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Amaç ve Kapsam / Aims and Scope

Türkiye Romatoloji Derneği'nin (TRD) yayın organı olan Ulusal Romatoloji Dergisi (önceki adı: RAED Dergisi) yılda üç kez, Türkçe ve İngilizce yayımlanan hakemli bir bilimsel dergidir (p-ISSN: 2651-2653; e-ISSN: 2651-2661). Dergi, romatoloji biliminin bütün konularında orijinal deneysel ve klinik araştırmaları, olgu sunumlarını, derlemeleri, tanıtım ve haberleri, yazarlara ve editöre mektupların yanı sıra romatoloji camiasını ilgilendiren duyuruları yayımlar. Bunun dışında romatoloji alanındaki yenilik ve gelişmelere yönelik toplantıların konuşma metinlerini ya da bu gelişmeleri içeren yazıları ek vererek yayımlayabilir. Derleme yazılar genellikle davetli yazı konumunda olduğundan dergiye gönderilmeden önce editör ile iletişime geçilmesi gerekmektedir. Dergi, doğrudan gönderilen derleme türü yazıları kabul etmemektedir.

Ulusal Romatoloji Dergisi **EBSCO, Gale, Index Copernicus, J-Gate, Türk Medline ve TÜBITAK ULAKBİM TR Dizin** veritabanında İndekslenmektedir.

Ulusal Romatoloji Dergisi'nin amacı ülkemizde romatoloji ile ilgilenen diğer disiplinlerin de katılımıyla romatoloji alanında güncel bir bilimsel tartışma zemini ve arşiv oluşturmaktır. Dergi bu birikimini, saygın bir biyomedikal periyodik olarak uluslararası bilimsel paylaşıma sunmayı ve böylece romatoloji biliminin gelişmesine akademik katkı sağlamayı hedeflemektedir.

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Ulusal Romatoloji Dergisi'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve editör, editörler kurulu ya da yayıncının görüşü değildir; Editör, editörler kurulu ve yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

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Aims and Scope / Amaç ve Kapsam

Journal of Turkish Society for Rheumatology (formerly RAED Journal), the official organ of Turkish Society for Rheumatology, is a peer-reviewed scientific journal published quarterly in Turkish or English (p-ISSN: 2651- 2653). The journal publishes three times in a year original contributions in the form of basic and clinical research articles, case reports, reviews, news, letters to the editor and authors as well as announcements related to all topics of rheumatology. Also, abstracts or full texts of scientific meetings in rheumatology can be published as supplements of the journal. The reviews are usually invited; therefore it is necessary to contact the editor before sending them to the journal. The journal does not accept unsolicited reviews.

Journal of Turkish Society for Rheumatology is indexed in **EBSCO, Gale, Index Copernicus, J-Gate, Turkish MEDLINE and ULAKBİM.**

Journal of Turkish Society for Rheumatology aims to constitute a current scientific discussion platform and archive in rheumatology with the contribution of the disciplines related to rheumatology together. The journal intends to share its experiences with the international scientific community in a prestigious way and to provide academic contribution to the development of rheumatology science.

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Dergide yer alan bölümler aşağıda aşağıdaki gibi sınıflandırılmaktadır:

- Klinik Araştırma
- Deneysel Çalışma
- Olgu Sunumu
- Derleme
- Editöre Mektup
- Öneri
- Yazara Mektup
- Kitap Tanıtımı
- Haberler
- Özetler

ETİK VE HAKEM DEĞERLENDİRMESİ

Ulusal Romatoloji Dergisi bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan süreli bir yayın organıdır. Makale baş editöre ulaşınca bilimsel kalitesi değerlendirilir ve ön değerlendirmeyi geçen yazılar yardımcı editöre gönderilir. Bölüm editörü makaleyi 2 hakeme gönderir. Hakemler 21 gün içinde kararlarını belirtmelidirler. Yardımcı editör hakem kararlarına kendi değerlendirme ve önerisini ekleyerek baş editöre gönderir ve son kararı baş editör verir. Hakemlerin kararları çatışıyorsa dergi editörü yeni hakem atayabilir.

Derginin alıntı kontrolü "Crossref Similarity Check" tarafından geliştirilen "iThenticate" programı kullanılarak yapılmaktadır. İntihal raporuna göre makale yazara geri gönderilebilir ya da reddedilebilir.

Yayınlanmak üzere dergiye gönderilen yazılar daha önce başka bir dergide yayınlanmamış veya yayınlanmak üzere eş zamanlı olarak herhangi bir dergiye gönderilmemiş olmalıdır. Bilimsel toplantılarda sunulmuş bildirilerden hazırlanan yazılar, tamamı yayınlanmamış olmak koşuluyla dergiye gönderilebilir. Gelen yazılar Yayın Kurulu tarafından ön incelemeden geçirilir. Derginin yayın amacına uygun olmayan yazılar doğrudan reddedilebilir ya da hakem değerlendirmesine alınmadan yayın amacına ve yayın kurallarına uygun hale getirilmesi amacıyla yazara geri gönderilir. Dergi kapsamına uygun görülen yazılardan klinik araştırma, deneysel çalışma, derleme ve olgu sunumu sınıfı yazılar hakem değerlendirme (eş değerlendirme/*peer review*) sürecine girerler. Yayın Kurulu, hakem yorum ve önerileri doğrultusunda dergiye gönderilen yazıların yayına hazırlanması aşamalarında gerekli gördüğü düzeltme ve değişiklikleri önermeye yetkilidir. Dil birliğini sağlamak amacıyla cümlenin bilimsel anlamını değiştirmeyen kelime değişikliklerini yapabilir. Eş değerlendirme sürecinde gerekli düzelti aşamalarını geçtikten sonra sayfa düzeni yapılıp yayına hazır hale getirilen yazıların provası, son baskı onayı için ilgili (yazışmaların yapıldığı) yazara göndeilir.

Araştırma Etiği

Yazar(lar), insanlar üzerinde yapılan çalışmalarda katılımcı bireylerden Bilgilendirilmiş Olur alındığını yazılarında belirtmeli ve çalışmanın yapıldığı kurumun Etik Kurulu veya eşdeğeri bir kuruldan alınan onay belgesini yazıyla birlikte göndermelidir(ler). Olgu sunumlarında, her olgunun kendisine ait bilgilerin yayın amacıyla kullanılacağına dair bilgilendirildiğini gösterir bir belgenin sunulması gerekir. Tüm çalışmalar Helsinki Deklarasyonu'nun son değişiklikleri işlenmiş şekline uygun yapılmış olmalıdır. Hasta bilgileri 01.08.1998 tarih ve 23420 sayılı Resmi Gazete'de yayımlanan Hasta Hakları Yönetmeliği'ne uygun olarak alınmış olmalıdır. Hayvanlar üzerindeki sonuçları bildiren deneysel çalışmaların, Hayvan Hakları Evrensel Bildirgesi, Deneysel ve Diğer Bilimsel Amaçlarla Kullanılacak Omurgalı Hayvanların Korunması Hakkındaki Avrupa Konvansiyonu (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose), T.C. Tarım ve Köy İşleri Bakanlığı'nın Deneysel ve Diğer Bilimsel Amaçlar İçin Kullanılan Deney Hayvanlarının Üretim Yerleri ile Deney Yapacak Olan Laboratuvarın Kuruluş Çalışma Denetleme Usul ve Esaslarına Dair Yönetmelik, Laboratuvar Hayvanları Biliminin Temel İlkeleri (Principles of Laboratory Animal Science), laboratuvar hayvanlarının bakım ve kullanılmasıyla ilgili el kitaplarında yer alan kural ve ilkelere uygun olarak ve çalışmanın yapıldığı kurumda mevcut ise, Deney Hayvanları Etik Kurulu'ndan alacakları onay sonrasında yapılmış olması gerekir. Etik Kurul onayı yazı ile birlikte sunulmalıdır. Yazılarda, insan ve hayvanlarda yapılan çalışmalarda kullanılan ameliyat sonrası ağrı giderici tedavi yöntemleri hakkında da bilgi verilmelidir.

Yayın Etiği ve Kötüye Kullanım Bildirgesi

Ulusal Romatoloji Dergisi yayın etiğini en yüksek standartlarda uygulamayı ve Yayın Etiği ve Kötüye Kullanım Bildirgesinin aşağıdaki ilkelerine uymayı taahhüt eder. Bu bildirge Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) ve International Committee of Medical Journal Editors (ICMJE) adlı birlik ve inisiyatiflerin, dergi editörleri için geliştirdikleri öneri ve kılavuzlar temel alınarak hazırlanmıştır. Yayımlanmak üzere dergiye gönderilen yazılar daha önce başka bir dergide yayımlanmamış (bilimsel toplantılarda sunulmuş ve tam metin yayımlanmış bildiriler dahil) veya yayımlanmak üzere eşzamanlı olarak herhangi bir dergiye gönderilmemiş olmalıdır. Dergiye gönderilen yazılar, bir editör ve en az iki danışman (hakem) tarafından incelenmek suretiyle tek-kör eş değerlendirme *(peer review)* sürecine alınır. Dergimiz gönderilen yazıların herhangi bir aşamada, amaca yönelik bir yazılım aracılığıyla intihal açısından incelenebileceği hakkını saklı tutar. Bu amaçla intihale yönelik izinsiz alıntı ya da düzmece veriler, sahtecilik (tablo şekil ya da araştırma verilerinin uydurma ya da manipüle edilmiş olması) ve araştırmada uygunsuz insan ya da hayvan denekler kullanımına yönelik incelemeler söz konusu

olabilir. Bu standartlara uygun olmayan yazılar dergide yayımlanmaz. Bu standartlara uygun olmayan yazılar dergide yayımlanmaz. Bu kural, yayımlanma sonrası aşamada saptanabilecek bu standartlarla ilgili herhangi bir uyumsuzluk durumunda da geçerlidir ve yazının yayımdan geri çekilmesini gerektirir. Yayın etiği gereği dergimiz intihal ya da duplike yayın şüphesi durumlarını rapor edecektir. Dergimiz, yayın etiğinin kötüye kullanımı ya da ihlali ile ilgili olası durumlarda COPE tarafından geliştirilen Yayın Etiği Akış Şemalarını temel alır.

Yazar Sorumluluğu

Yazarlar gönderdikleri yazıların özgünlüğünü teminat altına almalıdır. Yazının daha önce herhangi bir yerde, herhangi bir dilde yayımlanmadığı ya da yayımlanmak üzere değerlendirmeye alınmış olmadığını beyan etmelidirler. Geçerli telif hakkı sözleşme ve yasalarına uymalıdırlar. Dergimizde tablo, şekil ya da diğer katkı sunan alıntılar gibi telifli materyal ancak geçerli izin ve telif onayı ile yayımlanır. Yazarlar; başka yazarlar, katkı sağlayıcılar ya da kaynaklara uygun bir biçimde atıf yapmalı ve ilgili kaynakları belirtmelidir. Araştırma türü yazıların (kısa raporlar dahil) yazar(lar)ı "çalışmayı tasarlama", "verileri toplama", "verileri inceleme", "yazıyı yazma" ve "verilerin ve analizlerin doğruluğunu onaylama" aşamalarından en az 3 tanesine katılmış olmak ve bu durumu beyan etmek zorundadır. Yazarlar, çalışma ile ilgili bilinmesi gereken ve çalışmanın bulgularını ya da bilimsel sonucunu potansiyel olarak etkileyebilecek bir mali ilişkiyi ya da çıkar çakışması (conflict of interest) veya rekabet (competing interest) alanlarını açıklamakla yükümlüdür. Çalışmaya yapılan tüm mali katkıları, sponsorlukları ya da proje desteklerini açıklıkla bildirmelidirler. Derginin Çıkar Çakışması Politikası ile ilgili ayrıntılı bilgiyi de içeren ve olası çıkar çakışması durumunda kullanılabilecek "Çıkar Çakışması Beyan Formu"na PDF dokümanı olarak erişilebilir. Yazar yayımlanmış yazısında anlamlı bir bilimsel hata ya da uygunsuzluk saptadığında, yazıyı geri çekme ya da hatayı düzeltme amacıyla olabildiğince hızlı bir şekilde editör ile temasa geçme yükümlülüğünü taşır.

Hakem Sorumlulukları

Hakemler gelen yazıları, yazarlarının etnik köken, cinsiyet, cinsiyet tercihi, tabiyet, dini inanış ya da politik felsefelerini dikkate almaksızın bilimsel içerik açısından değerlendirir. Hakemler açısından; araştırma, yazarları ya da destekleyiciler ile ilgili bir çıkar veya rekabet çakışması bulunmamalıdır. Hakem kararları nesnel olmalıdır. Hakemler yazar tarafından atıf yapılmamış yayımlanmış ilintili yayınları belirtmelidir. Gönderilen yazı ile ilgili tüm bilgilerin gizli tutulması ve yazar tarafından yapılan telif hakkı ihlali ve intihal durumlarının farkına vardığında Editöre bildirilmesi ile yükümlüdürler. Hakem, gönderilen bir yazının içeriğinin kendi bilimsel alanı ya da birikimi ile uyumsuz olduğunu düşündüğünde ya da hızlı bir değerlendirme yapamayacağı durumlarda Editörü bilgilendirmeli ve değerlendirme sürecinden affını istemelidir.

Editör Sorumlulukları

Editörler gelen yazıları, yazarlarının etnik köken, cinsiyet, cinsiyet tercihi, tabiyet, dini inanış ya da politik felsefelerini dikkate almaksızın bilimsel içerik açısından değerlendirmelidir. Gönderilen yazıların yayımlanması için adil bir eş değerlendirme süreci sağlamalıdırlar. Gönderilen yazı ile ilgili tüm bilgilerin yayımlanana kadar gizli tutulmasını garanti altına almalıdırlar. Editörler yayının içeriği ve toplam kalitesinden sorumludur. Erratum sayfaları yoluyla gerektiğinde düzeltme yayımlamalıdırlar. Editör; yazarlar, editörler ve hakemler arasında olabilecek herhangi bir çıkar veya rekabet çakışmasına olanak vermemelidir. Ulusal Romatoloji Dergisinde hakem atamasında sadece Editör tam yetkiye sahip olup yazıların yayımlanması ile ilgili sonuç kararından da kendisi sorumludur.

YAYIN POLİTİKASI

Tüm makaleler bilimsel katkıları, özgünlük ve içerikleri açısından bilimsel komite tarafından değerlendirilecektir. Yazarlar verilerinin doğruluğundan sorumludurlar. Dergi gerekli gördüğü yerlerde dil ve uygun değişiklik yapma hakkını saklı tutar. Gereğinde makale revizyon için yazara gönderilir. Daha önce herhangi bir dilde yayınlanmış makaleler dergide yayınlanmak üzere kabul edilmeyecektir. Yazarlar bir başka dergide yayınlanmak üzere olan makaleyi teslim edemez. Tüm değişiklikler, yazar ve yayıncının yazılı izin alındıktan sonra yapılacaktır. Tüm makalelerin tam metinleri derginin www.manuscriptmodule.com/raed web sitesinden indirilebilir.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2013, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır:

Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097) (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting "Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12).

GENEL KURALLAR

Aşağıda belirtilen özelliklerin dışında yazılarla ilgili ilkeler açısından "International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts" dokümanları (www.icmje.org) esas alınmalıdır.

Dergiye gönderilecek yazılarda bulunması gereken bölümler sırası ile şunlardır ve her biri ayrı sayfada başlayacak şekilde sunulmalıdır:

Sayfa 1: Başlık sayfası

Sayfa 2: Türkçe Başlık, Özet ve Anahtar Sözcükler

Sayfa 3: İngilizce Başlık (Title), Özet (Abstract) ve Anahtar Sözcükler (Key words)

Sayfa 4 ve sonrası: Temel Metin

Sonraki sayfa: Kaynaklar

Sonraki sayfa: Tablo Açıklama Yazısı ve Tablo (her tablo ayrı sayfada belirtilmelidir)

Sonraki sayfa: Şekil ve Resim Alt Yazıları ve Resim/Şekiller (her şekil ayrı sayfada belirtilmelidir)

Başlık Sayfası

Başlık sayfasında aşağıdaki sıralama gözetilmelidir:

1- Yazının gönderildiği kategori (klinik araştırma, deneysel çalışma, derleme, olgu sunumu vb)

2- Yazının başlığı (başlık 80 karakteri geçmemeli ve standart dışı kısaltmalar içermemelidir)

3- Yazarların ad, soyad, iletişim adresleri ve araştırmanın yapıldığı sırada çalıştıkları kurum

4- Yazının, dergide yayınlandığında devam sayfalarının üst tarafında görünmesi arzu edilen ve 40 karakteri geçmeyen kısaltılmış başlığı

5- Varsa destekleyen kurum ve kuruluşlar

6- Yazı daha önce sunulmuşsa, sunulduğu toplantının ayrıntıları

7- İletişim kurulacak yazarın haberleşme bilgileri

8- Eğer varsa yazının içeriğiyle ilgili maddi desteğin belirtilmesi

Türkçe Özet

Araştırma yazılarında Amaç, Yöntem, Bulgular ve Sonuç bölümlerinden oluşmalı ve 250 kelimeyi geçmemelidir. Derleme ve olgu bildirilerinde yapılandırılmamış özet verilmelidir. Olgu sunumlarının özeti 100 kelimeyi geçmemelidir. Türkçe özet sayfasında en az 3 en fazla 6 anahtar kelime belirtilmelidir.

İngilizce Özet

Araştırma yazılarında "Objectives", "Methods", "Results", and "Conclusions" bölümlerinden oluşmalıdır ve 250 kelimeyi geçmemelidir. İngilizce Özet sayfasında en az 3 en fazla 6 İngilizce anahtar sözcük belirlenmeli, yazının İngilizce başlığı eklenmelidir.

Temel Metin

Giriş, Hastalar/Gereç ve Yöntem, Bulgular, Tartışma ve Kaynaklar bölümlerinden oluşmalıdır. Kısaltmalar standart olmalı ve ilk kullanıldığında parantez içinde açıklanmalıdır. Ölçümlerde uluslararası kabul edilmiş birimler kullanılmalıdır.

Tablo, Şekil ve Resimler

Metinde kullanılış sırasına göre numaralandırılmalı ve gereksiz kullanımdan kaçınılmalıdır. Olgularda kullanılan fotoğraflarda izin alınmalı ve tanınmayı önlemek için gerekli tedbirler uygulanmalıdır. Fotoğraf ve varsa çizim kalitesine özen gösterilmelidir. Yayın Kurulu yeterli kalitede olmadığı gerekçesiyle tablo, şekil ve resimlerde düzeltme veya yenileme isteğinde bulunabilir. Şekil ve resimlerin orijinal olmaları gerekir. Başka bir yayın içinde kullanılmış bulunan resim, şekil ve grafiklerin dergimizde yayımlanabilmesi için, gerekli izinler yazarlar tarafından ve makale başvurusu yapılmadan önce alınmalıdır. İznin alındığını gösterir belgenin kopyası yazıyla birlikte dergiye gönderilmelidir.

Kaynaklar

Kaynaklar güncel ve yazı için gerekli olanlardan seçilmelidir. Yazı metninde kaynaklar parantez içinde gösterilmeli ve kullanılış sırasına göre numaralandırılmalıdır. Süreli yayın adları PubMed kurallarına uygun olarak kısaltılmalı, burada yer almayan dergilerin adlarında kısaltma kullanılmamalıdır. Bildiri özetlerinin kaynak gösterilmesinden kaçınılmalıdır. Bir dergi tarafından kabul edilmiş fakat henüz yayımlanmamış olan yazılar gerektiği şekilde belgelendirilerek kaynak olarak kullanılabilir. Kabul edilmemiş yazılar da dahil olmak üzere bunun dışındaki bilgi, yazı içinde "yayınlanmamış gözlem" olduğu belirtilerek kullanılabilir. Kaynaklar aşağıdaki örneklere göre yazılmalı ve 6 yazara kadar olan kaynaklarda yazarların tamamı sunulmalı, daha fazla yazarı olan kaynak künyeleri, ilk 3 yazar ve sonuna ve ark. (yabancı dildeki kaynakların künyelerinde et al.) kısaltması gelecek şekilde düzenlenmelidir. Kaynakların doğruluğu açısından sorumluluk yazarlara aittir.

Örnekler

Türkçe süreli yayın örneği:

Göksedef D, Ömeroğlu NÖ, Denli Ş, Üreyen C, Sayılgan C, İpek G. Sistemik lupus eritematozuslu bir olguda aort yetmezliği nedeniyle aort kapak replasmanı. Cerrahpaşa Tıp Dergisi 2008;39:73-5.

Yabancı dilde süreli yayın örneği:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arhritis: a 14-year prospective evaluatin of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Elektronik dergide yayımlanan süreli yayın örneği:

Yurdakul S. Is there really a higher risk for infection with anti TNF-alpha agents or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Kitap bölümü örneği:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-8.

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Hazırlanan yazıların dergiye gönderilmeden önce aşağıdaki kontrol listesine göre gözden geçirilmesi önerilir:

1- Başlık sayfası

2- Özetler (Türkçe ve İngilizce; olgu sunumlarında en fazla 100 sözcük, diğerlerinde en fazla 250 sözcük; araştırma yazılarında yapılandırılmış)

3- Anahtar sözcükler (en az 3'er adet)

4- Temel metin (alt başlıklar)

5- Kaynaklar (ICMJE kurallarına uygunluk)

6- Şekil, tablo ve resimler (numaralandırma; alt yazılar; özgünlük/izin yazısı)

7- Başvuru mektubu

8- Telif Hakkı Devir Formu (tüm yazarlar tarafından imzalanmış)

9- Çıkar Çakışması Beyan Formu (gereğinde)

Journal of Turkish Society for Rheumatology (formerly RAED Journal), the official organ of Turkish Society for Rheumatology, is a peer-reviewed scientific journal published three times in a year in Turkish or English (p-ISSN: 2651- 2653). The journal publishes original contributions in the form of experimental and clinical research articles, case reports, reviews, news, letters to the editor and authors as well as announcements related to all topics of rheumatology. Also, abstracts or full texts of scientific meetings in rheumatology can be published as supplements of the journal. The reviews are usually invited; therefore it is necessary to contact the editor before sending them to the journal. The journal does not accept reviews which are directly submitted.

The article types in the journal are classified as below:

- Clinical Research Article
- Experimental Study
- Case Report
- Review
- Letter to the Editor
- Recommendation
- Letter to the Author
- Book Review
- News
- Abstracts

ETHICS & PEER-REVIEW

Journal of Turkish Society for Rheumatology is an independent journal based on double-blind peer-review principles. The manuscript is assigned to the Editor-in-Chief, who reviews the manuscript and makes an initial decision based on manuscript quality and editorial priorities. Manuscripts that pass initial evaluation are sent to an Associate Editor. The Associate Editor assigns the manuscript to two reviewers (internal and/or external reviewers). The reviewers must review the manuscript within 21 days. The Associate Editor recommends a decision based on the reviewers' recommendations and sends the manuscript to the Editor-in-Chief. The Editor-in-Chief makes a final decision based on editorial priorities, manuscript quality, and Associate Editor's and reviewers' recommendations. If there are any conflicting recommendations from reviewers, the Editor-in-Chief can assign a new reviewer.

All manuscripts submitted are screened for plagiarism using Crossref Similarity Check powered by "iThenticate" software. Results indicating plagiarism may cause manuscripts being returned or rejected.

Manuscripts sent to the journal for publication should not have been previously published in another journal or sent to any journal simultaneously to be published. Manuscripts prepared from papers presented at scientific meetings can be sent to the journal, provided that they are not fully published. Incoming articles are pre-examined by Editorial Board. Manuscripts that are not suitable for publication purposes may be rejected directly or sent back to the author for publication and publication rules without being evaluated by the reviewer. Among the articles deemed appropriate for the scope of the journal, clinical research, experimental study, review and case report class articles enter the peer-review process. The Editorial Board is empowered to propose the corrections and changes it deems necessary during the preparation of the articles sent to the journal in line with the comments and suggestions of the reviewers. In order to ensure language unity, he/she can make word changes that do not change the scientific meaning of the sentence. After the necessary correction steps have passed in the peer evaluation process, the proof of the articles that are made ready for publication and the page layout is sent to the relevant author (for whom correspondence is made) for the final print approval.

