısında ve semptomatolojisinde etkili olabilmektedir. Çalışmamızda Akdeniz diyeti (AD) alışkanlıklarının DEHB grubu ve sağlıklı kontroller arasında karşılaştırılması ve DEHB semptom şiddetine etkisinin incelenmesi amaçlanmıştır. **Yöntem:** Tüm katılımcılar yarı-yapılandırılmış psikiyatrik görüşmelerle incelenmiş ve toplam 113 DEHB olgusu ile 120 sağlıklı kontrol çalışmaya alınmıştır. İki grubun da sosyoekonomik ve klinik özellikleri araştırılmıştır. AD'ne uyumları Akdeniz Diyeti Kalite İndeksi (KIDMED) ve DEHB semptomatolojisi Turgay Ölçeği ile değerlendirilmiştir. **Bulgular:** DEHB gurubunun daha düşük KIDMED puanlarına ve daha kötü AD uyum düzeylerine sahip oldukları saptanmıştır. AD'ne "iyi düzeyde uyuma" göre "orta düzeyde uyum" DEHB tanı riskini iki kat, "düşük düzeyde uyum" ise beş kat arttırmaktadır. Ayrıca toplam KIDMED puanları ve AD'ne uyum düzeyleri ile dikkatsizlik semptomları arasında negatif korelasyon gözlenmiştir. **Sonuç:** Sağlıklı bir diyete (AD) uyumun daha düşük DEHB tanı oranları ve daha düşük şiddette dikkatsizlik problemleriyle ilişkili olduğu gözlenmiştir ve bu "sağlıklı bir diyetin" yalnızca DEHB'nin ortaya çıkmasında değil, kliniğinde de etkili olduğunu göstermektedir. Ancak nedensellik ilişkisini açığa çıkarmak ve diyetsel girişimlerin DEHB bulgularını düzeltip düzeltemeyeceklerini saptamak için ileri araştırmalara ihtiyaç vardır.

Anahtar Sözcükler: Akdeniz diyeti, dikkat eksikliği ve hiperaktivite bozukluğu, semptomatoloji

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD); is a relatively common neurodevelopmental disorder of child and adolescent age group which can persist through adulthood and it is characterized by symptoms such as; inattention during academic and/or daily life tasks, distractibility, hyperactivity and inadequate impulse control (1). In DSM-IV classification system, ADHD is divided into three diagnostic categories based upon the severity of the symptom clusters such as; "predominantly inattentive type", "predominantly hyperactive type" and "combined type" (2). Worldwide prevalence of ADHD is reported to be between 5.9% - 7.1% among children and adolescents and these rates tend to change according to age and gender (3). ADHD is more common among males compared to females and younger age groups compared to older age groups (4).

Much like other neurodevelopmental disorders, etiology of ADHD is multifactorial. Despite the dominant role of the genetic factors in ADHD etiology; numerous studies report that environmental factors such as gestational, perinatal and diet related features are also important (5). Lead/mercury exposure, organophosphates, nutrition qualities, lifestyle features and psychosocial factors are some of the environmental factors which are thought to be effective in the pathophysiology of ADHD (6). Even though the exact effect of nutritional factors on ADHD is still unclear; several studies have shown that they play an important role on the emergence of certain behavioral disorders of childhood and adolescence (7). Low blood zinc/iron/copper levels, inadequate omega-3 fatty acid intake, artificial food colorants, chemical food preservatives and unhealthy diet (high refined sugar/saturated fatty acid intake, low fruit and/or vegetable consumption) are some of the nutritional factors which are reported to be related to ADHD (8–11).

In the light of these literature findings, a healthy diet can have positive effects in the context of diagnosis and clinical features of ADHD and Mediterranean diet (MD) is the best-known and well-acknowledged type of healthy diet which includes almost all of the nutritional elements in the best balanced proportions (12). In this aspect, primary aim of our study is to determine if there are any differences between ADHD and control groups regarding their adherence to MD. Secondary aim of our study is to explore the effects of MD on the symptom severity of patients with ADHD diagnosis.

METHOD

Study Design

Our case group consisted of children and adolescents between the ages of 6 – 18 who were referred to Child and Adolescent Psychiatry unit of the institution, did not use any psychiatric treatment previously and received ADHD diagnosis according to semi-structured psychiatric interviews (Schedule for Affective Disorders and Schizophrenia for School Aged Children Kiddie-SADS-lifetime Version [K-SADS-PL]) done by trained professionals. Children and adolescents between the ages of 6 – 18 who were referred to our unit, did not use any psychiatric treatment previously and did not receive any psychiatric diagnosis according to semi-structured psychiatric interviews (K-SADS-PL) were included in the control group. Power analysis was conducted using G*Power analysis program and for effect size (d) 0.5, Type I Error (α) 0.05, Type II Error (β) 0.05 and power (1-β) 95%; the sample size was calculated as 105 for each group (total sample size of 210) (13). Informed consent was obtained from both the children/adolescent and his/her parent/legal guardian prior to the study. Individuals with mental retardation or autism spectrum disorder diagnosis, psychotic symptoms, previous ADHD diagnosis and/or treatment and history of using nutritional supplements (vitamins/minerals) were excluded from the study. Total of 233 participants (113 for case and 120 for control group) were included in our study and their heights and weights were measured and recorded. Their corresponding body-mass index (BMI) percentiles were calculated according to the study of Neyzi et al. (2008) done in Turkish population (14).

Measurement Tools

Sociodemographic and Clinical Data Form: This form was designed by researchers in order to examine the age, gender, height, weight, BMI value/percentile, are of living, physical illnesses, age of mother/father, education level of mother/father, employment status of mother/father, marital status of mother/father and level of family income of the participants.

Schedule for Affective Disorders and Schizophrenia for School Aged Children Kiddie-SADS-Lifetime Version (K-SADS-PL): This semi-structured psychiatric interview was adapted from original K-SAD-P by Kaufman et al. (1997) in order to use for evaluating the psychiatric disorders seen in childhood and adolescence (15). This interview is administered to both the children/adolescents and their parents and it includes five diagnostic appendices (mood disorders, psychotic disorders, anxiety disorders, conduct disorders and substance use/other disorders) and their their sub-diagnostic appendices. K-SADS-PL was found to be a reliable and valid tool in Turkish language (16).

Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale – Parent form (Turgay): This scale, which was originally developed by Turgay, is used to screen for disruptive behavior disorders based on the diagnostic criteria of DSM-IV (17). Validity and reliability study of Turgay Form in Turkish population was done by Ercan and colleagues (18). It consists of total of 41 items which include; 9 items screening for "inattention" (Turgay–IA), 9 items screening for "hyperactivity and impulsivity" (Turgay–HAI), 8 items screening for "oppositional defiant behavior" (Turgay–OD) and 15 items screening for "conduct disorder" (Turgay–CD). All items are scored between 0 – 3 points. It indicates clinically important situations which need further evaluation if the individual receives 2 or 3 points from at least 6 items of Turgay-IA, at least 6 items of Turgay-HAI, at least 4 items of Turgay-OD or at least 3 items of Turgay-CD.

Mediterranean Diet Quality Index (KIDMED): This scale was developed by Serra-Majem et al. (2004) in order to examine the adherence of children and adolescents to MD and it includes total of 16 items (19). In consists of 12 favorable and 4 unfavorable items; answering "yes" to a favorable item is scored as +1 whereas answering "yes" to an unfavorable question is scored as -1. Answering "no" to any item is scored as 0 and total KIDMED scores range between 0 – 12. Total KIDMED scores of ≥8 represent "high adherence", 4 – 7 represent "medium adherence" and ≤3 represent "low adherence" to MD. Kabaran et al. (2013) successfully translated and used KIDMED in Turkish children and adolescents (20).

The study was conducted in accordance with the ethical guidelines, including the World Medical Association (1975) Declaration of Helsinki 2008, and the legal requirements of the Ethics Committee of the institution it was conducted in (approval no: 2021/123).

Statistical Analysis

Statistical analysis of our study was done with Social Sciences software version 21.0 (21). Mean and standard deviation (±SD) values were given for continuous data; whereas number and percentages were given for categorical data. Kolmogorov-Smirnov test was used to check whether the continuous data were normally distributed. In order to compare continuous data between groups; Independent T-test was used for parametric and Mann Whitney-U (MWU) test was used for non-parametric data. Categorical data were analyzed using Chi-Square or Fisher's Exact test. Evaluation of the correlations between variables was done by Pearson Correlation test for continuous data and Spearman Correlation test for ordinal data. Correlation coefficient values between ±0.50 and ±1 are considered as a "high degree (strong)", between ±0.30 and ±0.49 are considered as a "moderate degree (medium)" and between ±0.01 and ±0.29 are considered as a "low degree (small)" correlation. Effect of adherence to MD on ADHD diagnosis was evaluated by logistic regression analysis and odds ratio (OR) and 95% confidence intervals (95% CI) were given. The value of $p<0.05$ was accepted as statistically significant.

Table 1: Comparison of sociodemographic features and Mediterranean diet habits between attention deficit - hyperactivity disorder patients and healthy controls.

	Case	Control	Z	p
	Mean (–SD)	Mean (–SD)		
Age (Years)	9.16 (–2.82)	9.35 (–3.25)	-0.058	0.954
Weight (kg)	36.88 (–15.36)	37.93 (–16.21)	-0.450	0.653
Height (cm)	136.63 (–15.94)	138.69 (–19.18)	-0.570	0.569
Mother s Age (Years)	37.99 (–6.08)	38.66 (–5.70)	-1.147	0.251
Father s Age (Years)	42.82 (–6.69)	42.19 (–6.72)	-0.763	0.446
BMI	18.97 (–4.31)	19.06 (–4.48)	-0.128	0.898
KIDMED (Total Score)	4.48 (–2.49)	6.05 (–2.32)	-4.697	**<0.001**
Fruit or fruit juice daily	0.57 (–0.50)	0.73 (–0.44)	-2.675	**0.007**
Second serving of fruit daily	0.47 (–0.50)	0.46 (–0.50)	-0.099	0.921
Fresh or cooked vegetables daily	0.33 (–0.47)	0.69 (–0.46)	-5.561	**<0.001**
Fresh or cooked vegetables >1/day	0.20 (–0.40)	0.45 (–0.50)	-4.095	**<0.001**
Regular fish consumption (?2-3/week)	0.40 (–0.49)	0.37 (–0.49)	-0.443	0.658
Fast-food more than once a week	-0.38 (–0.49)	-0.29 (–0.46)	-1.338	0.181
Legumes/Pulses more than once a week	0.57 (–0.50)	0.71 (–0.46)	-2.234	**0.025**
Pasta or rice consumption ?5/week	0.73 (–0.45)	0.37 (–0.49)	-5.410	**<0.001**
Cereals or cereal product (bread) for breakfast	0.58 (–0.50)	0.56 (–0.50)	-0.397	0.691
Regular nut consumption (?2-3/week)	0.61 (–0.49)	0.65 (–0.48)	-0.734	0.463
Use of olive oil at home	0.73 (–0.45)	0.89 (–0.31)	-3.255	**0.001**
Skipping breakfast	-0.27 (–0.44)	-0.08 (–0.27)	-3.739	**<0.001**
Dairy products for breakfast	0.63 (–0.48)	0.73 (–0.45)	-1.504	0.132
Commercially baked goods or pastries for breakfast	-0.62 (–0.49)	-0.29 (–0.46)	-4.959	**<0.001**
Two cups of yogurt and/or >40 g cheese	0.63 (–0.49)	0.72 (–0.45)	-1.486	0.137
Sweets and candy several times everyday	-0.73 (–0.45)	-0.62 (–0.49)	-1.714	0.087

SD, standard deviation; kg, kilogram; cm, centimeter; BMI, body-mass index; KIDMED, Mediterranean Diet Quality Index
Mann-Whitney U test, statistically significant p values are written in bold.

RESULTS

There were no statistically significant differences between groups regarding their age, gender, area of living, physical illnesses, weight, height, BMI score/percentile, ages/education level/employment status/marital status of their mothers/fathers and level of family income (Table 1 and 2). ADHD group scored significantly worse on KIDMED-Total compared to control group ($p<0.001$, MWU test, Table 1). There was also a statistically significant difference between groups regarding their levels of adherence to MD [$\chi2(1, N=233) =17.891$, $p<0.001$, Table 2]. ADHD group consumed vegetables less ($p<0.001$, MWU test), legumes/pulses less ($p=0.025$, MWU test), olive oil less ($p=0.001$, MWU test), pasta/rice more ($p<0.001$, MWU test), commercially baked goods/pastries more ($p<0.001$, MWU test) and skipped breakfast more often ($p<0.001$, MWU test). All item differences of KIDMED between groups are summarized on Table 1.

Table 2: Comparison of categorical data between ADHD patients and healthy controls.

	Number (Percentage)		?²	p
	Case (*n=120*)	Control (*n=113*)		
Gender				
Female	41 (34.2%)	45 (39.8%)	0.800	0.371
Male	79 (65.8%)	68 (60.2%)		
Area of Living				
High Population	60 (50%)	57 (50.4%)		
Medium Population	48 (40%)	48 (42.5%)	0.667	0.716
Low Population	12 (10%)	8 (7.1%)		
Physical Illness				
Not Present	108 (90%)	94 (83.2%)	2.343	0.126
Present	12 (10%)	19 (16.8%)		
Marital Status of Parents				
Married/Together	113 (94.2%)	110 (97.3%)		0.335
Divorced/Separated	7 (5.8%)	3 (2.7%)		
Education Level of Mother				
Primary/Middle School	64 (53.3%)	67 (59.3%)		
High School	31 (25.8%)	21 (18.6%)	1.783	0.410
University/Degree	25 (20.8%)	25 (22.1%)		
Employment of Mother				
Working in a Job	21 (17.5%)	17 (15.0%)	0.257	0.612
Unemployed	99 (82.5%)	96 (85.0 %)		
Education Level of Father				
Primary/Middle School	53 (44.2%)	53 (46.9%)		
High School	47 (39.2%)	38 (33.6%)	0.839	0.657
University/Degree	20 (16.7%)	22 (19.5%)		
Employment of Father				
Working in a Job	96 (80.0%)	88 (77.9%)		
Unemployed	13 (10.8%)	16 (14.2%)	0.648	0.723
Retired	11 (9.2%)	9 (8.0%)		
Level of Family Income				
Low	16 (13.3%)	11 (9.7%)	0.736	0.391
Middle/High	104 (86.7%)	102 (90.3%)		
Adherence to MD				
Low Adherence	45 (37.5%)	18 (15.9%)		
Medium Adherence	59 (49.2%)	61 (54.0%)	17.891	**<0.001**
High Adherence	16 (13.3%)	34 (30.1%)		
BMI Percentile				
<5	8 (6.7%)	13 (11.5%)		
5 15	5 (4.2%)	9 (8.0%)		
15 25	6 (5.0%)	4 (3.5%)		
25 50	20 (16.7%)	16 (14.2%)	7.603	0.369
50 75	27 (22.5%)	14 (12.4%)		
75 85	13 (10.8%)	16 (14.2%)		
85 95	18 (15.0%)	20 (17.7%)		
>95	23 (19.2%)	21 (18.6%)		

MD, Mediterranean diet; BMI, body-mass index
Chi-Square test, statistically significant p values are written in bold.
Fisher s Exact Chi-Square test, statistically significant p values are written in bold.

In the correlation analyses conducted in ADHD group; there were negative correlations between KIDMED-Total and Turgay-IA scores ($r=-0.202$, $p=0.027$, Pearson correlation); legumes/pulses consumption and Turgay-HAI scores ($r=-0.222$, $p=0.010$, Pearson correlation), Turgay-OD scores ($r=-0.205$, $p=0.024$, Pearson correlation), Turgay-CD scores ($r=-0.187$, $p=0.041$, Pearson correlation); and adherence level to MD and Turgay-IA scores ($\rho=-0.251$, $p=0.006$, Spearman correlation). Results of the correlation analyses are summarized on Table 3. Furthermore we examined the effect of adherence to MD on ADHD diagnosis and found that compared to "high adherence" to MD; "medium adherence" to MD increased the likelihood of ADHD diagnosis 2.06 fold (95% CI = 1.03 – 4.11, $p=0.042$) whereas "low adherence" to MD increased the likelihood of ADHD diagnosis 5.31 fold (95% CI = 2.73 – 11.91, $p<0.001$, Table 4).

DISCUSSION

In this study, we found that ADHD patients had lower overall KIDMED scores and worse adherence to MD compared to healthy controls. In fact, according to our analyses, individuals with "medium adherence" to MD were twice likely and individuals with "low adherence" to MD were five times likely to be diagnosed with ADHD. In addi-

Table 3: Correlations between Mediterranean diet habits and attention deficit - hyperactivity disorder symptoms.

Correlations		Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale Parent form				
		Inattention	Hyperactivity/ Impulsivity	OD Behavior	Conduct Disorder	Total Score
KIDMED Total Score	r	**-0.202**	0.015	0.042	-0.002	-0.043
	p	**0.027**	0.870	0.646	0.980	0.643
Fruit or fruit juice daily	r	-0.152	0.023	0.008	0.045	-0.028
	p	0.097	0.803	0.935	0.626	0.761
Second serving of fruit daily	r	-0.054	-0.008	0.100	0.025	0.018
	p	0.555	0.931	0.277	0.788	0.846
Fresh or cooked vegetables daily	r	0.280	0.046	0.099	0.148	0.016
	p	0.060	0.620	0.280	0.106	0.858
Fresh or cooked vegetables >1/day	r	-0.151	-0.040	0.060	-0.003	-0.044
	p	0.100	0.668	0.514	0.977	0.637
Regular fish consumption (?2-3/week)	r	-0.051	0.083	0.071	0.022	0.053
	p	0.582	0.369	0.443	0.808	0.567
Fast-food more than once a week	r	-0.056	0.082	-0.025	-0.135	-0.015
	p	0.540	0.374	0.788	0.142	0.872
Legumes/Pulses more than once a week	r	-0.092	**-0.233**	**-0.205**	**-0.187**	**-0.241**
	p	0.318	**0.010**	**0.024**	**0.041**	**0.008**
Pasta or rice consumption ?5/week	r	-0.018	-0.013	-0.121	-0.054	-0.067
	p	0.846	0.892	0.188	0.559	0.465
Cereals or cereal product (bread) for breakfast	r	0.025	0.080	0.092	0.067	0.086
	p	0.784	0.383	0.317	0.466	0.352
Regular nut consumption (?2-3/week)	r	-0.030	0.000	0.006	-0.017	-0.012
	p	0.746	0.996	0.945	0.856	0.899
Use of olive oil at home	r	-0.162	0.055	0.091	0.140	0.045
	p	0.076	0.549	0.323	0.053	0.625
Skipping breakfast	r	0.088	-0.024	0.134	0.170	0.100
	p	0.336	0.793	0.143	0.051	0.277
Dairy products for breakfast	r	-0.067	0.088	0.051	-0.043	0.028
	p	0.469	0.337	0.583	0.641	0.763
Commercially baked goods or pastries for breakfast	r	0.140	0.028	-0.120	-0.107	-0.114
	p	0.053	0.763	0.191	0.244	0.217
Two cups of yogurt and/or >40g cheese daily	r	0.015	0.084	0.023	0.000	0.048
	p	0.871	0.360	0.806	1.000	0.604
Sweets and candy several times every day	r	-0.042	-0.141	0.003	-0.104	-0.091
	p	0.649	0.123	0.974	0.258	0.324
Adherence to Mediterranean diet	?	**-0.251**	0.010	0.061	-0.020	-0.029
	p	**0.006**	0.917	0.508	0.826	0.755
BMI Percentiles	?	0.102	0.022	0.113	0.107	0.096
	p	0.267	0.810	0.219	0.243	0.295

OD, oppositional-defiant; KIDMED, Mediterranean Diet Quality Index; BMI, body-mass index

Pearson correlation coefficients (r) were given for continuous data, Spearman correlation coefficients (?) were given for categorical data, statistically significant p values are written in bold.

tion, total KIDMED scores and adherence level to MD were negatively correlated with inattention scores on Turgay scale. Research done by Martin et al. (2018) is one of the few studies which investigate the relationship between MD and ADHD and they found that ADHD patients scored significantly lower on KIDMED overall (7). Also number of individuals who scored 8 and higher on KIDMED (indicative of a healthy diet) was significantly lower in ADHD group compared to healthy controls (7). Rios-Hernandez et al. (2017) have also reported lower KIDMED scores in ADHD patients and children and adolescents with a "low adherence" to the MD were more likely to be associated with an ADHD diagnosis (RR: 2.80; 95% CI: 1.54–5.25)

Table 4: Logistic regression for attention deficit - hyperactivity disorder diagnosis by categories of adherence to Mediterranean diet.

	p	Odds Ratio	95% Confidence Interval
Adherence to Mediterranean Diet			
High (n=50)	-	1 (reference)	-
Medium (n=120)	**0.042**	2.06	1.03 4.11
Low (n=63)	**<0.001**	5.31	2.37 11.91
Constant	0.013	0.47	

(22). A cohort study examining the effects of an unhealthy dietary pattern ("Western Type" which includes high intakes of fat, refined sugars and sodium and low intakes of fibre, folate and omega-3 fatty acids) has found significant associations with ADHD diagnosis (9). Another case-control study showed that traditional-healthy Korean dietary pattern was associated with a lower probability of ADHD diagnosis compared to an unhealthy dietary pattern (11). In addition to all of these previous data, we found a direct effect of MD on both ADHD diagnosis and also inattention symptoms. Adherence to a healthy diet (MD in this case) seems to be related to lesser inattention problems and this indicates the importance of a "healthy diet" not only in the occurrence of the disorder, but also in the clinical symptomatology.

When we investigated the items included in KIDMED; we found that ADHD patients had lower vegetables, legumes and olive oil and higher pasta/rice and commercially baked good/pastry consumption rates. Regarding these features, studies in this field report varying results: Martin et al. (2018) reported higher commercially baked good/pastry and lower fish and cereal consumption; whereas Rios-Hernandez et al. (2017) reported lower fruit, vegetable, pasta/rice and higher fast-food consumption in ADHD group compared to control group (7,22). Lower vegetable intake in our ADHD group is parallel with the study done by Park et al. (2012) in which a negative correlation between vegetable consumption rates and inattention scores was observed (10). In addition, one clinical trial have also reported an association between high intake of vegetables and fewer attentional/behavioral problems in children and adolescents with ADHD (23). There are numerous evidence on positive effects of vegetables on cognitive function and psychological well-being which are attributed to their high content of antioxidant and anti-inflammatory properties (24–26).

Another important difference between our study groups was regarding their pulse/legume intake. In addition to significantly lower pulse/legume consumption rates seen in our ADHD group, we also found negative correlations between pulse/legume consumption rates and hyperactivity/impulsivity, oppositional-defiant and conduct problems. To our

knowledge this study is the first one report a direct relationship between pulse/legume intake and ADHD symptomatology; but these findings should be approached with caution because data regarding effects of legumes/pulses on psychological well-being are paradoxical. On one hand pulses/legumes are low in fat and rich in protein/fibre/minerals/vitamins, have low glycaemic index and certain amounts of non-nutritional factors (such as isoflavones); all of which link them with various health-promoting properties (27). On the other hand pulses/legumes contain a large number of unhealthy components, including phytates which could block the body's uptake of essential minerals like magnesium, calcium, iron and especially zinc (28). Also isoflavone content of pulses/legumes can potentially be problematic as the chemical structure of isoflavones is similar to that of oestrogen, so they can mimic oestrogen's effect on the human body (29). Testosterone is suggested as a particularly relevant risk factor for disruptive behavior disorders (oppositional-defiant and conduct disorder) and linked to hyperactive-impulsive ADHD symptoms in preschool-age children (30). In the light of these literature findings, reverse relationship between pulse/legume intake and hyperactivity/impulsivity, oppositional-defiant and conduct symptoms that we observed might reflect the possible protective effect of a high-oestrogenic state caused by pulse/legume consumption. Along with potential hormonal effects of pulses/legumes; hormonal factors underlying pathophysiology and symptomatology of ADHD and disruptive behavior disorders are candidates for further investigation.

Furthermore, our ADHD patients reported significantly lower olive oil intake rates compared to healthy volunteers. Several studies have found that olive oil has mild anti-anxiety and memory enhancing effects together with their antioxidant properties (31). In laboratory experiments, it was shown that olive oil improves learning and memory in mice (32). Researchers have explained the memory-enhancing effects of olive oil in terms of antioxidant properties of active components, including hydroxytyrosol, tyrosol, oleuropein, deacetoxyligstroside aglycon, and acetoxypinoresinol (33). In addition, olive oil consumption was associated with decreased brain serotonin and dopamine metabolisms which play major role in pathophysiology of ADHD and this potentially shed light on relationship between low olive oil intake and ADHD (4,34).

Several researchers have reported an association between increased risk of ADHD and sugar, artificial food colorants and preservatives (8,35). Junk foods (which are generally high in fat, sugar, additives, artificial food colorings and preservatives) might negatively affect ADHD symptoms (36). Wiles et al. (2009) have demonstrated a possible longitudinal relationship between a 'junk food' diet at age 4 and hyperactivity at age 7 (37). Furthermore, Lien et al. (2006) found a general relationship between sugar consumption and hyperactive behavior in a large sample of adolescents (38). We showed that children and adolescents with ADHD consumed more pasta/rice (which include high carbohydrate) and commercially baked goods/pastries (which also include high carbohydrate and possibly artificial food colorants and/or preservatives). Even though our findings are conflicting with the previous research on MD/ADHD interaction; it can be speculated that high pasta/rice and commercially baked good/pastry intake of ADHD patients might fall into same scope as a diet with high sugar, artificial food colorants and preservatives (7,22).

Another major difference between ADHD group and healthy controls which has been repeatedly observed in both our study and previous studies on ADHD/MD interaction is "skipping breakfast". All of the evidence on this subject suggests that children and adolescents with ADHD skipped breakfast more often compared to their counterparts (7,22). Wesnes et al. (2003) have found that skipping breakfast or substituting it for a sugary drink impairs attention and episodic memory in children (39). Several researchers suggested that in addition to analyzing the impact that a single food component may have on ADHD, the role of dietary patterns as a whole (e.g. three regular meals a day) can be more informative (40). Public health authorities promote provision-of-breakfast initiatives since three regular meals, especially breakfast, improve cognitive function and academic performance (41). Park et al. (2012) found that children who usually have three regular meals a day showed

lower odds of probable ADHD compared to the children who seldom have them (10). Another study reported that ADHD patients displayed more disruptive patterns of eating behaviors and exhibited markedly diminished adherence to a traditional breakfast, lunch, and dinner schedule, which was linked to a significantly higher frequency of irregular eating times (42). Even though direct interaction between "skipping breakfast" and ADHD is widely unclear; unbalanced diet can lead to deficiencies in essential nutrients or substituting it with a snack might result in higher intakes of certain food components (e.g. food additives, sugar) (43). However, possible reverse causation between ADHD and disrupted dietary patterns should not be overlooked in this matter (9). Impulsivity and oppositional-defiant/conduct problems which are frequently seen among ADHD patients, may result in a more chaotic lifestyle, noncompliance with parents' instructions about eating behaviors and less structured meal times (10). Skipping regular meals and/or substituting them with unhealthy food can potentially lower the diet quality and eventually lead to a low intake of certain nutrients which may induce certain nutritional subclinical deficiencies and, hence, worsen ADHD symptoms. In return, individuals with ADHD might experience more severe behavioral problems and end up in a vicious cycle of symptom exacerbation – unhealthy dietary patterns (7,44,45).

To our knowledge, this is one of the few studies done on MD habits of ADHD patients and first one to evaluate the effects of MD on ADHD symptomatology. By including drug naïve ADHD patients and matching them with healthy controls regarding their age/sex/height/weight/BMI, we minimized the effects of possible confounding factors and we believe this is the major strength of our study. Apart from these, some limitations of our research should also be acknowledged. Major limitation of our study is the case – control design which may hinder our ability to establish a causal relationship between the parameters that were analyzed. It should also be emphasized that, even though ADHD diagnoses were done according to semi-structured psychiatric interviews; other data which we explored were gathered according to self-reports and for this reason they are prone to some disruptions. Furthermore, our study was conducted in a single center so it might reflect only a portion of the population rather than a more comprehensive observation.

CONCLUSION

In conclusion, we found a positive relationship between a lower adherence to the MD and ADHD diagnoses. Also MD habits seem to be related to the inattention symptoms seen among ADHD patients. Another curious finding is the possible relationship between pulse/legume consumption and hyperactivity-impulsivity, oppositional-defiant behavior and conduct problems which warrants further research due to the potential hormonal effects of pulses/legumes. Our results suggest that certain dietary habits may play a role in both ADHD development and clinical appearance; but further evaluation is needed to shed light on causality and to determine if dietary manipulation could ameliorate ADHD symptoms.

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ARAŞTIRMA MAKALESİ

COVID-19 pandemi öncesi ve sırasında bir üniversite hastanesi çocuk psikiyatri polikliniğine yapılan başvuruların karşılaştırması

Evaluation of the psychiatric diagnosis of children and adolescents before and during the COVID-19 pandemic: A sample from a university hospital

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ÖZET

Amaç: Çin'de başlayan ve tüm dünyayı etkileyen COVID-19 salgını global bir sağlık krizine dönüşmüştür. Bu çalışmanın amacı, COVID-19 pandemisi sırasında psikiyatri polikliniğine başvuran çocuk ve ergenlerin sosyodemografik özelliklerini ve psikiyatrik tanılarını belirlemektir. **Yöntem:** AFSÜ çocuk psikiyatri polikliniğine Eylül 2019-Mart 2020 ve Eylül 2020-Mart 2021 tarihleri arasında başvuran hastalar çalışmaya dahil edilmiştir. Hastalar retrospektif olarak Nucleus® poliklinik sistemi ile taranmıştır. Veriler SSPS 21.0 ile analiz edilmiştir. Vakaların yaş, cinsiyet ve psikiyatrik tanıları incelenmiştir. **Bulgular:** Çalışmaya 1157 hasta dahil edilmiştir. Hastaların yaş ortalaması 10,8 yıl ve %61,5'i erkek cinsiyetteydi. Hastaların %53,8'i (n=622) pandemi öncesinde, %46,2'si (n=535) pandemi sonrasında başvuru yapmıştır. Pandemi sonrası dönemde, pandemi öncesi döneme göre başvurular kız cinsiyet yönünde artmıştır (p=0,017) ve başvuranların yaş ortalaması azalmıştır (p=0,035). Pandemi öncesinde başvuranların %40,0'ı Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB), %16,1'i Anksiyete Bozukluğu (AB), %5,1'i Otizm Spektrum Bozukluğu (OSB) ana tanısı alırken, pandemi sonrası başvuranların %27,3'ü DEHB, %19,3'ü AB, %5,6'sı OSB ana tanısı almıştır. Pandemi sonrasında pandemi öncesine göre DEHB tanısı alma sıklığı azalmıştır (p<0,001), AB (p=0,024) ve Major Depresif Bozukluk (MDB) (p=0,001) tanılarında artış görülmüştür. **Sonuç:** Çalışmamızda pandemi sonrası AB ve MDB tanılarının artış gösterdiği, DEHB tanısının ise azaldığı görülmüştür. Pandemi sırasında uzaktan eğitim sürecine geçilmesi, DEHB belirtileri nedeniyle yapılan başvuruları azaltırken ortaya çıkan fiziksel ve sosyal kısıtlılıklar AB ve MDB tanılarını arttırmış olabilir. Bu dönemde DEHB gibi mevcut psikiyatrik bozukluğu olan hastaların takiplerinin ve tedavilerinin aksatılmaması uzun dönemde gidişat için önem arz etmektedir.

Anahtar Kelimeler: COVID-19, pandemi, psikolojik etki, çocuk, ergen.

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SUMMARY

Objective: The aim of this study is to determine the sociodemographic characteristics and psychiatric diagnoses of children and adolescents who refered to the psychiatry outpatient clinic during the COVID-19 pandemic. **Method:** This study enrolled the patients who were presented to the Child and Adolescent Psychiatry outpatient clinic between September 2019 and March 2020 and between September 2020 and March 2021. The patients were scanned retrospectively with the Nucleus® outpatient clinic system. The data were analyzed with SSPS 21.0. Age, gender and psychiatric diagnosis of patients were examined. **Results:** This study enrolled 1157 patients with 10.8 mean age and 61.5% male participants. 53% (n=622) of patients was diagnosed before pandemia and 46.2% (n=535) of patients was diagnosed during pandemia. Before pandemia: patients were diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) 40%, Anxiety Disorder (AD) 16.1%, Autism Spectrum Disorder (ASD) 5.1%. During pandemia: patients were diagnosed with ADHD 27.3%, AD 19.3%, ASD 5.6%. During the pandemia the number of female patients increased (p=0.017), mean age of patients decreased (p=0.035), the diagnosed ADHD rates decreased (p<0.001) and the diagnosed AD (p=0.024), Major Depressive Disorder (MDD) (p=0.001) rates increased. **Conclusion:** In our study the diagnosis of AD and MDD during pandemia increased and the diagnosis of ADHD decreased. Because of the online education during pandemia, number of ADHD patients decreased and increasing in diagnosis of AD and MDD might caused by phsycial and social limitations. İn this period it is important to follow and treat the patients that already have psychiatric disorder like ADHD.

Key Words: COVID-19, pandemic, psychological effects, child, adolescents

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GİRİŞ

COVID-19 virüsü, SARS-CoV ve MERS-CoV'unda içinde bulunduğu beta-coronavirus ailesi içinde yer alan bir virüs türüdür (1). 2019 yılının sonunda Çin'in Wuhan kentinde ortaya çıkan COVID-19 hastalığı, Dünya Sağlık Örgütü tarafından Mart 2020'de "pandemi" olarak ilan edilmiştir (2). Dünya çapında yüz binlerce insanın enfekte olmasıyla birlikte çoğu ülke sayısız ölümle karşı karşıya kalmış ve pandemi ile mücadelede kısıtlayıcı birçok tedbir uygulamıştır.

Pandemi sürecinde okulların kapatılması ve sokağa çıkma yasağı gibi uygulanan tedbirler, çocuklar ve gençlerin günlük yaşantıları ve rutinlerinde önemli değişiklikler meydana getirmiştir (3). UNESCO verilerine göre, 8 Nisan 2020 itibariyle 188 ülkede eğitime ara verilmiş ve tüm dünyada öğrencilerin %90'ından fazlası (1,5 milyar genç) eğitimden mahrum kalmıştır (4). Türkiye'de de 11 Mart 2020'de ilk vakanın görülmesinin ardından, virüsün yayılmasını önlemek için pek çok önlem alınmıştır. Bu önlemler kapsamında 23.03.2020 tarihinde okullar kapatılarak uzaktan eğitim sistemine geçilmiş ve 20 yaş altı için 04.04.2020 tarihi itibariyle sokağa çıkma yasağı uygulanmıştır (5). Ayrıca bu önlemlerin gençlerde sosyal uzaklaşma, anksiyete ve korku gibi psikolojik sorunlara yol açabileceği düşünülerek öğrenciler ve aileler için çeşitli psikososyal rehberler hazırlanmıştır (6).

Çocuklar ve gençlerin hızla değişen bilişsel ve fiziksel süreçleri, sosyal ortamlarda kurulan sağlıklı ilişkiler ile gelişir. Bu nedenle çocukların akranları ile sosyal temas ve ilişki içinde olmaları normal psikolojik gelişimlerinde önemli bir rol oynar (7). Okullar örgün eğitim ve öğretimin yanı sıra çocuk ve gençlerin akranları ile sosyal ilişki kurmalarını sağlayan, bilişsel ve duygusal gelişimi destekleyen ortamlardır. Ergenlikte ön plana çıkan ayrışma/bireyleşme sürecinin önemli bir kısmı okullarda ve akran ilişkilerinin gerçekleştiği ortamlarda yaşanmaktadır. Okulların eğitim dışında sosyalleşme ve zamanı yapılandırma açısından da önemli olduğu göz önüne alındığında, uzaktan eğitim çocukların akran ilişkilerini kısıtlayabilmekte, stres düzeyini artırabilmekte, uyku- uyanıklık döngüsünü bozarak depresyon ve kaygı gibi içe yönelim sorunlarını artırabilmektedir (8,9). Pandemi sırasında çocukların ve gençlerin psikolojik tepkileri yetişkinlerinkine oldukça benzesede; çocuğun yaşı, algılama yeteneği, doğuştan sahip olduğu baş etme becerileri ve hali hazırda psikolojik rahatsızlıklarının olması psikolojik tepkilerinde farklılıklar doğurabilir. (7,10). Pandemi sürecinde ortaya çıkan tüm bu yaşam tarzı değişiklikleri çocuk ve gençlerin hali hazırda olan ruhsal sorunlarını kötüleştirebilir. Bu nedenle pandeminin ruh sağlığını nasıl etkilediğine veya bu tür pandemi dönemlerinde ruhsal bozukluk riskini veya dayanıklılığı artıran faktörlere ilişkin araştırmalara ihtiyaç doğduğu görülmektedir. Çalışmamızın hipotezi: pandemi sürecinde alınan önlemler ile akranlarından ve okuldan uzaklaşmak zorunda kalan çocuklar ve ergenlerde, depresyon ve kaygı bozukluğu tanılarının artacağıdır.

Çalışmamızda çocuk psikiyatri polikliniğine pandemi öncesi ve pandemi sırasında başvuran çocuk ve gençlerin dosyaları incelenerek, pandemi döneminde uygulanan kısıtlamaların, alınan önlemlerin ve değişen koşulların çocuk ve gençlerin ruh sağlığına etkisini araştırmayı hedefledik.