Research Ethics

The author(s) should indicate in their articles that Informed Consent was received from the participating individuals in the studies conducted on people and send the approval document(s) received from the Ethics Committee or equivalent board of the institution where the study was conducted. In case reports, a document must be presented, indicating that each case is informed that their information will be used for publication. All work must have been done in accordance with the final amendments to the Helsinki Declaration. Patient information should be obtained in accordance with the Patient Rights Regulation published in the Official Gazette dated 01.08.1998 and numbered 23420. The European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose, by the Universal Declaration of Animal Rights, which reports results on animals, for the Protection of Vertebrates to be Used for Experimental and Other Scientific Purposes, T.C. The Regulation of the Ministry of Agriculture and Rural Affairs on the Production Areas of the Experimental Animals Used for Experimental and Other Scientific Purposes and the Regulation on the Establishment Operation Control Procedures and Principles of the Laboratory to Experiment, the Principles of Laboratory Animal Science, by the care and use of laboratory animals. If it is available in accordance with the rules and principles contained in the relevant manuals and in the institution where the study is carried out, it should be made after approval from the Experimental Animals Ethics Committee. Ethics Committee approval must be submitted with the letter. In the articles, the information should be given about post-operative pain-relieving treatment methods used in human and animal studies.

Publication Ethics and Malpractice Statement

Journal of Turkish Society for Rheumatology undertakes to apply the publication ethics to the highest standards and to comply with the following principles of the Publication Ethics and Abuse Declaration. This declaration is prepared based on the suggestions and guidelines developed by the journal on editors of the Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) and International Committee of Medical Journal Editors (ICMJE). Manuscripts sent to the journal for publication should not have been previously published in another journal (including papers presented at scientific meetings and published in full text) or simultaneously not sent to any journal for

publication. Manuscripts sent to the journal are taken into the peer review process by an Editor and at least two consultants (reviewers). Our journal reserves the right to examine the submitted articles at any stage in terms of plagiarism through a purposeful software. For this purpose, unauthorized quotations or fraudulent data regarding plagiarism, fraudulence (made up or manipulated in the form or research data of the table) and investigations may be subject to inappropriate human or animal subjects. Manuscripts that do not comply with these standards are not published in the journal. This rule also applies in case of any incompatibility with these standards which can be determined at the post-publishing stage and requires the withdrawal of the article from the publication. Due to publication ethics, our journal will report cases of plagiarism or duplicate publication. Our journal is based on Publication Ethics Flowcharts developed by COPE in possible situations related to malpractice or violation of publication ethics.

Author Responsibility

Authors should ensure the authenticity of the articles they send. They must declare that the manuscript has not been published in any language, or has been evaluated for publication. They must comply with applicable copyright contracts and laws. In our journal, copyrighted material such as tables, figures or other contributory citations is published only with valid permission and copyright approval. Authors; other authors, contributors or sources should cite appropriately and indicate relevant sources. Participating in at least three stages of research type articles (including short reports) "designing the study", "collecting data", "reviewing data", "writing the article" and "confirming the accuracy of data and analysis" must declare. The authors are responsible for disclosing a financial relationship or areas of conflict of interest or competing for interest that should be known about the study and potentially affect the findings or scientific outcome of the study. They must explicitly report all financial contributions, sponsorships or project supports to the study. The "Conflict of Interest Conflict Declaration Form", which contains detailed information about the journal's Conflict of Interest Policy and can be used in case of potential conflict of interest, is available as a PDF document. When the author detects a meaningful scientific error or incompliance in his published article, he has an obligation to contact the Editor as quickly as possible for the purpose of withdrawing or correcting the article.

Reviewer Responsibilities

Reviewers evaluate incoming articles in terms of scientific content, regardless of their authors' ethnicity, gender, gender preference, nationality, religious belief, or political philosophy. For the reviewers; there should be no conflict of interest or competition regarding research, authors or promoters. Reviewer decisions must be objective. The Reviewers should indicate the related publications that have not been cited by the author. They are obliged to keep all information regarding the submitted article confidential and inform the Editor when they become aware of copyright infringement and plagiarism by the author. The reviewer should inform the Editor and ask for forgiveness from the evaluation process when he considers that the content of a sent article is incompatible with his or her scientific field or knowledge, or when he cannot make a quick evaluation.

Editor Responsibilities

Editors should evaluate incoming articles in terms of scientific content, regardless of their authors' ethnicity, gender, gender preference, nationality, religious belief, or political philosophy. They must provide a fair peer-review process for the publication of the submitted articles. They must ensure that all information regarding the submitted letter is kept confidential until it is published. Editors are responsible for the content and overall quality of the publication. If necessary, they should publish a correction through the Erratum pages. The Editor should not allow any conflicts of interest or competition between authors, editors and reviewers. Only the Editor has full authority in the assignment of the reviewers in the Journal of Turkish Society for Rheumatology and is also responsible for the final decision on the publication of the articles.

PUBLICATION POLICY

All articles will be evaluated by the scientific committee in terms of their scientific contributions, originality and content. Authors are responsible for the accuracy of their data. The journal reserves the right to change the language and appropriate changes where it deems necessary. If necessary, the article is sent to the author for revision. Articles previously published in any language will not be accepted for publication in the journal. Authors cannot submit an article that is about to be published in another journal. All changes will be made after the written permission of the author and publisher. The full text of all articles can be downloaded from the journal's website, www.manuscriptmodule.com/raed.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

GENERAL RULES

Apart from the features mentioned below, "International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts" documents (www.icmje.org) should be taken as a basis.

The sections that should be included in the articles to be sent to the journal are as follows and should be presented in a way that each starts on a separate page:

Page 1: Title page

Page 2: Turkish Title, Abstract and Keywords

Page 3: Title, Abstract and Key Words in English

Page 4 and afterwards: Main Text

Next page: Resources

Next page: Table Explanation and Table (each table should be specified on a separate page)

Next page: Figure and Image Subtitles and Image / Shapes (each shape must be specified on a separate page)

Title Page

The title page should be considered in the following order:

1- The category in which the article was sent (clinical research, experimental study, review, case report, etc.)

2- Title of the article (the title should not exceed 80 characters and should not contain non-standard abbreviations)

3- Name, surname, contact addresses of the authors and the institution they work at the time of the research

4- The abbreviated title of the article, which is desired to appear at the top of the continuation pages when published in the journal and does not exceed 40 characters.

5- Supporting institutions and organizations, if any

6- If the article has been submitted before, details of the meeting it was presented

7- Communication information of the author to be contacted

8- Indicating the financial support regarding the content of the article, if any

Turkish Abstract

The research articles should consist of the "Objectives", "Methods", "Results", and "Conclusions" sections and should not exceed 250 words. An unstructured abstract should be provided in reviews and case reports. The abstract of case reports should not exceed 100 words. A minimum of 3 and a maximum of 6 keywords should be specified in the Turkish abstract page.

English Abstract

The research articles should consist of "Objectives", "Methods", "Results", and "Conclusions" sections and should not exceed 250 words. At least 3, maximum of 6 English keywords should be determined in the English Abstract page, and English title of the article should be added.

Main Text

The introduction should consist of the Patients / Materials and Methods, Results, Discussion and References sections. Abbreviations should be standard and should be explained in parentheses when they are used first. Internationally accepted units should be used in the measurements.

Tables, Figures and Images

It should be numbered in the order of use in the text, and unnecessary use should be avoided. In the photographs used in the cases, permission should be obtained, and necessary measures should be applied to prevent recognition. Attention should be paid to the quality of photographs and drawings if any. Editorial Board may request correction or renewal in tables, figures and pictures on the grounds that it is not of sufficient quality. Figures and pictures must be original. In order for the pictures, figures and graphics used in another publication to be published in our journal, the necessary permissions must be obtained by the authors and before applying for an article. A copy of the document indicating that the permit has been obtained must be sent to the journal with the article.

References

References should be selected from the ones that are up to date and necessary for the article. References in the text should be indicated in parentheses and numbered according to the order of use. Name of the journals should be abbreviated in accordance with PubMed rules, and abbreviations should not be used in the names of journals which are not included here. Citation of proceedings should be avoided. Manuscripts accepted by a journal but not yet published can be documented as required and used as a source. Information other than this, including unaccepted articles, can be used by stating that there is "unpublished observation" in the article. References should be written according to the examples below, and all the authors should be presented in references up to 6 authors, references which have more authors should be arranged in a way that ''et al.'' abbreviation will be placed at the end of the first three authors. The responsibility for the accuracy of the references belongs to the authors.

Examples

Periodical publication example in Turkish:

Göksedef D, Ömeroğlu NÖ, Denli Ş, Üreyen C, Sayılgan C, İpek G. Sistemik lupus eritematozuslu bir olguda aort yetmezliği nedeniyle aort kapak replasmanı. Cerrahpaşa Tıp Dergisi 2008;39:73-5.

Periodical publication example in a foreign language:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow-acting antirheumatic therapy in rheumatoid arhritis: a 14-year prospective evaluatin of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Example of periodical publication published in an online journal:

Yurdakul S. Is there really a higher risk for infection with anti TNF-alpha agents or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Example of book section:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-8.

It is recommended that the prepared articles are reviewed according to the following checklist before being sent to the journal:

1- Title page

2- Abstracts (Turkish and English; maximum 100 words in case reports, maximum 250 words in others; structured in research papers)

3- Keywords (at least three each)

4- Main text (subheadings)

5- Resources (Compliance with ICMJE rules)

6- Figures, tables and pictures (numbering; subtitles; originality/ permission letter)

7- Application letter

8- Copyright Transfer Form (signed by all authors)

9- Conflict of Interest Declaration Form (if required)

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İçindekiler / Contents

Orijinal Araştırmalar / Original Articles

Olgu Sunumları / Case Reports

Editöre Mektup / Letter to the Editor

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Sevgili Okurlarımız,

Ulusal Romatoloji Dergimiz (Eski adıyla RAED dergisi) 2022 yılı ikinci sayısı ile karşınızdayız. Her geçen sayı ile içeriğimiz daha da zenginleşiyor.

Orijinal makalelerimizden ilkinde Mehmet Ali Balcı ve Lütfi Akyol 2010-2020 yılları arasında izledikleri RA hastalarında, ülkemizde ilk kez standart mortalite oranını (SMR) değerlendiren çalışmalarında, özellikle konvansiyonel DMARD kullananlarda SMR'nin arttığını gösteriyorlar. İkinci çalışmamızda Reyhan Bilici Salman ve Şeminur Haznedaroğlu SLE hastalarında oto-antikor pozitifliği ile çeşitli klinik bulgular arasındaki ilişkiyi araştırıyorlar. Çalışmada Diskoid raş anti-Sm, Raynaud ve oral ülser anti-RNP, alopesi, lupus pnömonisi ve perikardit anti-Ro ve plörit anti- La pozitifliği ile ilişkili bulunuyor. Sonraki çalışmamızda Andaç Komaç ve ark. Dev-hücreli arterit'in 2 ana altgrubu olan kraniyal ve ekstra-kraniyal tutulum (EKT) arasındaki klinik farklılıkları inceliyorlar. Özellikle konstitüsyonel bulgular ve PET pozitifliği EKT ile ilişkili saptanıyor. Behçet hastalarında uyku kalitesinin hastalık aktivitesi, depresyon ve hayat kalitesi ile ilişkisi ise Ozge Polat-Korkmaz ve ark. sonraki çalışmasının konusunu oluşturuyor. Beşinci yazımızda Ceren Tuncer Sakar ve ark. Romatoid artritte biyolojik ilaçlara yanıtı değerlendiriyor ve izlemde çok-kriterli modellerin kullanılmasını öneriyorlar. Nilüfer Tekgöz ve ark. PFAPA sendromunun klinik seyrinde *MEFV* gen mutasyonlarının etkisini araştırdıkları çalışmada özellikle atipik olgularda gen taramasının önemini vurguluyorlar. Son olarak Hakan Babaoğlu vaskülit hastalarında SAA düzeyi ölçümünün potansiyel bir biyobelirteç olabileceğini gösteriyor. Ayrıca yine 2 ilginç olgu sunumu da bu sayıda yer alacak.

Önümüzdeki dönemde de yine orijinal makalelerinizi, derleme ve olgu sunumlarınızı bekliyoruz.

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Assessment of the effect of DMARD use on the mortality of patients with rheumatoid arthritis

Romatoid artrit hastalarında DMARD kullanımının mortalite üzerine etkisinin araştırılması

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Abstract

Objective: The aim of this study was to investigate the causes of mortality in patients diagnosed with rheumatoid arthritis (RA) and the effects of disease-modifying antirheumatic drugs (DMARDs) to be used for treating RA on mortality.

Methods: A total of 743 patients with RA over the age of 18 who attended between 2010 and 2020 in the hospital where this study was conducted, were included in the study. The patients' clinical and laboratory information were obtained from the hospital database, whereas the relevant mortality and population data were obtained from the Turkish Ministry of Health system and the Turkish Statistical Institute, respectively. The standardized mortality ratio (SMR) was calculated by dividing the number of mortality observed in the cohort by the number of mortality in the Turkish population of the same age and gender. Patients were divided into two groups: Those who used only conventional (cDMARDs) and those who took cDMARDs plus biological (bDMARDs).

Results: Mortality occurred in 61 patients from the 743 patients with RA. SMR of the patients with RA was found to be 1.42 [confidence interval (CI) 1.09-1.81)] in the Turkish population. SMR was determined to be higher in the cDMARD cohort than in the bDMARD cohort [2.05 (CI 1.53-2.69) and 0.66 (CI 0.37-1.11), respectively]. The most common causes of mortality in patients with RA were determined as cardiovascular diseases 18 (29.5%), infectious diseases 13 (21.3%) and respiratory system diseases 12 (19.7%).

Conclusion: This study is the first mortality study reported from Turkey in patients with a diagnosis of RA. Generally, there is an increased mortality in patients with RA compared with the Turkish population. Therefore, to reduce mortality in patients with RA, patients with RA should be followed more carefully, and treated more effectively in terms of both RA and any comorbid diseases they might have.

Keywords: Rheumatoid arthritis, mortality, antirheumatic agents

Öz

Amaç: Çalışmamızın amacı romatoid artrit (RA) tanılı hastaların mortalite nedenlerinin ve tedavide tercih edilen ilaçların mortalite üzerine etkisinin araştırılmasıdır.

Yöntem: Hastanemizde 2010-2020 yılları arasında takip edilmiş RA tanılı 18 yaşından büyük 743 hasta çalışmaya alındı. Hastaların klinik ve laboratuvar verileri hastane veritabanından, mortalite verileri Türkiye Sağlık Bakanlığı sisteminden ve nüfus verileri Türkiye İstatistik Kurumu'ndan alındı. Standartlaştırılmış ölüm oranı (SMR) kohortta gözlemlenen ölüm sayısının aynı yaş ve cinsiyetteki Türk toplumunda görülen ölüm sayısına bölünmesiyle hesaplandı. Hastalar sadece konvansiyonel hastalık modifiye edici antiromatizmal ilaç (cDMARD) kullanan hastalar ve cDMARD ile birlikte biyolojik (bDMARD) kullanan hastalar olmak üzere iki gruba ayrıldı.

Bulgular: Takip süreci boyunca 61 hastada mortalite gerçekleşti. RA hastalarının SMR'si 1,42 [güven aralığı (GA) 1,09-1,81] olarak Türk toplumuna göre daha yüksek tespit edildi. cDMARD kohortunda SMR, bDMARD kohortuna göre daha yüksek tespit edildi [sırasıyla; 2,05 (GA 1,53-2,69) ve 0,66 (GA 0,37-1,11)]. RA hastalarında genel olarak en sık ölüm nedeni kardiyovasküler hastalıklar 18 (%29,5), enfeksiyon hastalıkları 13 (%21,3) ve solunum sistemi hastalıkları 12 (%19,7) tespit edildi.

Sonuç: Çalışmamız RA tanılı hastalarda Türkiye'den bildirilen ilk mortalite çalışmasıdır. RA tanılı hastalarda genel olarak Türk toplumuna göre artmış bir mortalite mevcuttur. RA tanılı hastalarda mortaliteyi azaltmak için hem RA'nın kendisi hem de komorbidit hastalıklar daha dikkatli ve etkin bir şekilde takip ve tedavi edilmelidir.

Anahtar Kelimeler: Romatoid artrit, mortalite, antiromatizmal ajanlar

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Introduction

Rheumatoid arthritis (RA) is a symmetrical, inflammatory and peripheral polyarthritis of unknown etiology. Studies conducted with patients with RA revealed that the mortality rates in patients with RA are higher than the mortality rates in the general population.[1-3] In the literature, cardiovascular diseases, malignant diseases, respiratory and infectious diseases have been cited as the main causes of mortality in patients with RA.[1,4,5] Chronic inflammation, disability, comorbidities and drugs used in treatment can be listed as causes of increased mortality. Recently, biological disease-modifying antirheumatic drugs (bDMARDs) have been used in addition to conventional (cDMARDs) for the treatment of RA. Although the effects of bDMARDs used in addition to cDMARDs on mortality have been studied in different societies, no study has been conducted on this subject in Turkish society.[3,4,6] Therefore, is aimed this study to investigate the causes and incidences of mortality, the mortality rates in patients with RA compared to the general population, and the effects of the medications preferred according to local and international guidelines to be used for treating RA on mortality.

Materials and Methods

The sample of this study consisted of 743 patients with RA who were older than 18 years and followed up in the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital between 2010 and 2020. RA diagnoses of all 743 patients conformed to the American College of Rheumatology Criteria.[7] Records of these patients, i.e. their demographic, clinical and laboratory data, the treatments they received, their follow-up periods, disease courses, disease outcomes and related complications, were obtained from the hospital database, and analyzed retrospectively. Treatment durations of the patients were checked from the hospital database. The compliance of the patients with the treatment was checked from the hospital database. The patient who did not attend regular follow-ups was excluded from the study. Diagnoses of RA and comorbid diseases were obtained from the hospital database, in accordance with the International Statistical Classification of Diseases and Related Health Problems Tenth Revision [ICD-10 (B16-B18), (J45), (I10), (I24-I25), (E13-E14), (E78), (M05-M06), (M80-M81), (N18)]. Death records were obtained from the National Death Reporting System of the Ministry of Health of the Republic of Turkey (NDRS).[8] NDRS is an institutional web-based application that allows data exchange among the relevant units of the Ministry of Health, the General Directorate of Population and Citizenship Affairs and the Turkish Statistical Institute in order for the compilation of the death statistics established by the Government of the Republic of Turkey. Additionally, national population records were obtained from the Turkish Statistical Institute (TSI).[9] TSI is the national institution established to compile, evaluate, analyze and publish statistics in the respect of the economy, society, demographics, culture, environment, science and technology and other fields deemed necessary. The incidence-based mortality (IBM) was calculated by dividing the total number of mortality by the aggregate value of patient-time in the cohort. The 95% confidence intervals (CIs) for IBMs were calculated using Byar's formula.[10] The treatment of patients with RA was started with cDMARDs and bDMARDs were added to the treatment if the target remission was not achieved in line with the recommendations of the "EULAR recommendations for managing RA with synthetic and bDMARDs".[11] Patients were divided into two groups: those who only used cDMARDs and those who took cDMARDs plus bDMARDs. That is, the bDMARDs group uses both cDMARDs and bDMARDs together. Head-to-head comparisons were made between with a new mechanism of action (rituximab, tocilizumab) versus cycling to tumour necrosis factor inhibitors (TNFi) (adalimumab, etanercept, golimumab, infliximab) among patients with RA in which mortality occurred, within the bDMARD cohort. The standardized mortality ratio (SMR) was calculated by dividing the number of mortality observed in the cohort by the number of mortality in the Turkish population of the same age and gender. The number of mortality observed in the Turkish population of the same age and gender was obtained from the TSI's database.[9]

Statistical Analysis

Statistical analysis were performed using the SPSS 21.0 (Statistical Package for the Social Sciences, Version 21.0, IBM, Armonk, NY) software package. Cumulative survival curves were created using the Kaplan-Meier method. All-cause mortality risk factors such as gender, age, disease activity score of 28 joints (DAS28) score, RF, anti-CCP positivity, comorbidities, bDMARD and cDMARD use analyses were performed using the Cox regression analysis. Probability (p) values of <0.05 were considered to indicate statistical significance.

Results

A total of 743 patients, of whom 338 (261 women, 77 men) were using bDMARDs and 405 (325 women, 80 men) were using cDMARDs, were included in the study. The mean age at diagnosis of the cDMARD cohort was found to be higher than the mean age of the bDMARD cohort (56.8

years and 49.2 years, respectively; p=0.00). The mean follow-up period of the patients using cDMARDs was found to be longer than the mean follow-up period of the patients using bDMARDs (56.8 months and 49.9 months, respectively; p=0.00). DAS28 scores of the patients using bDMARDs and cDMARDs were found to be similar (3.29 and 3.28, respectively; p>0.05). At least one comorbidity such as diabetes, hypertension, and coronary disease, was detected in 26% of the patients included in the study. Hypertension (23.1% and 15.3%, respectively; p=0.06) and hyperlipidemia (10.9 and 5.3, respectively; p=0.07) were found to be more frequent in the cDMARD cohort than in the bDMARD cohort. There was no significant difference between the cohorts in terms of other comorbidities.

The risk of mortality was found to be higher in patients with comorbidities [hazard ratio (HR) was 2.20 (1.04-4.65), p=0.039 in the presence of one comorbidity, whereas HR was 17.67 (5.31-58.82), p=0.00 in the presence of five comorbidities]. The clinical and laboratory characteristics of the patients who use cDMARDs and bDMARDs as well as the treatment modalities administered to these patients are summarized in Table 1.

Out of the 743 patients, mortality occurred in 61 patients. Thirteen of these patients were using bDMARDs whereas 48 patients of them were using cDMARDs, during the treatment period. Cardiovascular disease was found to be the most common cause of death in both the bDMARD cohort and the cDMARD cohort (23.1% and 31.3%, respectively). The mortality rate due to infectious diseases was determined to be higher in the bDMARD cohort compared to that the cDMARD cohort (30.8% and 18.8%, respectively; p>0.05), whereas the mortality rate due to cardiovascular causes was determined to be higher in the cDMARD cohort compared to the bDMARD cohort (31.3% and 23.1%, respectively; p>0.05), albeit not statistically significantly in either of the cases. Data on the underlying causes of the mortality are shown in Table 2. Kaplan-Meier survival curves of patients who have been using bDMARDs and cDMARDs are shown in Figure 1A.

The retrospective analysis of the follow-up periods of the patients with RA included in this study revealed that they were followed up for a total of 3.690 patient-years. Of the patients with RA, the patients who have been using cDMARDs were followed up for 2.240 patient-years and the patients who have been using bDMARDs were followed up for 1.450 patient-years. Additionally, IBM was found as 16.53 per 1000 person-years in patients with RA in general. IBM of the patients who have been using cDMARDs was found as 21.34 per 1000 person-years, whereas IBM of the patients who have been using bDMARDs was found as 8.96 per 1000 person-years. It was determined that 52 patients (15.4%) in the cDMARD cohort had switched from one biological to another. It was mostly the patients who had been using infliximab (34.5%) who switched to another biological. Diagnosis, clinical characteristics,

Table 1. The clinical and laboratory characteristics of, and the treatment modalities administered to, the patients that use cDMARDs and bDMARDs

	bDMARD	cDMARD	p
Number of patients (t/f/m)	338/261/77	405/325/80	>0.05
Age (years), mean	49.2±15.3	56.8±15.1	0.00
Disease duration (months), mean	49.9±39.3	76.7±41.9	0.00
Disease activity score, mean	3.29±1.23	3.28±1.33	>0.05
Gender (female), (%)	77.2	80.2	>0.05
RF positivity, (%)	69.2	66.2	>0.05
Anti CCP positivity, (%)	62.7	54.8	0.03
Diabetes, (%)	8.0	8.2	>0.05
Hypertension, (%)	15.3	23.1	0.09
Hyperlipidemia, (%)	5.3	10.9	0.07
Coronary artery disease, (%)	8.9	12.3	>0.05
Chronic renal failure, (%)	1.5	2.7	>0.05
Osteoporosis, (%)	4.7	4.2	>0.05
Asthma, (%)	2.7	2.5	>0.05
Hepatitis B, (%)	2.1	1.2	>0.05
Steroid use, (%)	71.9	51.9	0.00
Methotrexate use, (%)	47.9	72.1	0.00
Leflunomide use, (%)	37.6	25.7	0.01
Sulfasalazine use, (%)	20.1	38.0	0.00
Hydroxychloroquine use, (%)	47.6	60.5	0.00

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, t/f/m: Total/female/male

incidence-based mortality rates of, and the treatment modalities administered to, the patients who have been using bDMARDs are given in Table 3.

SMR of the patients with RA was found to be 1.42 (CI 1.09-1.81) in the general Turkish population. However, SMR was determined to be higher in the cDMARD cohort than in the bDMARD cohort [2.05 (CI 1.53-2.69) and 0.66 (CI 0.37-1.11), respectively]. The age group with the highest SMR was the 35-44 age group with an SMR of 3.31 (0.55-10.97). The 35-44 age group was also the age group with the highest SMR in the bDMARD cohort with a SMR of 3.26 (0.16-16.11) and in the cDMARD cohort with a SMR of 3.37 (0.16-16.63). SMR of the 18-34 age group compared to the general population could not be calculated as no mortality was observed in this age group in the respective cohorts. Detailed data on the SMRs are given in Table 4. The mortality risk was found to be higher in the cDMARD cohort compared to the bDMARD cohort, albeit not statistically significantly [HR 1.59 (0.85-2.97), p=0.1].