YÖNTEM

Çalışmaya Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Hastanesi Çocuk Psikiyatri Polikliniği'ne 1 Eylül 2019- 1 Mart 2020 tarihleri arasında (pandemi öncesinde) başvuran 622 hasta ve 1 Eylül 2020-1 Mart 2021 tarihleri arasında (pandemi sırasında) başvuran 535 hasta dahil edilmiştir. Ülkemizde 1 Haziran 2020 tarihinden sonra "kontrollü normalleşme" sürecine geçilmesinin ardından, hastanemizde 1 Temmuz 2020 tarihinden sonra çocuk psikiyatri polikliniğine kabul edilen hasta sayısı pandemi öncesindeki dönem ile aynı sayıya getirilmiştir. Bu nedenle pandemi öncesi dönemde başvuran hasta sayısına yakın bir hasta sayısı elde etmek için 1 Eylül 2020 tarihinden sonra polikliniğe başvuran hastalar pandemi sırasında başvuranlar olarak çalışmaya dahil edilmiştir. Katılımcıların yaş, cinsiyet gibi demografik verileri ve aldıkları tanıları, psikiyatrik tedavileri Nucleus® poliklinik sistemi ile retrospektif olarak taranmış ve incelenmiştir.

Bu araştırma Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Etik Kurul'u tarafından 02.04.2021 tarih ve 2021/228 sayılı karar ile onaylandı.

İstatistiksel Analiz

Araştırmanın istatistiksel analizi Statistical Package

Tablo 1. Sosyodemografik veriler ve pandemi öncesi/sonrası verilerin karşılaştırması

		Toplam n (%)	Pandemi öncesi n (%)	Pandemi sonrası n (%)	χ^2/u	p
Cinsiyet	Erkek	711 (%61,5)	402 (%64,6)	309 (%57,8)	5,736/-	**0,017**[a]
	Kız	446 (%38,5)	220 (%35,4)	226 (%42,2)		
Yaş (yıl)		10,83±4,51	11,13±4,41	10,49±4,59	-/154472,5	**0,035**[b]

[a]Pearson ki kare testi uygulanmıştır [b]Mann whitney u testi uygulanmıştır

for Social Science (SPSS) 21.0 programı kullanılarak yapılmıştır. Normal dağılıma uygunluk Kolmogrov,Smirnov testi, histogram ve Skewness-Kurtosis katsayılarına göre değerlendirilmiştir. Tanımlayıcı sayım verileri yüzde ve sayı ile, ölçüm verileri ortalama, standart sapma, ortanca, en az ve en çok değerleri ile sunulmuştur. Sayım verilerinde iki grubu karşılaştırmak için Pearson ki kare testi ve Fisher's exact testi, ölçüm verilerinde normal dağılıma uymadığı için iki grubu karşılaştırmada Mann Whitney U testi uygulanmıştır. Tip 1 hata düzeyi α=0,05 alınmıştır.

BULGULAR

Çalışmada 1157 hastanın verilerine erişilmiştir. Hastaların %53,8'i (n=622) pandemi öncesinde başvurmuştur. Pandemi sırasında, pandemi öncesi döneme göre kız başvuranların sayısı erkek başvuranlara göre artmıştır (p=0,017) ve başvuranların yaş ortalaması azalmıştır (p=0,035) (Tablo 1).

Pandemi öncesi başvuran hastaların %31,4'üne (n=195) ek tanı konulurken pandemi sırasında başvuran hastaların %22,2'sine (n=119) ek tanı konulmuştur. Hastaların pandemi öncesi ve sonrası dönemdeki başlıca ana tanı ve ek tanıları Şekil 1'de verilmiştir. Pandemi öncesinde başvuranların %40,0'ı Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB), %16,1'i Anksiyete Bozukluğu (AB), %11,7'si Mental Retardasyon (MR), %5,1'i Otizm Spektrum Bozukluğu (OSB) ana tanısı alırken pandemi sırasında başvuranların %27,2'si DEHB, %19,5'i AB, %5,6'sı OSB ana tanısı almıştır. Pandemi sırasında pandemi öncesine göre başvuran hastalar arasında DEHB tanısı alma sıklığı istatistiksel olarak anlamlı şekilde azalırken (p<0,001), AB (p=0,024) ve Major Depresif Bozukluk (MDB) (p=0,001) tanısı alma sıklığı artmıştır (Tablo 2).

Hastaların %58,8'inde (n=680) psikotrop ilaç reçete edilmiştir. Hastaların %57,7'sine stimülan ve non-stimülan, %27,9'una antidepresan, %11,5'ine antipsikotik ilaç reçete edildiği saptanmıştır. Pandemi sırasında, pandemi öncesi döneme göre stimülan ve non-stimülan ilaç reçetelerinin azaldığı (p<0,001), antidepresan ilaç reçetesinin arttığı (p=0,001) saptanmıştır (Tablo 3).

TARTIŞMA

Çalışmamızda COVID-19 pandemi döneminde psikiyatri polikliniğine yapılan başvurularda, psikiyatrik tanı ve tedavi özelliklerinin incelenmesi ve pandemi öncesi başvurular ile karşılaştırılması amaçlanmıştır. Pandemi sırasında, pandemi öncesi

Tablo 2. Pandemi öncesi ve sonrası başvuranlarda DEHB, AB, MDB, OSB ve OKB tanılarının karşılaştırılması

		Total (n, %)		Kız (n, %)		Erkek (n, %)	
		Pandemi öncesi	Pandemi sonrası	Pandemi öncesi	Pandemi sonrası	Pandemi öncesi	Pandemi sonrası
DEHB	Var	279 (44,9)	153 (28,6)	65 (29,5)	42 (18,6)	214 (53,2)	111 (35,9)
	Yok	343 (55,1)	382 (71,4)	155 (70,5)	184 (81,4)	118 (46,8)	198 (64,1)
	χ^2	32,490		7,345		21,099	
	p	**<0,001**		**0,007**		**<0,001**	
Anksiyete Bozukluğu	Var	130 (20,9)	142 (26,5)	82 (37,3)	93 (41,2)	48 (11,9)	49 (15,9)
	Yok	492 (79,1)	393 (73,5)	138 (62,7)	133 (58,8)	354 (88,1)	260 (84,1)
	χ^2	5,091		0,703		2,276	
	p	**0,024**		0,402		0,131	
MDB	Var	10 (1,6)	26 (4,9)	9 (4,1)	18 (8,0)	1 (0,2)	8 (2,6)
	Yok	612 (98,4)	509 (95,1)	211 (95,9)	208 (92,0)	401 (99,8)	301 (97,4)
	χ^2	10,090		2,941		7,656	
	p	**0,001**		0,086		**0,012***	
OSB	Var	32 (5,1)	31 (5,8)	6 (2,7)	4 (1,8)	26 (6,5)	27 (8,7)
	Yok	590 (94,9)	504 (94,2)	214 (97,3)	222 (98,2)	376 (93,5)	282 (91,3)
	χ^2	0,236		0,466		1,305	
	p	0,627		0,539*		0,253	
OKB	Var	3 (0,5)	6 (1,1)	0 (0,0)	3 (1,3)	3 (0,7)	3 (1,0)
	Yok	619 (99,5)	529 (98,9)	220 (100,0)	223 (98,7)	399 (99,3)	306 (99,0)
	χ^2	1,522		2,940		0,105	
	p	0,316*		0,248*		1,000*	

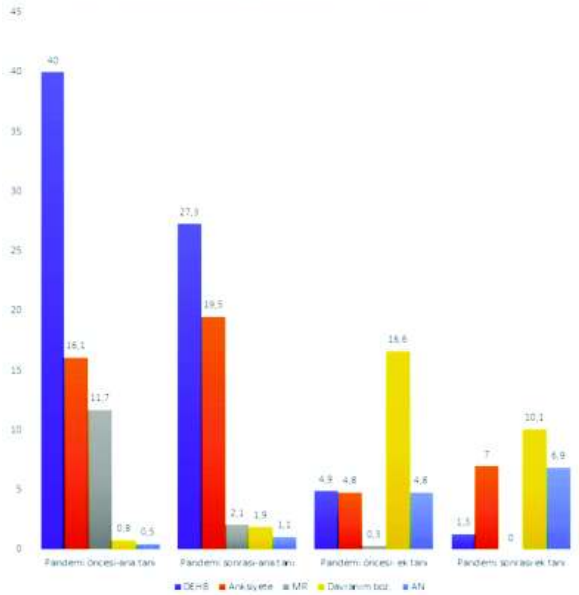
Tablo 3. Katılımcıların ilaç kullanımı ile özellikleri ve pandemi öncesi/sonrası duruma göre ilişkisi

	Toplam		Pandemi öncesi		Pandemi sonrası			
İlaç	**n**	**%**	**n**	**%**	**n**	**%**	**χ^2**	**p**
Stimülan-Nonstimülan	391	57,7	248	63,4	143	36,6	19,646	**<0,001**
Metilfenidat	264	38,9	172	65,2	92	34,8		
Atomoksetin	127	18,8	76	59,8	51	402		
Antipsikotik	79	11,5	37	46,8	42	53,2	3,168	0,075
Risperidon	49	7,2	24	49,0	25	51,0		
Arıpıprazol	24	3,5	8	33,3	16	66,7		
Ketiyapin	2	0,3	2	100,0	0	0,0		
Olanzapin	3	0,4	2	66,7	1	33,3		
Amilsülpirid	1	0,1	1	100,0	0	0,0		
Antidepresan	190	27,9	87	45,8	103	54,2	11,555	**0,001**
Sertralin	64	9,4	27	42,2	37	57,8		
Fluoksetin	103	15,1	54	52,4	49	47,6		
Essitalopram	10	1,5	5	50,0	5	50,0		
Mirtazapin	2	0,3	0	0,0	2	100,0		
İmipramin	4	0,6	1	25,0	3	75,0		
Venlafaksin	6	0,9	0	0,0	6	100,0		
Klomipramin	1	0,1	0	0,0	1	100,0		
Anksiyolitik	1	0,1	0	0,0	1	100,0	1,284	0,438*
Benzodiazepin	1	0,1	0	0,0	1	100,0		
Mood stabilizatör	2	0,3	0	0,0	2	100,0	2,571	0,192*
Lityum	2	0,3	0	0,0	2	100,0		
Valproik asit	0	0,0	0	0,0	0	0,0		
Diğer								
Hidroksizin	12	1,8	8	66,7	4	33,3		
Desmopressin	5	0,7	2	40,0	3	60,0		

döneme göre kız cinsiyette başvuruların arttığı ve başvuran hastaların yaş ortalamasının düştüğü görülmüştür. Pandemi öncesi ve sırasındaki tanı dağılımı karşılaştırıldığında; DEHB tanısının azaldığı, AB ve MDB tanılarının artmış olduğu görülmektedir.

DEHB olan çocukların işlevselliklerini bozan sorun davranışları yaşıtları ile bir arada oldukları, denetlenmeye daha çok ihtiyaç duyulan okul gibi ortamlarda daha sık göze çarpmaktadır (11). Okul döneminde dikkat eksikliği ve öğrenme güçlükleri nedeniyle akademik başarıda düşüklük olması da kliniğe sık başvuru nedenlerindendir (12). DEHB olan çocuklarda mevcut psikiyatrik bozukluğun

Şekil 1. Pandemi öncesi ve sonrası başvuranlarda ana ve ek tanı özellikleri



getirdiği güçlüklerin sınıf ortamında daha çok ortaya çıkabileceği göz önünde bulundurulduğunda; okulların pandemi sürecinde kapatılması ile DEHB'li çocuklarda güçlüklerin azalması ya da öğretmenlerin sınıf ortamında yaptıkları gözlemlerin azalmış olması çalışmamızda bulduğumuz DEHB tanısındaki azalmayı açıklayabilir. Fransa'da karantina döneminde DEHB olan çocuk ve ergenlerin COVID-19 sürecindeki psikolojik iyilik hallerinin değerlendirildiği bir anket çalışmasında; DEHB olan çoğu çocuk ve ergenin ebeveyni, bu dönemde okulla ilgili zorlanmanın daha az olduğunu, okulla ilgili kaygının azaldığını ve genel iyilik hallerinde bozulma olmadığını belirtmişlerdir (13). Bunun yanı sıra, COVID-19 pandemisi nedeniyle uzaktan eğitime geçilmesinin, DEHB olan ve olmayan ergenlerde etkisinin incelendiği bir çalışmada; DEHB'li ergenlerin, DEHB'si olmayan ergenlere göre daha fazla öğrenme güçlüğü yaşadığı ve DEHB'li ergenlerin ebeveynlerinin uzaktan öğrenmeyi yönetme ve ev-okul iletişimini destek-lemede daha fazla zorluk yaşadığı bildirilmiştir (14). COVID-19 pandemi sürecinin, normal gelişim gösteren çocuklara göre DEHB gibi mevcut nörogelişimsel bozukluğu olan çocuklar ve ailelerinde daha fazla zorlanma doğuracağı üzerinde durulmaktadır (15). Çalışmamızda DEHB'li çocuklarda ve gençlerde pandemi sürecinin psikolojik ve davranışsal etkisini değerlendiren bir ölçek kullanılmamış olması, COVID-19 pandemi sürecinin ve okulların kapanmasının DEHB'li çocuklar ve aileleri

üzerindeki etkisini yorumlamamızı güçleştirmektedir. Pandemi sürecinde evlere kapanma ile rutinlerin bozulması ve yapılandırılmış zamanın azalması, ekran bağımlılığı gibi davranışsal bağımlılıklar için riski artırabilir (16). DEHB ile internet bağımlılığı gibi davranışsal bağımlılıkların sık eşlik eden bozukluklar oldukları (17) göz önüne alındığında pandemi süreci ile DEHB'li çocuk ve ergenlerde davranışsal bağımlılıklar artabilir. Okulların açılması ile DEHB'li çocuklarda sorunların daha çok belirginleşeceği ve DEHB belirtileri ile çocuk psikiyatri polikliniklerine yapılan başvuru sayısında artış görülebileceğini ön görmekteyiz.

DEHB'nin klinik ve epidemiyolojik örneklemde cinsiyet oranına bakıldığında kızlara oranla erkeklerde daha sık görüldüğü bilinmektedir. Klinik örneklemde erkek/kız oranı 9/1 iken epidemiyolojik örneklemde 3/1 olarak bildirilmiştir (18). Pandemi öncesi döneme göre pandemi sırasında başvuruların kız cinsiyet yönünde artmasının bir açıklaması; DEHB tanısının erkek cinsiyette daha sık görülmesi nedeniyle pandemi öncesine göre polikliniğimizde DEHB tanısının azalmasıyla birlikte erkek cinsiyet başvurularının da azalmış olabileceğidir. Almanya'da COVID-19 pandemisi sırasında 7-17 yaş arası çocuk ve ergenler ve aileleri ile yapılan çevrimiçi bir anket çalışmasında; 11-13 yaş arası çocukların, 14-17 yaş arası çocuklara göre pandemiden daha olumsuz etkilenme bildirdikleri ve pandeminin olumsuz etkisinin kızlarda daha fazla olduğu ve kız cinsiyette yaşla birlikte duygusal sorunların arttığı belirtilmiştir (19). Çalışmamızda da benzer şekilde pandemi öncesine göre pandemi sırasında başvuruların yaş ortalamasının düştüğü ve kız cinsiyet yönünde arttığı görülmüştür. Pandemi öncesine göre pandemi döneminde başvuruların kız cinsiyet yönünde artmasının bir diğer açıklaması da pandemi sürecinden kızların erkeklere göre daha olumsuz etkilenmiş olabileceğidir.

Ülkemizde pandeminin erken döneminde (18-30 Nisan 2020 tarihleri arası) yapılan bir çalışmada; pandemi sonrası nörogelişimsel bozukluğu olan çocuklarda duygusal, davranışsal sorunların ve uyku, iştah sorunlarının arttığı, nörogelişimsel bozukluğu olan çocukların ebeveynlerinde ise anksiyete ve depresyon riskinin arttığı belirtilmiştir (20). Aynı çalışmada OSB grubunun duygusal ve davranışsal sorunlarının diğer gruplara göre (Zihinsel Gerilik, Özgül Öğrenme Bozukluğu, İletişim Bozuklukluğu) daha sık olduğu belirtilmiştir. Bu çalışmadan farklı olarak çalışmamız pandeminin daha geç dönemlerinde yapılan bir çalışma olup, çalışmamızda pandemi öncesine göre pandemi sürecinde OSB tanısı sıklığında değişiklik gözlenmemiştir. Çalışmamızda çocuk ve ergenlerin mevcut psikiyatrik bozukluklarına ait klinik belirtilerinin şiddeti ya da ek sorunları araştırılmamış olup hasta kayıtları incelenerek tanı dağılımları karşılaştırılmıştır. Bu nedenle çalışmamızda OSB tanısında artış görülmesede, pandemi sürecinin OSB tanılı çocuk ve ergenlerin hali hazırda olan sorunlarına ve genel işlevselliklerine etkisini yorumlamak mümkün değildir.

Yazında COVID-19 pandemi sürecinin çocuk ve gençlerin ruh sağlığı üzerine etkisinin incelendiği birçok çalışmada; özellikle gençlerin pandemi öncesine göre daha yüksek kaygı ve daha fazla depresif belirtiler tarifledikleri bildirilmiştir (15,21,22). Ülkemizde 12-18 yaş aralığında ergenlerin özbildirim formları ile değerlendirildiği bir online anket çalışmasında; okulların kapanmasının ve karantinanın ergenlerde kaygıyı artırdığı bildirilmiştir (22). Türkiye'de ve Avusturya'da COVID-19 pandemisinin ruh sağlığı üzerine etkisinin araştırıldığı çok merkezli bir çalışmada; Avusturya'daki gençlere göre Türkiye'deki gençlerin kaygı ve depresyon düzeylerinin daha yüksek olduğu bildirilmiştir. Türkiye'de yaşayan gençlerin kaygı ve depresyon düzeylerinin daha yüksek olması, Avusturya'da uygulanan karantina kısıtlamalarının Türkiye'de uygulanan kısıtlamalara göre daha esnek olması ile açıklanmıştır (21). Almanya'da yetişkin popülasyonda COVID-19 pandemisinden önce ve pandemi sırasında AB tanısının sıklığının karşılaştırıldığı bir çalışmada; pandemi öncesine göre AB tanısının arttığı ancak pandemi öncesi döneme göre yeni AB tanısı alanlara daha az antidepresan reçete edildiği belirtilmiştir (23). İngiltere'de ise karantinanın hemen ardından 6 aylık dönemde yetişkinlere reçete edilen antidepresan ilaçların pandemi öncesi döneme göre birinci basamakta arttığı, ancak üst basamaklara sevklerin azaldığı bildirilmiştir (24). Ülkemizde pandemi öncesinde yapılan bir çalışmada; çocuk psikiyatri polikliniğine başvuran çocuklarda psikotrop ilaç kullanım sıklığı incelenmiş ve en yüksek oranda reçetelenen ilaç grubunun %32,7 ile antipsikotikler

ve %32,5 ile stimulan ilaçlar olduğu, antidepresan ilaç grubunun ise %14,8 oranında reçetelendiği bildirilmiştir (25). Ülkemizde çalışmamız ile yaş ve cinsiyet açısından benzer bir örneklem üzerinde yapılan bir diğer çalışmada; çocuk psikiyatri polikliniğine başvuran ve tanı alan hastaların %61,8'inin psikotrop ilaç kullandığı, %71,3'ünün monoterapi aldığı bildirilmiştir. Monoterapiler arasında %34,3 ile en çok reçetelenen ilaçların stimülan ilaçlar olduğu, %24,0'ının antipsikotikler ve %16,0'ının antidepresanlar olduğu belirtilmiştir (26). Çalışmamızda ise polikliniğimize başvuran hastaların %58,8'ine psikotrop ilaç reçete edildiği; bu ilaçların %38,9 ile stimülan, %27,9 ile antidepresan, %11,5 ile antipsikotik ilaçlar olduğu saptanmıştır. Çalışmamızdan elde ettiğimiz sonuçlar pandemi öncesinde ülkemizde yapılan bu iki çalışma sonuçları ile karşılaştırıldığında; benzer oranlarda stimülan reçete edildiği görülürken, antidepresan ilaç oranının arttığı görülmektedir. Çalışmamızda COVID-19 pandemi sonrası yapılan çalışmalarla da uyumlu şekilde pandemi sonrası çocuk ve gençlere konulan AB ve MDB tanıların ve bu doğrultuda antidepresan ilaç reçetesinin artmış olduğu görülmüştür. Pandemi sürecinde okulların kapanması ile çocuk ve gençlerin günlük rutinlerinden ve akranlarından uzaklaşmasının AB ve MDB tanılarında artışa neden olabileceği düşünülmüştür.