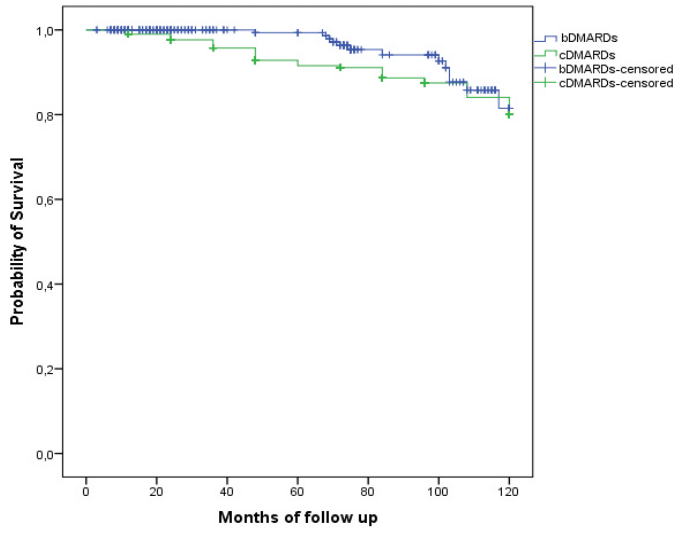

Figure 1A. Kaplan-Meier survival curves of patients who have been using bDMARDs and cDMARDs

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs

Table 2. Data on underlying causes of death in patients with rheumatoid arthritis

Cause of death	Death in the cDMARD cohort (n=48)	Death in the bDMARD cohort (n=13)	Death in all patients with RA (n=61)
Cardiovascular diseases, n (%)	15 (31.3)	3 (23.1)	18 (29.5)
Infectious diseases, n (%)	9 (18.8)	4 (30.8)	13 (21.3)
Respiratory system diseases, n (%)	3 (23.1)	9 (18.8)	12 (19.7)
Malignant diseases, n (%)	7 (14.6)	2 (15.4)	9 (14.8)
Renal diseases, n (%)	4 (8.3)	0 (0)	4 (6.6)
Neurological diseases, n (%)	2 (4.2)	0 (0)	2 (3.3)
Other causes, n (%)	2 (4.2)	1 (7.7)	3 (4.9)

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, RA: Rheumatoid arthritis

Table 3. Clinical characteristics and incidence-based mortality rates of the patients with RA in general, and the patients with RA who have been using bDMARDs or cDMARDS

	Gender (f/m/t)	Age (year) at diagnosis mean ± SD	Duration of treatment (mounth), mean ± SD	Follow-up patient-years,	Incidence of mortality/per 1.000 years	Switch, n (%)	≥1 Comorbidity, n (%)	Death, n
Abatacept	5/5/10	55.5±17.1	56.5±26.6	52	NA	3 (30)	2 (20)	0
Adalimumab	43/15/58	43.7±15.7	63.1±42.9	312.5	9.6	13 (22.4)	3 (5.2)	3
Etanercept	42/15/57	43.4±13.6	63.6±40.8	312	6.41	8 (14.0)	15 (26.3)	2
Golimumab	32/6/38	46±14.6	36.9±26.4	132	NA	9 (23.7)	5 (13.2)	0
Infliximab	22/7/29	49.9±14.8	98.4±26.9	225.5	13.3	10 (34.5)	9 (31)	3
Rituximab	45/11/59	56.7±13.8	42.6±38.1	200.5	14.6	3 (5.1)	15 (26.8)	3
Certolizumab	11/2/13	43.7±16.8	16.4±8.6	22	NA	1 (7.7)	0 (0.0)	0
Tofacitinib*	29/3/32	55.1±11.5	21.3±15.2	63	NA	0 (0.0)	6 (18.7)	0
Tocilizumab	32/13/45	52.5±15.2	32.6±25.4	132	15.15	5 (11.1)	19 (46.2)	2
All bDMARD patients	261/77/338	49.2±15.3	49.9±39.3	1.450 (total)	8.96	52 (15.4)	74 (21.8)	13
All cDMARD patients	325/80/405	56.8±15.1	76.7±41.9	2.240 (total)	21,34	NA	119 (29.4)	48
All patients with RA	586/157/743	53.36±15.57	64.51±42.87	3.690 (total)	16.53	NA	193 (26)	61

*bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, , F: Female, M: Male, n: Number, RA: Rheumatoid arthritis, SD: Standard deviation, T: Total, *Tofacitinib: b/tsDMARD*

Head-to-head comparisons of the treatment groups within the group of patients who have been using bDMARDs revealed that the patients who have been using tocilizumab had the highest increase in the mortality risk increase compared with the patients who have been using etanercept (HR 21.701, CI 1.931-243.893, p=0.013). Detailed data on the head-to-head comparisons of various bDMARD treatments indicated for RA in terms of the associated mortality risks are given in Table 5.

Additionally, individual survival analyses based on the type of bDMARD the patients have been using are shown in Figure 1B.

Discussion

The mortality data were analyzed according to the treatment modalities administered to the patients with RA during the 10-year follow-up period. This study is the first mortality study reported from Turkey in patients with a diagnosis of RA. Mortality occurred in 61 patients with RA during the follow-up period. SMR of the patients with RA included in this study was found to be 1.42 (CI 1.09-1.81) in the general Turkish population. However, SMR of the patients with RA who have been using bDMARDs was found to be 0.66 (CI 0.37-1.11) and lower than the SMR of the general Turkish population. In comparison, SMR in patients with RA was reported as 1.65 (95% CI 1.44-1.87) in a study conducted in South Korea, [1] as 1.49 (95% CI 1.36-1.63) in a study conducted in Germany[12] and as 1.54 (95% CI 1.41-1.67) in a study conducted in the Netherlands.

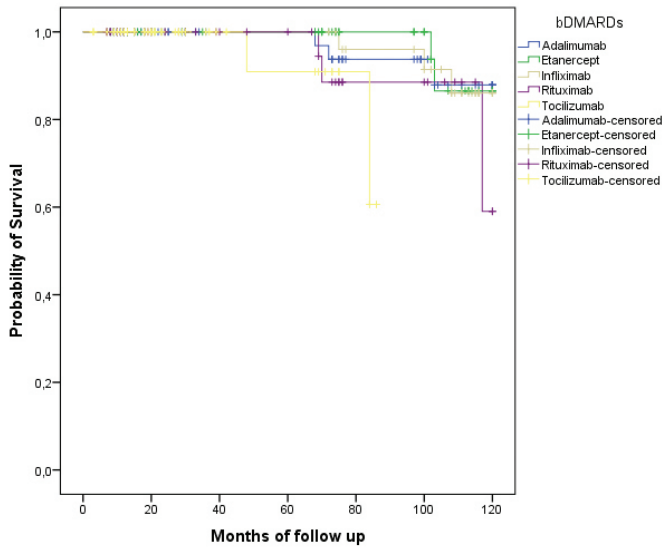

Figure 1B. Individual survival analyses of the patients based on the type of bDMARD they have been using

bDMARDs: Biologic disease-modifying antirheumatic drugs

Table 4. SMRs by the age group

Age bracket	bDMARD (number of deaths/patients)	SMR (CI)	cDMARD (number of deaths/patients)	SMR (CI)	All patients (number of deaths/patients)	SMR (CI)
18-24	0/20	NC	0/4	NC	0/24	NC
25-34	0/45	NC	0/23	NC	0/68	NC
35-44	1/64	3.26 (0.16-16.11)	1/62	3.37 (0.16-16.63)	2/126	3.31 (0.55-10.97)
45-54	3/78	1.87 (0.47-5.11)	3/86	1.70 (0.43-4.63)	6/164	1.78 (0.72-3.71)
55-64	2/74	0.62 (0.10-2.05)	10/101	2.28 (1.15-4.06)	12/175	1.58 (0.85-2.68)
65-74	6/47	0.96 (0.39-2.01)	13/79	1.24 (0.69-2.07)	19/126	1.14 (0.70-1.74)
75+	1/10	0.41 (0.02-2.05)	21/50	1.74 (1.11-2.62)	22/60	1.52 (0.98-2.27)
Total	13/338	0.66 (0.37-1.11)	48/405	2.05 (1.53-2.69)	61/743	1.42 (1.09-1.81)

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, CI: Confidence interval, NC: Not calculated, SMR: Standardized mortality ratio

Table 5. Head-to-head comparisons of various bDMARD treatments indicated for RA in terms of the associated mortality risks

bDMARDs	HR	CI	p
Adalimumab vs Etanercept	1.379	0.230-8.277	0.724
Adalimumab vs Infliximab	1.050	0.210-5.239	0.952
Infliximab vs Etanercept	1.178	0.196-7.072	0.858
Rituximab vs Adalimumab	2.091	0.419-10.436	0.368
Rituximab vs Etanercept	2.760	0.458-16.629	0.268
Rituximab vs Infliximab	1.870	0.373-9.388	0.440
Tocilizumab vs Adalimumab	4.159	0.567-30.476	0.161
Tocilizumab vs Etanercept	21.701	1.931-243.893	0.013
Tocilizumab vs Infliximab	9.291	0.801-107.800	0.034
Tocilizumab vs Rituximab	2.186	0.305-15.650	0.436

bDMARD: Biological disease modifying antirheumatic drug, CI: Confidence interval, HR: Hazard ratio, RA: Rheumatoid arthritis

[5] In a study conducted in Sweden, [13] the mortality rates of patients with RA were investigated on the basis of their use of TNFi and compared with the mortality rates of the general population. Consequentially, SMRs in both groups were found to be similar, as the SMR in patients with RA who had been using TNFi was 1.50 (95% CI 1.03-1.96) and SMR in patients with RA who had not been using TNFi was found as 1.50 (95% CI 1.14-1.86). However, in a study conducted in the United States, SMR in patients with RA using TNFi was found to be 0.95 (95% CI 0.73-1.17) and lower than the SMR of the general population,[14] similar to the findings of this study. Considering the age group, the greatest SMR in patients with RA was reported to be 2.56 (95 percent CI 0.00-7.59) in the 30-34 age range in a study conducted in South Korea.[1] This result is different from the respective results of this study, in that the age group with the highest SMR in this study was found to be the 35-44 age group with an SMR of 3.31 (95% CI 0.55-10.97).

In this study, IBM was found as 16.53 per 1000 person-years in patients with RA in general. Additionally, IBM of the patients who have been using cDMARDs was found as 21.34 per 1000 person-years, whereas the IBM of the patients who have been using bDMARDs was found as 8.96 per 1000 person-years. In a study conducted in Canada, all-cause IBM in patients with RA was reported to be between 17.10 per 1000 person-years (95% CI 14.77-19.44) and 21.04 per 1000 person-years (95% CI 18.03-24.05)[2] and in another study conducted in a Sweden, the IBM of patients with RA was found to be 19 (17 to 21) per 1000 person-years.[3] Thus, the overall IBM in patients with RA found in this study is a comparable finding to the respective findings reported in the literature.

In another study, which has been conducted in the United States on patients with RA who use anti-TNF, i.e. infliximab, etanercept, and adalimumab, IBM was found as 5.34 per 1000 person years in the said patient groups (95% CI 4.20-6.69).[14] In comparison, the respective findings in this study, that is IBM in the bDMARD cohort, was found as 8.96 per 1000 person-years, and is thus a comparable finding.

When we performed subgroup analysis in the bDMARD cohort, the IBM in patients using adalimumab was found to be 9.6 per 1000 years in our study. In comparison, in the studies conducted in Sweden,[15] and United States,[16] IBMs in patients with RA who use adalimumab were reported as 13 per 1000 person-years and 3.3 per 1000 person-years, respectively, which are similar to our study. IBM in RA patients who use etanercept was reported as 9 per 1000 person-years (95% CI 7-12), which is higher than the respective findings of this study mentioned above; in another study conducted in Sweden.[15] IBM in RA patients who use infliximab was reported as 12 per 1000 person-years (95% CI 9-15), which is comparable to the respective findings of this study mentioned above; and in the study conducted in England.[17] IBM in RA patients who use rituximab was reported as 53 per 1000 person-years (95% CI 22.9-104.6), which is higher than the respective findings of this study mentioned above. Furthermore, in this study, IBM in patients with RA who have been using tocilizumab was found to be 15.15 per 1.000 person-years. However, a thorough literature review did not reveal any other study with a result on IBM of RA patients who have been using tocilizumab, therefore no comparison could be made in that regard.

As for the patient groups that have been abatacept, golimumab, certolizumab pegol, or tofacitinib, IBMs in these patient groups could not be calculated since no mortalities occurred in any of these groups.

However, head-to-head comparisons of the patient groups within the bDMARD cohort included in this study in terms of different types of bDMARDs the patients have been using revealed a significant increase in the risk of mortality in patients using tocilizumab compared to with patients using etanercept (HR 21.701, CI 1.931-243.893, p=0.013) and infliximab (HR 9.291, CI 0.801-107.800, p=0.034). This result may be attributed to the fact that the number of patients who have been using tocilizumab and the follow-up durations of these patients was lower than other patient groups included in the bDMARD cohort. Another reason is; it may be that comorbidity is higher in the tocilizumab group than in the other groups (46.2%). In head-to-head comparisons, no significant difference in mortality was detected between the other therapies. In head-to-head comparisons with infliximab, etanercept, and adalimumab in the literature, no significant difference in mortality was detected.[18]

As for the patients who have changed from one treatment modality to another, it was determined that 52 patients (15.4%) had switched from one biological to another. A detailed analysis of these patients revealed that 34.5% of the 52 patients have been using infliximab in the first place before switching to another treatment modality, whereas 22.4% of them have been using adalimumab, and 14.0% of them have been using etanercept. According to the literature, 19% of patients on etanercept, 35% of patients taking infliximab, and 25% of patients taking adalimumab experienced a switch from one biological to another.[15] These findings are comparable to the respective findings of this study.

Last but not least, analysis of the mortality in patients with RA included in this study by the causes of mortality revealed that the most common cause of mortality was cardiovascular diseases, which caused mortality in 29.5% of the fatalities, followed by infectious diseases, which caused mortality in 21.3% of the fatalities, and respiratory system diseases, which caused mortality in 19.7% of the fatalities. In comparison, in the study conducted in South Korea, the most common cause of mortality in patients with RA was reported as the malignant diseases, which caused mortality in 17.8% of the fatalities, followed by respiratory system diseases that caused mortality in 16.9% of the fatalities and cardiovascular diseases that caused mortality in 14.2% of the fatalities;[1] whereas in the study conducted in the Netherlands, the most common cause of mortality in patients with RA was reported as the cardiovascular diseases (n=172), followed by malignancies (n=112), and respiratory system diseases (n=62).[5] These findings are comparable to the respective findings of this study.

Study Limitations

The study strength is that it is the first mortality study reported from Turkey in patients with RA. However, the limitations of this study are that first, it was a retrospective study and secondly, the total number per 1000 person-years was low due to the relatively small number of patients despite a 10-year follow-up period.

Conclusion

This study is the first mortality study reported from Turkey in patients with a diagnosis of RA. The results of this study indicated that the SMR and IBM of patients with RA were higher than the SMR and IBM observed in the general Turkish population, yet were comparable to the respective findings reported in the literature. Additionally, SMRs in the cDMARD and bDMARD cohorts were found to be higher and lower, respectively, as compared to the SMR observed in the general Turkish population. In conclusion, to reduce mortality in patients with RA, they be followed more carefully and treated more effectively in terms of both RA and any comorbid diseases they might have.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval number: 837, date: 09.07.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.A.B., Design: M.A.B., Data Collection or Processing: M.A.B., L.A., Analysis or Interpretation M.A.B., L.A., Literature Search: M.A.B., L.A., Writing: M.A.B.

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Sistemik lupus eritematozusta antikor ve klinik bulgular arasındaki ilişkinin araştırılması

Relationship between antibodies and clinical manifestations in systemic lupus erythematosus

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Öz

Amaç: Bu çalışmanın amacı ekstrakte edilebilir nükleer antikorlar (ENA) ile sistemik lupus eritematozus (SLE) hastalarından oluşan bir kohorttaki klinik belirtiler arasındaki ilişkiyi araştırmaktır.

Yöntem: Çalışmaya romatoloji polikliniğinde takip edilen 2012 SLE sınıflandırma kriterlerini karşılayan 187 erişkin hasta dahil edildi. Ayrıntılı tıbbi öykü, muayene ve laboratuvar incelemeleri kaydedildi. Hastaların tanı anında serumlarında bulunan otoantikorların [antinükleer antikor, anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-Sm ve anti-ribonükleoproteinler (RNP)] analizleri üniversite hastanesi rutin klinik immünoloji laboratuvarı tarafından yapıldı.

Bulgular: Ortanca yaş 38 yıldı ve 176 (%94,1) hasta kadındı. Ortanca hastalık süresi ise 120 aydı. Ortalama serum anti-dsDNA, kompleman 3 ve 4 seviyeleri sırasıyla 211,7 IU/μL,78 mg/dL ve 12,3 mg/dL olarak bulundu. Bu hastalarda en sık görülen klinik bulgu muskülоskletal bozukluklar (%60,4), sonrasında sırası ile mukokutanöz bozukluklar (%57,8), nefrit (%37,4), hematolojik (%18,7) ve nörolojik bozukluklar olarak görüldü (%12,3). SLE olgularının sırasıyla %15, %24, %26,7 ve %11,8'inde anti-Sm, anti-RNP, anti-Ro ve anti-La pozitifliği vardı. Çok değişkenli analizde diskoid raşın anti-Sm pozitifliği ile, Raynaud fenomeninin ve oral ülserin anti-RNP pozitifliğiyle, alopesi, lupus pnömonisi ve perikarditin anti-Ro pozitifliğiyle ve plöritin anti- La pozitifliği ile ilişkili olduğu gösterilmiştir.

Sonuç: ENA'lara karşı oluşan antikorların varlığı SLE'li hastaların takibinde oluşabilecek bulguları predikte edebilir ve takipte yarar sağlayabilir.

Anahtar Kelimeler: Sistemik lupus eritematozus, klinik özellikler, immünolojik özellikler

Abstract

Objective: To investigate the role between antibodies to extractable nuclear antigens (ENA) and clinical manifestations in a cohort of systemic lupus erythematosus (SLE) patients.

Methods: The study included 187 adult patients with a diagnosis of SLE. Patients fulfilled the 2012 classification criteria for SLE. Full medical history, general examination, and laboratory investigations were recorded. Analyses of the autoantibodies [antinuclear antibody, anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-Sm and anti-ribonucleoproteins (RNP)] in the serum of the patients at diagnosis were also undertaken by the routine clinical immunology laboratory at University Hospital.

Results: The median age was 38 years, and 176 (94.1%) patients were women. Median disease duration was 120 months. Median levels of serum anti-dsDNA, complement 3 and 4 were found 211,7 IU/μL,78 mg/dL and 12,3 mg/dL. The most frequent clinical manifestation of these patients was musculoskeletal disorders (60.4%) the others were mucocutanous disorders, respectively (57.8%), nephritis (37.4%), haematological (18.7%), neurological disorders (12.3%). Anti-Sm, anti-RNP, anti-Ro and anti-La positivity were found in 15%, 24%, 26.7% and 11,8% of SLE cases. Multivariable analysis revealed that discoid rash was independent predictors of anti-Sm positivity; Raynaud phenomenon and oral ulcer were independent predictors of anti-RNP positivity; alopecia, lupus pneumonia and pericarditis were independent predictors of anti-Ro positivity and pleuritis was independent predictors of anti-La positivity.

Conclusion: Presence of antibodies against ENAs may predict findings that may occur in the follow-up in patients with SLE and It may be useful for follow-up.

Keywords: Systemic lupus erythematosus, clinical characteristics, immunological characteristics

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Giriş

Sistemik lupus eritematozus (SLE) klinik ve serolojik bulguların heterojen bir spektrumu ile karakterize sistemik otoimmün bir hastalıktır. Anti-nükleer antikorlar (ANA) ve ekstrakte edilebilir nükleer antijenlere (ENA) karşı oluşan antikorlar SLE'li hastalarda oldukça değişken bir şekilde ortaya çıkabilir ve hastalığın oluşturduğu patolojik değişikliklere doğrudan katkıda bulunduğu gösterilmiştir.[1] Otoantikorlar hastalık patogenezinin merkezinde olduğu için, gelişimleri klinik hastalıktan önce oluşabilir veya hastalıkla birlikte olabilir.[2] Anti-çift sarmallı DNA antikoru (anti-dsDNA) ise sistemik lupuslu kişilerin yaklaşık %30'unda bulunan spesifik bir ANA antikoru türüdür ve patogenezde direkt role sahiptir. Sağlıklı bireylerin %1'inden daha azında bu antikor bulunur ve bu da sistemik lupus tanısını doğrulamada yardımcı olur. Anti-dsDNA antikorlarının varlığı genellikle lupus nefriti düşündürür ve hastalık aktif olduğunda, özellikle böbreklerde, genellikle yüksek miktarda anti-dsDNA antikoru bulunur. Ancak anti-dsDNA testi, lupus aktivitesini izlemek için kullanılamaz, çünkü anti-dsDNA herhangi bir klinik aktivite olmaksızın mevcut olabilir.[3] 2019 Avrupa Romatizma Birliği/Amerikan Romatoloji Derneği kriterlerine göre SLE tanısında ve sınıflandırmada immünolojik parametreler kullanılabilir ve ENA'lar içerisinde anti-Smith antijenler (Sm) antikor varlığı bu anlamda önem arz etmektedir.[4]

Literatürde ENA'ya karşı oluşan antikorlar ile SLE'deki hastalık aktivitesi arasındaki ilişki çok net olarak gösterilememiştir.[5] Anti-ENA antikorlarının primer antijenik hedefleri U1-ribonükleoproteinler (RNP), Sm, topoizomeraz I, Jo-1, Ro (SS-A) ve La'dır (SS-B).[6] SLE nadiren negatif bir ANA ile birliktelik göstermektedir. ENA'ya karşı oluşan antikorlar bazen negatif ANA'ya rağmen istenebilmektedir ve SLE veya diğer bağ doku hastalıklarının diğer formlarının tanısına katkıda bulunabilmektedir.[7] Sm'leri küçük nükleer RNA'lar ile kompleks oluşturmuş nükleer non-histon protein serileridir.[8] Anti-Sm antikorları çoğunlukla sadece SLE hastalarında bulunur. SLE hastalarının sadece %25-30'unda saptanabildikleri için sensitiviteleri çok yüksek olmasa da spesifiteleri oldukça yüksektir ve hastalık tanısını dışlamada başarılı olmasa da, hastalık tanısını koymada oldukça yararlıdır.[9] Anti-RNP sadece U1-RNA içeren antijenlere bağlanır ve SLE'li kişilerde yaygın olarak anti-Sm antikorları ile birlikte bulunur. Lupuslu kişilerde anti-RNP antikorlarının insidansı yaklaşık %25 iken sağlıklı bireylerin %1'inden azında bu antikor bulunur. Bununla birlikte, anti-dsDNA ve anti-Sm antikorlarının aksine, anti-RNP antikorları lupusa özgü değildir; romatoid artrit, sistemik skleroz, Sjögren sendromu ve polimiyozit gibi diğer romatizmal durumlarda bulunabilirler. Anti-Sm ve anti-RNP antikorlarının varlığının tanıyla birlikte çeşitli klinik prezentasyonlarla ilişkili olduğu gösterildiği için başlangıçta pozitif olmaları takipte önem arz etmektedir. Bununla birlikte, anti-RNP antikorları, Raynaud fenomeni olan hastalarda daha yaygındır ve daha hafif böbrek tutulumu ile ilişkilidir. Aksine, anti-Sm antikorları böbrek tutulumunun şiddeti ve aktivitesi ile ilişkilidir.[10] Anti-Ro (SS-A) ve La (SS-B) antikorları küçük nükleer RNA'lar ile kompleks oluşurmuş hücresel proteinleri hedef almaktadır. Anti-Ro/SSA ve Anti-La/SSB, çoğunlukla SLE ve primer Sjögren sendromu olan kişilerde bulunan antikorlardır. Anti-Ro ve anti-La sistemik skleroz, romatoid artrit ve polimiyozit gibi diğer romatizmal hastalıklarda da görülebilir ve sağlıklı bireylerin yaklaşık %15'inde düşük titrelerde bulunur.[9] Konjenital kalp bloklu bebeğe sahip annelerin %80'inde romatizmal hastalık olmasa bile anti-Ro/SS A ve anti-La/SS B antikorları görülebilir.[9] Tüm seropozitif annelerin ise, sadece %1'inde neonatal lupus sendromu veya konjenital kalp bloğu izlenmiştir.