Çalışmamızın en önemli kısıtlılığı küçük bir örneklem ile yapılmış kesitsel bir çalışma olmasıdır. COVID-19 pandemisinin çocuk ve ergenlerin ruh sağlığı üzerindeki etkisini daha büyük örneklemlerde araştıran çok merkezli çalışmalara ihtiyaç vardır. Ülkeler arası karşılaştırmayı içeren uluslararası araştırmalar, pandeminin ele alınmasına ilişkin farklı politikaların çocukları ve gençlerin ruh sağlığını nasıl etkilediğini anlamak için faydalı olacaktır. Kısıtlılıklarına rağmen çalışmamızda, verilerin iki farklı klinisyenin psikiyatrik görüşmeleri sonrası elde edilmesi ve pandemi öncesi dönemde başvuran hastaların özellikleri ile karşılaştırılması çalışmamızın güçlü yönleridir. Bunun yanı sıra literatürde; COVID-19 pandemisinin erken döneminde çocuk ve gençlerin verdikleri ruhsal ve davranışsal tepkileri inceleyen çalışmaların olduğu görülürken, çalışmamızda pandeminin ilk 6 aylık döneminden sonra yapılan başvuruların incelemiş olması nedeniyle bulgularımızın pandeminin geç dönem etkileri hakkında literatüre katkı sağlayacağı düşünülmektedir.

Sonuç olarak, COVID-19 pandemisi ile bu süreçte uygulanan kısıtlamalar ve alınan önlemler nedeniyle polikliniğe başvuran çocuk ve ergenlerin tanı dağılımında değişiklik olduğu görülmüştür. Pandemi öncesine göre pandemi sürecinde; AB ve MDB tanılarında artış görülürken, DEHB tanısında azalma olduğu görülmüştür. Pandemi sürecinde hastalığın yayılımını engellemek için alınan zorunlu önlemlerin ruh sağlığı üzerine olumsuz etkileri göz önünde bulundurulduğunda; gerekli önlemler alınarak okula dönüşün hızlandırılması ve yüz yüze eğitimin kesintisiz, sürdürülebilir olması için gerekli çalışmaların yapılması, çocuklar ve ergenlerin ruh sağlığını koruması yönünden çok önemlidir. Pandemi sürecinde DEHB gibi hâlihazırda psikiyatrik bozukluğu olan çocuklar ve gençlerin tedaviden ve psikolojik destekten uzak kalmış olabilecekleri görülmektedir. Okula dönüşün ardından öncelikli olarak bu bireylerin ruh sağlığını destekleyici programların geliştirilmesi ve uygulanması mevcut hastalıklarının prognozu için önem arz etmektedir.

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Evaluation of the political psychological reflections of the COVID-19 process in the context of Turkey

COVID-19 sürecinin politik psikolojik yansımalarının Türkiye bağlamında değerlendirilmesi

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SUMMARY

The COVID-19 pandemic, with its rapid contagion and deadly effect, emerged in China and surrounded the whole world. This pandemic, unlike other pandemics has emerged in the global age. Due to the disappearance of borders as a result of globalization, both the physiological and psychological spread of the virus has been rapid. The transmission of the Covid-19 virus through contact and droplets has provided its physiological spread, while digital media channels have provided its psychological spread. The negativities experienced in health, economy, politics and cultural structures have shaken the societies in the context of political-psychology. Anxiety and fear caused by the pandemic have negatively affected the psychology of individuals and therefore the whole society. In this study, the effects of the COVID-19 process on Turkey and how Turkey responded to the pandemic were tried to be evaluated in the context of political psychology. By examining the researches published in the process, the improvements made in the field of health against the pandemic, the regulations covering the whole society and the measures to overcome the process with the least damage were mentioned. It has been concluded that, as a result of the negative factors that directly affect mental health such as compulsory social isolation, losses, death anxiety brought by the pandemic, as well as processes such as unemployment and bankruptcy caused by inadequate socio-economic policies, a pandemic of mental disorders may occur in future.

Key Words: COVID-19, Politics, Psychology

ÖZET

Çin'de ortaya çıkarak tüm dünyayı saran COVID-19 salgını, hızla bulaşması ve ölümcül etkisiyle dünya tarihideki en büyük pandemilerden biri olmuştur. Bu pandemi, diğer salgınlardan farklı olarak küresel çağda ortaya çıkmıştır. Küreselleşmenin bir sonucu olarak sınırların ortadan kalkması nedeniyle virüsün hem fizyolojik hem de psikolojik yayılımı hızlı olmuştur. COVID-19 virüsünün temas ve damlacık yoluyla bulaşması fizyolojik yayılmasını sağlarken, dijital medya kanalları psikolojik yayılmasını sağlamıştır. Sağlık, ekonomi, siyaset ve kültürel yapılarda yaşanan olumsuzluklar toplumları siyaset-psikoloji bağlamında sarsmıştır. Pandeminin yarattığı endişe ve korku, bireylerin ve dolayısıyla tüm toplumun psikolojisini olumsuz etkilemiştir. Bu çalışmada politik psikoloji bağlamında COVID-19 sürecinin Türkiye üzerindeki etkileri ve Türkiye'nin pandemiye nasıl tepki verdiği değerlendirilmeye çalışılmıştır. Bu süreçte yayımlanan araştırmalar ve raporlar incelenerek Türkiye'nin pandemi yönetiminde hangi alanlarda başarılı ya da başarısız olduğu tespit edilmeye çalışılırken özellikle ülkedeki psikopolitik durum üzerine yoğunlaşılmıştır. Pandeminin getirdiği zorunlu sosyal izolasyon, kayıplar, ölüm kaygısı gibi ruh sağlığını doğrudan etkileyen olumsuz faktörlerin yanı sıra yetersiz sosyo-ekonomik politikaların neden olduğu işsizlik ve iflas gibi süreçler sonucunda, gelecekte bir ruhsal bozukluk pandeminin ortaya çıkabileceği sonucuna varılmıştır.

Anahtar Sözcükler: COVID-19, Politika, Psikoloji

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INTRODUCTION

For viruses, country borders are meaningless, they are as imaginary as parallels and meridians. The virus, which can reach every part of the world in just a few months, proves that the world is a "global village"(1). The COVID-19 pandemic, which emerged in China, shocked the whole world with its deadly effect, rapid contagion, and difficulties in control and prevention. As in the past, the pandemic affects the societies from different perspectives and brings various experiences as well as the losses it causes. The COVID pandemic continues its course with various effects in health, social, economic and political fields in all nations of the world. We have experienced in the process that many countries are not prepared for the pandemic and that although they can take various measures in the field of health, they can be affected economically and socially. Different fields of science have conducted various studies on the biopsychosocial and political effects of the process and shared their experiences. Psychiatric, socio-economic effects and political reflections of the pandemic in Turkey have been the subject of various studies (2,3,4).

The pandemic will remain in mind not only during the period but also after the traces it will leave in the national and international arena. The anxiety created by the uncertainty that emerged in the first months of the pandemic infected the whole world before the virus and became the common agenda of the whole world. While trying to make sense of the dimensions of the horror they face in the virtual world, people who were simultaneously locked in their homes due to social isolation experienced the anxiety they had reached to levels that they could not cope with by being exposed to conspiracy theories. The anxiety of individuals who have been locked in their homes for a long time, become lonely and deprived of many activities they enjoy, has started to turn into a feeling of frustration and anger over time.

State officials, who tried to make decisions by prioritizing the health and safety of the society, had to make great efforts to overcome this psychological war and medical struggle with the least damage. While the pandemic caused psychological, economic and social collapse in the homes of ordinary people at the micro level, it also caused irreparable destructions in the economies, education systems, social and cultural areas of the states at the macro level.

The first feelings that generally appear in people in a pandemic are intense anxiety and fear. Some factors that evoke fear and anxiety in people are mentioned below:

(i) Unlike many viruses, this virus can be transmitted to individuals without showing any symptoms,

(ii) certain groups who have possibility of life risk,

(iii) the complete containment of the pandemic cannot be predicted with certainty,

(iv) the length of the vaccine development process and mistrust of the long-term consequences it may have in the human body,

(v) possibility of the virus mutating and the emergence of second and third waves in the pandemic, with short and long-term effects on the economy (5).

Many articles have been published on the COVID process from different disciplinary perspectives. The political-psychological effects of the world and especially Turkey in the COVID pandemic process will be tried to be reviewed by examining the studies that have been done in the process and presenting outputs within this framework. The purpose of this study is to evaluate the effects of the Covid-19 process on Turkey and how Turkey responded to the pandemic in the context of political psychology.

PSYCHOPOLITICS IN THE EVENT OF THREAT

After the world wars in the first half of the 20th century, the Cold War process, which left its mark on the second half of the century, and its unexpec-ted end caused the expectation of a peaceful world for the new century to reach its highest level. With the

fall of the Berlin Wall in 1989, a clean slate was expected to open. The bipolar world was over and the threat of nuclear war had disappeared. It was hoped that the new millennium would be different from the old one, but it did not. At the beginning of the new century, the whole world was shaken by the terrorist attacks on September 11, 2001 in the USA. Security concerns embodied in al-Qaeda and radical Islamic terrorism and the vision of a global enemy caused a serious sway on the economic, political and social levels. Economic resources began to be transferred to defense expenditures; at the social level, the securitization process caused the suspension of fundamental rights and freedoms, and the rise of anti-democracy waves even in the liberal world (6).

After 9/11, the second global crisis emerged in the field of economy. With the mortgage crisis that broke out in the USA in 2008, an economic depression began to be experienced all over the world. Finally, the pandemic started before we reached the first quarter of the 21st century. This new global crisis has had and continues to have effects in social, economic and political fields. Political Psychology examines the relationship between mass psychology and politics in these difficult processes. Jost et al. have tried to explain this relation with System Legitimation Theory. Their primary motivation is to explore why and how people acknow-ledge and sustain the social systems that penetrate them (7,8).

The pandemic triggers the fear of loss in people. This loss could be losing health, losing loved ones, losing a job, or losing sense of security. In the face of these threats, people panic and changes in their behavior may occur. These behaviors can occur not only in a social sense, but also in a political and economic sense. Throughout history, humanity has faced many visible threats, wars, bombardments, and environmental disasters. This time, however, the threat is invisible and the possible consequences are uncertain. The common anxiety and collective consciousness formed in the society also affect the political decisions. According to John Jost, events that threaten the system cause a tendency towards conservative views in social and political attitudes (9).

In a society, oppressed groups as well as rulers can rationalize everything thoroughly. They may realize that their living conditions are far from desirable; but they rationalize this phenomenon on the basis of the notion that they deserve to suffer, that everyone is in the same situation, that it is somehow inevitable, that what is to be replaced may be much worse, and so on (10). This makes the existing conditions for individuals bearable. John Jost, with his System Legitimation Theory, claims that people unconsciously support the preservation of the status quo through subconscious processes. Individuals who try to legitimize the system support the acceptance of existing political, economic, social systems as they are because they provide stability (11). Individuals who try to avoid uncertainty determine their political preferences to maintain the status quo. According to the system justification theory, there is a psychological motive to defend and justify the status quo (12).

The times when pandemics disrupt the social order are the times when the search for a new political beginning intensifies in history and today. Different societies may perceive the same pandemic differently. The reaction of the politicians to the pandemic, the restrictions applied, the securing of the economic and social concerns of the people are an important factor and are very effective in determining the political demands and choices of the people. Although there was resistance in some cases to the measures taken by the states during the pandemic, it was observed that the political legitimacy was not shaken during the pandemic times in the modern era, especially in Europe and the Islamic world, on the contrary, the measures taken strengthened the authority of the state over the people (13).

In Zizek's own words;

“COVID-19 has also affected enormous ideological viruses that are ready to explode inside communities, such as conspiracy theories, fake news and xenophobia. Maybe we can hope that a different and beneficial ideological virus will spread and infect us: a virus of the dream of an alternative society, a virus of society beyond the nation-state that will realize itself through global forms of solidarity

and cooperation. Just as the Chernobyl disaster started the events that brought the end of Soviet communism, the speculation that the coronavirus will end the communist rule in China is frequently voiced today. But there is a paradox here: the coronavirus will also force us to reinvent a communism based on trust in society and science. The communism in question here is more than an old-style communism, it will be possible with the existence of a superior global organization that can control the markets that will limit the sovereignty of nation states (14).

According to studies, there is a serious connection between people's political views and the threatening situations (15). A recent meta-analysis showed that exposure to objectively threatening situations such as terrorist attacks was associated with adopting more politically conservative attitudes (16). For example, terrorist attacks accelerated rightward shifts after each of the following events: the 1985 bombing of an AirIndia plane; the 1989 French airline bombings in Nigeria; the 1995 bombing of a federal office building in Oklahoma City; the 1998 bombing of the US embassies in Kenya and Tanzania; the 2001 September 11 terrorist attacks in New York and Washington DC; and like a train bombing in London, England in 2005. When people see that their social system is threatened, they try to preserve the status quo, even if they have previously criticised the system and accept the possibility of change (17). There may be some who assume that the COVID-19 pandemic will not have a similar effect, as the examples we have described are predominantly man-made traumas. However, it should not be completely ignored that similar political consequences can occur in traumas that affect the whole society.

THE IMPACT OF THE DIGITAL WORLD ON THE PSYCOPOLITICS OF THE PANDEMIC

Being confronted with COVID-19 in a digital world has caused information pollution, and therefore anxiety and horror. Pandemics have occurred many times in world history. The Spanish Flu, which emerged during World War I, spread to the world because of the USA's censorship of the news. When the USA joined World War I, the virus was transferred to Spain. In 1918, the Reuters news agency announced the news of the pandemic, which they thought started in Spain, to the whole world, and as a result, the name of the pandemic was heard as "Spanish Flu" (18). We can say that the same situation happened in the COVID-19 pandemic as the Presidents of the USA and Brazil initially chose the path of denial (19). Fake news or misdirection has led to more alarming situations in some countries that are more dangerous than the virus. Especially in the USA, Donald Trump was criticized for not handling the pandemic well, especially on social media (20). Gun sales, which rose sharply in the early months of pandemic, continued to rise in the United States, with first-time purchasers accounting for more than 20 % of Americans who buy guns. In March 2020, research by the FBI announced that gun sales had reached the highest level since 1998. A third study of data compiled by Northeastern University and the Harvard Injury Control Research Center and seen by the New York Times shows that in 2019, 6.5% of US adults purchased a gun in 2020 (21). It has been described that the reason for this sudden increase in gun sales in the USA is the bad world syndrome, in this case, symptoms such as avoidance, aggression or being depressed occur, and people who become aggressive try to reassure themselves and perceive everyone as a threat or even a virus, thinking that the world is getting worse (22).

The other sale, which was the most subject to the digital agenda during the pandemic, was related to toilet paper. Toilet paper hoarding, which was in the news in Australia, has also taken place in places worsened by the virus, such as Singapore, Japan and Hong Kong. Nitika Garg from the University of New South Wales states that this situation is related to mass psychology and that people do this in order not to lose their sense of control (23, 24). In this context, how leaders address their followers reveals how major issues are perceived, strengthens public confidence in government's competence, and elicits behavior change that is aligned with key policy measures (25). While most world leaders took COVID-19 seriously when the pandemic began, some leaders, including Donald Trump, did not take it seriously. Trump said he believed it was like the common flu and was accused of delaying responding appropriately. Many believe that late

government intervention is responsible for thousands of avoidable losses (26).

To distract attention from his failures, Trump blamed China for the virus, calling it the 'Chinese virus', and even blaming the World Health Organization (WHO), his political opponents and the campaign of Black Lives Matter for the spread of the virus (27). Madagascar President Andry Rajoelina rejected the treatment procedures carried out against the pandemic, putting forward an alternative COVID-19 treatment that most of the world does not take seriously. While four African country leaders ordered the 'cure' of Madagascar, most leaders did not show support at the African Union meeting in April (28). The pandemic has not only accelerated challenges in health care, social, educational, economic, political, environmental, cultural and socioeconomic systems, but has also accelerated numerous misinformation such as rumors, myths, superstitions, conspiracy theories and deceptions (29). Scientific facts and unconfirmed information have become indistinguishable among the public. Misinformation, allegations, and conspiracy theories have reduced trust in treatment or vaccines that caused xenophobia against Chinese, psychological destruction, and intolerance to measures such as quarantine and isolation.

In Turkey, there is no study on the effect of the digital world on the psychopolitics of the pandemic, but when we look at the indirectly related studies, the following studies have been found: More than 1.5 million posts on Twitter during the pandemic in Turkey were analyzed, and it was observed that there were deteriorations in the mood of the citizens during the pandemic. This negative mood was mostly expressed as emotions such as anxiety, panic and fear. Although the Minister of Health, who is managing the pandemic, has a reassuring and integrative speaking style, he preferred a one-way communication instead of two-way communication on Twitter, which is more effective in digital sense, and has been criticized in this sense. Studies have concluded that a communication model that will keep the communication dynamic between crisis managers and those affected by the crisis is necessary in the future (30). In another study, it was concluded that Facebook was the platform where the participants encountered the most false information among social Networks and among the traditional media types, the discussion programs gave the most false information. (31).