ENA'ya karşı oluşan antikorlar, SLE tanısı koydurmanın yanında hastalığın prognozu ve klinik bulgular hakkında fikir vermektedir. Literatürde bu konuda yapılan çalışmalar ise oldukça kısıtlı olup yeni çalışmalara gereklilik olduğu düşünülmüştür. Bizim bu çalışmadaki amacımız SLE hastalarında ENA'ya karşı oluşan antikorların klinik belirtiler ile arasındaki ilişkinin araştırılmasıdır.

Gereç ve Yöntem

Bu çalışmaya 2015 Ocak ve 2020 Aralık tarihleri arasında Gazi Üniversitesi Tıp Fakültesi Romatoloji Kliniği'ne ayaktan başvuran SLE hastaları dahil edilmiştir. Çalışmada 2012 Systemic Lupus International Collaborating Clinics klasifikasyon kriterlerine göre SLE kriterlerini karşılayan 187 yetişkin hasta değerlendirilmiştir. Detaylı bir anamnez ve genel muayene ile tam kan sayımı, karaciğer ve böbrek fonksiyon testleri, idrar analizi, 24 saatlik üriner proteinler, serum kompleman düzeyleri (C3 ve C4) gibi laboratuvar araştırmaları tüm hastalarda gerçekleştirildi. Romatoid faktör ve anti-CCP her hastaya bakılmadığı için analizlere dahil edilmedi. Klinik bulgular kümülatif olarak değerlendirildi. Laboratuvar değerlerinde ise tanı anındakiler kaydedildi. Otoantikorlardan anti-nükleer antikorlar indirekt immün floresan yöntemiyle, anti-dsDNA mikroeliza yöntemiyle ayrıca anti-Ro/SSA, anti-La/SSB, anti-Sm ve anti-RNP immünblot yöntemiyle üreticinin önerisi doğrultusunda üniversite hastanesindeki rutin klinik immünoloji laboratuvarındaki hasta serumlarında analiz edildi. Anti fosfolipid antikor sendromu tanı kriterleri; 12 hafta aralıkla bakılan antifosfolipid antikorları (lupus-antikoagülan, antikardiolipin IG, M ve anti-β2-glikoprotein IG, M)

varlığında vasküler tromboz ve/veya gebelik morbiditesinin olmasıdır.[11]

Floresan şiddeti negatif kontrol (0) ve pozitif kontrol (+4) baz alınarak +1'den +4'e kadar semikantitatif olarak değerlendirildi. Bant yoğunlukları EUROLINE SCAN programı kullanılarak değerlendirildi. Bu çalışma Gazi Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından (kabul tarihi: 21.09.2020, karar no: 639) kabul edilmiş ve Helsinki Bildirgesi'nde ileri sürülen ilkelere uygun olarak yürütülmüştür. Hastalardan bilgilendirilmiş onam formu alınmıştır.

İstatistiksel Analiz

Araştırma verilerinin istatistiksel analizleri için SPSS 22 istatistik paket programı kullanılmıştır. Tanımlayıcı istatistikler kısmında kategorik değişkenler sayı ve yüzde verilerek, sürekli değişkenler ise ortanca (minimum-maksimum) ile sunulmuştur. Bu çalışmada SLE klinik ve laboratuvar bulguları ile anti-Sm, anti-RNP, anti-Ro ve anti-La arasında öncelikle ki-kare ve Student's t-testleri yapıldı ve istatistiksel olarak anlamlı olanlar için lojistik regresyon analizleri yapıldı. Tek değişkenli analizde istatistiksel olarak anlamlı bulunanlar çok değişkenli analizde tekrar değerlendirildi. Bu çalışmada istatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edilmiştir.

Bulgular

SLE'li hastaların demografik klinik ve laboratuvar özellikleri Tablo 1'de sunulmuş olup, ortanca yaşları 38 yıl idi ve 176'sı (%94,1) kadındı. SLE tanı yaşı 28 yıl olarak bulunmuştur. Ortanca hastalık süreleri ise 120 aydı. Semptom süreleri de 120 ay olup, ortanca hastalık süresi ile eşit olarak saptandı.

Hastalarda %60,4 ile en sık musküloskeletal bozukluklar izlenmiş olup sonrasında sırasıyla mükokütanöz bozukluklar %57,8, nefritler %37,4, hematolojik bozukluklar %33,2, vasküler bozukluklar %23,5, nörolojik bozukluklar %12,3 ve serozal bulgular ise %9,1'inde görülmüştür. SLE hastaları içerisinde, lökolenfopenisi olanlar 45 (%24,1), hemolitik anemisi olanlar 42 (%22,5), trombositopenisi olanlar ise 17 (%9,1) idi.

SLE'li hastalarda anti nükleer antikor pozitifliği titreleri ve ENA'ya karşı oluşan antikorlar Tablo 2'de sunulmuş olup, anti-Sm, anti-RNP, anti-Ro ve anti-La pozitliği sırasıyla %15, %24, %26,7 ve %11'dir.

Anti-Sm pozitif ve negatif SLE hastalarında öncelikle tek değişkenli analizde anlamlı olan konstitusyonel bulgular, diskoid raş, perikardit ve overlap varlığına göre hasta sayıları ve yüzdeleri Tablo 3'te bildirildi. Sonrasında çok değişkenli analizde diskoid raşın anti-Sm pozitifliği ile (Tablo 4) ilişkili olduğu izlendi. Anti-RNP pozitif ve negatif SLE hastalarında tek değişkenli analizde anlamlı olan Raynaud fenomeni ve oral ülser varlığına göre hasta sayıları ve yüzdeleri Tablo 5'te bildirildi ve her ikisinin de çok değişkenli analizde anti-RNP pozitifliği ile ilişkili olduğu görüldü (Tablo 6). Anti-Ro pozitif ve negatif SLE hastalarında tek değişkenli analizde anlamlı olan alopesi, kuru ağız, kuru göz, Raynaud fenomeni, lupus pnömonisi, plörit ve perikarditin varlığına göre hasta sayıları ve yüzdeleri Tablo 7'de bildirildi ve alopesi, lupus pnömonisi ve perikarditin çok değişkenli analizde anti-Ro pozitifliği ile ilişkili olduğu görüldü (Tablo 8). Anti-La pozitif ve negatif SLE hastalarında tek değişkenli analizde anlamlı olan baş ağrısı, plörit, perikardit ve overlapın varlığına göre hasta sayıları ve yüzdeleri Tablo 9'da bildirildi ve plöritin anti-La pozitifliği (Tablo 10) ile ilişkili olduğu gösterildi.

Ortanca serum anti-dsDNA, kompleman 3 ve 4 düzeyleri sırasıyla 211,7 IU/µL, 78 mg/dL ve 12,3 mg/dL olarak bulunmuştur. Referans aralıkları sırası ile anti-ds-DNA (100-800 IU/µL), C3 (79-152 mg/dL) ve C4 (16-38 mg/dL) idi. Anti-dsDNA pozitif saptanan (>100 IU/µL) hasta sayısı 134 olup hastaların %71,7'sidir. Kompleman 3 düzeyi düşük olanların sayısı 97 olup oranları %51,9 idi, kompleman 4 düşüklüğü ise 141 hastada (%75,4) izlenmiştir.

Tartışma

Biz bu retrospektif SLE kohortumuzda yaptığımız araştırmada, ENA'ya karşı oluşan antikorların hastaların klinik ve laboratuvar özellikleri ile olan ilişkisini araştırdık. Özellikle SLE'de, ENA otoantikorlarının patogenezde potansiyel önemi ve hastalığın klinik başlangıcından önce ortaya çıktığı bilinmektedir. Öncelikle ANA, anti-Ro, anti-La ve antikardiyolipin antikorları, sonrasında anti-ds DNA antikorları, ardından da anti-Sm ve anti-RNP antikorları ortaya çıkar.[12-14] Ayrıca, asemptomatik SLE'lilerde hastalık başlangıcından önce ilerleyici bir spesifik otoantikor birikimi, hastalığın gidişatı ile ilgili fikir verdirebilir.[12] Anti-Ro, anti-La, antikardiyolipin antikor ve ANA aslında nispeten yaygın ama otoimmün romatizmal hastalık belirtileri olmayan normal kişilerde de saptanabilen antikorlardır. Buna karşılık, anti-dsDNA, anti-Sm ve anti-RNP antikorları ise normal kişilerde çok nadirdir.[15,16]

Bizim çalışmamızda anti-Ro pozitifliği %27, anti-RNP %24, anti-Sm %15 ve anti-La %11 olarak bulunmuştur. Literatürde 552 SLE hastası ile yapılan bir çalışmada ANA %99,8, ardından anti-dsDNA %81,3, anti-SSA/Ro %58,7, anti-RNP %36,8, anti-Sm %35,7 ve anti-SSB/La %15 hastada pozitif olarak saptanmıştır.[17]

Tablo 1. Sistemik lupus eritematozuslu hastaların demografik, klinik ve laboratuvar özellikleri

Değişkenler Medyan (çeyrekler arası aralık) ya da n (%)	SLE hastaları n=187	SLE hastaları (%)
Demografik özellikler		
Yaş, yıl	38 (31-47)	
Tanı yaşı, yıl	28 (21-36)	
Kadın cinsiyet	176	94,1
Hastalık süresi, ay	120 (60-180)	
Semptom süresi, ay	120 (81-180)	
Mukokütanöz	**108**	**57,8**
Sicca semptomları	55	29,4
Malar raş	92	49,2
Diskoid raş	9	4,8
Oral ülser	23	12,3
Fotosensitivite	118	63,1
Raynaud fenomeni	52	27,8
Livedo retikülaris	13	7
Alopesi	42	22,5
Musküloskeletal	**113**	**60,4**
Artrit	103	55,1
Myalji	39	20,9
Nefrit	**70**	**37,4**
Hematolojik bozukluk	**35**	**18,7**
Serozal	**17**	**9,1**
Plörit	14	7,5
Perikardit	9	4,8
Miyokardit	4	2,1
Lupus pnömoni	10	5,3
Nörolojik bozukluk	**23**	**12,3**
Baş ağrısı	8	4,3
Periferik nöropati	16	8,6
Vasküler bozukluk	**44**	**23,5**
Düşük öyküsü	33	17,6
Tromboz öyküsü	16	8,5
AFAS	27	14,4
Konstitusyonel semptomlar	104	55,6
Vaskülit	3	1,6
Otoimmün hepatit	5	2,7
İmmünolojik bozukluk	**171**	**92,4**
Laboratuvar değerleri		
ESH mm/saat	38 (4-119)	
CRP mg/L	7,3 (1-88)	
Kreatinin mg/dL	0,66 (0,4-6,5)	
AST IU/L	20 (8-881)	
ALT IU/L	17 (5-997)	
Albumin g/dL	4,1 (1,3-5,4)	
Anti-dsDNA IU/μL	211,7 (0-800)	
Kompleman 3, mg/dL	78,0 (14-174)	
Kompleman 4, mg/dL	12,3 (1,4-20,8)	
WBC sayısı, μL	5,9 (4,7-7,4)	
Lenfosit sayısı, μL	1,5 (0,2-4,7)	
PLT sayısı, x1000/μL	239,8 (5-663)	
Hgb g/dL	12 (5,8-17,3)	

Tabloda değerler medyan (minimum-maksimum) ya da sayı (%) olarak sunulmuştur, AFAS: Anti fosfolipid antikor sendromu, ALT: Alanin aminotransferaz, AST: Aspartat aminotransferaz, CRP: C-reaktif protein, ESH: Eritrosit sedimentasyon hızı, Hgb: Hemoglobin, PLT: Trombosit hücresi, WBC: Beyaz küre hücresi

Literatüre bakıldığında, antikorlar ile lupus nefriti arasındaki ilişkinin çelişkili olduğu net bir şekilde izlenmektedir.[18-21] Biz ise çalışmamızda renal bulgular ile antikorlar arasında net bir ilişki gözlemedik.

Bizim çalışmamızda anti-Sm pozitifliği ile diskoid raşın ilişkili olduğu saptandı. Bir araştırmaya göre hem anti-RNP hem de anti-SSA, SLE deri hasarının önemli göstergeleri olarak kullanılabileceği, pozitif anti-RNP'li SLE hastalarının başlangıç yaşının daha erken olduğu ve eritemli deri ve proteinüriye daha yatkın oldukları

Tablo 2. Sistemik lupus eritematozuslu hastaların serolojik özellikleri

Değişkenler n (%)	SLE hastaları n=187	SLE hastaları (%)
Anti nükleer antikor pozitifliği		
+	105	56,1
++	34	18,2
+++	40	21,4
++++	8	4,3
ENA pozitifliği		
Anti-Sm	28	15
Anti-RNP	45	24,1
Anti-Ro (SS-A)	50	26,7
Anti-La (SS-B)	22	11,8

ENA: Ekstrakte edilebilir nükleer antijenlere karşı oluşan antikorlar, SLE: Sistemik lupus eritematozus

Tablo 3. Anti-Sm pozitif ve negatif SLE hastalarında klinik bulguların varlığına göre hasta sayıları ve yüzdeleri

Değişkenler	Anti-Sm negatif SLE hastaları n (%)	Anti-Sm pozitif SLE hastaları
Konstitusyonel	88 (55,3)	16 (57,1)
Diskoid raş	5 (3,1)	4 (14,3)
Perikardit	5 (3,1)	4 (14,3)
Overlap	52 (32,7)	2 (7,1)

SLE: Sistemik lupus eritematozus

Tablo 4. SLE hastalarında klinik ve laboratuvar bulgularıyla anti-Sm antikorunun tek değişkenli ve çok değişkenli ikili lojistik regresyon analizi ile değerlendirilmesi

	Tek değişkenli analiz			Çok değişkenli analiz		
	RO	%95 GA	p değeri	RO	%95 GA	p değeri
Konstitusyonel	2,7	1,0-7,5	0,04			
Diskoid raş	5,1	1,2-20	0,02	5,21	1,2-22,3	0,02
Perikardit	2,26	1,1-4,5	0,02			
Overlap	0,15	0,03-0,69	0,014	0,15	0,03-0,69	0,015

Yaş ve cinsiyet modele dahil edilmiştir, GA: Güven aralığı, RO: Risk oranı, SLE: Sistemik lupus eritematozus

Tablo 5. Anti-RNP pozitif ve negatif SLE hastalarında klinik bulguların varlığına göre hasta sayıları ve yüzdeleri

Değişkenler	Anti-RNP negatif SLE hastaları n (%)	Anti-RNP pozitif SLE hastaları n (%)
Raynaud fenomeni	33 (23,2)	19 (42,2)
Oral ülser	12 (8,5)	11 (24,4)

SLE: Sistemik lupus eritematozus

Tablo 6. SLE hastalarında klinik ve laboratuvar bulgularıyla anti-RNP antikorunun tek değişkenli ve çok değişkenli ikili lojistik regresyon analizi ile değerlendirilmesi

	Tek değişkenli analiz			Çok değişkenli analiz		
	RO	%95 GA	p değeri	RO	%95 GA	p değeri
Raynaud fenomeni	2,41	1,1-4,9	0,015	2,5	1,2-5,3	0,01
Oral ülser	1,87	1,1-2,9	0,006	1,9	1,2-3,0	0,005

Yaş ve cinsiyet modele dahil edilmiştir, GA: Güven aralığı, RO: Risk oranı, SLE: Sistemik lupus eritematozus

düşünülmüştür. Anti-RNP SLE'de deri ve böbrek hasarının önemli bir göstergesi olarak kullanılabileceği yorumunda bulunmuşlardır.[22] Benzer şekilde başka bir araştırmada Chilblain lupusun, subakut kütanöz lupus eritematozus (SCLE), hipergamaglobulinemik purpura ve neonatal lupus eritematozus gibi SSA/Ro otoantikorları ile ilişkili olduğu gösterilmiştir.[23] Ayrıca başka bir çalışmada Ro/SSA'ya karşı yüksek titreli, presipitan antikorların SCLE için tipik ama diskoid lupus için atipik olduğu belirtilmiştir. Ro/SSA'ya karşı düşük titre, non-presipitan antikorlar ise diskoid lupusta yaygındır ve SCLE ile paylaşılan patojenik faktörlerin bir göstergesi olabilir. Bununla birlikte, düşük antiRo/SSA titreleri, SCLE deri lezyonları için önemli bir risk oluşturmaz.[24]

Afro-Karayipli bir kohortta SLE hastalarında raş, alopesi, oral ülserler, serozit, nörolojik, eklem ve böbrek tutulumu varlığı anti-Sm ve anti-RNP antikorları ile anlamlı olarak ilişkiliyken, eklem tutulumu ise anti-Ro ve anti-La

Tablo 7. Anti-Ro (SS-A) pozitif ve negatif SLE hastalarında klinik bulguların varlığına göre hasta sayıları ve yüzdeleri

Değişkenler	Anti-Ro (SS-A) negatif SLE hastaları n (%)	Anti-Ro (SS-A) pozitif SLE hastaları n (%)
Alopesi	22 (16,1)	20 (40)
Kuru ağız	47 (34,3)	27 (54)
Kuru göz	33 (24,1)	22 (44)
Raynaud fenomeni	32 (23,4)	20 (40)
Lupus pnömoni	2 (1,5)	8 (16)
Plörit	5 (3,6)	9 (18)
Perikardit	3 (2,2)	6 (12)

RO: Risk oranı, SLE: Sistemik lupus eritematozus

Tablo 8. SLE hastalarında klinik ve laboratuvar bulgularıyla anti-Ro (SS-A) antikorunun tek değişkenli ve çok değişkenli ikili lojistik regresyon analizi ile değerlendirilmesi

	Tek değişkenli analiz			Çok değişkenli analiz		
	RO	%95 GA	p değeri	RO	%95 GA	p değeri
Alopesi	1,86	1,2-2,6	0,001	1,6	1,1-2,4	0,01
Kuru ağız	2,24	1,1-4,3	0,016			
Kuru göz	2,47	1,2-4,8	0,009			
Raynaud fenomeni	2,18	1,0-4,3	0,026			
Lupus pnömoni	12,85	2,6-62,9	0,002	8,6	1,6-45,5	0,01
Plörit	2,40	1,3-4,2	0,003			
Perikardit	2,46	1,2-5,0	0,013	2,1	1,1-3,9	0,01

Yaş ve cinsiyet modele dahil edilmiştir, GA: Güven aralığı, RO: Risk oranı, SLE: Sistemik lupus eritematozus

Tablo 9. Anti-La (SS-B) pozitif ve negatif SLE hastalarında klinik bulguların varlığına göre hasta sayıları ve yüzdeleri

Değişkenler	Anti-La (SS-B) negatif SLE hastaları n (%)	Anti-La (SS-B) pozitif SLE hastaları n (%)
Baş ağrısı	5 (7)	3 (13,6)
Plörit	9 (5,5)	5 (22,7)
Perikardit	6 (3,6)	3 (13,6)
Overlap	43 (26,1)	11 (50)

SLE: Sistemik lupus eritematozus

Tablo 10. SLE hastalarında klinik ve laboratuvar bulgularıyla anti-La (SS-B) antikorunun tek değişkenli ve çok değişkenli ikili lojistik regresyon analizi ile değerlendirilmesi

	Tek değişkenli analiz			Çok değişkenli analiz		
	RO	%95 GA	p değeri	RO	%95 GA	p değeri
Baş ağrısı	1,22	1,0-1,4	0,035			
Plörit	2,25	1,2-4,1	0,008	2,3	1,2-4,3	0,007
Perikardit	2,04	1,1-4,2	0,05			
CRP mg/L	1,0	1,0-1,01	0,047			
Overlap	2,8	1,1-7,0	0,024	3,0	1,1-7,6	0,02

Yaş ve cinsiyet modele dahil edilmiştir, CRP: C-reatktif protein, GA: Güven aralığı, RO: Risk oranı, SLE: Sistemik lupus eritematozus

antikorlarının varlığı ile ilişkiliydi.[25] Başka bir araştırmada ise el deformiteleri gelişen SLE'li hastalar, SSA/Ro'ya (özellikle 52 kD bileşenine) ve SSB/La'ya karşı antikorları olan bir grup hasta olarak tanımlanmıştır.[26]Bizim kohortumuzda da Raynaud fenomeninin ve oral ülserin anti-RNP pozitifliğiyle, alopesi, lupus pnömonisi ve perikarditin anti-Ro pozitifliğiyle ve plöritin anti-La pozitifliği ile ilişkili olduğu gösterilmiştir. Araştırmalara göre anti-Sm antikoru perikardit ve kardiyak tutulum için risk faktörü olarak görülmüştür.[27,28] Ülkemizde Artim-Esen ve ark.'nın[29] 2014'te yaptığı bir çalışmada, Sm/RNP grubunda pulmoner hipertansiyon ve Raynaud fenomeni insidansı anlamlı olarak daha yüksekti. Anti-dsDNA grubu en yüksek renal tutulum insidansına sahipti. ACL/LAC grubunda ise nöropsikiyatrik tutulum, antifosfolipid sendromu, otoimmün hemolitik anemi ve trombositopenisi olan hasta sayısı daha fazla idi.

Anti-Sm ve anti-RNP antikorlar klinik pratikte çok önemlidir. Bunun yanı sıra bu antikorların üretimlerini tetikleyen mekanizmalara dair çalışmalar otoimmün bozuklukların patogenezini açıklamak için yeni bakış açıları açmıştır.[10] SLE'de otoantikorların üretimi ve immünopatolojisindeki rolleri oldukça karmaşıktır. Bu konulara olan ilgi sadece teorik bilgiden ibaret olmayıp, aynı zamanda yeni tanısal testlerin bulunması, doğru şekilde hastalık aktivitesinin değerlendirilmesi, daha önleyici veya spesifik tedavilerin geliştirilmesini hedeflemektedir. Bu anlamda tek merkez 187 SLE hastasını içeren bu klinik çalışmanın sonuçlarının literatüre ışık tutmasını ve ileri çalışmalar için yol gösterici olmasını umuyoruz.

Çalışmanın Kısıtlılıkları

Araştırmanın retrospektif kohort olması nedeni ile kayıp veriler olduğu için tüm hastalar analize dahil edilemedi. Bunun sonucunda da poliklinikte daha sık olarak karşılaştığımız daha hafif form olan musküloskeletal ve deri tutulumu ön planda olan hastaların kohorttaki sayıca yüzdesi daha fazla izlendi. Ağır organ tutulumu olan hastaların kohortta az sayıda izlenmesinin çalışmanın majör bir kısıtlılığı olduğunu düşünüyoruz.

Sonuç

ENA'lara karşı oluşan antikorlar SLE'nin klinik prezentasyonuna katkıda bulunuyor gibi görünmektedir. İleride bulgularımızı doğrulamak ve ENA'ların SLE hastalığının prognozundaki temel rolünü göstermek için daha geniş ölçekli longitudinal çalışmalar yapılması gerektiğini düşünmekteyiz.

Bizim çalışmamızda yaptığımız analiz sonuçlarına göre diskoid raşın anti-Sm pozitifliği ile, Raynaud fenomeninin ve oral ülserin anti-RNP pozitifliğiyle, alopesi, lupus pnömonisi ve perikarditin anti-Ro pozitifliğiyle ve plöritin anti-La pozitifliği ile ilişkili olduğu gösterilmiştir.

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Comparison of cranial and extra-cranial involvement of patients with giant cell arteritis

Dev hücreli arteritte kraniyal ve ekstra-kraniyal tutulumların karşılaştırılması

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Abstract

Objective: Giant cell arteritis (GCA) is a chronic granulomatous inflammation of medium and large sized arteries; it is also known as temporal arteritis. The aim of the study was to investigate the clinical, laboratory and radiological findings of the patients diagnosed with GCA and to compare cranial, extra-cranial (ECI) and either involvement patterns.

Methods: The study was designed as cross-sectional. The demographic and clinical data, laboratory results, imaging and biopsy findings were documented. The patients were divided into three groups according to the involved regions.

Results: Twenty-four patients with GCA were evaluated. When patients were divided into three groups as cranial (CI), ECI and both cranial and extra-cranial (CECI) involvement; vision loss, jaw claudication, scalp tenderness, temporal artery stiffness, tenderness and pulselessness were common in patients with CI. Weight loss was significantly higher in patients with ECI than in patients with CI. Positron emission tomography (PET) was performed in 50% of GCA patients; vasculitic involvement was found in all of the 5 patients with ECI and CECI, whereas it was not observed in 7 patients with CI.

Conclusion: GCA is a vasculitis that is among the large vessel vasculitides, but until recently, its CI findings were better defined than its systemic involvement. With the widespread use of modern imaging techniques, ECI involvement accompanying CI involvement and isolated ECI involvement has been better defined. Constitutional symptoms and positive PET findings were more prominent in patients with ECI, which is thought to be related to systemic disease pattern.