STATES' APPROACH TO THE PANDEMIC

Pandemics enter people's lives like an asteroid hitting a planet. They kill millions of people and leave many more with great losses, deep suffering, social and psychological collapse. They suspend and traumatize societies. They remove people from their normal patterns and cause societies to redefine themselves (32). An overly common sense of anxiety can activate strong dynamics that can also create a break in the society's relations with the market and the state. The state's test with this unexpected situation is a candidate to produce results as strong as the pandemic itself. The most important of these results is that the resulting uncertainty and risks increase the expectations of the state and the responsibilities of the state (33). With the WHO's declaration of a global pandemic on March 11, 2020, the first response of governments to this situation was to make an action plan to slow the spread of the virus. The states first closed their border gates, limited intercity movements, and imposed curfews. States use their authorities to impose various sanctions for the health of their citizens. These sanctions, which could be considered authoritarian, were tolerated by the society. At this point, it became important for leaders to provide accurate and understandable information to people who are confined to their homes, because during global pandemics such as COVID-19, politicians are responsible for communicating effectively with the public.

It is clear that there are effective responses to COVID-19 where leaders have succeeded in forging a sense of "us" that allows them to unleash the power of society and come together against the virus (34). The response of states and societies to the pandemic differs from region to region. The psychopolitical behaviors of societies also differentiate their responses to the pandemic and restrictions. Italy and Spain, which located on the Mediterranean coast, were late in taking precautions, and they were adversely affected by the pandemic and suffered many casualties. While

Germany applied the "controlled panic" principle, England tried to provide herd immunity with the free movement principle, but had to step back when it failed. It has implemented isolation and quarantine measures. Central and Eastern European countries, where the state practice and perception is more dominant, the pandemic was tried to be kept under control with more dominant measures. In this process, the restrictions of fundamental rights and freedoms, the medical interventions of the states in the pandemic, the competition between the states in vaccine studies and treatments, the mutual accusations between the USA and China, the loss of trust in the World Health Organization, the issue of "natural selection", which arises due to the high risk of elderly and chronic patients, and the moral and psychological state of societies have been the prominent topics of this process (35).

Mental health is a state of mental well-being in which people can cope well with many of life's stresses, realize their own potential, work productively and efficiently, and contribute to their communities (36). In order to protect and maintain this state of well-being during the pandemic, states have taken some initiatives for mental health and psychosocial support through NGOs and associations; In Lebanon, the Ministry of Public Health created an action plan that comprehensively addresses the mental health aspects of COVID-19, with teams from Egypt, Kenya, Nepal, Malaysia and New Zealand establishing emergency hotlines to reach people in need of mental health. The Government of the Bahamas decided to work with UN agencies to respond to the mental health and psychosocial causes of the COVID-19 pandemic. A non -governmental organization in Pakistan had to close the vocational training centers for economic strengthening, but people with mental health problems participating in training centers have started to plant face masks for health officials to support their communities. In Nigeria, the Nigerian Association of Psychiatrists and mental health NGOs have come together to form COVID-19 Partners in Mental Health and have worked with both government and civil society to provide education in mental health and teletherapy (37). The pandemic is a global problem. WHO has been the body that the whole world hoped to get information from since the beginning of the COVID-19 pandemic. When WHO defined COVID-19 as a serious pandemic, it had been a month since the pandemic started and most of the cases were in China, 98 cases were detected in 18 countries outside of China and no casualties were reported yet (38). At this point, WHO made a statement and announced that there was no need to restrict international trade and travel (39). On March 11, 2020, Covid-19 was designated a "pandemic" by WHO after the virus infected more than 118,000 patients in more than 100 countries and caused more than 4,200 deaths (40).

HOW DID TURKEY MEET THE PANDEMİC?

COVID-19 began to be experienced in Turkey with the first diagnosis on March 12, 1920. At the first stage, the state suspended primary and secondary schools, courses and exams were postponed in all universities. Full closure was implemented in various areas. On April 10, 2020, a curfew was declared in 31 provinces. The closure, which will last for 48 hours, caused interesting images to be experienced on the streets. People flocked to markets and bakeries in panic. Long queues formed in front of bakeries and markets for fear of starvation during the two-day closure. People were afraid of starving more than the virus. The end of the curfews caused a chaotic environment just like the beginning. The removal of bans was perceived as the abandonment of the rule-making in the hands of absolute power, and a carnival atmosphere was experienced with the removal of norms, rules and prohibitions. Although the virus threat has not disappeared, this environment can only be understood when those wild impulses that are suppressed in the unconscious go out of control (41). Turkey's response to the COVID-19 pandemic has set an example to the world and the region in the fight against this new virus and in solidarity. Turkey has one of the lowest case fatality rates (2.8% and 52.5% infections/million population), especially among the elderly aged 65 and over (high risk group). Although Turkey is both a European and an Asian country, it is also a Mediterranean country with its Mediterranean culture and heritage. Turkish people prefer close contact as a tradition. Gathering in social events and hugging are common in daily life. Preventing physical contact is essential for a virus that spreads through droplets and close contact.

Before the pandemic, Turkey had one of the most comprehensive universal health insurance plans. Health services were not only available to Turks, but also to more than 3.6 million Syrian refugees who took refuge in Turkey. Turkey's emphasis on health has a long history in the prevention and control of infectious diseases, starting with the early Ottoman Empire. Some health professionals have been trained and organized to provide psychosocial and mental health support to the society by being placed in a health institution in each province at least once.

A COVID-19 specific software module has been added to the Public Health Management System software to facilitate disease surveillance and contact tracing.

Mental Health Support System app has been developed by the Ministry of Health in order to provide a direct channel to protect mental health between mental health professionals and health workers. A mobile application called “Hayat Eve Sığar” was also developed by the Ministry of Health in order to inform, guide and protect the public about areas with high risk of exposure, and to warn about high-risk behaviors.

Turkey offers lessons and best practices that can be useful in contributing to the global health arsenal against the pandemic with the help of technical support of WHO (42). It is difficult to say that the success of the measures in the field of health described above is also in the economic field. It is thought that the studies carried out in this field are more affected in Turkey, which is one of the developing countries, and the real reflections of being affected will be seen in the long term. It can be said that Turkey is among the successful countries when the disease and death rates are compared in order to evaluate the effectiveness of the health measures taken within the scope of the pandemic process. However, as one of the objective criteria for the success of measures to affect other areas of life (social, economic, etc.), the influence on people's mental health can be considered. As can be seen in the two tables below, the proportional increase in mental disorders was higher in countries where socio-economic measures were insufficient (43).

In addition to illness and death anxiety, the most difficult psychological process that people experience during pandemics is economic inadequacy and job loss. This state of psychological anxiety also affects their economic behavior, their perception of

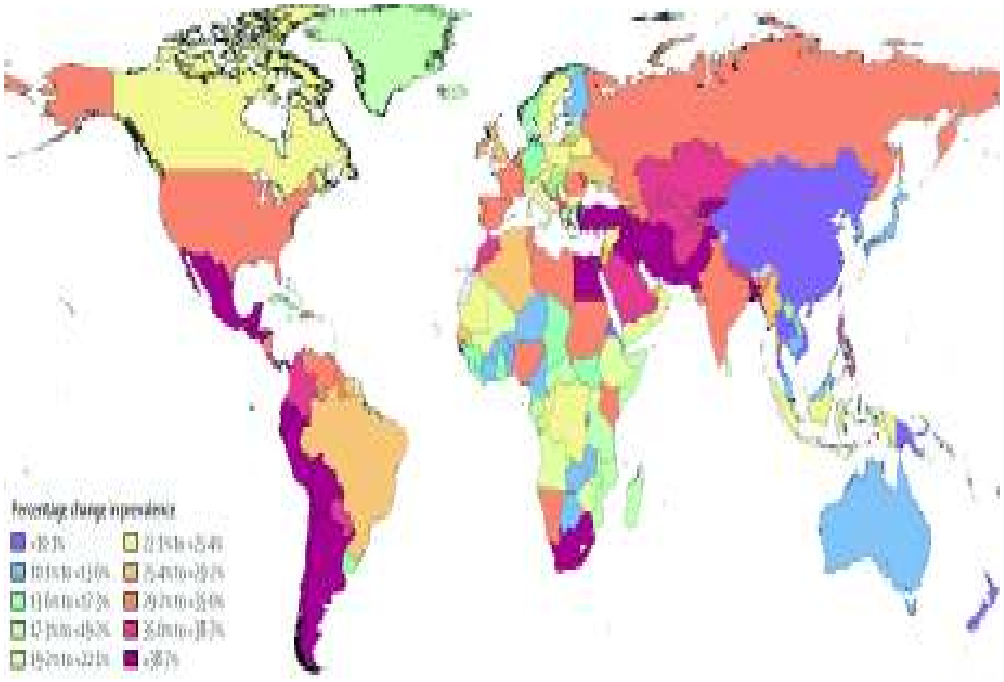

Figure 1: Change in the prevalence of major depressive disorder after adjustment for (ie, during) the COVID-19 pandemic

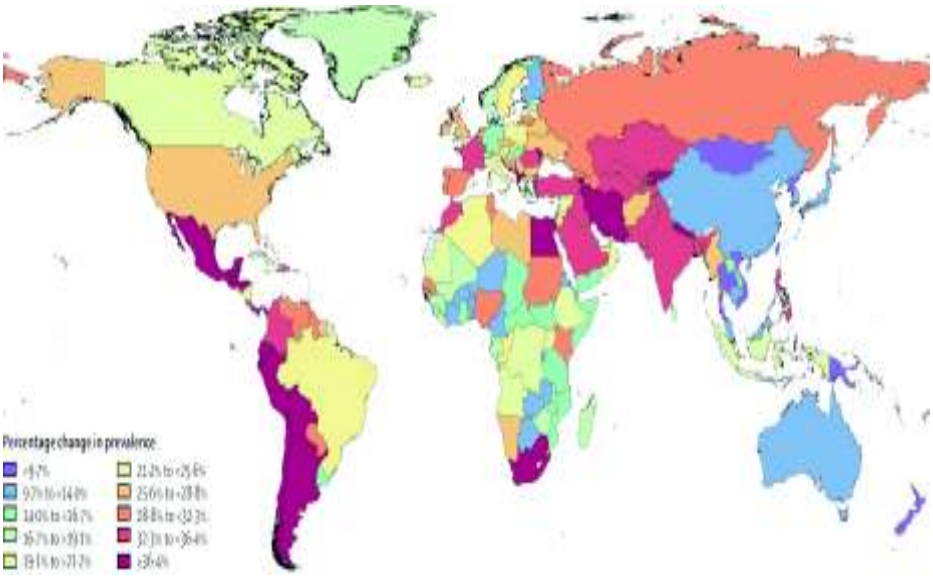

Figure 2: Change in the prevalence of anxiety disorders after adjustment for (ie, during)

the environment, thus their spending and living standards (46).

CONCLUSION

Pandemics, which were seen as the wrath of God before the modern age and believed to be met with resignation, have evolved into a perception that the state has to fight and all responsibility lies with the state in modern state systems (47). In this study, it has been tried to evaluate the process in the context of political psychology by referring to the policies and restrictions applied in the world and in Turkey in terms of health, economy and culture during the COVID-19 pandemic. In the fight against the COVID-19 pandemic, each country has responded to its own socio-cultural structure and economic power, depending on its competence in the field of health. It can be said that Turkey has achieved a successful graphic with its drug sufficiency in the field of health, ease of access to vaccines and treatment opportunities provided to the entire population. With the explanations made using different information channels, it is aimed to create a perception to the public that the status quo will be protected in the context of political psychology, that the pandemic is under the control of the state and that the necessary measures are taken in line with the maximum good of the people. Despite the successful health policies, it is understood from the published reports and research that the economic measures taken are insufficient and the effects of this on the psychological state of individuals will be seen in the long term. Pandemics have not lasted more than two years in world history, in other words, the pandemic is temporary, but the post-pandemic political processes will be determined by the political behaviors applied during the pandemic. Acquired COVID-19 pandemic experiences and national and international literature review have shown that; it is important to develop policies that will ensure preparedness for economic collapses that may develop secondary to the pandemic, as well as preventive health measures for pandemics. It can be said that, as a result of the negative factors that directly affect mental health such as compulsory social isolation, losses, death anxiety brought by the pandemic, as well as processes such as unemployment and bankruptcy caused by inadequate socio-economic policies, a pandemic of mental disorders may occur. It has been seen that many researches and articles have been published in the field of both health and social sciences regarding the COVID process, but it has been seen that there are no studies that address the pandemic, which affects people from a biopsychosocial perspective, from a psychopolitical framework and make recommendations. In this study, although there are some points that could not be addressed, Turkey's COVID process was evaluated from a psychopolitical window and it was tried to include determina-

tions that could be the subject of research in the future.

It is thought that WHO, which is accepted as the authority in the field of health in the world, informs about the pandemic by using all communication tools at the right time and in order to create a widespread effect, especially in order to make conspiracy theories that may lead to xenophobia. Politicians should also avoid making statements accusing the country where the pandemic started in the face of a common threat, such as the pandemic, in which countries must act together, and should not utter a claim that has not been proven by research such as the "chinese virus". Furthermore, It may also be advisable to have an anniversary or commemoration day, where the world humanity can share their pain related to the pandemic.

Academicians specialized in political psychology should conduct more research in this field and lead the development of national policies suitable for the cultural and specific structure of the society.

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Myoclonic seizures induced by antipsychotic drugs: A case series and literature review

Antipsikotik ilaçların neden olduğu miyoklonik nöbetler: Bir olgu dizisi ve literatür incelemesi

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SUMMARY

Introduction: The true frequency of myoclonic seizures caused by antipsychotics is unknown. Myoclonus associated with clozapine and other antipsychotics has been shown less frequently than tonic-clonic seizures in the literature and the treatment protocol is controversial. In this study, we have compiled current literature data by presenting our clinical experiences in patients who developed myoclonic seizures with antipsychotic use. **Case Series:** The patients were followed up in the inpatient service of Gazi University Hospital, Department of Psychiatry between 2014-2019. Demographic data, clinical variables, imaging methods and response to treatment of 10 patients with myoclonic seizures were analyzed. After clinical evaluation, psychiatric diagnoses were clarified according to DSM-5. Psychotropic drugs and doses, EEG, MRI examinations and follow-up data were recorded in these patients with myoclonic seizures.

While 6 of the patients (60%) were receiving clozapine treatment, other patients using olanzapine, amisulpride and quetiapine were seen as 2 (20%), 1 (10%) and 1 (10%), respectively. The mean chlorpromazine dose-equivalent of the antipsychotics used by all 10 patients was 876.66 mg per day. In addition to antipsychotic change, valproic acid was used (most frequently) for the control of myoclonic seizures in 8 of the patients (80%), due to insufficient response. **Conclusion:** Myoclonic seizures may be misdiagnosed as sudden falls resulting from generalized tonic-clonic seizures, dyskinesia, and clozapine induced hypotension. In patients with myoclonic seizures, use of antipsychotic drugs should be kept in mind, especially in additional medical conditions such as renal failure, as well as direct central nervous system pathologies.

Keywords: Myoclonic seizures, myoclonus, antipsychotics, schizophrenia, atypical antipsychotics

ÖZET

Giriş: Antipsikotiklerle oluşan miyoklonik nöbetlerin gerçek sıklığı bilinmemektedir. Klozapin ve diğer antipsikotiklerle ilişkili miyoklonus, literatürde tonik-klonik nöbetlere göre daha az sıklıkla gösterilmiş ve tedavi protokolü tartışmalıdır. Bu çalışmada antipsikotik kullanımı ile miyoklonik nöbet gelişen hastalarımızda klinik deneyimlerimizi sunarak güncel literatür verilerini derlemiş bulunmaktayız. **Olgu Sunumları:** Hastalar Gazi Üniversitesi Hastanesi Psikiyatri Anabilim Dalı' nda 2014-2019 yıllarında takip edilmiştir. Miyoklonik nöbetleri olan 10 hastanın demografik ve klinik verileri, görüntüleme yöntemleri ve tedavi yanıtları incelendi. Klinik değerlendirme sonrası DSM-5'e göre psikiyatrik tanıları netleştirildi. Miyoklonik nöbet görülen bu hastaların tedavilerinde yer alan psikotrop ilaçlar, dozları, EEG, MRG sonuçları ve takip verileri kaydedildi. Hastaların 6'sı (% 60) klozapin tedavisi alırken, olanzapin, amisülpirid ve ketiapin kullanan diğer hastalar sırasıyla 2(% 20), 1(% 10) ve 1(% 10) olarak görüldü. Kullanılan antipsikotiklerin ortalama klorpromazin doz eşdeğeri günde 876.66 mg olarak hesaplandı. Hastaların 8'inde (% 80) miyoklonik nöbetlerin kontrolü için antipsikotik değişimine ek olarak, yeterli cevap sağlanamaması nedenli, valproik asit (en sık olarak) kullanıldı. **Sonuç:** Miyoklonik nöbetler; jeneralize tonik-klonik nöbetler, diskinezi ve klozapine bağlı hipotansiyondan kaynaklanan ani düşmeler olarak yanlış tanı alabilmektedir. Miyoklonik nöbetleri olan hastalarda direkt santral sinir sistemi patolojilerinin yanı sıra -özellikle böbrek yetmezliği gibi ek tıbbi durumlarda- antipsikotik ilaç kullanımı akılda tutulmalıdır.

Anahtar kelimeler: Miyoklonik nöbetler, miyoklonus, antipsikotikler, şizofreni, atipik antipsikotikler

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INTRODUCTION

Myoclonus is defined as sudden, jerky, generally non-rhythmic, involuntary movements. It can present either a movement disorder or a seizure (1). Myoclonic seizures are characterized as the same, brief, jerking spasms of muscles with loss of consciousness in generalized types. On the other hand, consciousness is preserved in focal myoclonic seizures (2).

Some medications and multidrug usage predispose to these conditions. Among first-generation antipsychotics, the greatest seizure risk is considered to be chlorpromazine [3,4]. Among second-generation antipsychotics, clozapine is the one with the greatest risk for myoclonic conditions (5,6). Only a few reports of myoclonus induced by olanzapine, quetiapine is available in the literature (7,8).

We present our clinical experiences in ten patients who developed myoclonic seizures with the use of antipsychotics.

CASE SERIES

Subjects

All of the patients were followed up in the inpatient service of Gazi University Hospital, Department of Psychiatry between 2014-2019. Verbal consent was obtained from all patients and data were analyzed retrospectively. The diagnoses of the patients were evaluated according to DSM-5 after a clinical interview. However, Schizophrenia subtypes were also defined in order to provide partial detail in the diagnostic contents. Psychotropic drugs and doses, EEG (electroencephalography) and CT (computerized tomography), MRI (magnetic resonance imagining) diagnostic methods, drug therapies initiated, and clinical findings were recorded during the myoclonic event. Tests such as complete blood count, liver, kidney function tests, thyroid function tests, glucose, iron, folate, and vitamin B12 levels were performed to exclude other medical causes other than myoclonic seizures. The diagnosis and treatment of the patients were conducted in a multidisciplinary manner by psychiatry and neurology physicians. The patients did not have a primary neurological disease. However, sufficient information on medical comorbidities that may trigger myoclonic seizures could not be obtained in all patients because the relevant records could not be accessed adequately.

Statistical analysis

SPSS 23.0 version was used in the analysis of patient data. Sociodemographic and clinical characteristics of the patients were evaluated using descriptive statistical methods such as percentage, number, mean and standard deviation.

Case Analysis

The demographic characteristics, drug data, electrophysiological and radiological features of patients are summarized in Table 1. There were 10 patients with myoclonic epileptic seizures under antipsychotic treatment. Neither they nor their family had an epilepsy history. Two (20%) of the patients were female and 8 (80%) were male. The mean age was 24.2 years. Seven (70%) of them had a diagnosis of undifferentiated schizophrenia while 2 (20%) of them had a diagnosis of treatment-resistant schizophrenia and 1 (10%) was diagnosed as disorganized schizophrenia.

The mean duration of the disease was found to be

Table 1. Myoclonic seizure cases triggered by antipsychotics

Case number	Age/ Gender	Education	Marital Status	Dx	Duration of disease	Used Antipsychotic/ Dose during myoclonic seizure	CLP equivalent**	Used antiepileptic drug	Dose of antipsychotic after seizure	EEG/ Neuroradiological studies
1	21/M	University	Single	Undif. Sch	9 months	Clozapine/ 400 mg	800 mg	Valproic acid 800 mg	300 mg	Partial onset epileptic activity No acute cranial pathology on MRI
2	23/M	University	Single	Dez Sch	1 year	Clozapine/ 425 mg	850 mg	Valproic acid 600 mg	325 mg	Normal EEG findings No acute cranial pathology on MRI
3	20/M	University	Single	Undif. Sch	8 months	Olanzapine/ 15 mg	300 mg	Clonazepam 1 mg	10 mg	Bilateral synchronous symmetrical spike and polyspike and slow wave discharges No acute cranial pathology on MRI
4	23/F	Primary School	Single	Undif. Sch	1 year	Olanzapine/ 15 mg	300 mg	Lorazepam 2 mg	10 mg	Intermittent generalized slow wave activity (Larger amplitude in frontal electrodes) No acute cranial pathology on MRI
5	35/M	Secondary School	Married	Undif. Sch	5 years	Clozapine/ 450 mg	900 mg	Valproic acid 1000 mg	350 mg	Paroxysmal, bilateral synchronous symmetrical spikes No acute cranial pathology on MRI
6	21/F	Secondary School	Single	Undif. Sch	9 months	Clozapine/ 400 mg	800 mg	Valproic acid 1000 mg	300 mg	Normal EEG No acute cranial pathology on MRI
7	22/M	Secondary School	Single	Undif. Sch	4 years	Amisulpride/ 400 mg Quetiapine/ 800 mg	300 mg 1066.66 mg (Total: 1366,66mg)	Valproic acid 1000 mg	400 mg 400 mg	Paroxysmal, generalized high amplitude spike and slow wave activity No acute cranial pathology on MRI
8	27/M	Secondary School	Single	TR Sch	8 years	Clozapine/600 mg	1200 mg	Valproic acid 1000 mg	600 mg	Normal EEG No acute cranial pathology on MRI
9	22/M	Secondary School	Single	TR Sch	2.5 years	Clozapine /350 mg	700 mg	Valproic acid 1000 mg	350 mg	Normal EEG No acute cranial pathology on MRI
10	28/M	Secondary School	Married	Undif. Sch	6 years	Haloperidol/ 15 mg Quetiapine/ 600 mg	750 mg 800 mg (Total: 1550 mg)	Valproic acid 1000 mg	15 mg 300 mg	Normal EEG No acute cranial pathology on MRI

M: Male, F: Female, Dx: Diagnosis, Undif. Sch: Undifferentiated schizophrenia, Dez Sch: Disorganized schizophrenia, TR Sch: TreatmentResistant schizophrenia, CLP: Chlorpromazine, MRI: Magnetic resonance imaging, EEG: Electroencephalography

33.5 months (between 8 and 96 months). Six (60%) of the patients were under clozapine treatment while others using olanzapine, amisulpride, and quetiapine, haloperidol, and quetiapine were found to be 2 (%20), 1 (%10), and 1 (10%) respectively. The average dose of clozapine use during myoclonic activity was found to be 437.5 mg per day. It was 15 mg per day for those using olanzapine. On the other hand, the average chlorpromazine dose equivalent of antipsychotics used by all 10 patients was found to be 876.66 mg per day. Those treated by clozapine were using 875 mg chlorpromazine equivalent antipsychotic per day while the chlorpromazine equivalent doses of those using olanzapine, amisulpride + quetiapine, and haloperidol + quetiapine were found to be 600 mg, 1366.66 mg, and 1550mg per day respectively. In 8 (80%) of the patients, valproic acid was used for the treatment of the myoclonic states. Lorazepam and clonazepam were the other two choices in two patients. After the myoclonic event, the average dose of clozapine use was found to be 370.8 mg per day, while this dose for olanzapine was 10 mg per day.

DISCUSSION

Myoclonic seizures are observed in patients with specific myoclonic epileptic syndromes or occur as a result of hypoxic, infective, inflammatory, neurodegenerative, and toxin/ drug-associated conditions (9,10). The percentage of drug-related myoclonic seizures is substantial. Besides, it is frequently encountered, especially as one of the reasons for frequent consultation from non- neurologist physicians (10).

Older ages, neurodegenerative comorbidities, history of epilepsy, impaired renal functions, electrolyte imbalance, drugs (opioids, levodopa, quinolones, phenytoin, carbamazepine, amantadine, etc.), and multidrug usage predispose to this condition (9,10).

We detected that this situation occurred under the use of atypical antipsychotics in 9 patients and both typical and atypical antipsychotic combinations in 1 patient. Atypical antipsychotics lower the seizure threshold more and they are preferred more in clinical practice nowadays (11).

Six patients were using clozapine. Clozapine is known as the antipsychotic that reduces the epilepsy threshold mostly (12). It has also been reported to create any kind of seizure activity, and it is known to cause focal awareness seizures, focal impaired awareness seizures, atonic, tonic-clonic, or myoclonic seizures (3,5). Although generalized tonic-clonic seizures are frequently observed, we want to emphasize that myoclonic seizures may occur and may be encountered in daily practice (2).

While all patients who had a seizure with clozapine experienced these seizures at doses of 400 mg and above, in two patients using olanzapine seizures were seen on 15 mg doses. Seizures were observed in one patient using amisulpride 400 mg and quetiapine 800 mg; and in another patient, using 15 mg haloperidol and 600 mg quetiapine. In previous studies, with high doses (1,000 mg/day chlorpromazine equivalent), seizures were seen in 9% of the patients; with moderate doses, in 0.7% patients; and with low doses 0.3% of the patients (200 mg/day chlorpromazine equivalent) (13,14). Although rare, epileptic seizures can be observed even with low doses of antipsychotics, depending on the patient's epilepsy threshold and additional factors. In a report, status epilepticus was documented with minimal doses of CPZ (~1000 mg/d) in patients (15). The equivalent dose of chlorpromazine in which myoclonic seizures occurred was found to be 850 mg per day. This result seems to be consistent with the findings in the literature. Nevertheless, these EEG changes and seizures have been generally believed to be related to both the dose and plasma concentration. Also, it is possibly happening with rapid drug titration (1-4). EEG changes corresponded to the myoclonic events time wisely, especially in seizures. EEG recordings can be normal in these conditions (1).

In the treatment of these myoclonic events, the priority should be to reduce the dose or change the triggering drug (10). However, in daily practice, drug switching is compelling because the psychotic conditions of these patients were resistant, an agent such as clozapine had been switched on intentionally. So, we reduced the doses of these antipsychotics, and valproic acid (500-100mg/ day) was added to the treatment in 8 patients, benzodiazepine (lorazepam 2mg/day, clonazepam 1mg/day) in 2 patients. As with other seizure types, the use of GABAergic drugs has been effectively treated these myoclonic seizures due to the assumption that the underlying pathology is GABAergic inhibition (16,17). Levetiracetam is also used in myoclonic conditions, but it is rarely preferred with these psychiatric patients because of the dose-independent aggression and/ or psychotic side effects (18,19,20).

Our access to some data in our cases (time of onset of the seizure, comorbidities) was incomplete due to various reasons (time-lapse, wrong remembering, missing notes, etc.). The incompleteness of these data creates a limitation and the results should be interpreted carefully in this direction.

CONCLUSION

It shouldn't be forgotten that myoclonic seizures may occur in the form of sudden, jerky, involuntary movements. Symptoms of myoclonic events can sometimes be misdiagnosed as tonic-clonic seizures, dyskinesia, and sudden falls that result from hypotension. Antipsychotic drug usage has to be kept in mind in a patient with myoclonic states besides primary central nervous system pathologies.

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L-Carnitine use as a trigger for the onset of Kleine-Levin syndrome: A case presentation

Kleıne- Levin sendromu'nda bir tetikleyici olarak L-Karnitin: Bir olgu sunumu

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SUMMARY

Kleine- Levin Syndrome (KLS) is a rare phenomenon characterized by repeating episodes of hypersomnia, cognitive and behavioral impairments, compulsive eating behavior, and hypersexuality. Postinfectious processes, alcohol consumption, sleep deprivation, psychological stress, getting vaccinated, head injury and genetic factors have been identified possible etiological factors. Abnormal metabolism of serotonin and dopamine have also been reported. Alcohol and cannabis have been listed among triggering factors. With its role as a mediator required to transport long-chain fatty acids to mitochondrial matrix and its contributions in increasing oxidation of fatty acids, L-carnitine helps to produce more energy from burning fat while maintaining economic use of muscle glycogen stocks. Animal studies have shown a continous increase in dopamine discharge within nucleus accumbens via acetyl L-carnitine application. Carnitine supplementation is known to cause increased dopamine levels within cortical, hippocampal and striatal regions of the rat brain. One case report reported severe psychotic symptoms in a patient with bipolar disorder, following acetyl L-carnitine use. In this case presentation, we have aimed to present clinical course of an adolescent using L-carnitine for ergogenic support, as a possible trigger for the onset of a KLS episode.

Keywords: Kleine- Levin Syndrome, l-carnitine, triggering factor, child, adolescent, ergogenic supplement

ÖZET

Kleine-Levin Sendromu (KLS) tekrarlayan hipersomnia ve çeşitli derecelerde bilişsel ve davranışsal bozulmalar, kompulsif yeme davranışı ve hiperseksüalite ile karakterize nadir bir hastalıktır. Postenfeksiyöz düzenekler, alkol kullanımı, uykusuz kalma, psikolojik stres, aşılanma, kafa travması ile genetik etkenler altta yatan olası nedenler olarak sunulmuştur. Etiyoloji için serotonin ve dopamin metabolizmasında anormallikler bildirilirken alkol ile esrar da olası tetikleyiciler arasında tanımlanmıştır. L-karnitin, uzun zincirli yağ astilerinin mitokondri matriksine taşınmasında gerekli bir aracı olarak görev yapma ve yağ asitlerinin oksidasyonunun artırılmasında rol almaktadır. Bu özelliğinden dolayı, hem yağlardan daha fazla enerji üretilmesine hem de kas glikojen depolarının ekonomik kullanımına yardımcı olmaktadır. Hayvan çalışmalarında asetil L-karnitin uygulaması ile nucleus accumbens bölgesinde süreğen biçimde dopamin deşarjında artışın elde edildiği gösterilmiştir. Sıçan çalışmaları ile karnitin takviyesi sonucu beynin korteks, hipokampus ve striatumunda dopamin seviyelerinin arttığı saptanmıştır. Bir olgu sunumunda bipolar bozukluğu olan bir bireyde asetil L-karnitin kullanımı sonrasında şiddetli psikotik belirtilerin ortaya çıktığı bildirilmiştir. Bu olgu sunumunda, olası bir tetikleyici olarak, ergojenik amaçlı L-karnitin kullanımı ardından KLS epizodu başlayan bir erkek ergenin klinik gidişinin paylaşılması ve tartışılması hedeflenmiştir.

Anahtar Kelimeler: Kleine- Levin Sendromu, L- karnitin, tetikleyici faktör, çocuk, ergen, ergojenik madde

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INTRODUCTION

Kleine-Levin Syndrome (KLS) is a rare disorder of episodic nature that is characterized by hypersomnia, and alterations in cognition, eating and behavior (1). Although exact prevalance is unknown, the disorder is estimated to have affected 1-5/1000000 individuals worldwide (2). Generally encountered in adolescents and young adults, KLS has been reported to show a male predominance. In a review of 239 cases, mean age of onset for the disorder was 15 years old, regardless of gender (3).

Etiology of the disorder still remains largely unknown and while there have been reported triggering factors for the disorder, no causal link has yet been determined. Commonly underlined triggering conditions for the onset and recurrence of the disorder have been listed as infection, fever, alcohol and marijuana consumption, sleep deprivation, psychological stress, head injury, menstruation and lactation, and situations involving heavy physical effort, general or local anesthesia (4). Along with these, abnormalities in serotonin and dopamine metabolism have also been reported, therefore, an imbalance of neurotransmitters within serotonergic or dopaminergic pathways has also been suggested as a possible mechanism (5).

A non-specific generalized slow-wave pattern in the baseline electroencephalography (EEG) has been reported in 70% of the cases during the episode, while normal brain waves are present in between the episodes, in general. Polysomnography (PSG) might reveal decreased sleep index along with increased number of arousals (6). Despite increasing number of imaging and laboratory tests in order to better understand the disorder, no specific diagnostic tool or results have yet been maintained. Therefore as for today, KLS diagnosis is mainly made by a thorough assessment and review of clinical symptoms.

According to International Classification of Sleep Disorders-IIIrd Edition criteria (ICSD3, 2014), that is commonly used to formally diagnose KLS, the individual needs to experience at least two episodes of recurrent hypersomnia or increased sleep-time that would continue for a period of 2 days to 5 weeks for each episode identified; episodes recurring at least once in every 18 months and generally, in a period of less than once a year; maintaining normal levels of consciousness, awareness, cognitive functioning, behavior pattern and mood in between the episodes; while presenting with at least one of the following during an episode; 1) cognitive deficits, 2) perceptual alterations, 3) eating problems (not eating or overating), 4) dysinhibitated behavior (i.e, hypersexuality), and hypersomnia and other related symptoms should not be caused by the clinical course of another sleep disorder, or other medical, neurological or psychiatric disorder (specifically bipolar disorder), or should not be present secondary to a substance or drug use of any kind (7).

For cases with mild- moderate episodes, supportive interventions such as reducing stress, avoiding dangerous situations and treatment of comorbid conditions have been recommended, in those with much more severe form of the disorder, pharmacological agents such as modafinil, risperidone, aripiprazole, lithium, sodium valproate and carbamazepine have been tried with favorable clinical outcome (1,8). In a study where 186 KLS cases were assessed, clinical response to amphetamine was 70%, while 20% for methylphenidate, especially when tested during the symptomatic phase. As for treatment options to prevent the emergence of episodes, clinical response was 41% for lithium, and 21% for carbamazepine (4).

Dietary supplements have been used by many individuals who are professionally involved in sports, in order to maintain better performance. L-carnitine has gained more popularity recently as a potential ergogenic aid due its role of converting fat into energy (9). L-carnitine exists naturally in all mammal species, and takes part in mitochondrial oxidation of fatty acids (10). Due to its charge in acting as a mediator required to transport long chain fatty acids to the mitochondrial matrix as well as being involved in the process of increasing the oxidation of fatty acids, L-carnitine facilitates energy production from fat and aids in economic use of muscle glycogen storage (11). L-carnitine has two esther forms called acetyl L-carnitine and propionyl L-carnitine, and both forms have high bioavailability (10).

Since L-carnitine supplementation was hypothesized to have a potential of increasing lipid oxidation, reserved muscle gycogen and exercise performance, a number of studies focusing on the given action mechanism of the compound have been conducted (11,12). Apart from recent studies that cover L-carnitine being used as an ergogenic supplement, different derivatives of the compound have also been evaluated, to be used for diverse purposes and conditions. Among these forementioned forms is acetyl L- carnitine; the short chained esther form of L-carnitine. Acetyl L-carnitine is produced from carnitine and acetyl-CoA, via carnitine acetyl transferase enzyme (13). This compound has vastly been studied in different neuropsychiatric conditions, specifically. Among such conditions are depression, fibromyalgia, fatigue, male infertility and sexual dysfunction, Alzheimer's Disease, alcohol abuse and Attention Deficit Hyperactivity Disorder (13). Aside from the psychiatric conditions mentioned above, manic episode and psychotic episode in two separate cases each diagnosed with bipolar disorder have been identified, following acetyl L-carnitine use (14,15).

With this case report, we have aimed to discuss the possibility of L-carnitine supplement acting as a triggering factor for the onset of a KLS episode, in a male adolescent who had started to use the compound on his own for its ergogenic action, along with a review of relevant literature.

CASE HISTORY

The case was a 13 year old male adolescent who had applied to a child psychiatry outpatient unit in the company of his parents with primary complaints as irritability, increase in total sleep time, angry outbursts whenever family members would try to wake him, overeating, mood swings and dysinhibitated behavior that was mainly inappropriate and sexual in nature.

In the clinical interview, the family reported that the case had been sleeping excessively for the past couple of days prior to application, only to be woken up for meeting his basic daily needs. He was reported to eat excessive amounts of food during the time he would be awake, and had behavioral disruptions such as talking to himself about things that were unreal and engaging in meaningless monologues, inappropriate laughing, defiant behavior, inappropriate sexual talk and conduct. Reported symptoms had a sudden onset, and due to similar complaints and symptoms, they had actually applied to an emergency unit of a university hospital 4 months ago, followed by an admission to the intensive care unit for further diagnostic procedures. Data collected from the hospital records at that time revealed the case was followed up with preliminary diagnoses as psychotic episode, manic episode, possible drug intoxication and encephalopathy, following his initial evaluation in the emergency unit, from where he was transfered to the intensive care unit of the same hospital for differential diagnostic procedures and treatment. His EEG result was nonspecific, indicating a generalized slowing in the baseline wave. All other laboratory tests were normal. The case had been followed up for nearly 10 days with none other than supportive treatment, and following remarkable reduction in the symptoms, was discharged with nearly full remission. A review of his personal history revealed that he had been going to the gym for a few months before the onset of symptoms, and had started himself on L-carnitine for ergogenic purposes, and continued using for approximately 4 weeks.