Keywords: Giant cell arteritis, temporal arteritis, cranial, extra-cranial, imaging, positron emission tomography

Öz

Amaç: Dev hücreli arterit (DHA), orta ve büyük çaplı arterlerin kronik granülomatöz enflamasyonudur; temporal arterit olarak da bilinir. Çalışmanın amacı DHA tanısı konulan hastaların klinik, laboratuvar ve radyolojik bulgularının araştırılması ve kraniyal (CI), ekstra-kraniyal (ECI) ve her iki bölgede tutulum paternlerinin karşılaştırılmasıdır.

Yöntem: Çalışma kesitsel olarak tasarlanmıştır. Demografik ve klinik veriler, laboratuvar sonuçları, görüntüleme ve biyopsi bulguları kaydedilerek, hastalar tutulum bölgelerine göre üç gruba ayrılmıştır.

Bulgular: DHA'lı yirmi dört hasta değerlendirildi. Hastalar CI, ECI ve kraniyal ve ekstrakraniyal (CECI) tutulum olarak üç gruba ayrıldığında; görme kaybı, çene kladikasyosu, saçlı deride hassasiyet, temporal arterde sertlik, hassasiyet ve nabızsızlık CI grubunda daha yaygındı. Kilo kaybı ECI'lı hastalarda CI'lı hastalara göre anlamlı olarak daha yüksekti. Pozitron emisyon tomografisi (PET), DHA hastalarının %50'sine çekilmişti; ECI ve CECI'lı 5 hastanın tümünde vaskülitik tutulum bulunurken, CI'lı yedi hastada tutulum gözlenmedi.

Sonuç: DHA, büyük damar vaskülitleri arasında yer alan bir vaskülittir ancak yakın zamana kadar kraniyal bulguları sistemik tutulumdan daha iyi tanımlanmıştır. Modern görüntüleme tekniklerinin yaygınlaşması ile kraniyal tutulumlara eşlik eden ECI tutulumlar ve izole ECI tutulumlar daha iyi tanımlanmıştır. Konstitüsyonel semptomlar ve pozitif PET bulguları ECI olan hastalarda daha belirgin olup, bu daha sistemik bir hastalık paterni ile ilişkili olarak değerlendirilmiştir.

Anahtar Kelimeler: Dev hücreli arterit, temporal arterit, kraniyal, ekstra-kraniyal, görüntüleme, pozitron emisyon tomografisi

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Introduction

Giant cell arteritis (GCA) is a chronic granulomatous arteritis of medium and large sized arteries; it is also known as temporal arteritis.[1] It is more common in females, with an incidence ratio of approximately 2-3:1. GCA affects people over 50 years old, and the disease peaks between the ages of 70-79.[2] Constitutional symptoms, headache, jaw claudication, tenderness in the scalp, visual findings, musculoskeletal system involvement are common.[3] Polymyalgia rheumatica (PMR) often coexists with GCA, seen in approximately 40 to 50 percent of patients.[4] Although the temporal arteries are the most commonly affected vessels in GCA; the carotid arteries, vertebral arteries, subclavian, axillary and proximal brachial arteries, the ascending aorta and coronary arteries may be affected.[5] With the widespread use of positron emission tomography (PET) in patients with GCA and PMR, the frequency of observation of extra-cranial involvement (ECI) accompanying cranial involvement (CI) or isolated ECI has increased.[6] In this study, we compared the clinical, laboratory and imaging findings of patients with different involvement patterns.

Materials and Methods

Study Design and Study Population

The study design was cross-sectional. The medical records of all patients with GCA followed up between January 2010 and September 2021 at Kocaeli University Hospital, Clinic of Rheumatology, were reviewed. The patients who fulfilled the American College of Rheumatology 1990 GCA classification criteria were included the study.[7] The local ethics committee of Kocaeli University approved the study protocol (date: 13.09.2021, approval number: 2021/232).

Data Collection

The demographic and clinical characteristics, including age, gender, symptoms, disease duration, physical examination findings at the time of diagnosis, laboratory, imaging and biopsy results, and treatments, were obtained from medical records. Laboratory results at the time of diagnosis, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count and lipid levels were recorded. The findings of imaging modalities, including temporal artery ultrasonography (USG), PET/computed tomography (PET/CT), thorax and abdominal magnetic resonance (MR) angiography and CT angiography, and cranial MR imaging were noted.

PET/CT Analysis Method

PET imaging was performed with a GE healthcare discovery PET/CT 690 scanner using F-18 fluorodeoxyglucose as a radiopharmaceutical. Images were obtained from the hospital PACS system.

Statistical Analyses

Statistical analysis was performed by SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to evaluate the demographic variables and clinical data. The normality of continuous variables was checked by Shapiro-Wilk test. In numerical data, mean and standard deviation for normal distributions and median (IQR) for non-normal distributions were given. Group comparisons were made by Kruskal-Wallis H and ANOVA test for continuous variables and chi-square test for categorical variables.

Results

The data of 24 patients with the diagnosis GCA were analyzed. Thirteen (54%) of these patients were female. The mean age at diagnosis was 72.4±8.75 years. The median disease duration was 33 (14.3-83) months and the median time between the onset of symptoms and the diagnosis of disease was 1 (0-4.8) month.

Constitutional symptoms were present in 11 (46%) patients. Among the common symptoms of GCA; the most common was visual loss, observed in 18 (75%) patients, followed by headache in 13 (54%), scalp tenderness in 9 (37.5%) and jaw claudication in 9 (37.5%). In the temporal artery examination, 6 (25%) patients had tenderness, 3 (13%) had stiffness and 7 (29%) had temporal pulselessness. In one patient who described extremity claudication, there was a lack of pulsation in the left upper extremity and a blood pressure difference between the extremities; and this patient had both CI and ECI. Two (8.3%) patients had a murmur in the branches of the aorta and 2 (8.3%) had an abdominal aortic aneurysm.

The PMR findings were accompanied in 25% of the patients with GCA. The mean ESR was 72.64±25.48 mm/h, and median CRP level was 50.5 (19.2-128) mg/L. All patients had elevated ESR and CRP values. There were no patients whose ESR and CRP values were within normal limits at the time of diagnosis. No difference was found between the presence of PMR and ESR or CRP elevation (p=0.538, p=0.193; respectively).

Temporal artery USG was performed in 15 (62.5%) patients, and halo sign was observed in 20% of these 15 patients. In 2 (8.3%) patients, intima media thickness compatible with vasculitis was observed in carotid Doppler USG. The vasculitic involvement was detected in 5 (20.8%) of 12 patients in whom PET/CT was performed. All of these 5 patients had thoracic aorta involvement, 3 patients had involvement of the aortic arch and its branches, 3 patients had abdominal aorta involvement, and 2 patients had a femoral artery involvement. Supratentorial and periventricular white matter T2 hyperintense foci, which may be compatible with vasculitis, were detected in 7 of 10 (41.6%) patients in whom cranial MR imaging was performed. Vasculitic involvement was seen in 2 of 7 (29.2%) patients who underwent thoraco-abdominal MR angiography. In these 2 patients, celiac artery and superior mesenteric artery were affected. No significant involvement was observed in 2 (8.3%) patients who underwent thoraco-abdominal CT angiography.

Temporal artery biopsy (TAB) was performed in 14 (58.3%) patients and the diagnosis was confirmed by biopsy in 13 (54.1%) of them. Among these 14 patients who had TAB, all of them had CI involvement. TAB was not performed in 3 patients with cranial symptoms in the cranial and extra-cranial involvement (CECI) group, the diagnosis was confirmed by imaging. One patient was diagnosed with GCA after total hysterectomy and salpingo-oophorectomy. Non-necrotizing vasculitis characterized by giant cells and granulomas on the walls of myometrial tubal and ovarian small to medium sized arteries were found in the pathology specimen. This patient had no cranial symptoms, large vessel vasculitis was also confirmed by PET/CT.

Hypertension, which is the most common comorbidity, was present in 17 (71%) patients, 7 (29.2%) patients had diabetes mellitus and 7 (29.2%) patients had coronary artery disease. The demographic and clinical data of the patients were given in the Table 1.

Among the 24 patients followed up with the diagnosis of GCA, 18 had isolated CI, 3 had ECI, and 3 had CECI. These 3 groups were compared in terms of clinical, radiological findings and treatment regimens they received. However, statistics could not be made because the number of patients in the groups was low (Table 2). There was no difference between the groups in terms of age at the diagnosis, time from onset of symptoms to diagnosis, gender, and smoking habits. Constitutional symptoms and weakness were more common in patients with ECI. Weight loss was detected more frequent in the ECI group than in the CI group. Vision loss, jaw claudication, scalp tenderness, temporal artery stiffness, tenderness and pulselessness were common in patients with CI, as expected. These examination findings were not observed in patients with ECI. The frequency of accompanying PMR was similar in all 3 groups.

When the laboratory findings were examined, no significant difference was found between the groups in terms of elevated ESR and CRP, leukocytosis, anemia and thrombocytosis.

Although the proportion of patients with a halo sign on temporal artery USG was low, all of these patients had CI. Two of these 3 patients underwent PET/CT, and both were negative in terms of vasculitic involvement.

Table 1. Demographic variables and clinical data of the study group

Demographic variables	
Age at diagnosis (years)	72.4±8.75
Female	13 (54.2)
Clinical findings	
Constitutional symptoms	11 (45.8)
Fever	2 (8.3)
Weight loss	7 (29.2)
Night sweats	2 (8.3)
Weakness	11 (45.8)
Headache	13 (54.2)
Jaw claudication	9 (37.5)
Visual loss	18 (75)
Tenderness on temporal artery	3 (12.5)
Temporal artery stiffness	2 (8.3)
Temporal pulselessness	7 (29.2)
PMR	6 (25)
Laboratory findings	
Sedimentation rate (mm/h)	72.64±25.48
C reactive protein (mg/L)	50.5 (19.2-128)
Total cholesterol (mg/dL)	204.3±46.7
LDL (mg/dL)	129.3±42.7
HDL (mg/dL)	44 (39.5-51.8)
Leukocytosis	7 (29.2)
Anemia	19 (79.2)
Thrombocytosis	8 (33.3)
Biopsy	
Temporal artery biopsy	14 (58.4)
Compatible	13 (54.2)
Incompatible	1 (4.2)
Biopsy from different area	1 (4.2)
Treatment	
Pulse steroid	11 (45.8)
Methotrexate	16 (66.7)
Azathioprine	2 (8.3)
Leflunomide	3 (12.5)
Tocilizumab	2 (8.3)

Values are given as n (%), median (IQR) or mean ± SD, HDL: High density lipoprotein, LDL: Low density lipoprotein, PMR: Polymyalgia rheumatica, SD: Standard deviation

Table 2. Comparison of the clinical data of the groups

	Cranial (n=18)	Extra-cranial (n=3)	Cranial and extra-cranial (n=3)
Demographic variables			
Age at diagnosis (years)	71.7±9.1	66 (61-66)	67 (62-67)
Symptom duration (months)	58.9±42.6	18 (6-18)	31 (1-31)
Symptom-diagnosis duration (months)	1 (0-4.25)	4 (4-4)	3 (0-3)
Female	9 (50)	2 (67)	2 (67)
Smoking	7 (39)	2 (67)	1 (33)
Clinical findings			
Constitutional symptoms	6 (33)	3 (100)	2 (67)
Fever	1 (6)	1 (33)	-
Weight loss	2 (11)	3 (100)	2 (67)
Night sweats	1 (6)	1 (33)	-
Weakness	6 (33)	3 (100)	2 (67)
Headache	10 (56)	1 (33)	2 (67)
Scalp tenderness	7 (39)	-	1 (33)
Jaw claudication	9 (50)	-	-
Visual loss	16 (89)	-	2 (67)
Tenderness or stiffness on temporal artery	9 (50)	-	-
Temporal pulselessness	5 (27)	-	2 (67)
PMR	3 (17)	1 (33)	2 (67)
Extremity claudication	-	-	1 (33)
Peripheral pulselessness	-	-	1 (33)
Tension difference between extremities	-	-	1 (33)
Murmur	-	1 (33)	1 (33)
Aneurysm in aortic branches	3 (16)	-	-
Diabetes mellitus	7 (39)	-	-
Hypertension	14 (78)	1 (33)	2 (67)
Coronary artery disease	7 (39)	-	-
Laboratory findings			
Erythrocyte sedimentation rate (mm/h)	69.4±24.5	88.3±27	61.7±31.5
C-reactive protein (mg/L)	46 (18.5-74)	133 (100-133)	20 (12-20)
Leukocytosis	6 (33)	1 (33)	-
Anemia	14 (78)	3 (100)	2 (67)
Thrombocytosis	6 (33.3)	1 (33)	1 (33)
Biopsy			
Compatible temporal artery biopsy	13/14 (92)	-	-
Biopsy from different area	-	1/1 (100)	-
Imaging			
Halo sign on temporal artery USG	3/11 (27)	0/1	0/3
Positive finding in PET/CT	0/7	3/3 (100)	2/2 (100)
Positive finding in cranial MR	5/8 (63)	1/1 (100)	1/1 (100)
Positive finding in MR angiography	0/3	1/2 (50)	1/2 (50)
Positive finding in CT angiography	0	0/1	0/1
Treatment			
Pulse steroid	10 (56)	0	1 (33)
Methotrexate	11 (61)	3 (100)	2 (67)
Azathioprine	1 (6)	0	1 (33)
Leflunomide	2 (11)	0	1 (33)
Tocilizumab	1 (6)	0	1 (33)
Acetylsalicylic acid	13 (72)	1 (33)	2 (67)
Anti-hyperlipidemic agent	3 (17)	1 (33)	1 (33)

Values are given as n (%), median (IQR) or mean ± SD, CT: Computed tomography, MR: Magnetic resonance, PET: Positron emission tomography, PMR: Polymyalgia rheumatica, SD: Standard deviation, USG: Ultrasonography

PET/CT was performed in 12 patients with a pre-diagnosis of GCA. The vasculitic involvement was found in all the 5 patients with ECI and CECI, while it was not observed in 7 patients with isolated CI. Although these data are meaningful, statistics could not be made due to the absence of PET/CT evidence in the CI group. Nine patients did not undergo CT or MR-angiography and PET/CT to evaluate large vessel involvement. All these patients were diagnosed with signs of CI. Only 1 of 12 patients who underwent PET/CT had PMR related musculoskeletal involvement. This patient also had vascular involvement. In addition, PET/CT was performed in 5 of 6 patients with PMR findings, one patient had PMR related musculoskeletal involvement. All patients received medium-high dose steroid therapy, 45.8% of them received pulse steroid (1 gram/day for three days). All patients who received pulse steroid therapy had CI with acute vision loss. All patients received conventional synthetic disease modifying anti-rheumatic drug therapy. 66.7% of them received methotrexate, 12.5% leflunomide, and 8.3% azathioprine as steroid sparing agent. Anti-interleukin-6 treatment was given to 2 patients (1 patient with CI and, 1 patient with CECI). 66.7% of the patients were taking acetylsalicylic acid and 20.8% were taking anti-hyperlipidemic treatment.

Discussion

GCA is a vasculitis that is among the large vessel vasculitides, but until recently, its cranial findings were better defined than its systemic involvement. With the widespread use of modern imaging techniques, ECI accompanying CI and isolated ECI have been better defined. Patients with isolated ECI often present with non-specific symptoms. While there may be localized ischemic manifestations, only systemic constitutional symptoms may be present.[3] When Schmidt et al.[8] compared GCA patients with CI and ECI, they found more constitutional symptoms and unclear inflammation in patients with ECI, while they reported more visual loss, headache, and temporal artery examination findings in the CI group. Also, the median time until the diagnosis was found to be longer in the ECI group. In our study, although it did not reach statistical significance (except for weight loss), constitutional symptoms were observed in all patients with ECI and this finding was more frequent in this group. As expected, loss of vision and pathological temporal artery examination was found more frequently in patients with CI. Muratore et al.[9] grouped patients as cranial GCA (C-GCA) and large vessel GCA (LV-GCA). LV-GCA group was younger than the C-GCA group, the duration of symptom-diagnosis period was longer, PMR symptoms and relapse rate were higher. In our study, symptom-disease duration and accompanying PMR were similar between the groups.

There was no specific laboratory test for the GCA. At least one of the acute phase values (CRP or ESR) is high in 96% of the TAB-positive GCA patients in the literature. Kermani et al.[10] also reported that acute phase values were higher in patients with accompanying PMR symptoms. Another study noted that sensitivity of the ESR and CRP together was 99% in TAB-positive GCA patients.[11] Czihal et al.[12] and Ghinoi et al.[13] found no significant difference between acute phase values in patients with CI and ECI. Considering the laboratory values of our patients, it was observed that the CRP value was higher in patients with ECI, but statistical significance could not be achieved. This was attributed to the small sample size and the wide range of CRP results.

Since the systemic symptoms and elevated acute phase reactants seen in elderly patients may often suggest an underlying malignancy, vasculitis can be diagnosed incidentally with imaging studies, especially with PET/CT. There are many studies in the literature evaluating the use of PET/CT in GCA. PET/CT seems to be a useful diagnostic modality for ECI, but not for CI.[14,15] Van der Geest et al.[14] recommends the use of PET/CT with TAB-negative patients or patients with isolated clinical PMR symptoms. Considerable progress has occurred in diagnostic imaging modalities since the GCA 1990 ACR diagnostic criteria were established.[7] This classification set excludes imaging methods. Recently, 2022 ACR/EULAR classification criteria for GCA were defined. Imaging findings that were missing in the previous classification set, such as the halo sign on temporal artery USG, involvement of axillary arteries, and FDG-PET activity in the aorta, were added to new classification criteria. This has increased the role of imaging modalities in the diagnosis of GCA.

The lack of objective clinical examination findings in ECI makes difficult the diagnosis. De Boysson et al.[16] evaluated the imaging findings of patients with cranial and extra-cranial GCA and found a more large vessel involvement in PET/CT scans in patients with ECI. Similar to the literature, while vasculitic involvement in PET/CT was observed in all patients with ECI and CECI, no PET/CT findings were observed in the isolated CI group in this study. Temporal artery USG has significant sensitivity and specificity in the diagnosis of GCA, particularly for patients with CI. Hypoechoic edematous wall swelling, also called a halo sign, is observed in those patients.[17] Temporal artery USG is an easily accessible method that can be performed in patients with cranial and visual symptoms. In our

study, temporal artery USG was performed in 62.5% of the patients, and a halo sign was detected in 20% of these patients. Recently, increased use and experience of USG by the rheumatologists will allow the evaluation of these patients in the symptomatic period.

The diagnosis can be made more easily with suggestive clinical findings in patients with CI. In addition, TAB provides the definitive diagnosis. TAB is the gold standard for GCA diagnosis by showing the typical histopathologic findings, namely, mononuclear cell infiltration of the artery wall.[18] Although stated as the gold standard, focal and segmental involvement of the vessel wall and technical pitfalls of the procedure make it difficult to confirm the diagnosis. However, the absence of suggestive clinical findings in ECI and the inability to determine the appropriate site for biopsy lead to diagnostic delay. Brack et al.[19] compared the TAB of the patients CI and ECI, they found a positivity rate of 100% and 42%, respectively. TAB findings were negative in 42% of patients with large-vessel GCA.

In some studies, TAB was also performed in patients without cranial findings and pathology results consistent with GCA were obtained.[20] This suggests that the disease has a systemic course even if it does not show any obvious symptoms. TAB was performed in 14 of 18 CI patients with visual findings, and diagnostic pathological findings were found in 92% of them. One patient presented with systemic symptoms and acute phase elevation, total abdominal hysterectomy and bilateral salpingo-oophorectomy performed with a suspicion of malignancy. The patient was diagnosed with GCA by pathological evaluation and PET/CT.

The shortcomings of our study are the small number of patients and the retrospective design. Due to the small number of patients in the groups, statistics could not be made. In addition, CT or MR angiography and PET/CT were not performed in 9 patients. If those patients had undergone these imaging modalities, accompanying ECI could have been detected.

Conclusion

As a conclusion, CI is common and diagnosed more easily due to its demonstrative clinical findings. ECI has begun to be defined better with the widespread use of imaging studies. ECI in GCA may present with different clinical findings, laboratory results, and may be defined as a different clinical entity as LV-GCA. The significant difference in terms of vasculitic involvement in PET/CT between C-GCA and LV-GCA is promising for the future studies in this regard.

Ethics

Ethics Committee Approval: The local ethics committee of Kocaeli University approved the study protocol (date: 13.09.2021, approval number: 2021/232).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.K., Ö.Ö.I., A.Y., A.Ç., Design: A.K., Ö.Ö.I., A.Y., A.Ç., Data Collection or Processing: A.K., Ö.Ö.I., A.Y., A.Ç., Analysis or Interpretation: A.K., Ö.Ö.I., A.Y., A.Ç., Literature Search: A.K., Ö.Ö.I., A.Y., A.Ç., Writing: A.K., Ö.Ö.I., A.Y., A.Ç.

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Sleep quality and its association with disease activity, depression and quality of life in Behçet's disease patients

Behçet hastalarında uyku kalitesinin hastalık aktivitesi, depresyon ve hayat kalitesi ile ilişkisinin değerlendirilmesi

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Abstract

Objective: Quality of sleep is one of the main predictors of quality of life (QoL). Data on sleep quality and associated factors are limited in Behçet's disease (BD), a systemic inflammatory disorder with different organ manifestations. In this study, we assesed depression, anxiety and sleep disorders and their associations with disease activity of Turkish patients with BD to establish the relationship between sleep quality, BD activity and QoL scales.

Methods: A cross-sectional study of 105 BD and 85 healthy controls was conducted. All subjects completed short form (SF-36), health assessment questionnaire, hospital anxiety and depression scale, multidimensional assessment of fatigue scale (MAF), American College of Rheumatology 2010 fibromyalgia criteria and sleep quality assessed with the Pittsburgh sleep quality index (PSQI). Behçet's syndrome activity score was used to determine the disease activity of BD.

Results: PSQI scores of patients with BD were significantly higher compared to the control group (p=0.001). Among patients BD patients, groups with poor or good sleep quality had similar patient characteristics in terms of gender, education level, smoking, depression level, major organ involvement and presence of fibromyalgia. Among the clinical features, only genital ulcers were associated with poor sleep quality (p=0.036). After regression analysis, mean PSQI score of patients with BD was associated with age, mental component score of SF-36 and MAF score. The disease activity was not associated with sleep quality but correlated with fatigue, depression, anxiety, QoL scales (p<0.005).

Conclusion: Sleep quality is poor among patients with BD and is associated with increased fatigue, lower QoL. As sleep is an important predictor of QoL, it should be among the patient-reported outcome measures for assessing BD.

Keywords: Behçet's disease, depression, fatigue, sleep quality

Öz

Amaç: Uyku kalitesi, hayat kalitesinin en önemli belirleyicilerinden biridir. Farklı organ tutulumları ile seyreden sistemik enflamatuvar bir hastalık olan Behçet hastalığında hastaların uyku kalitesi ve bunu etkileyen faktörlerle ilgili yayınlanmış çalışmalar sınırlıdır. Bu çalışmada Behçet hastalarında depresyon, anksiyete ve uyku bozukluklarının belirlenmesi ve uyku kalitesi ile hastalık aktivitesi ve yaşam kalite indeksleri arasındaki ilişkisinin değerlendirilmesi amaçlanmıştır.

Yöntem: Kesitsel çalışmamızda 105 Behçet hastası ve 85 sağlıklı kontrol değerlendirilmiştir. Tüm katılımcılara kısa form (KF-36), sağlık değerlendirme anketi, hastane anksiyete ve depresyon anketi, yorgunluk çok boyutlu değerlendirme anketi, Amerikan Romatoloji Derneği 2010 fibromiyalji kriterleri, uyku kalitesi değerlendirilmesi için Pittsburg uyku kalite indeksi (PUKI), hastalık aktivite değerlendirilmesi için Behçet sendrom aktivite skoru uygulandı.

Bulgular: Behçet hastalarının PUKI skorları sağlıklı kontrole göre anlamlı olarak daha yüksekti (p=0,001). İyi ve kötü uyku kalitesine sahip Behçet hastaları değerlendirildiğinde cinsiyet, eğitim düzeyi, sigara içiciliği, depresyon seviyesi, fibromiyalji ve majör organ tutulumu benzerdir. Klinik özellikler arasında ise sadece aktif genital ülserin varlığı kötü uyku kalitesi ile ilişkili bulunmuştur (p=0,036). Regresyon analizinde Behçet hastalarının ortalama PUKI skoru yaşla, KF-36'nın mental bileşen özeti ve yorgunlukla ilişkili bulunmuştur. Hastalık aktivitesinin uyku kalitesi ile ilişkisi bulunmamakla birlikte yorgunluk, depresyon ve anksiyete ve yaşam kalite ölçütleri ile korelasyonu saptanmıştır (p<0,005).