No significant feature was identified regarding medical, developmental and family history of the case. Neither did he meet any criteria for the diagnoses of other sleep related disorders, mood disorder, substance use disorder or any other psychiatric and neurological disorders. Results of physical examination, laboratory tests including complete blood count, biochemical test panel, and thyroid function tests, along with magnetic resonance imaging (MRI) of the brain were normal. Although non-specific, only difference was observed in EEG results, where there was a generalized slowing of baseline brain activity during symptomatic phase, EEG activity was measured to be completely normal in between episodes. Sudden onset of symptoms, episodic nature of the clinical picture, almost full remission in between symptomatic phases, characteristics of reported and observed clinical symptoms along with test results were all suggestive of KLS as the primary diagnosis. The case was

started on 400 mg/day carbamazepine, and admitted to the inpatient unit where he was monitored for 2 weeks. Since none of the symptoms at application were observed and improved daily functioning was maintained, the case was discharged, to be followed up in the outpatient unit. 3 months into his last episode, the case is still on 400 mg/day carbamazepine and yet remains symptom-free.

DISCUSSION

An uncommon disorder frequently misdiagnosed as other certain psychiatric and medical conditions, KLS might pose severe negative impact on daily functioning and quality of life in the face of severe symptoms (1). The case we have presented had no problems prior to the emergence of KLS symptoms, only to have become unable to attend school, meet his basic everyday needs, resulting in significant functional impairment following the onset of frequent and severe episodes caused by the disorder. A thorough review of diagnostic criteria for other psychiatric conditions ruled out depressive disorder, bipolar disorder, schizophrenia and related disorders. Normal neurological examination results and negative results for infectious markers ruled out the possibility of encephalitis and/or menengitis; while other neurological conditions such as epileptic seizures and lesions of temporal lobe had also been excluded via neurological examination, brain MRI and EEG. Based on data from relevant literature that suggested the syndrome generally presented during adolescence and predominantly affected males, we might suggest that our case fit the typical case profile, as previously described in relevant literature. In a study where 108 KLS cases were evaluated, main symptoms of the condition have been identified as hypersomnia, cognitive disturbances, alterations in perception, odd behavior and emotional problems (8). A review of relevant literature indicated that most commonly identified behavior profiles in KLS were overeating and inappropriate sexual conduct (16) that were similarly among the most striking clinical symptoms our case had presented with.

In some of the cases with KLS, it is possible to determine an underlying cause acting as a facilitator for the emergence of symptoms related to the syndrome (4,7). As we mentioned before, infection, fever, alcohol and/or marijuana use, sleep deprivation, psychological stress, head trauma, menstruation or lactation, physical effort and general/local anesthesia jave previously been reported as triggering factors for the onset or recurrence of a KLS episode (4). Even though forementioned factors have not been mentioned in our case's history, presence of a temporal relationship between onset of KLS symptoms and starting himself on L-carnitine for ergogenic purposes might indicate a causal link, in between.

Probable causal relationship between L-carnitine use and emergence of an index KLS episode might be explained through possibility of creating an imbalanced serotoninergic and/or dopaminergic system caused by L-carnitine use as suggested in literature, similar to what has so far been postulated as the hypothetical etiological base of the disorder. It has long been suggested that cases with KLS might reflect an imbalance in both dopaminergic and serotoninergic systems, though clinical importance was predominantly attributed to the imbalanced dopaminergic system. For instance, an imaging study on KLS reported reduced striatal dopamine binding potentials throughout symptomatic attack phase of the disorder (17). Again, 5-hydroxyindolacetic acid (5-HIAA, metabolite of serotonin) and homovanilic acid (HVA, dopamine metabolite) levels in cerebrospinal fluid (CSF) were measured in a sample of patients with periodic hypersomnolance. Results indicated increased or slightly increased HVA levels i CSF of patients with KLS, which was interpreted as a sign of increased dopamine cycle, by the researchers (18). Another study suggested a decline in dopaminergic hypothalamic tone, during symptomatic phase (5). Such findings support the need to better focus on dopaminergic and serotoninergic systems, specifically on the dopaminergic system. At this point, depicting the effects of L-carnitine and its derivatives on dopaminergic and serotoninergic system have mainly been limited to animal studies. While L-carnitine supplementation increased the status of carnitine located in various localizations of the study- animal's brain, no significant increase was observed among young rats. Again, L-carnitine supplementation was observed to cause significant increase in cortical, hippocampal and striatal

dopamine of the rat brain (19). Another study reported acetyl L-carnitine increased the level of 5-HIAA, as well as acetyl L-carnitine administration prior to 3,4-Methylenedioxymethamphetamine (MDMA, extacy) injection prevented serotonin (5-HT) loss in rats (20). Acetyl L-carnitine was shown to exert its potential agonistic effects on 5-HT1A receptors (20). Moreover, chronic acetyl L-carnitine supplementation was reported to increase 5-HT levels in the cerebral cortex, and caused a reduction in serotonin turnover through a decrease in 5-HIAA/5HT ratio. Long term acetyl L-carnitine use was shown to increase dopamine and serotonin output within mesocorticolimbic area of the brain and protected against exposure to acute stress (21).

As a conclusion, supplementation of L-carnitine and its derivatives were shown to create an effect on dopaminergic and serotoninergic systems, in animal studies conducted so far. We might only speculate that same or similar effects might develop in humans and some individuals might in particular be vulnerable to the effects caused by such compounds, due to their genetic profile or being exposed to early life environmental manipulation and damage.

Another probable explanation to consider L-carnitine use as a triggering factor is linked to catabolic processes. One common denominator in conditions that have been reported to trigger KLS episodes such as infection, fever, alcohol and head trauma, is increased levels of catabolism in all. Therefore, these nonspecific events might facilitate emergence of given clinical picture, by causing accumulation of toxic aminoacid or protein concentrations within metabolic pathways with partially erroneus enzymatic activity (16). Current biochemical data states L-carnitine plays a part specifically in catabolic processes of fatty acids. In that sense, we might only hypothesize that L-carnitine might be regarded as a candidate for the place of other yet-undetermined triggering factors of KLS, with its common feature of being linked to catabolic processes.

Although we have conceptualized L-carnitine supplementation as a triggering factor for our case, we also believe that our report needs to be cautiously addressed, in the sense that it consists of findings from only one case with nearly no replicated findings from other studies, making it even harder to confirm an actual causal relationship existed between L-carnitine use and KLS. We believe future studies including case reports, case series and hopefully researches designed to be conducted in larger samples, employing rigorous methodology shall provide more insightinto this mysterious clinical entity we have identified as Kleine- Levin Syndrome.

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Fonksiyonel yürüme bozukluğu olan bir olguya yaklaşım

Approach to a case with functional gait disorder

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ÖZET

Fonksiyonel yürüme bozukluğu psikojenik hareket bozukluğu olan hastaların %8-10'unda görülen yaygın bir bozukluktur. Birçok fonksiyonel yürüme bozukluğu, nörolojik hastalıkları taklit etmektedir. En kolay tespit edilen bulgu olan astazi-abazi bu hastalarda sıklıkla izlenir. Hastalar sendeler, anlık olarak denge kurarlar, düşme tehlikeleri var gibi görünseler de son anda hep kendilerini kurtarırlar ve genellikle yaralanmazlar. Diğer tüm fonksiyonel bozukluklar gibi yürüme bozuklukları da bir psikososyal stresörü takiben akut bir şekilde ortaya çıkabilir. Semptomların dalgalı seyri, hareketlerde anormal yavaşlama, dizlerde ani bükülmeler ve psikojenik Romberg gibi bazı ipuçları ayırıcı tanı açısından yardımcıdır. Dikkatli bir inceleme ile bozukluğun fonksiyonel doğası tanınsa da bu hastaların uygun tedavisi yeterli zaman ve çaba gerektirir. Hasta ile terapötik bir ilişki kurmak, belirtiler ve tanı arasındaki ilişkiyi yalın ve saldırgan olmayan bir dille açıklamak oldukça önemlidir. Bu fonksiyonel bozukluk bireyselleştirilmiş bir tedavi yaklaşımı gerektirir. Bu yazıda ayağa kalkamama, yürüyememe, her iki kol ve bacağında sıçrama tarzında hareketler ve sürekli yan tarafına eğilme nedeniyle anormal bir postür gibi yakınmalarla başvuran ve hafif mental retardasyonu olan 23 yaşında bir kadın hasta anlatılmıştır. Kliniğimizde uygulanan tedavi ile tam bir iyileşme gösteren hastanın klinik belirtileri, belirtilerin altında yatan olası etkenler, tedavi girişimleri, klinik izlemi ve tedavi başarısını etkileyen faktörler bu yazıda tartışılmıştır.

Keywords: Fonksiyonel yürüme bozukluğu, fonksiyonel hareket bozukluğu, konversiyon, psikojenik yürüme bozukluğu

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SUMMARY

Functional gait disorder is a common disorder seen in 8-10% of patients with psychogenic movement disorder. Many functional gait disturbances mimic neurological diseases. Astasis-abhasia, which is the most easily detected finding, is frequently observed in these patients. Patients stumble, balance momentarily and even though they seem to be in danger of falling, they always rescue themselves at the last moment and generally do not get hurt. Like all functional disorders, gait disorders can occur acutely following a psychosocial stressor. Some clues such as the fluctuating course of symptoms, abnormal slowing of movements, sudden bends in the knees and psychogenic Romberg are helpful in terms of differential diagnosis. Although the functional nature of the disorder can be recognized with careful examination, appropriate treatment of these patients requires sufficient time and effort. It is very important to establish a therapeutic relationship with the patient, to explain the relationship between symptoms and diagnosis in a plain and non-aggressive language. This functional disorder requires an individualized treatment approach. In this article, a 23-year-old female patient with mild mental retardation who presented for evaluation of complaints such as inability to stand up and walk, jerk-like movements in both arms and legs, and an abnormal posture due to continuous lateral bending is described. Clinical symptoms, possible underlying factors, treatment attempts, clinical follow-up and factors affecting the treatment success of the patient who had a complete recovery with the treatment applied in our clinic are discussed in this article.

Anahtar Kelimeler: Functional gait disorder, functional movement disorder, Conversion, psychogenic gait disorder

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GİRİŞ

Postür ve yürüme ile ilişkili fonksiyonel bozukluklar oldukça yaygın olup, psikojenik hareket bozukluğu olan hastaların %8-10'unda görülmektedir (1). Anksiyete ve depresyon, fonksiyonel yürüme bozukluklarına eşlik eden en yaygın psikiyatrik morbiditelerdir (2). Tanıyı ayırt edici özellikler ve yürümenin gözlemlenmesine dayanarak koymak sıklıkla mümkündür. Nörolojik hastalıkları taklit eden bazı tipik bulgular olabilmekle birlikte, sıklıkla anatomi ya da fizyoloji bilgileri ile uyumsuz nörolojik belirtiler mevcuttur (3). Diğer nörolojik ve tıbbi hastalıkları taklit eden özelliklerinden ötürü, bu hastalar sıklıkla psikiyatri dışındaki bölümlere başvurmaktadır ve bu da tanı ve tedavi sürecini geciktirmekte, prognozu olumsuz etkileyebilmektedir. Bu hastaların bir kısmında, önerilen tedavi yaklaşımları olan psikoterapötik müdahaleler, gerekli durumlarda psikofarmakolojik tedaviler ve rehabilitasyon uygulamalarına rağmen tedavi yanıtı hızlı olmayabilir. Yakınmaları 6-12 aydan uzun süren hastalarda prognozun iyi olmadığı ve uzun süreli defisitlerin görülebileceği bilinmektedir (1). Bu nedenle, hastalığın erken tanı ve tedavisi önem arz etmektedir. Biz bu yazımızda, ayakta durma ve yürüme bozukluğu olan, psikiyatri dışındaki bölümlerde birkaç kez değerlendirilerek yakınmalarında iyileşme görülmeyen 23 yaşındaki bir kadın hastanın belirtilerini, bu belirtilerin ortaya çıkmasında etkili olabilecek etkenleri, tedavi yaklaşımını ve izlem sürecini aktardık.

Bu vaka raporunun paylaşılması için hastadan yazılı aydınlatılmış onam alınmıştır.

OLGU

F.S., 23 yaşında, kütüphane görevlisi olarak çalışan, özel eğitim ve iş okulu mezunu, bekar kadın hasta, ayağa kalkamama, yürüyememe, sürekli yan tarafına eğilerek yürüme ve anormal postür, her iki kol ve bacağında devamlı anormal kasılmalar gibi yakınmalarla kliniğimize başvurdu.

F'nin yakınmaları ilk olarak 7 ay önce dedesinin yüz felci geçirdiğini görmesinin ardından, sağ bacağında bir ağrı ile başlamış. Ağrı ile birlikte yürümesinde aksama olmuş ve ayakta durmakta zorluk çekmiş. Ailesi ve kendisinden alınan bilgiye göre bu ağrıdan önce yürümesine ilişkin hiçbir sorun olmamış. Hastanın zamanla yürümesi daha da bozulmuş, özbakımını ve kendi işlerini yapamamaya başlamış. Zaman zaman semptomlarında değişiklikler oluyormuş. Bazen birden bir ağrı başlıyor, kollarında ve bacaklarında uyuşma hissediyor, daha sonra kol ve bacakları yaklaşık on dakika kasılı halde kalıyormuş. Ardından kasılan ekstremite gevşiyor, başka bir yerinde kasılma hissetmeye başlıyormuş. Yakınmalarına idrar inkontinansı eşlik etmemiş. Hasta, dedesinin tedavi sürecinde hastanelere genellikle birlikte gitmiş ve bu süreçten olumsuz etkilenmiş.

Hasta bu yakınmalarla önce ortopedi bölümüne başvurmuş. Ortopedik herhangi bir sorun saptanmaması üzerine bacak ağrıları ve postür bozukluğu nedeniyle fizik tedavi ve rehabilitasyona yönlendirilmiş. Çekilen lomber vertebra MRG'sinde minimal düzeyde lomber disk hernisi ile uyumlu bulgular saptanması üzerine 2 hafta kadar fizik tedavi görmesine rağmen şikayetlerinde bir gerileme olmamış.

Bir süre sonra bacak ağrıları azalmış; ancak yürüyememe şikayeti devam etmiş. Yeniden ortopediye, ardından nörolojiye başvuruları olmuş. 18 yaşındayken epilepsi tanısı konulan; ancak dört yıl antiepileptik tedavi sonrası medikal tedavisi sonlandırılan hastanın yapılan EEG, EMG ve kranyal MRG tetkiklerinin normal olması üzerine belirtileri açıklayacak nörolojik bir tanı düşünülmemiş ve belirtilerin epileptik bir aktiviteden kaynaklanmadığı da belirtilmiş. Ardından beyin ve sinir cerrahisine başvuruları olmuş, şikayetlerini açıklayacak bir tanı konulamayınca psikiyatriye yönlendirilmiş. Başvurdukları psikiyatri kliniğinde yatarak izlenmesi önerilmiş; ancak hasta ve yakınları kabul etmemiş. Hastaya 10 mg/gün essitalopram ve 0.5 mg/gün klonazepam reçete edilmiş.

Hastanın şikayetlerinde belirgin gerileme olmaması üzerine yeniden psikiyatriye başvuruları olmuş, ardından kliniğimize yönlendirilmiş.

Psikiyatrik muayenesinde hastanın yaşından küçük gösterdiği, ayakta durmakta zorlandığı,

özbakımının ve kişisel hijyeninin normal, görüşmeciye karşı tutumunun işbirlikçi olduğu gözlendi. Hastanın bilinci açık, oryantasyonu yere, zamana, kişiye ve hastalığına karşı yeterliydi. Dikkati ile anlık, yakın ve uzak belleğinin yeterli olduğu görüldü. Hastada herhangi bir algı patolojisi saptanmadı. Hastanın klinik olarak hafif düzeyde zihinsel yetersizliği olduğu izlenimi edinildi. Gerçeği değerlendirmesi, yargılama ve soyutlaması ise sağlamdı. Hastanın düşünce akışı duraksamalı ve soru-cevap tarzında, cevapları amaca uygundu, çağrışım bozukluğu saptanmadı. Düşünce içeriğini daha çok hastalığının düzelmeyeceğine dair kaygılı temalar oluşturuyordu. Duygulanımında labilite ve uygunsuzluk izlenmedi. Duygudurumu ötimikti. Psikomotor aktivitesinin ise azalmış olduğu izlendi.

Hastanın nörolojik muayenesinde anlama, tekrarlama ve isimlendirme normaldi. Ense sertliği yoktu, göz hareketleri her yöne tamdı ve nistagmus saptanmadı. Fasiyal asimetrisi olmayan hastanın kas tonusu global normotonustu, spastisite ve bradikinezi izlenmedi. Kas gücü global 5/5 olan hastada lateralizan duyu defisiti yoktu. Serebellar testler üst ekstremitede değerlendirilebildiği kadarıyla normaldi, koopere olamadığından alt ekstremitede değerlendirilemedi. Hastanın derin tendon refleksleri global normoaktif izlendi. Hastada astazi – abazi (ayakta durmada ve yürümede güçlük çekme) ve psikojenik Romberg (muayene eden hekimin kollarına düşme) bulguları saptandı. Yürürken anlık olarak denge kurduğu; sıklıkla düşme tehlikesi var gibi görünse de son anda kendini kurtarabildiği gözlemlendi. Yürürken gövde aşırı ekstansiyon, lateral deviasyon ve antepulsiyon şeklinde farklı postürler sergilemekteydi. Sağ ayak bileği içe deviasyonda, her iki diz eklemi fleksiyonda ve adım aralığı değişkendi. Her iki ayakta taban derisi cevabı fleksör izlendi.

Hasta normal spontan vajinal yol ile beklenen zamanında, köyde doğmuş. Uzamış doğum ve hipoksi öyküsü olan hasta, doğum sonrasında 15 gün küvözde takip edilmiş. Konuşma haricinde gelişim basamaklarını zamanında tamamlamış. 4 yaşında hala konuşamaması sebebiyle çocuk psikiyatrisine başvuruları olmuş. Yapılan psikometrik testler sonucunda bilişsel gelişimde gecikme saptanmış, özel eğitim ve konuşma terapisi önerilmiş ve 4-5 yaşlarındayken konuşmaya başlamış.

Arkadaşlık ilişkileri iyi olan, kurallara uyum sağlayabilen bir çocukmuş. Çevresi ile sosyal ilişki kurmakta zorlanmazmış.

2015 yılında 17 yaşındayken hastaya Ailevi Akdeniz Ateşi (FMF) tanısı konmuş ve bu nedenle kolşisin kullanmaya başlamış. 2016 yılında 18 yaşındayken ise hastanın annesinin fark ettiği, bazen gözünün bir noktaya dalması şikayetiyle başvurdukları nöroloji hekimi tarafından epilepsi tanısı konularak levetirasetam 3000 mg/gün dozunda önerilmiş; ancak hastanın kliniğimize başvurmasından beş ay önce aynı hekim tarafından artık medikal tedavi gerekliliğinin olmadığı söylenerek kesilmiş. Başka ek hastalığı yokmuş.