Sonuç: Uyku kalitesi Behçet hastalarında sağlıklı populasyonla karşılaştırıldığında daha kötüdür ve yorgunluk, düşük hayat kalitesi ile ilişkilidir. Uykunun hayat kalitesinin önemli bir belirleyicisi olduğu düşünüldüğünde Behçet hastalarının değerlendirme ölçütleri arasında olması önemlidir.

Anahtar Kelimeler: Behçet hastalığı, depresyon, yorgunluk, uyku kalitesi

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Introduction

Behçet's disease (BD) is a chronic, systemic inflammatory disease characterized by recurrent oral and urogenital aphthous ulcers, ocular, musculoskeletal, vascular and central nervous system involvement.[1] Although the etiology is unknown, infectious agents, autoimmunity and genetic factors are thought to be associated with the disease. Many studies suggested that physical and psychological stresses also have some influence on the development of immune dysregulation in BD.[1-4]

Chronic inflammation, treatment toxicities and disease-related damage in chronic inflammatory diseases can affect patients' quality of life (QoL) and functional status seriously. Modern health care has focused on the association of mental and social health with physical health, which are all important predictors of QoL and it is essential to evaluate the health-related QoL of patients. One of the important items of QoL is the quality of sleep and a recent study revealed that sleep quality was the most important factor for wellness rated by patients themselves.[5] Psychiatric disorders, depression and anxiety can also affect sleep quality, as well as the disease itself.

There are very limited data of patients with BD with disturbed sleep quality, increased depressive symptoms and anxiety.[6-8] In this study, we assessed depression, anxiety and sleep disorders and their associations with disease activity of Turkish patients with BD to establish the relationship between sleep quality, BD activity and QoL scales.

Materials and Methods

BD patients (n=105) classified using International Study Group (ISG) criteria and 85 healthy controls were recruited to our study between May 2012 and September 2013.[9] Patients who weren't classified as BD according to ISG criteria, with age <18 or more than 65 years, diagnosed psychiatric disease and pregnancy are excluded from our study.

Patient, disease characteristics and demographic information were recorded into study form.

Parameters Used in the Study

Behcet's Syndrome activity score (BSAS) comprised 10 questions, containing visual analog scales for patient's level of discomfort due to oral ulcers, genital ulcers, skin lesions and current disease activity.

Also, the BSAS categorizes the number of oral ulcers, genital ulcers, and skin lesions present and evaluates whether there is an eye, gastrointestinal, or vascular involvement. Physician's global assessment was scored from 0 (inactive) to 10 (active) to assess the disease activity.[10]

Turkish validated short form (SF-36), health assessment questionnaire (HAQ) score, both validated for Turks, were used.[11-14] Hospital anxiety and depression scale (HADS), Multidimensional assessment of fatigue scale (MAF) were also assessed.[15-17] Fibromyalgia is diagnosed on the basis of American College of Rheumatology 2010 criteria.[18]

The Pittsburgh Sleep Quality index (PSQI) evaluates the patient's self-reported sleep quality over the last month. The scale has 19 items and measures 7 components of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. By using these 7 individual scores, a total PSQI score is calculated (range=0-21). The diagnostic specificity of the test for clinical sleep disturbances was high, scores above 5 indicated poor sleep quality.[19,20]

Statistical Analyses

The statistical program SPSS version 21.0 was used for data processing and statistical analysis. Categorical variables are presented as frequencies and percentages. Histogram, normal quantile plot, Kolmogorov-Smirnov, and skewness kurtosis tests were used for normality evaluation of continuous variables. Mann-Whitney U and Kruskal-Wallis tests were used to compare the groups with continuous variables. Correlations for continuous variables were evaluated with the Spearman test, where both rho and p values were presented. As multivariate analysis, binary logistic and ordinal regression models were used, and odds ratios with 95% confidence interval.

Univariate regression analysis showed that age, disease duration, MAF, HAQ, PCS, MCS and HADS-A ($p<0.05$) were statistically significant variables for poor sleep quality, and all these variables were included for multivariate regression analysis.

The institutional review board of the Medical School approved the study (09.2012.202), and all participants gave informed consent.

Results

Demographic and clinical characteristics of the study population are described in Table 1. There was no difference between BD and control groups regarding gender and age. Thirty (28.6%) of patients with BD were under the immunosuppressive drugs during the study. PSQI scores of patients with BD were significantly higher compared with the control group. The median MAF score also increased in patients with BD compared with the control group ($p=0.001$, Table 1).

BD (29.5%) patients had increased depression than the control group (13.1%, p=0.008), but there was no difference between the groups in terms of anxiety (18.1% and 11.9% for BD and control group respectively, p>0.05) (Table 1).

Clinical and demographic characteristics of patients with BD with poor or good sleep quality are presented in Table 2. Although there was no difference between the groups in terms of disease activity (BSAS score), among clinical features, only genital ulcers were associated with sleep quality (83% of patients with BD having one or more genital ulcer over last month of evaluation had poor sleep quality compared to 50% in patients without genital ulcers, p=0.036). BSAS was positively correlated with MAF (r:0.39, p=0.000), HAQ (r:0.343, p=0.000) and negatively associated with MCS (r:-0.289, p=0.003) and PCS (r:-0.479, p=0.000).

Mean PSQI score of patients with BD had positively correlated with age (r:0.311, p=0.001), disease duration (r:237, p=0.015), HAQ (r:0.38, p=0.000), MAF (r:0.37, p=0.000), HADS-A (r:0.31, p=0.000) and negatively associated with all subgroups of SF-36, physical, and mental component score: PCS, MCS (r:-0.308 and -0.268 respectively, p<0.005).

Table 1. Demographic and clinical features of patients with BD and healthy controls

		BD (n=105)	HC (n=85)	p
Male		64 (61%)	48 (56.5%)	0.556
Age (years)		39.7±11.2	41.8±10.6	0.190
Smoking		32 (31.1%)	28 (32.9%)	0.875
Disease duration in years		8.8±6.8		
BSAS (median, 25-75 percentile)		20 (7-35)		
The type of disease (n:102)	Mucocutaneous	59 (59.8%)		
	Major organ	43 (42.2%)		
PSQI global score		5.7±3.2	3.4±2.8	**0.000**
Bad sleep quality according to the PSQI		50 (47.6%)	12 (14.1%)	**0.000**
Fibromyalgia		21 (20.4%)	6 (7.1%)	**0.012**
MAF score (median, 25-75)		21 (0-30)	13.3 (0-21.5)	**0.001**
HADS-A (0-21)		6.3±3.7	5.1±3.4	**0.020**
HADS-D (0-16) (median, 25-75 percentile)		5 (2-7)	3 (1-5)	**0.007**
SF-36	PCS	43.3±10.2	52.3±7.5	**0.000**
	MCS	45.1±9.9	51.6±8.0	**0.000**
	HAQ (median, 25-75 percentile)	0.1 (0-0.33)	0.0 (0-0.1)	**0.000**

BD: Behçet's disease, BSAS: Behcet syndrome activity score, HADS-A/HADS-D: Hospital anxiety/depression scale, HAQ: Health assessment questionnaire, HC: Healthy control, MAF: Multidimensional assessment of fatigue scale, MCS: Mental component score, PCS: Physical component score, PSQI: Pittsburgh sleep quality index, SF-36: Short form

Table 2. Clinical and demographic characteristics of patients with BD with good and bad sleep quality

Behçet's disease patients				
		Good sleep quality (n=55)	**Bad sleep quality (n=50)**	**p**
Male		29 (52.7%)	35 (70%)	0.076
Age (years)		36.5±10.7	43.3±10.9	**0.000**
Smoking		15 (28.3%)	17 (34%)	0.670
Disease duration in years (mean ± SD)		7.1±5.3	10.7±7.7	**0.006**
Type of involvement				
Major organ		26 (49.1%)	17 (34.7%)	0.164
Mucocutaneous		27 (50.9%)	32 (65.3%)	
Immunosuppressive usage		20 (37%)	10 (20%)	0.082
BSAS (median, 25-75 percentile)		15 (5-34)	21 (11.5-35)	0.148
SF-36	PCS	46.3±10.4	40±9	**0.001**
	MCS	48±8.7	41.8±10.2	**0.001**
Anxiety		5 (9.1%)	14 (28%)	**0.021**
Depression		13 (23.6%)	18 (36%)	0.201
Fibromyalgia		7 (13%)	14 (28.6%)	0.055

BSAS: Behçet syndrome activity score, MCS: Mental component score, PCS: Physical component score, SD: Standard deviation

However, there was no correlation between PSQI score and doctor/patient global assessment (p>0.05). Multivariate logistic regression analysis revealed that increased age, MCS and MAF score statically significantly related to poor sleep quality (Table 3).

Fifty-nine (59.8%) of patients with BD had mucocutaneous and 43 (42.2%) had a major organ involvement. There was no difference between these two groups in terms of PSQI score, MAF score and the rate of depression.

PSQI include subgroup evaluation about subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Table 4 shows a subgroup evaluation of the index between the groups. Most parameters were disturbed for patients with BD compared with the control group.

Discussion

Our study results showed that BD had higher degree of poor sleep quality, depression, and fatigue scores with significantly lower QoL.

Our results support previous studies in the literature. Koca et al.[21] demonstrated higher PSQI scores in patients with BD from Turkey. Another study from Korea also reported decreased sleep quality for patients with BD.[8] Like our study, previous studies revealed that more than 40% of patients with BD have poor sleep quality.[8,22]

Senusi et al.[23] reported poor sleep quality in patients with BD. In this study, female patients with BD had worse sleep quality compared with males, opposite to our study, which showed no difference between gender groups in terms of sleep quality. This difference could be a result of increased fatigue in female patients as fatigue is closely correlated with poor sleep. In our study female and male patients with BD had similar fatigue scores. Unlike our study, Senusi et al.[23] showed no effect of age on sleep quality.

Our results also showed that patients with BD scored significantly higher in sub-components of PSQI with decreased subjective sleep quality-sleep duration, increased sleep latency-sleep disturbances- daytime dysfunction. Yazmalar et al.[22] reported similar disturbances in sleep characteristics for patients with BD.

Previous studies showed different results about the association between disease activity and sleep scores of patients with BD. Senusi et al.[23] and Koca et al.[21] showed a positive correlation between bad sleep quality and high disease activity.[21,23] In contrast to these studies our study like research from Korea, showed no association between sleep quality and disease activity.[8] These conflicting results may be explained by the challenges of evaluating disease activity of patients with BD because of its fluctuating clinical course and different tools were used in our research and the other studies. The only clinical finding correlated with lower sleep quality was genital ulcers in our study, complaining of one or more genital ulcers increased the risk of having poor sleep quality. Tascilar et al.[6] also reported a positive correlation between genital ulcers and wake before sleep, non-REM sleep latency and percentage of REM sleep.

One-fifth of patients with BD had fibromyalgia in our study and even it is not statically significant, patients with BD with poor sleep quality had increased fibromyalgia than patients with good sleep quality (Tables 1, 2). Previous studies showed increased fibromyalgia in patients with BD and increased central sensitization, which is disturbed in fibromyalgia.[24,25] Because of cross-sectional nature of the

Table 3. Logistic regression analysis for factors affecting poor sleep quality in patients with BD

	Multivariate analysis OR (95% CI)	p-value
Age	1.068 (1.023-1.114)	**0.003**
MAF	1.067 (1.031-1.104)	**0.000**
MCS	0.946 (0.899-0.996)	**0.033**

BD: Behçet's disease, CI: Confidence interval, MAF: Multidimensional assessment of fatigue scale, MCS: Mental component score, OR: Odds ratio

Table 4. Comparison of sleep quality components between groups

	BD	Healthy control	p
Subjective sleep quality	1 (0-3)	1 (0-3)	**0.001**
Sleep latency	1 (0-3)	0 (0-3)	**0.000**
Sleep duration	1 (0-3)	0 (0-3)	**0.008**
Habitual sleep efficiency	0 (0-3)	0 (0-3)	**0.062**
Sleep disturbances	1 (0-3)	1 (0-2)	**0.000**
Use of sleeping medication	0 (0-3)	0 (0-3)	**0.166**
Daytime dysfunction	1 (0-2)	0 (0-2)	**0.004**

All values are presented as medians (min-max), BD: Behçet disease

study, we could not conclude whether poor sleep quality is the cause or result of fibromyalgia in patients with BD. Previous studies searching for the frequency of fibromyalgia in patients with BD showed similar results to our study but the most patients with BD with fibromyalgia were females, unlike our study; 10% of our female patients with BD and 27% of male patients had fibromyalgia (p=0.046).[25,26]

Twenty-nine percentage of our patients with BD had depression. Previous studies have confirmed a higher prevalence of depression in patients with BD similar to other inflammatory rheumatic diseases such as RA and psoriasis.[7,27] Depression score and disease activity assessed with BSAS correlated, similar to the results reported by Melikoglu and Melikoglu[27] The interaction between physical and emotional health during rheumatic diseases is well-known and stressful life events can cause depression and relapse of BD. Stressful life events may precipitate relapses and may occur just before increased disease activity.[28]

An increased fatigue was present in patients with BD similar to other inflammatory diseases[29,30] and in our study, MAF score and bad sleep quality association was still statistically significant after regression analysis. Our study also revealed that mental, and physical well-being in patients with BD were decreased compared with healthy individuals. Moreover, patients with BD with poor sleep quality had decreased QoL scores although this correlation is only statically significant for MCS after multivariate regression analysis (Tables 2 and 3). A recent study showed that sleep quality is the most important predictor of patients with BD' self-rated wellness and another study found a deterioration in QoL for patients with BD with sleep disturbances and high disease activity. Our study showed an association between QoL and disease activity of patients, too.[5,8] This may suggest that patients' QoL can be eased by sustaining the low disease activity and using patient-reported measures such as patient-global, fatigue, MAF, and PSQI as a part of routine clinical practices.

Study Limitations

As the limitations of the study, patients with BD were from a hospital population and can minimally represent the full spectrum of BD in the community. Although we excluded all patients with active psychiatric disorder, we did not have a detailed psychiatric histories of the patients. Also, cross-sectional analysis of disease activity, MAF, PSQI, depression and anxiety evaluation can be affected by other potential influencers. The lack of data for obesity and cumulative steroid dosage, which can be a possible effector of sleep quality, is another limitation for our study.

Conclusion

Poor sleep quality and increased depression were detected among patients with BD compared with healthy persons. Poor sleep quality was affected by age, fatigue, and a lower mental component score of SF-36. As sleep is an important predictor of QoL, it may affect the patient's perception of the disease and expectations of treatment outcome. The patient reported measures can be used in routine clinical practice and treatment plans should also incorporate them.

Ethics

Ethics Committee Approval: The institutional review board of the Medical School approved the study (09.2012.202).

Informed Consent: All participants gave informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.P.K., A.A., B.I., F.A.O., H.D., Design: Ö.P.K., A.A., B.I., F.A.O., H.D., Data Collection or Processing: Ö.P.K., A.A., B.I., F.A.O., H.D., Analysis or Interpretation: Ö.P.K., A.A., B.I., F.A.O., H.D., Literature Search: Ö.P.K., A.A., B.I., F.A.O., H.D., Writing: Ö.P.K., A.A., B.I., F.A.O., H.D.

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Predicting the response to bDMARD treatment in RA: Then what?

Romatoid artritte bDMARD yanıtını öngörmek: Peki sonrasında?

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Abstract

Objective: Biologic disease-modifying antirheumatic drugs (bDMARDs) offer promising results for rheumatoid arthritis (RA) patients in general, but a substantial percentage of patients do not respond to them. It is important to predict the response before the treatment so that unnecessary adversities for the patients and costs for the healthcare system can be avoided. This study aims to develop a machine learning (ML) model that works with readily-available demographic and clinical factors for prediction of response to bDMARDs, and discusses additional non-pharmacological practices.

Methods: Several ML models were tested in 190 RA patients from Turkey, and the logistic regression model was found to be superior. The relation between long-term and short-term responses were also analyzed.

Results: Predictors of the logistic regression model were age, sex, coronary artery disease, spine surgery, steroid treatment, sulfasalazine treatment and baseline health assesment questionnaire score. The model displayed 79.5% accuracy and an area under receiver operating characteristic curve of 0.82. 87% of the patients who were good-responders in six-month follow-up were also good responders in one-year follow-up. Among non-responders in six-month follow-up, 75% were also non-responders in one-year follow-up.

Conclusion: Making the prediction at an early stage is crucial for the patients as well as the healthcare system. However, it is equally important to determine how to proceed with the patients who are unlikely to respond to bDMARDs. Current literature does not adequately answer this question. Additional treatment options and multiple evaluation criteria for these options should be considered; multiple criteria models can provide useful decision support for this purpose.

Keywords: Rheumatoid arthritis, treatment decision, bDMARD, response prediction, logistic regression

Öz

Amaç: Biyolojik hastalık modifiye edici antiromatizmal ilaçlar (bDMARD'lar) genel olarak romatoid artrit (RA) hastaları için umut verici sonuçlar sunar; ancak hastaların önemli bir yüzdesi bunlara yanıt vermez. Yan etkilerin azaltılması ve sağlık sistemi için maliyetlerden kaçınılabilmesi için yanıtın tedavi öncesi tahmin edilmesi önemlidir. Bu çalışmada, bDMARD'lara yanıtı tahmin etmek için demografik ve klinik faktörlerle çalışan bir makine öğrenimi (ML) modeli geliştirme ve ek farmakolojik olmayan uygulamaların tartışılması amaçlanmıştır.

Yöntem: Yüz doksan Türk RA hastasında birkaç ML modeli test edilmiştir ve lojistik regresyon modelinin üstün olduğu bulunmuştur. Uzun ve kısa vadeli sonuçlar arasındaki ilişki de analiz edilmiştir.

Bulgular: Lojistik regresyon modelinde, cinsiyet, koroner arter hastalığı, omurga cerrahisi, steroid tedavisi, sülfasalazin tedavisi ve başlangıç sağlık değerlendirme anketi skoru prediktör olarak saptanmıştır. Model, %79,5 doğruluk ve 0,82'lik bir alıcı işletim karakteristiği eğrisi altında kalan alan sergilemiştir. Altı aylık takipte iyi yanıt veren hastaların %87'sinin, bir yıllık takipte de iyi yanıt verdiği gözlemlenmiştir. Altı aylık takipte yanıt vermeyenlerin %75'inin bir yıllık takipte yanıt vermediği gözlemlenmiştir.

Sonuç: Tedavi yanıtlarının erken aşamada öngörülmesi hastalar için olduğu kadar sağlık sistemi için de çok önemlidir. Bununla birlikte, bDMARD'lara yanıt verme olasılığı düşük olan hastalarda nasıl bir yol izleneceğini belirlemek de aynı derecede önemlidir. Mevcut literatür bu soruya yeterince cevap vermemektedir. Ek tedavi seçenekleri ve çoklu değerlendirme kriterleri göz önünde bulundurulmalıdır; çok kriterli modeller bu amaç için faydalı karar desteği sağlayabilir.

Anahtar Kelimeler: Romatoid artrit, tedavi kararı, bDMARD, yanıt tahmini, lojistik regresyon

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Introduction

With the advances in technology and informatics, artificial intelligence (AI) methods have become increasingly useful in medical decision making. One of their uses is to predict the risk of patients to develop some diseases and the success rates of treatments.[1,2] Another use is to predict the complications that can arise after the onset of diseases.[3] AI is also used to determine personalized treatments for patients that have been diagnosed with a disease, such as cancer.[4] It is also possible to use AI methods in clinical research and drug development. A review of AI methods in healthcare can be found in.[5]

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease that causes pain, disability, and social and economic disadvantages for approximately one percent of the world population. RA is a heterogeneous disease; the clinical symptoms, progress of the disease and response rate to treatment differ substantially among patients.[6] Therefore, clinicians and patients of this disease can benefit from AI methods that will support their decisions. Many AI methods used for RA aim to diagnose patients that exhibit certain complaints and predict patients with high risks of developing RA (see[7] for fuzzy logic;[8] for rule-based;[9] for clustering;[10] for decision tree and feature selection applications; and[11] for a review of computational methods).

This paper focuses on the prediction of response to treatment in RA patients. In the AI domain, machine learning (ML) models that can work with several factors related to the patients and their conditions come forward as suitable and useful tools for this prediction. In RA, firstly the factors that can determine the response to treatment should be discovered.[12] Several trials with methotrexate (MTX), cyclosporine plus MTX and combination treatment were made in.[13] They found that disease duration, prior use of disease-modifying antirheumatic drugs (DMARDs), higher disease functional class, low disease activity and female sex had a negative effect on the likelihood of patient response. A logistic regression model was used to predict response to MTX, steroids, and combination of DMARD treatments in.[14] They tested their model in a UK randomized controlled trial, and the significant variables to predict remission measured as the disease activity scores in 28 joints (DAS28) <2.6 were discovered as age, sex and tender joint count. The results had high specificity (98%) but low sensitivity (13%). The evidence on predictors of response to MTX and other synthetic DMARDs was reviewed in.[15] Even though they found high discrepancy between the results of different studies, they stated that the factors that are more likely to lead to lower response are female sex, smoking, established disease, previous DMARD use, high disease activity and the absence of concomitant corticosteroids. Biomarker search for the prediction of response to treatment in RA was summarized.[16] Regularized regression, random forest and a pathway-supported approach were used to study the association between early treatment lipidomic measurements and response to MTX, but the results did not support an evident association.[17]

Biologic therapies offer more promising results in RA treatment. It was discussed that biologic therapies offer increased efficacy, but their use is limited by cost concerns.[18] Therefore, predictive models for identifying patients that are most likely to benefit from them is important. But it is also stated that many predictive models are hindered by their complexity and the need for biomarkers that are not routinely measured. For example,[19] reported that circulating cell-free DNA can predict the early therapeutic effects of biologic DMARDs (bDMARDs) in RA patients. However, more work is needed to integrate this prediction to clinical practice. In addition,[20] reported that different markers were effective in the prediction in different studies. They observed that currently no biomarkers can predict response to bDMARDs with high certainty.

Other studies used demographic and clinical factors to build prediction models for bDMARDs. Multivariate ordinal logistic regression was applied to identify clinical factors that can predict response to anti-tumor necrosis factor (TNF)-α therapy; and DAS28 scores were used to assess patients and found lower response rate among smokers and females.[21] The response to anti-TNF agents was studied using DAS28 scores and it was found that poorer response was associated with female sex, the number of DMARDs previously used, baseline erythrocyte sedimentation rate, tender joint count, and long RA history.[22] Different ML models such as lasso, ridge, support vector machine (SVM), random forest, and XGBoost were used to predict response.[23] It was discovered different predictors for different bDMARDS; accuracy rates were between 52.8-72.9%.

Even though bDMARDs are generally accepted to provide better results for the patients, a significant number of patients do not respond to them.[6] As discussed, clinical trials often show that bDMARDs are not effective for approximately 30-40% of patients; and the response rate decreases with subsequent biologic drugs.[23] This situation has drawbacks for the patients and the healthcare system. First, ineffective treatments cause pain and unnecessary side effects for the patients. In addition, as some of the reviewed studies discussed, disease duration can have a negative effect on the success of the treatment. Therefore, an unsuccessful

treatment period can lower the chance of remission for the patients in the future as well. As another drawback, bDMARDs cause a significant cost burden on the healthcare system. Considering these issues, it is evident that early intervention and detection of non-responders are crucial in the treatment of RA with biologics.

This paper proposes to use an ML model to predict the response to bDMARDs for RA patients who have been registered to Hacettepe University Rheumatology Biologic (HUR-BIO) Registry system in Turkey. The aims of the paper are to i) assess the performances of different ML models, ii) develop a model that uses demographic and clinical factors that are readily available in clinical practice, iii) investigate the relation between long-term and short-term responses, and iv) discuss additional non-pharmacological practices such as physiotherapy and rehabilitation, psychotherapy, dieting, daily exercise, and pain education for the patients who are not likely to benefit from biologics.

Materials and Methods

First the information on the study population is provided and then, the ML models used for predicting the response to treatment are explained.

Data Collection

In this study, HUR-BIO Registry where patients on bDMARD treatment have been recorded was used. RA diagnosis was based on American College of Rheumatology/ The European League Against Rheumatism 2010 Classification Criteria. The response was measured based on the difference in health assesment questionnaire (HAQ) scores of the patients at the baseline (at the beginning of the bDMARD treatment) and at six-month follow-up. HAQ is reported as a good representation of disease activity[24] and assessment of function in RA patients.[25] Although DAS28 and HAQ scores are both commonly used in RA studies, the latter was selected to measure the response as HAQ was considered to reflect the patients' self-evaluations better. This self-evaluation is expected to guide additional non-pharmacological treatment selections.

Among 1101 RA patients registered in the HUR-BIO database, the ones who started bDMARD treatment in 2013 and later and having a HAQ score of at least 0.5 were selected and included in the analysis. 2013 was selected as the starting year since consistent data on bDMARDs were available after this date in the database. In order to assess the improvement due to treatment, a threshold in the starting HAQ score was necessary to avoid misinterpreting patients having good initial scores. Therefore, a threshold of 0.5 was selected for the starting HAQ score. After excluding patients with missing data and those whose follow-up durations deviated from six months, 190 patients remained for the analysis. All of these patients were at least 22 years old, so no more exclusion due to age was needed.

ML Models

While measuring the response to treatment, the patients having a change in their HAQ score of at least 0.22, which was validated in a cohort of 1.645 RA patients, were labelled as "good responders"[26] whereas the others were labelled as "non-responders".

To predict the response, four commonly used ML models that are suitable for the available data are selected: namely Kernel naïve Bayes (NB), fine decision tree (DT), logistic regression (LR), and linear SVM. Accuracy is estimated following a 10-fold cross validation approach. To test the performances of the ML models, Classification Learner App in MATLAB was utilized; thus, the guidelines of MATLAB were used for the parameterization of the algorithms.

Results

Cohort Characteristics

The ages of the selected patients were between 22-79 and 86.3% were female. Of the 190 selected patients, 137 were identified as good responders. The baseline characteristics are summarized in Table 1.

Performances of the ML Models

The accuracy levels of the algorithms were found as 72.6%, 70.5%, 75.3%, and 74.2% for NB, DT, LR and SVM, respectively. Since LR is the best performer among the four ML models and is widely used in the literature, it was selected to be used in the further analysis. Hence, an LR model was constructed to identify predictors (important features) of being good responder/non-responder. The assumptions of LR such as independence of observations, linearity between independent variables and log odds, the existence of no multicollinearity and extreme outliers are checked. A p-level of 0.10 was used as in[22] and age, sex, coronary artery disease, spine surgery, steroid treatment, sulfasalazine treatment, baseline HAQ score were selected as predictors. Although there is not a commonly used set of predictors in the literature, age and sex were prominent in almost all studies. The final model is as follows: 1.451 - 0.063*age + 1.933*sex - 0.939*coronary artery disease - 1.268*spine surgery - 0.627*sulfasalazine treatment +

1.086*steroid treatment + 2.151*HAQ. According to the model, a higher likelihood of being a non-responder is associated with higher age, female sex, having coronary artery disease, having spine surgery, previous exposure to sulfasalazine treatment, and having a lower baseline HAQ score. The model resulted in 79.5% accuracy, 90.5% sensitivity, and 50.9% specificity. The receiver operating characteristic (ROC) curve and the corresponding area under ROC curve value are provided in Figure 1.

Prediction of the Long-term Responses Based on Short-term Responses

In prediction of response levels (good responder/non-responder) of the patients to bDMARDs, those whose follow-up durations were about six months were analysed.

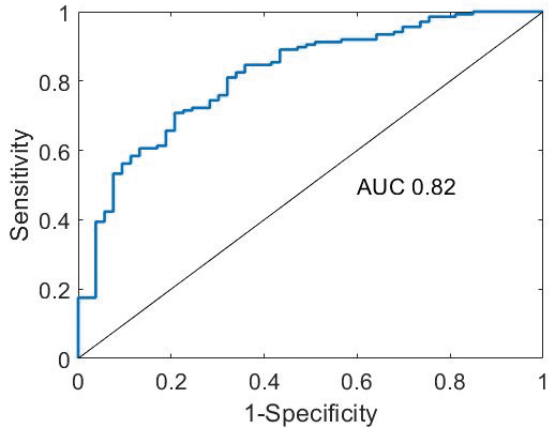

Figure 1. ROC curve of LR model to predict the response

AUC: Areu under the curve, ROC: Receiver operating characteristic, LR: Logistic regression

Table 1. Baseline characteristics of 190 patients treated with bDMARDs

Variable	Overall (n=190)	Good responder (n=137, 72.1%)	Non-responder (n=53, 27.9%)
Female, n (%)	164 (86.3)	114 (83.2)	50 (94.3)
Age, mean ± SD	52.1±12.9	50.6±12.9	56.2±12.0
Married, n (%)	170 (89.5)	123 (89.8)	47 (88.7)
Smoking pack-year, mean ± SD	6.9±14.3	6.1±13.9	9.0±15.2
BMI, mean ± SD	30.7±6.8	30.6±6.9	30.9±6.6
Anti-CCP or RF positivity, n (%)	147 (77.4)	106 (77.4)	41 (77.4)
Interstitial lung disease, n (%)	1 (0.5)	1 (0.7)	0 (0.0)
Coronary artery disease, n (%)	18 (9.5)	9 (6.6)	9 (17.0)
Spine surgery, n (%)	21 (11.1)	12 (8.8)	9 (17.0)
Orthopedic surgery, n (%)	23 (12.1)	15 (10.9)	8 (15.1)
Chronic kidney disease, n (%)	1 (0.5)	0 (0.0)	1 (1.9)
Thyroid diseases, n (%)	26 (13.7)	17 (12.4)	9 (17.0)
Cerobrovascular event, n (%)	2 (1.1)	2 (1.5)	0 (0.0)
Hypertension, n (%)	71 (37.4)	44 (32.1)	27 (50.9)
Diabetes, n (%)	27 (14.2)	15 (10.9)	12 (22.6)
Tuberculosis history, n (%)	3 (1.6)	2 (1.5)	1 (1.9)
Sjogren, n (%)	8 (4.2)	5 (3.6)	3 (5.7)
Cancer, n (%)	7 (3.7)	5 (3.6)	2 (3.8)
Methotrexate treatment, n (%)	161 (84.7)	115 (83.9)	46 (86.8)
Sulfasalazine treatment, n (%)	120 (63.2)	83 (60.6)	37 (69.8)
Hydroxychloroquine treatment, n (%)	141 (74.2)	103 (75.2)	38 (71.7)
Leflunomide treatment, n (%)	103 (54.2)	71 (51.8)	32 (60.4)
Steroid treatment, n (%)	164 (86.3)	121 (88.3)	43 (81.1)
Sedimentation, mean ± SD	50.8±26.3	52.0±26.2	47.6±26.6
CRP, mean ± SD	4.3±4.6	4.7±4.5	3.4±4.6
Swollen joints, mean ± SD	5.2±3.3	5.0±3.3	5.7±3.5
Tender joints, mean ± SD	9.8±4.5	9.6±4.6	10.3±4.2
VAS global assessment, mean ± SD	71.0±15.8	71.9±15.8	68.8±16.0
VAS fatigue, mean ± SD	67.3±24.5	67.6±24.4	66.6±25.0
VAS pain, mean ± SD	73.8±16.7	76.1±15.0	68.1±19.3
HAQ, mean ± SD	1.4±0.6	1.4±0.6	1.1±0.5

Anti-CCP: Anti cyclic citrullinated peptide, BMI: Body mass index, CRP: C-reactive protein, HAQ: Health assessment questionnaire, RF: Rheumatoid factor, SD: Standard deviation, VAS: Visual analogue scale

To check the effectiveness of the model for long-term prediction, patients who had records for one-year follow-up were identified. One hundred thirty one out of 190 patients satisfied the requirement and were included in further analysis. After checking the responses of these 131 patients with respect to their baseline HAQ scores, it was observed that 87% of the patients who were classified as good responders for six-month follow-up were also classified as good responders at the end of one-year follow-up. Moreover, 75% of the patients who were classified as non-responders for six-month follow-up were also classified as non-responders at the end of one-year follow-up. This implies that the response prediction based on six-month follow-up is a good representative for that of one-year follow-up.

Discussion

In this study, HUR-BIO database which is the oldest and one of the most comprehensive registry systems in Turkey, was used to predict the responses of the RA patients to bDMARD treatment. In the first part of the study, four different ML models were analysed using a sample of 190 patients with a total of 31 demographic and clinical features. Then, further analysis was conducted with LR to identify important features for predicting non-responders.

Predictors

Age, sex, coronary artery disease, spine surgery, steroid treatment, sulfasalazine treatment, and baseline HAQ score were selected as predictors. As stated in the introduction, higher age and female sex are commonly associated with poor outcomes in RA. Besides, baseline HAQ score was expected to be a predictor of future scores. On the other hand, the others -having coronary artery disease, having spine surgery, and previous exposure to sulfasalazine treatment- were not obvious predictors at the start of the study.

Study Limitations

There were several limitations in this study, some of which are common to all studies in this area. It is not possible to generalize the findings to all RA patient groups as different cohorts can result in different predictors and models. Only clinical and demographic characteristics were included in the examined data set. In this study, the aim of using HAQ score as a response criterion was to consider "functional status" as a better surrogate factor of overall health status of the patient. As another limitation, since the learning performance of ML models increases with sample size, better results could have been obtained with a larger sample. In addition, drug-specific predictions could not be made with the available sample.

Study Implications

There are several studies that predicted the response to bDMARD treatment for RA patients, but a consensus on important predictors and models has not been reached. It is clear that more studies are needed to determine common predictors and best models of prediction. They will help to distinguish patients who are most likely to benefit from bDMARDs from patients who need more careful evaluation. This is critical not only for the well-being of patients but also for the monetary position of the healthcare system, especially for developing countries such as Turkey where bDMARDs are very costly. For the same reasons, making the prediction at an early stage is beneficial. This study predicted the short-term response, and showed that it is a good representative of the long-term response.

Another critical issue is developing treatment plans for patients who will not achieve good outcomes from bDMARDs. The current literature does not sufficiently address this issue; the studies end with the prediction and do not answer the question of what to do next. This question is not straightforward to answer; there can be several options to improve the condition of non-responders and multiple factors to consider when making a decision. Due to the nature of RA, which is a chronic disease, patients can benefit from non-pharmacological practices such as physiotherapy and rehabilitation, psychotherapy, dieting, daily exercise and pain education.[27] There can also be other pharmacological options, e.g. injection and surgery. The best option for each patient can be different, and the decision should be made considering different factors like side effects, cost, expected improvement in pain and function, psychosocial improvement and difficulty in implementation. Since there are multiple options and factors to consider, this decision presents itself as a multiple criteria decision making (MCDM) problem.

Although MCDM methods have been used for medical decision making problems (see[28] for a review), their application in treatment selection is limited. In RA context, they have high potential in terms of eliciting the preferences of the patients, reflecting the expertise of the clinicians and providing decision support in an interactive setting. Therefore, the collaboration between prediction and MCDM methods can provide more useful outcomes. In future studies, the development of a decision support tool and its validation with both clinicians and patients will impact the literature and clinical practice.

Conclusion

The prediction of response to bDMARD treatment in RA patients at an early stage is critical for two main reasons: The patients should be spared from ineffective treatments that will worsen their condition in the long-term, and the healthcare budget should be allocated in an efficient way. Therefore, prediction models should be studied more to discover powerful and easy-to-use predictors. In addition, decision support tools should be developed to make best use of the predictions. These tools can assist the clinicians and RA patients in the formation of patient-specific treatment plans. This study contributed to the literature by proposing a practical response prediction model with the available data, and discussing the potential of a decision support tool to select non-pharmacological treatments considering multiple criteria.

Ethics

Ethics Committee Approval: Ethical approvals for this study were obtained from Hacettepe University Non-Interventional Clinical Researches Ethics Board (2019/28-36).

Informed Consent: Written consent was obtained from each patient participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.B., L.K., U.K., Concept: C.T.S., G.K., E.B., L.K., U.K., Design: C.T.S., G.K., E.B., L.K., U.K., Data Collection or Processing: C.T.S., G.K., E.B., L.K., U.K., Analysis or Interpretation: C.T.S., G.K., E.B., L.K., U.K., Literature Search: C.T.S., G.K., L.K., U.K., Writing: C.T.S., G.K., E.B., L.K.

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PFAPA sendromunun klinik seyrinde *MEFV* gen mutasyonlarının ilişkisi

The effect of *MEFV* gene mutations on the clinical course of PFAPA syndrome

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Öz

Amaç: Periyodik ateş, aftöz stomatit, farenjit ve adenopati ile karakterize tablo olan periyodik ateş, aftöz stomatit, farenjit, adenit (PFAPA) otoenflamatuvar bir sendromdur. Ülkemiz Ailevi Akdeniz ateşinin (AAA) sık görüldüğü coğrafyada bulunmaktadır. Bu çalışmada MEFV mutasyonu taşıyıcılığının, PFAPA sendromunun klinik özelliklerine ve tedavisine etkisinin araştırılması amaçlanmıştır.

Yöntem: 2019-2021 yılları arasında, çocuk romatoloji kliniğinde en az 6 ay takip edilen PFAPA sendromlu hastaların dosyaları geriye dönük olarak tarandı. Demografik veriler, klinik bulgular, atak sıklığı ve süresi, *MEFV* gen analiz sonuçları hazırlanan formlara kaydedildi.

Bulgular: Hastaların 43'ü (%51,8) kızdı. Ortanca semptom başlama yaşı 1,5 (0,3-7) yıl, tanı yaşı 3,5 (0,5-8) yıl ve tanı konulmasına kadar geçen süre 1,5 (0-7) yıldı. Altmış sekiz hastadan (%82) *MEFV* gen analizi gönderilmiş ve 25 hastada (%36) heterezigot mutasyon saptanmıştır. En sık saptanan mutasyon E148Q'dur. Ortalama tanı yaşı, semptom başlama yaşı, atak süresi ve atak sıklığı açısından iki grupta anlamlı fark gözlenmedi.

Sonuç: Bu çalışmada, ülkemizde oldukça sık görülen MEFV mutasyon taşıyıcılığının, hastalığın seyrine ve kolşisin yanıtına etkisi gösterilememiştir. Yine de AAA'nın ülkemizde sık görüldüğü göz önüne alınarak PFAPA sendromunun kliniği ve seyri ile uyuşmayan bulguları olan hastalarda *MEFV* gen analizinin istenmesi düşünülmelidir.

Anahtar Kelimeler: PFAPA sendromu, MEFV mutasyonu, periyodik ateş

Abstract

Objective: Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) is an autoinflammatory syndrome characterized by periodic fever, aphthous stomatitis, pharyngitis and adenopathy. Our country is located in a geography where Familial Mediterranean fever (FMF) is common. In this study, it was aimed to investigate the effect of MEFV mutation carrying on the clinical features and treatment of PFAPA syndrome.

Methods: The files of patients with PFAPA syndrome who were followed up in the pediatric rheumatology clinic for at least 6 months between 2019 and 2021 were retrospectively reviewed. Demographic data, clinical findings, frequency and duration of attacks, *MEFV* gene analysis results were recorded in the prepared forms.

Results: Forty-three (51.8%) of the patients were girls. The median age of symptom onset was 1.5 (0.3-7) years, the age at diagnosis was 3.5 (0.5-8) years, and the time to diagnosis was 1.5 (0-7) years. *MEFV* gene was analysed in 68 (82%) patients, and heterozygous mutations were detected in 25 (36%) patients. The most frequent mutation was E148Q. There was no significant difference between the two groups in terms of mean age at diagnosis, age of symptom onset, duration of attack and frequency of attacks.

Conclusion: In this study, the effect of MEFV mutation carriyng, which is very common in our country, on the course of the disease and the response to colchicine could not be demonstrated. Considering that FMF is common in our country, *MEFV* gene analysis should be considered in patients with findings inconsistent with the clinical and course of PFAPA syndrome.

Keywords: PFAPA syndrome, MEFV mutations, periodic fever

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Giriş

Periyodik ateş, aftöz stomatit, farenjit ve adenopati ile karakterize tablo olan periyodik ateş, aftöz stomatit, farenjit, adenit (PFAPA) otoenflamatuvar bir sendromdur. İlk olarak Marshall ve ark.[1] tarafından 1987 yılında tanımlanmıştır. Genellikle erken çocukluk döneminde görülür ve puberteden önce kendiliğinden düzelme eğilimindedir. Ateş atakları arasında çocuklar tamamen sağlıklıdır ve büyüme gelişmeleri normal olarak izlenir. Tanısal bir testi yoktur, tanı klinik özelliklere göre konulur.

Ailevi Akdeniz ateşi (AAA), tekrarlayan ateş ataklarına eşlik eden ve 6-72 saat süren, kendini sınırlayan serözit kliniği ile seyreder. Hastalık pirin proteinini kodlayan Mediterrenian Fever *(MEFV)* genindeki mutasyonlar sonucunda oluşan, kalıtsal, monogenik bir otoenflamatuvar tablodur.

Ülkemiz AAA'nın sık görüldüğü coğrafyada bulunmaktadır. Ozen ve ark.[2] ülkemizdeki çocukluk çağı AAA insidansını %0,095 (1/1071) olarak bildirmiştir. Sağlıklı bireylerde, MEFV mutasyonu taşıyıcılık oranı da yüksektir (%20).[3] Bu oranın yüksek olması çocukluk çağının en sık görülen otoenflamatuvar sendromu olan PFAPA'da da bu mutasyonların görülme sıklığını artırmaktadır.

Bu çalışmada MEFV mutasyonu taşıyıcılığının, PFAPA sendromunun klinik özelliklerine ve tedavisine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem

Çalışmamızda, 2019-2021 yılları arasında, çocuk romatoloji kliniğinde en az 6 ay takip edilen PFAPA sendromlu hastaların dosyaları geriye dönük olarak tarandı. PFAPA tanısı modifiye Marshall kriterlerine göre; tekrarlayan ateş ataklarına eşlik eden eksudatif tonsillit, aftöz stomatit veya lenfadenitten birinin bulunmasıyla konuldu. Hastalar ataklar arasında sağlıklıydı ve büyüme gelişme hızları normaldi.[4]

Hastaların en az iki atağı aynı doktor tarafından değerlendirilerek boğaz kültürü alındı. İmmün yetmezlik, siklik nötropeni, bakteriyel ve viral üst solunum yolu enfeksiyonu ekarte edildi. Etiyolojide herhangi bir neden saptanmayan hastalarda steroid yanıtı değerlendirildi. Steroid yanıtı, 1 mg/kg metilprednizolon tedavisi sonrasında 24 saat içerisinde ateşin düşmesi olarak kabul edildi. Steroid tedavisi tanısal amaçlı kullanıldı ve atak sıklığını artıracağından dolayı tedavide kullanılmadı.

Atak süresi, atak sıklığı ve steroid tedavisine yanıt değerlendirildi. Hastaların demografik verileri, klinik bulgular, akut faz belirteçleri ve genetik analiz sonuçları kaydedildi.

PFAPA ile uyumlu olmayan hasta yaşı, aile öyküsü, göğüs ağrısı, karın ağrısı, döküntü ve artrit varlığı pozitif genetik test belirleyicileri olarak kabul edilerek *MEFV* gen analizi gönderilen hastaların, sonuçları dosyalarından geriye dönük olarak kaydedildi.[5] *MEFV* gen analizi için 2, 3 ve 10. ekzon mutasyonları tarandı. Heterozigot MEFV mutasyonu olan ve mutasyonu olmayan PFAPA hastaları, klinik özellikler ve tedavi yanıtı açısından karşılaştırıldı.

Marshall tanı kriterlerini karşılamayan ve *MEFV* gen analizinde homozigot ya da birleşik heterozigot mutasyonu hastalar çalışma dışı bırakıldı.

Ailelere hastalık ve tedavi yöntemleri hakkında bilgi verildi. Tonsillektomi uygulananlar ve profilaktik kolşisin tedavisi kullananlar kaydedildi.

Kolşisin tedavisine yanıt, tedavi sonrası atakların olmaması olarak tanımlandı. Kısmi yanıt ise tedavi sonrası atak sıklığında ve süresinde azalma olarak belirlendi. Atak sıklığı ve süresinde belirgin değişiklik olmayan hastalar, yanıtsız olarak kabul edildi.

Bu çalışma için Ankara Şehir Hastanesi'nden 01.09.2021 tarihli etik kurul onayı alındı (E2-21-751). Çalışmamız geriye dönük olduğu için hastalardan onam alınmadı. Tüm prosedürler Helsinki Bildirgesi ilkelerine ve insan ve hayvan haklarına göre yapılmıştır.

İstatistiksel Analiz

İstatiksel değerlendirmede IBM SPSS Statistics 26.0 (SPSS, Inc, Chicago, IL, USA) kullanıldı. Normal dağılan sürekli değişkenler ortalama ± standart sapma, normal dağılmayan süreli değişkenler ortanca (minimum-maksimum) olarak hesaplandı. Kategorik değişkenler ki-kare testi ile değerlendirildi, sayılar ve yüzde olarak hesaplandı. Mann-Whitney U testi, bağımsız değişkenleri karşılaştırmada kullanıldı. Anlamlılık düzeyi $p < 0,05$ olarak kabul edildi.

Bulgular

Periyodik ateş, aftöz stomatit, farenjit, adenit sendromu tanısı konulan ve en az 6 ay takip edilen 83 hasta çalışmaya alındı. Hastaların 43'ü (%51,8) kızdı. Ortanca semptom başlama yaşı 1,5 (0,3-7) yıl, tanı yaşı 3,5 (0,5-8) yıl ve tanı konulmasına kadar geçen süre 1,5 (0-7) yıl olup detaylı demografik veriler, klinik bulgular ve uygulanan tedaviler Tablo 1'de verilmiştir.

Hastaların tamamında ateş mevcuttu. Ateşi takiben en sık görülen klinik bulgular sırasıyla kriptik tonsillit (%97,6), farenjit (%91,6) ve servikal lenfadenopati (%80,7) olarak bulundu. Baş ağrısı (%1,2) en az görülen semptom iken, artrit hastaların hiçbirinde yoktu. Tüm hastalarda ataklar esnasında bakılan akut faz belirteçleri yüksekti.

Altmış sekiz hastadan (%82) *MEFV* gen analizi gönderilmiş ve 25 hastada (%36) heterezigot mutasyon saptanmıştır. Hastaların 11'inde E148Q, 8'inde M694V, 2'sinde M680I, 2'sinde V726A, 1'inde R761H ve 1'inde P369S heterezigot mutasyonu saptandı.

PFAPA hastalarının 57'sine (%69) profilaktik kolşisin tedavisi başlandı ve 45 (%79) hastada kolşisine yanıt görüldü. Kolşisine kısmi yanıt veren 3 hastaya ve yanıt vermeyen 2 hastaya, ilaç kullanmayı istemeyen bir hastaya tonsillektomi önerildi. Tonsillektomi yapılan 6 hastanın tamamında, ameliyat sonrasında atak gözlenmedi. Yirmi altı hasta ilaçsız takip edildi ve ataklar kendiliğinden sonlandı.

Tablo 1. PFAPA sendromlu hastaların demografik, klinik verileri ve tedavi yanıtının değerlendirilmesi

Demografik veriler	**Hasta Sayısı**
Hasta sayısı	83
Kız cinsiyet, n (%)	43 (%51,8)
Semptom başlama yaşı (ay), ortanca (min-maks)	18 (4-84)
Tanı yaşı (yıl), ortanca (min-maks)	3,5 (0,5-8)
Tanıya kadar geçen süre (yıl), ortanca (min-maks)	1,5 (0-7)
Ateş süresi (gün), ortanca (min-maks)	4 (1-10)
Yıllık atak sayısı, ortanca (min-maks)	12 (4-24)
Takip süresi (ay), ortanca (min-maks)	6 (6-72)
Klinik veriler	
Ateş, n (%)	83 (100)
Kriptik tonsillit, n (%)	81 (97,6)
Aftöz stomatit, n (%)	38 (45,8)
Servikal lenfodenopati, n (%)	67 (80,7)
Farenjit, n (%)	76 (91,6)
Karın ağrısı, n (%)	26 (31,3)
Kusma/Mide bulantısı, n (%)	9 (10,8)
Artralji, n (%)	16 (19,3)
İshal, n (%)	4 (4,8)
Artrit, n (%)	0 (0)
Baş ağrısı, n (%)	1 (1,2)
Akut faz yüksekliği, n (%)	83 (100)
***MEFV* gen mutasyon%)**	25/68 (36)
E148Q/Normal	11 (44)
M694V/Normal	8 (32)
M680I/Normal	2 (8)
V726A/Normal	2 (8)
R761H/Normal	1 (4)
P369S/Normal	1 (4)
Tedavi ve tedaviye yanıt	
Kolşisin, n (%)	57 (69)
Kolşisin yanıt, n (%)	45 (79)
Kolşisin kısmi yanıt, n (%)	6 (%10,5)
Kolşisin yanıtsız, n (%)	6 (%10,5)
Tonsillektomi, n (%)	6 (7,2)
Tonsillektomi yanıt, n (%)	6 (100)

Maks: Maksimum, MEFV: Mediterranean fever, Min: Minimum, PFAPA: Periyodik ateş, aftöz stomatit, farenjit, adenit

MEFV mutasyonu saptanan hastaların %77'si, saptanmayan hastaların ise %35'i kız hastaydı. MEFV taşıyıcılığı olan grupta kız sıklığı daha fazlaydı fakat istatiksel olarak anlamlı fark bulunmadı (p=0,6). Ortalama tanı yaşı, semptom başlama yaşı, atak süresi ve atak sıklığı açısından iki grupta anlamlı fark gözlenmedi. Servikal lenfadenopati ve ishal, MEFV taşıyıcılığı olan hastalarda daha az sıklıkta saptandı, ancak istatiksel olarak anlamlı değildi (sırasıyla %8-%74, %0-%9,3). Diğer klinik özellikler ve tedavi açısından her iki grupta fark görülmedi. Bu iki grubun demografik verileri, klinik özellikleri ve uygulanan tedaviler açısından karşılaştırılması Tablo 2'de verilmiştir.