Anne ve babası 24 yıl önce görücü usulü ile tanışarak ve anlaşarak evlenmişler, evlendiklerinde anne 14 baba 23 yaşındaymış. Aile 2 çocuklu çekirdek bir aileymiş. Anne şu an 38 yaşında, lise mezunu ve otel işletmecisi olarak çalışıyor, kızının hastalık ve tedavi süreci nedeniyle 7 aydır işine ara vermek durumunda kalmış. Baba 47 yaşında, meslek lisesi mezunu ve oto tamircisi olarak çalışıyor. Hastanın kardeşi 20 yaşında erkek, ön lisans mezunu, annesi ile birlikte çalışıyor. Aile, maddi sorunlarının olmadığını, orta gelir grubunda olduklarını ifade ediyor. Aile, hastanın önceden kendisine yetebilen bir çocuk olduğunu ve mevcut durumuna çok üzüldüklerini belirtiyor. Annesi "Onun bunları isteyerek yapmadığını biliyorum, babası ve babaannesi çok üzerine gidiyor, F. anlaşılamadığı için üzülüyor." diyor. Ailede bilinen bir psikiyatrik hastalık öyküsü yok.

KLİNİK İZLEM

Hasta iki hafta süre ile konsültasyon-liyezyon psikiyatrisi servisinde yatırılarak takip edildi. Rutin tetkiklerine ek olarak MRG, EEG ve EMG tetkikleri tekrarlandı ve tamamı normal olarak raporlandı. Hastanın ayakta duramama ve yürüyememe yakınmalarının nöroanatomi ile uyumsuz olması, sözgelimi ayakta durmakta güçlük çekmesine rağmen kas gücünün global olarak 5/5 olması, farklı kaslardaki kasılmalarla uyumlu spastisitenin

ve kontraktürlerin yokluğu, tüm derin tendon reflekslerinin normoaktif olması, denge sağlamada güçlük çekmesine rağmen serebellar testlerinin normal olarak değerlendirilmesi belirtilerin fonksiyonel olduğu yönünde önemli ipuçları olarak değerlendirildi. Ek olarak yürümeye başlamada tereddüt, sürekli farklı bir postür alma ve muayene sırasında hareketlerin amplitüd, frekans ve dağılımındaki tutarsızlık (4) ile birlikte yapılan tetkiklerin tamamının normal olması, vücudundaki anormal hareketlerin başlamasından önce tanımlanabilen bir psikososyal stresörün varlığı (dedesinin yüz felci geçirmesine tanık olması) nedeniyle hastada konversiyon bozukluğu (fonksiyonel nörolojik belirti bozukluğu) ön planda düşünüldü.

Hastanın tedavisine anksiyetesine yönelik olarak başlanan 2 mg/gün klonazepam ile davranışçı tedavi ve telkin kullanıldı. Psikoeğitime aile de dahil edilerek daha kapsamlı bir tedavi yaklaşımı uygulandı. Aileye yapılan tüm tetkiklerin normal olduğu, bu şikayetleri açıklayacak bedensel bir hastalık bulunmadığı ve psikososyal stresörler ile mevcut yakınmalar arasındaki ilişki anlatılarak hastalığa ilişkin bilgi verildi.

Ardından hastanın ayağa kalkmasına ve yürümesine yönelik fiziksel egzersizler uygulandı. Hastaya günde iki kez yarım saat süre ile ayakta durma ve yürüme egzersizleri yaptırıldı. İlaç saatlerinde hasta tedavi ekibi tarafından tedavi odasına çağrılarak ilacını almak üzere yürümesi ve ayakta durması teşvik edildi. Bu sırada etrafındaki ilginin azaldığı zamanlarda hastanın yürümesinin daha normal olduğu, tedavi odasına geldiğinde ise yürüyüş bozukluğunun yeniden arttığı izlendi. Hastanın dik durabilmesi, tedavi saatlerinde ilaçlarını almak üzere yardımsız yürümesi, fiziksel egzersizlere uyum sağlaması ve tamamlayabilmesi, özbakımını ve kendi işlerini yapabilmesi, bireysel ve grup psikoterapilerinde duygularını ifade etmeye başlaması gibi davranışlarındaki sağlıklı gelişmeler olumlu yönde pekiştirildi. Zamanla hastanın tedavi ekibi ile ilişkisinin güçlenmesi, yürümeye yönelik çabalarının desteklenip ödüllendirilmesi ve ailenin hastalıkla ilgili yanlış düşüncelerinin azalması ile tedavide işbirliği arttı. İki haftalık hastane izleminden sonra hastanın yürümesi belirgin derecede düzeldi. Ardından Covid-19 salgını nedeniyle taburcu edilerek ayaktan takiplerine devam etmesi önerilen hastanın ailesine, sekonder kazançları önlemek amacıyla hastanın kendi kendine yürümesi, yürümesine destek olunmaması ve yakınmalarına ilgi gösterilmemesi anlatılarak birtakım ev ödevleri verildi. Covid-19 salgını nedeniyle düzenli kontrollerine gelemeyen hastanın son kontrolünde, yakınmalarının neredeyse tamamen düzeldiği, psikiyatrik muayenesinin normal olduğu ve kendi işlerini yapabildiği görüldü.

TARTIŞMA

Fonksiyonel yürüme bozukluğu yaygın ve her yaşta izlenebilen bir hastalıktır. Fonksiyonel yürüme bozukluğu olan hastalar genellikle zorlayıcı hastalardır ve uygun tedavi için yeterli zaman ve çaba gerekir.

Hastalardan anamnez alırken yakınmaların nörolojik ve psikiyatrik taraflarına özellikle dikkat etmek önemlidir. Belirtilerin akut ya da kademeli bir şekilde şiddetlenmiş olması önemli olabilir. Yine, yakınmaların başlamasından önce hastanın yaşamında önemli bir stresör olup olmadığı önemli bir ipucu olabilir. Sorunun bacaklardaki kuvvet, hareket, duyu ya da denge ile ilgili olup olmadığını anlamak yararlı olur. Üriner inkontinansın varlığı özellikle organik etyolojiyi düşündürür (5). Ailede benzer bir bozukluğun olması ya da hastanın yakınında olan bir arkadaş veya aile üyesinin benzer yakınmalarla giden bir nörolojik hastalığı bulunması da fonksiyonel bir etyoloji lehinedir (6). Bazen hastanın belirtilerine neyin sebep olduğunu düşündüğünü sormak faydalı olabilir. Bazı hastalarda fibromiyalji ve kronik yorgunluk sendromu gibi bilinmeyen etyolojiye sahip tıbbi hastalıkları sormak, hastaya belirtilerinin gerçekliğini inkar etmediğimize yönelik bir rahatlatma sağlayabilir.

Psikojenik yürüme bozukluğunun altı karakteristik özelliği vardır. Bunlar bozukluğun dalgalı bir seyir göstermesi (%51), hareketlerde aşırı yavaşlık (%35), psikojenik Romberg varlığı (%32), buzda yürür gibi yürüme (%30), kas enerjisinin boşa harcanması ile uygunsuz bir postür varlığı (%30) ve dizlerde ani bükülmelerdir (%27) (7). Bizim hastamızda da belirtilerin dalgalı bir seyir göster-

mesi, hareketlerin belirgin yavaşlamış olması, uygunsuz bir postür ve dizlerde ani bükülmeler saptanabilen anormal özelliklerdi.

Bu hastalarda mevcut yakınmalarının nedeninin kısa sürede anlaşılabilmesi bile hastaya zaman ayırmak ve yakın ilişki kurmanın önemini azaltmamaktadır. Bazen dramatik bir iyileşme izlense de belirtiler genellikle hızla düzelmez. Hastanın üstünkörü bir muayenin ardından ciddi bir sorunu olmadığı belirtilerek gönderilmesinin ise birtakım başka şikayetlerle yeniden başvurmasına neden olacağı neredeyse kesindir.

Öncelikle hastaya açık, anlaşılır ve saldırgan olmayan bir açıklama yapılmalıdır. Bu amaçla bazı klinisyenler bu tür bozuklukları 'psikojenik' olarak değil, 'fonksiyonel' olarak adlandırırlar. Tanının yalın ve yargılayıcı olmayan bir dille anlatılması terapötik ilişkiyi güçlendirir. Hasta şüpheci bir tutum içindeyse, değerlendirmenin bazı aşamalarını ya da terapötik müdahaleleri sonraki seanslara bırakmak uygun olabilir.

Fonksiyonel yürüme bozukluğunun kesin bir tedavisi olmayıp tedavinin bireyselleştirilmesi gerekir. Genellikle destekleyici görüşme ya da psikiyatrik tedavi ile birlikte rehabilitasyona dayalı müdahaleler uygulanır. Hastaların çoğu hızlı iyileşme ya da plaseboya yanıt gösterse de, kanıtlar semptomları bir yıldan fazla süren hastalarda prognozun iyi olmadığını bildirmektedir (8). Slater, fonksiyonel bozuklukları olan bir hasta grubuna ait uzun süreli bir izlem çalışmasında, hastaların yarısında belirtilerin majör bir defisit ya da psikiyatrik hastalığa evrildiğini saptamıştır (9). İngiltere'de yapılan 6 yıllık bir çalışma ise psikojenik nörolojik bozukluğu olan hastaların %28'inin semptomlarının tamamen iyileştiğini, %20'sinin kısmen düzelme gösterdiğini ve %52'sinde değişiklik olmadığını ya da kötüleştiğini bildirmiştir (10).

Sonuç olarak fonksiyonel bozukluklar çok şiddetli yakınma ve bulgularla karşımıza çıkabilir. Bu hastaların yanlış nörolojik tanı alması ya da psikiyatri dışı bölümlere başvurması ve tanınmayarak doğru yönlendirmenin yapılmaması; tanıda ve tedavide gecikmelere yol açarak prognozu olumsuz yönde etkileyebilir (11). Hastaların zamanında tanınıp psikiyatriye yönlendirilmemesi, aynı zamanda sağlık sistemi üzerinde de yük oluşturmaktadır. Bu nedenle klinisyenlerin hastalığın nörolojik ve psikiyatrik taraflarını ayırt etmek üzere dikkatli olması, bulguları yorumlayabilecek düzeyde bir nöroanatomi bilgisine sahip olması, dikkatli bir psikiyatrik muayene ile altta yatan bir psikopatoloji varlığına odaklanılması ve bölümler arası işbirliğinin varlığı oldukça önemlidir.

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Clarithromycin induced psychotic disorder with catatonic-like features in an adolescent girl: Case report

Bir kız ergende Klaritromisin kullanımında katatoni-benzeri belirtiler ile kendini gösteren psikotik bozukluk: Olgu sunumu

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SUMMARY

Delusions and/or hallucinations developed during exposure to a medication are diagnosed medication induced psychotic disorder. Antibiotic-induced psychotic disorder have been well documented among adults. The etiology is not clear, clinical presentation is variable and catatonia-like symptoms can be seen. The prognosis is good, the symptoms decrease with the discontination of the drug, and long-term treatment is often not required. In this case, 16-year-old girl who presented with acute catatonia-like symptoms will be described. Family history of clarithromycin-induced behaviour changes accelerated the diagnosis process. Medication induced psychotic disorder should be thought in differential diagnosis of young people with acute psyhotic symptoms.

Keywords: Psychosis, clarithromycin, catatonia, adolescent

ÖZET

Sanrı ve/veya varsanılar ilaç kullanımı sırasında ortaya çıktığında ilaçla indüklenen psikotik bozukluk tanısı konulmaktadır. Antibiyotik kullanımı sırasında psikotik belirtilerin görülebileceği erişkinlerde bilinmektedir. Bu durumun etiyolojisi belli değildir; klinik görünümü değişkendir, katatoni benzeri belirtiler de olabilir. Uzun süreli tedavi çoğu zaman gerekmez, belirtiler ilaç kesilince ortadan kalkar. Bu olgu sunumunda klaritromisin kullanımı sırasında katatoni benzeri akut psikotik belirtilerle başvuran kız ergen tartışılacaktır. Olgunun kuzeninde klaritromisin kullanımı sırasında benzer belirtiler olduğunun öğrenilmesi tanı koyma sürecini hızlandırmıştır. Gençlerde katatoni dahil her türlü akut psikotik belirtide ayırıcı tanıda ilaçla indüklenen psikotik bozukluk düşünülerek kullanılan ilaçlar sorgulanmalıdır.

Anahtar Kelimeler: Psikoz, klaritromisin, katatoni, ergen

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INTRODUCTION

Clarithromycin is a semi-synthetic macrolide that used frequently in the treatment of bacterial infection. Although, gastrointestinal system adverse effects are common, neuropsychiatric adverse effects can not be ignored, especially among adults (1). Here we described acute psychotic symptoms with catatonic-like features attributed to medication in an adolescent girl.

CASE

A 16-years-old girl was brought to Emergency Department at night because of intense fear from being taken by devils. She was using 1000 mg/day oral clarithromycin for 5 days because of tonsillitis. That day, she also took another medicine that contained 60 mg pseudoephedrine and 2.5 mg desloratadine because of common cold and itchy rashes on her legs. No other behavioral changes were mentioned by the family, except sleeping less since the beginning of clarithromycin treatment. The mother told that nearly two hours after the night dose, the girl was staring in her room for nearly one and a half hours without talking or moving, then suddenly started to run to a woodland 200 m away from the house. The family said that she refused to come back because of her belief that her father was a devil. Police was called and an ambulance brought her to the hospital.

During the examination, she was very agitated, not compatible, refused to talk and consistently saying "Go away devils. I will not give you my soul." She seemed disoriented to time, place and person. Neurological examination was normal, vital signs and laboratory tests were within normal range. Neither her nor any family member had a psychiatric history. However, the family blamed clarithromycin because some behavior changes were seen in one of her cousin due to clarithromycin in the past. Haloperidol 5 mg im was given. Her symptoms were gradually improved, and approximately half an hour later she was normal except not recalling what had happened and how she arrived at hospital. She remained eight hours in emergency department. Clarithromycin was stopped, and no other medication was given. After a week from discharge, the family said that she was completely normal during the whole week but she refused to come to hospital because of Covid-19 pandemic and her prejudice towards psychiatry. So she was talked via telephone. Her orientation, speech, thought process and content seemed normal. It has been nearly one and a half year, and she still has no any psychiatric symptoms. Informed consent was obtained from the patient and the patient's parents.

DISCUSSION

In DSM-5, diagnostic criteria of substance/medication-induced psychotic disorder are delusions and/or hallucinations developed during or soon after exposure to a medication. Delirium, withdrawal or intoxication should be excluded (2). Hoigne syndrome is firstly referred to pseudo-anaphylactic reactions characterised by acute psychological and neurological manifestations after procaine penicillin injection (3). This phenomenon has also been named as antibiomania (4). However, these features may occur after some other medications (3). Neuropsychological side effects seem mostly during clarithromycin treatment, though it is considered as safe and effective (5). Albeit the etiology has not been detected, direct effect of antibiotics on neurotransmitters or indirect effect via cytokines are some hypothesis. For clarithromycin, GABA-A antagonism and drug interactions via CYP3A4 inhibition have been proposed (1).

Antibiotic-induced psychiatric reactions have been well documented among adults (1), but few cases of neuropsychological side effects have been reported among children. A 18-year-old teenager was the first pediatric case of antibiotic-induced psychosis, whose acute psychosis symptoms after anesthesia were resolved with the discontinuation of clarithromycin and/or amoxicillin (6). Hypomania, mania, visual hallucinations were described among children during clarithromycin treatment. (Table 1)

In this case, the vital symptoms were within normal range, so as the neurological examination. The dose of pseudoephedrine was within normal range, as the neuropsychiatric adverse effects mostly seen in overmedication (12). There was no drug interac-

Table 1. Clarithromycin-induced psychiatric symptoms among children

Age, Gender,	Diagnosis for treatment	Dosage	Time to psychiatric symptoms	Psychiatric symptoms	Other drugs	History of any disorder	Family history of psyhiatric disorder
18 y, Boy	For H.pylori infection, started after cholecystectomi operation	1000 mg/day	Two days	Acute pyshcosis (Anxiety, insomnia, delusional thoughts, fear)	Amoxicillin	No	No
12 y, Boy	Pneumonia	500 mg/day	After first dose	Mania	No	No	No
6 y, Girl	Acute sinusitis	15mg/kg bid	After second dose	Visual hallucinations (animals)	No	No	No
7 y, Boy	Acute otitis media		After five days	Visual hallucinations (spiders)	No	No	No
3 y, Boy	Pneumonia	15 mg/kg	After second dose	Hypomania (psychomotor agitation, pressured speech, irritability, agrresive behavior, insomnia)	No	No	No
16 y, Girl	Upper respiratory tract infection	500 mg/day (for 13 days)	After 7 days	Mania	Inhaled steroid	Asthma	No
4 y, Girl	Respiratory drug infection	20 mg/kg (250 mg morning, 125 mg evening)	Shortly after the second dose	Visual hallucinations (snakes), fear	No	Multiple allergies	No

tion between pseudoephedrine and clarithromycin (13). Desloratadine is a non-sedating antihistamine which penetrates less to central nervous system and acts especially on H1-receptors. Psychosis is not expected as an adverse effect of desloratadine (14). The familial risk of clarithromycin-induced behavioral changes in this case should also be taken into consider. Therefore clarithromycin-induced psychosis is most likely.

Clarithromycin-related psychiatric symptoms are acute, while the prognosis is excellent. The symptoms seem to be age-related as fears and hallucinations, especially concerning animals, are seen among children (8,11) while psychosis and mania are seen among youths (15,16). Duration of symptoms are variable, in most cases withdrawal of clarithromycin was enough (6,8,9,11), while olanzapine was needed in one case (7) and risperidone with valproat were needed in another (10). Haloperidol had been used for acute agitation in a clarithromycin-induced psychotic state (16). Although the examination of the case was compatible only with psychosis, the sudden onset of marked agitation after unresponsiveness (might be considered as stupor and mutism) could be defined as unspecified catatonia. In DSM-5, unspecified catatonia is diagnosed when symptoms cause significant impairment even though full criteria of catatonia are not met and/or underlying medical condition is unclear. No duration has been mentioned (2). The category of unspecified catatonia is believed to increase early identification and appropriate treatment of pediatric catatonia (17). Since GABA-A agonists seem to alleviate catatonic symptoms (18), clarithromycin can cause catatonia via GABA-A antagonism.

Psychosis itself is still a mystery, that both diagnosis of substance/medication-induced psychotic disorder and unspecified catatonia in DSM-5 are open to discussion with unclear borders. Any presentation of neuropsychiatric symptoms, including catatonia, can be seen during many medications. Some of the questions that come to mind are; what are the differences between substance/medication-induced psychotic disorder and other psychotic disorders, what makes these children vulnerable to psychosis even without any family history of psychiatric disorder?, does this reaction be an indicator of an elevated risk for any psychiatric disorder during the whole life?, do all the medications lead to psychiatric symptoms via the same mechanisms? The studies that referred these questions are spare (19), because of many factors like heterogenity and short duration of clinical presentation. As the manifesta-

tion of psychiatric symptoms are different among children, it is even more difficult to identify and distinguish psychiatric symptoms during medications. Acute psychotic symptoms are not common among young children, and drugs should be thought in differential diagnosis. Since early discontinuation of clarithromycin may result in quick recovery of neuropsychiatric side effects, it is important for clinicians to be aware of them during treatment.

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