Tartışma

Periyodik ateş, aftöz stomatit, farenjit, adenit sendromu 3-8 haftada bir 3-6 gün süren ateş atakları ile karakterize poligenik/multifaktöriyel bir hastalıktır.[1] Çocukluk çağında dünyada en sık görülen periyodik ateş sendromudur. Bir başka periyodik ateş nedeni olan AAA'nın patogenezinden sorumlu *MEFV* gen mutasyonu taşıyıcılığı ülkemizde %20 oranındadır.[3] *MEFV* gen mutasyon varlığında, enflamatuvar bağırsak hastalığı, vaskülit, juvenil idiopatik artrit gibi hastalıkların seyri değişmektedir.[6] Geriye dönük ve kesitsel yaptığımız bu çalışmada PFAPA sendromlu hastalarda MEFV mutasyon taşıyıcılığının hastalığın kliniği, seyri ve tedavi seçenekleri üzerinde etkisi olmadığını belirledik.

Çalışmamızda semptomların başlama yaşından tanıya kadar geçen süre 1,5 yıl olarak saptandı ve bu süre önceki çalışmalara benzer olarak bulundu. Semptomların başlamasından, tanı konulmasına kadar geçen süre, önceki çalışmalarda da 18-24 ay arasında değişmekteydi.[7-9] PFAPA sendromu için tanı koydurucu klinik ve laboratuvar parametrelenin olmaması tanı sürecini uzatmaktadır. Atakların farklı hekimler tarafından değerlendirilmesi sonucu periyodisitenin fark edilememesi ya da ülkemizde ateşlenme nedeniyle yapılan başvuruların çoğunluğunun çocuk acil polikliniklerine yapılması, tanıda gecikmenin nedeni olabilir.

Çalışmamızdaki hastaların tamamında ataklarda ateş ve yüksek akut faz belirteçleri mevcuttu. Kriptik tonsillit (%97) ve farenjit (%91,6) en sık görülen klinik bulgulardı. Literatürden farklı olarak servikal lenfadenit (%80,7) sıklığı daha yüksek, aftöz stomatit (%45) sıklığı ise daha düşüktü.[8-9] Hastaların üçte birinde ateş ataklarına eşlik eden karın ağrısı bulunmaktaydı. Bu durum AAA hastalığı ve taşıyıcılığı sık olan ülkemizde tanı zorluğuna ve karışıklığına neden olabilir. Özellikle AAA'nın endemik olduğu bölgelerden biri ülkemizde, birbirinden tamamıyla farklı olan bu iki hastalık için tanımlayıcı çalışmalar mevcuttur. Adrovic ve ark.[10] AAA için tipik olan karın ağrısının, PFAPA ataklarına daha nadir

Tablo 2. *MEFV* gen mutasyonu olan ve olmayan PFAPA sendromlu hastaların karşılaştırılması

	Mutasyon var (n=25)	Mutasyon yok (n=43)	p
Kız cinsiyet n (%)	14 (77,7)	21 (35)	0,6*
Tanı yaşı (yıl), ortanca (min-maks)	4 (1-8)	3 (0,5-8)	0,5**
Semptom başlama yaşı (yıl), ortanca (min-mak)	1,5 (0,25-6,5)	1 (0,4-5)	0,8
Tanıya kadar geçen süre (yıl), ortanca (min-maks)	1,75 (0,3-4,5)	1,5 (0-7)	0,7
Ateş süresi (gün), ortanca (min-maks)	4 (2-9)	4 (2-10)	0,7
Atak sayısı (yıl), ortanca (min-maks)	12 (6-36)	12 (4-24)	0,1
Artralji, n (%)	4 (16)	6 (14)	0,8
Bulantı/Kusma, n (%)	4 (16)	5 (11,6)	0,6
Döküntü, n (%)	1 (4)	1 (2,3)	0,7
Farenjit, n (%)	24 (96)	38 (88,3)	0,28
Aftöz stomatit, n (%)	12 (48)	17 (39,5)	0,6
Kriptik tonsilit, n (%)	25 (100)	41 (95,3)	0,27
Servikal lenfadenopati, n (%)	20 (8)	34 (79)	1
İshal, n (%)	0 (0)	4 (9,3)	0,11
Karın ağrısı, n (%)	9 (36)	12 (28)	0,4
Kolşisin, n (%)	19 (76)	33 (76,7)	1
Kolşisin yanıt, n (%)	16 (84)	25 (75,7)	0,7
Tonsillektomi, n (%)	3 (12)	1 (2,3)	0,1
Tonsillektomi yanıt, n (%)	3 (100)	1 (100)	0,1

**Ki-kare testi, **Mann-Whitney U testi, Maks: Maksimum, MEFV: Mediterranean fever, Min: Minimum, PFAPA: Periyodik ateş, aftöz stomatit, farenjit, adenit*

eşlik ettiğini, mezenter lenfadenitten kaynaklandığı için akut serozite göre daha hafif olduğunu bildirmiştir. AAA ataklarında, PFAPA'dan farklı olarak üst solunum yoluna ait semptomun görülmediği bildirilmiştir. Bu nedenle PFAPA tanısı konulmadan önce hastaların atakta değerlendirilmesi, öyküyle birlikte detaylı fizik muayene yapılması tanıda oldukça kıymetlidir.

Tekrarlayan ateş ataklarına karın ağrısı, göğüs ağrısı, artrit ve döküntü semptomlarının eşlik ettiği ve semptomların erken yaşta başladığı hastalarda, diğer otoenflamatuvar hastalıkların ayırıcı tanısını yapabilmek için genetik analiz de oldukça önemlidir.[5]

Semptomların erken başlangıçlı olması (<2 yaş) ve PFAPA kliniğine uymayan atipik semptomlar varlığında *MEFV* gen analizi istenmiştir. Genetik analiz istenen 68 hastanın %63'ünde erken başlangıç, %37'sinde ise eşlik eden karın ağrısı, döküntü, ishal gibi atipik semptomlar bulunmaktaydı. *MEFV* gen analizi çalışılan 68 hastanın %36,7'sinde heterezigot mutasyon saptandı. Heterozigot mutasyon saptanan hastaların hiçbirinde AAA'yı düşündürecek klinik bulgular yoktu. Heterozigot MEFV mutasyonu ve PFAFA birlikteliği için önceki çalışmalarda bu oran %24-65 arasında değişmektedir.[11,12] Gunes ve ark.'nın[11] *MEFV* gen analizi yapılan 231 PFAPA hastasını incelediği çalışmada hastaların 57'sinde (%24,7) MEFV taşıyıcılığı olduğu saptandı. MEFV taşıyıcılığı olan hastaların; %40'ında M694V, %12,2'sinde E148Q olduğunu gösterdiler. Bu çalışmadan farklı olarak bizim çalışmamızda E148Q (%44) taşıyıcılığı, M694V (%32) taşıyıcılığından daha sık görüldü. Bunun nedeni mutasyonların dağılımında bölgesel farklılıklar olması ve sağlıklı Türk toplumunda en sık görülen (%12) heterozigot mutasyonun E148Q olması ile açıklanabilir.[3]

AAA ile ilişkili MEFV mutasyonlarının, bazı hastalıkların ve klinik durumların seyrini etkilediği gösterilmiştir. Yalçınkaya ve ark.'nın[13] 29 poliarteritis nodosa (PAN) hastasını içeren serisinde, hastaların %38'inde *MEFV* geninde mutasyon bulunmuştur ve MEFV mutasyonunun PAN gelişimi için risk faktörü olabileceği öne sürülmüştür. Ülkemizde immünoglobulin A vasküliti olan 1.120 çocuk hastayı içeren bir çalışmada, MEFV mutasyon taşıyıcılığı %15,6 olarak bildirilmiştir. Taşıyıcıların yarısına yakını ekzon 10 mutasyonudur. Ekzon 10 mutasyonu taşıyan grupta; karın ağrısı, artrit, skrotal tutulum, relaps oranı ve yüksek akut faz belirteçleri daha sık görülürken, ekzon 2 ve 3 mutasyonu olan grupta anlamlı fark gözlenmemiştir.[14] Zhong ve ark.'nın[15] sistemik juvenil idiopatik artrit hastalarında, MEFV mutasyon taşıyıcılığının etkisini incelediği çalışmasında, M694V taşıyıcılığı risk faktörü olarak gösterilirken, ekzon 2 ve 3 taşıyıcılığının risk faktörü olmadığı bildirilmiştir. Yakın zamanda Özdel ve ark.[7] PFAPA sendromu olan 70 hastada, %47 oranında MEFV mutasyon taşıyıcığı bulmuştur. En sık saptanan mutasyon M694V'dir. Mutasyonu olan hastaların atak süresi ve sıklığının daha fazla, bununla birlikte kolşisin tedavisine yanıtın daha iyi olduğu görülmüştür. Başka bir çalışmada diğer varyantlara oranla ekzon 10 mutasyonu olan hastaların,

PFAPA başlangıç yaşının daha büyük ve atak sürelerinin daha kısa olduğu bildirilmiştir.[16] Bunun tersine literatürde mutasyon taşıyıcılığının hastalığın kliniği ve tedavisi üzerine etkisinin olmadığını bildiren çalışmalar vardır.[17] Bizim çalışmamızda mutasyonu olan ve olmayan iki grup arasında, semptom süresi, sıklığı, klinik bulgular ve kolşisin tedavisine yanıt açısından anlamlı fark gözlenmedi. Bunun nedeni çalışmamızda en sık saptanan mutasyonunun, bir 2. ekzon mutasyonu olan E148Q olması ile açıklanabilir. Daha fazla ekzon 10 ve diğer mutasyon taşıyıcılarını içeren çalışmaların yapılması, mutasyonun PFAPA sendromu üzerindeki etkisini belirlemede yardımcı olacaktır.

PFAPA sendromunun tedavisine yönelik fikir birliği bulunmamaktadır. Tedavi seçenekleri merkezlere göre değişmektedir. CARRA (Childhood Arthritis and Rheumatology Research Alliance) çalışma grubunun PFAPA tedavisine yönelik yayınladığı çalışma raporunda, semptomatik tedavi için antipiretik veya kortikosteroid, profilaksi için simetidin veya kolşisin, cerrahi tedavi olarak da tonsillektominin seçilebileceğini bildirmiştir.[18]

Profilakside kolşisin kullanımının etkili olduğunu belirten çalışmalar bulunmaktadır. Dusser ve ark.[19] kolşisin profilaksisi başladığı 25 PFAPA hastasının 9'unda atak sıklığının 2 atak/yılın altına indiğini ve atakları azalan grupta MEFV mutasyon taşıyıcılığı oranının, yanıtsız olan gruba göre daha fazla olduğunu bildirmiştir. Başka bir çalışmada profilaktik kolşisin başlanan 356 PFAPA hastasının %85'inde, atak sıklığında anlamlı bir azalma görülmüş ve bu oran MEFV mutasyon taşıyıcısı olan grupta istatiksel açıdan anlamlı olarak yüksek bulunmuştur.[11] Özdel ve ark.[7] MEFV mutasyonunun PFAPA'nın seyri ve şiddeti üzerine etkisini araştırdığı bir çalışma da, heterozigot MEFV mutasyonu olan grupta kolşisin profilaksisinin atak sıklığını ve uzunluğunu anlamlı derecede azalttığı bildirilmiştir. Çalışmamızda 57 (%69) hastaya kolşisin profilaksisi başlanmıştı ve profilaksi alan hastaların %79'unda kolşisin yanıtı görüldü. Kolşisin tedavisine yanıtsız 6 hastanın tamamında tonsillektomi yapıldı ve sonrasında atak görülmedi. Kolşisin kullanımının, atak sıklığını azalttığını gösteren başka çalışmalarda bulunmaktadır.[9,11,20] Bununla birlikte medikal tedaviye dirençli olgularda ise tonsillektomi etkili bir yöntemdir.[21,22]

Çalışmanın Kısıtlılıkları

Bu çalışmanın kısıtlılığı tek merkezli ve geriye dönük olarak yapılmasıdır. *MEFV* gen mutasyonun PFAPA sendromu üzerine etkisinin net anlaşılabilmesi için daha geniş kohortlu ve çok merkezli çalışmalara ihtiyaç vardır.

Sonuç

Sonuç olarak bu çalışmada, ülkemizde oldukça sık görülen MEFV mutasyon taşıyıcılığının hastalığın seyrine ve kolşisin yanıtına etkisi gösterilememiştir. AAA sıklığı göz önüne alınarak PFAPA sendromunun başlangıç yaşı, kliniği ve seyri ile uyuşmayan bulguları olan hastalarda *MEFV* gen analizinin istenmesi düşünülmelidir. Kolşisin profilaksisi, literatürle uyumlu olarak bizim çalışmamızda da etkili görülmüştür. Cerrahinin bir seçenek olamayacağı hastalarda tedavi seçenekleri arasında değerlendirilebilir.

Ayrıca PFAPA sendromu, çocukluk çağının en sık periyodik ateş nedenidir ancak tanı alması gecikebilir. Bu nedenle gereksiz ve sık antibiyotik kullanımını engellemek için, PFAPA sendromu akılda tutulmalı, çocuk acil ve genel çocuk doktorlarının farkındalığı artırılmalıdır.

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Serum amyloid A may be a potential biomarker for vasculitis

Serum amiloid A vaskülit değerlendirmede potansiyel bir biyobelirteç olabilir

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Abstract

Objective: There are still unmet needs for ideal biomarkers for management of vasculitis. This study aimed to analyze the potential utilities of the S100A12 and Serum Amyloid A (SAA) as diagnostic or activity-specific biomarkers of vasculitis.

Methods: A total of 18 clinically active vasculitis patients [giant cell arteritis (n=6), Takayasu arteritis (n=6), and granulomatosis with polyangiitis (n=6)] and 12 healthy controls (HCs) were enrolled. Disease activity was assessed using the Birmingham disease activity score (BVAS). The correlation between SAA, S100A12, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and BVAS was analyzed. Receiver operating characteristics analysis was used to evaluate the diagnostic utility of each marker.

Results: Patients with active vasculitis had significantly higher levels of CRP, S100A12, and SAA, and higher ratios of NLR and PLR compared to HCs. S100A12 did not correlate with disease activity and other biomarkers. SAA had the most significant correlation with BVAS ($r=0.63$, $p<0.05$). All biomarkers have the capability of effectively discriminating patients with vasculitis from HCs. The area under the curve (AUC) of CRP, SAA, S100A12, NLR and PLR was 0.95 (95% confidence interval 0.88-0.99), 0.82 (0.65-0.98), 0.77 (0.60-0.95), 0.90 (0.79-0.99) and 0.89 (0.76-0.99), respectively. SAA had better AUC compared to S100A12. A level of 7.5 mg/L (sensitivity 78%, specificity 83%) for SAA and 24 ng/mL (sensitivity 89%, specificity 67%) for S100A12 were found as the optimum cut-off points for defining active vasculitis.

Conclusion: SAA could be proposed as a more potential biomarker than S100A12. Both discriminative value for active vasculitis and correlation with disease activity of SAA were more significant than S100A12. Our results point to the need of further longitudinal researches regarding utility of SAA and SAA-like proteins in the assessment of vasculitis.

Keywords: Serum amyloid A, S100A12, vasculitis, biomarker

Öz

Amaç: Vaskülitlerin takibinde ideal biyobelirteç için hala karşılanmamış ihtiyaçlar vardır. Bu çalışmada S100A12 ve Serum Amilod A'nın (SAA) vaskülitlerin tanı veya hastalık aktivasyonunda biyobelirteç olarak geçerliliklerini değerlendirmeyi amaçladık.

Yöntem: Klinik olarak aktif 18 vaskülit hastası [dev hücreli arterit (n=6), Takayasu arteriti (n=6) ve granülomatoz polianjit (n=6)] ve 12 sağlıklı kontrol çalışmaya dahil edildi. Hastalık aktivitesi Birmingham hastalık aktivite skoru (BVAS) kullanılarak değerlendirildi. SAA, S100A12, C-reaktif protein (CRP), nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve BVAS arasındaki korelasyon araştırıldı. Her biyobelirteçin tanısal geçerliliğini değerlendirmek için alıcı işlem karakteristiklerinin analizi yapıldı.

Bulgular: Aktif vaskülitli hastalarda, sağlıklı kontrollere kıyasla CRP, S100A12 ve SAA düzeyleri ile NLR ve PLR oranları anlamlı derecede yüksek saptandı. S100A12, hastalık aktivitesi ve diğer biyobelirteçler ile korele değildi. Hastalık aktivitesi ile en anlamlı korelasyona SAA'nın sahip olduğu saptandı ($r=0,63$, $p<0,05$). Tüm biyobelirteçlerin vaskülit hastalarını sağlıklı kontrollerden etkin bir şekilde ayırt edebildikleri saptandı. Eğri altındaki alan (EAA); CRP, SAA, S100A12, NLR ve PLR için sırasıyla 0,95 (%95 güven aralığı 0,88-0,99), 0,82 (0,65-0,98), 0,77 (0,60-0,95), 0,90 (0,79-0,99) ve 0,89 (0,76-0,99) olarak saptandı. SAA, S100A12 ile karşılaştırıldığında daha iyi bir EAA'ya sahipti. SAA için 7,5 mg/L (duyarlılık %78, özgüllük %83) ve S100A12 için 24 ng/mL (duyarlılık %89, özgüllük %67) aktif vaskülit tanımlamak için en uygun değerler olarak saptandı.

Sonuç: SAA, S100A12'den daha potansiyel bir biyobelirteç olarak önerilebilir. SAA'nın, hem aktif vaskülit ayırt edici özelliği hem de hastalık aktivitesi ile korelasyonu S100A12'den daha anlamlı olarak saptandı. Sonuçlarımız, SAA ve SAA benzeri proteinlerin vaskülit değerlendirmesinde kullanımıyla ilgili daha ileri araştırmalara ihtiyaç duyulduğunu göstermektedir.

Anahtar Kelimeler: Serum amiloid A, S100A12, vaskülit, biyobelirteç

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Introduction

Vasculitides are a heterogeneous group of diseases, characterized by inflammation of blood vessels, causing severe tissue destruction and organ/system failure. Given the variability of the location and size of the involved vessels, there is a great diversity of clinical presentation and severity. This heterogeneity and insidious natural history make the management of vasculitis challenging.[1] Vasculitis related damage causes significant mortality, morbidity and economic burden.[2] The prompt and accurate treatment of patients regarding their organ involvement is crucial to prevent damage. Therefore, identifying the disease and relapse is quite important. Despite our increasing knowledge about vasculitis, there are still unmet needs for ideal biomarkers. Available markers, including antineutrophil cytoplasmic antibodies,[3] erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are unreliable and inaccurate for diagnosis, assessing disease activity and defining relapse. For instance ESR and CRP can be quite normal in some clinically active Takayasu and histopathologically active giant cell arteritis (GCA) patients.[4-6]

Serum amyloid A (SAA) is an acute-phase protein that belongs to the apolipoprotein family. SAA is synthesized primarily in the liver by activated monocytes and macrophages in response to proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α).[7] The S100 protein family is a unique class of calcium-binding proteins which are expressed and released at local sites of inflammation.[8-10] Members of the S100 protein family are the most abundant danger-associated molecular patterns (DAMPs), which participated in an inflammatory reaction during stress, and associated with various receptors (e.g. Toll-like receptor 4) and advanced glycosylation end products (RAGE).[11] S100A12 is more restricted to granulocytes with several important extracellular roles including activating the NF-κB pathway, which results in the expression of the proinflammatory cytokines and adhesion molecules.[12,13] The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have emerged as a markers of inflammation and are found to be a useful indices for estimating the current inflammatory burden and disease activity of vasculitis.[14,15]

The capability of neither SAA nor S100A12 in the assessment of vasculitis has not been fully elucidated. In particular, we are not aware of any study that compares S100A12 and SAA in that field. In light of this background, this study analyzed the plasma levels of SAA and S100A12 in patients with active vasculitis and healthy controls (HCs) and we aimed to investigate their correlation with disease activity and other biomarkers, and to identify the potential utilities as identifying diagnosis or relapse in patients with GCA, Takayasu arteritis, and granulomatosis with polyangiitis (GPA).

Materials and Methods

Eighty-five consecutive vasculitis patients, whether newly diagnosed or relapsing, were admitted to the clinic during the study period. The inclusion criterion was clinically active disease. Exclusion criteria were refusal to participate, having inactive disease, other autoimmune conditions or malignancies, being under 18 years of age and being pregnant. Sixty-seven of them were excluded because they met the exclusion criteria or reached the target number per group. Total of eighteen consecutive active vasculitis patients (six patients for each) who fulfilled the American College of Rheumatology classification criteria for GCA,[16] Takayasu arteritis[17] and GPA[18] were enrolled in this cross-sectional study. Twelve healthy controls (HCs), who had no signs or symptoms that direct an inflammatory disease, participated in this study (Figure 1). The study was conducted after the ethical approval of the local ethics committee (approval number: 98, date: 27/01/2020) complied with the declaration of Helsinki. Informed consent was obtained from all patients and HCs before the initiation of the study.

Demographic data were collected. The disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS v3), which is composed of nine major items.[19] BVAS>0 was accepted as active disease. Conventional inflammatory biomarkers included CRP, NLR and PLR analyzed by use of in-house method. CRP was studied with the nephelometric method and under 5 milligrams per liter (mg/L) is considered normal. Peripheral venous samples were obtained; after clothing, the tubes were centrifuged at 3000x for 5 min, and sera were stored at -80^{0}C for further analyses. S100A12 and SAA were analyzed by enzyme-linked immunosorbent assay (ELISA) methods. Human S100A12 was studied with a commercially available ELISA kit (Boster Immunoleader En Rage PicoKineTMCA, USA). The assay detection range was 31.2 pg/mL-2000 pg/mL and sensitivity was <10 pg/mL. SAA was studied with commercially available SAA ELISA Kit (Assay Pro, MO, USA). The assay detection range was 0.125-2 ug/mL and sensitivity was 6 ug/mL.

Statistical Analyses

We conducted all statistical analyses with SPSS software (version 15 for Windows; SPSS INC., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine the distribution of data. Continuous variables were expressed as a median

values with minimum-maximum (min-max). Categorical data are summarized as absolute frequencies and percentages. We compared the biomarker levels across different subgroups by either Kruskal-Wallis (>2 groups) or Mann-Whitney U (2 groups) tests, when appropriate. Spearman's correlations were calculated to define the association between biomarkers and disease activity. Receiver operating characteristic (ROC) curve analysis was performed to establish the optimal discriminatory threshold for identifying patients with vasculitis from HCs. A two-tailed p-value <0.05 was considered statistically significant.

Results

Table 1 details the characteristics and biomarker levels of both groups. Patients were significantly older than HCs [52 (28-80) vs. 36 (26-56), respectively, p=0.01]. Gender distribution and body mass index (BMI) were comparable. Median BVAS of the patients was 4 (min-max, 1-14). CRP, SAA, S100A12, NLR and PLR were significantly higher in patients than in HCs [61.4 (3-306) vs. 2.2 (1.24-4.15), p<0.001; 26.0 (0.07-42) vs. 2.0 (0.49-15.62), p=0.004; 60.8 (17.1-125.3) vs. 21.4 (16.1-82.2), p=0.013; 5.1 (1.3-20.8) vs. 1.6 (1.2-4.5) p<0.001; and 304.5 (72.2-1322.5) vs. 107.0 (67.8-230.8), p<0.001, respectively].

The patient population comprised six patients with GCA, Takayasu arteritis and GPA. Further subgroup analyses showed a statistical difference between these groups in terms of CRP, SAA, NLR, and PLR, unlike S100A12 (p=0.083) (Table 2). Correlation analysis between biomarkers and BVAS were performed separately for the patients and HCs.

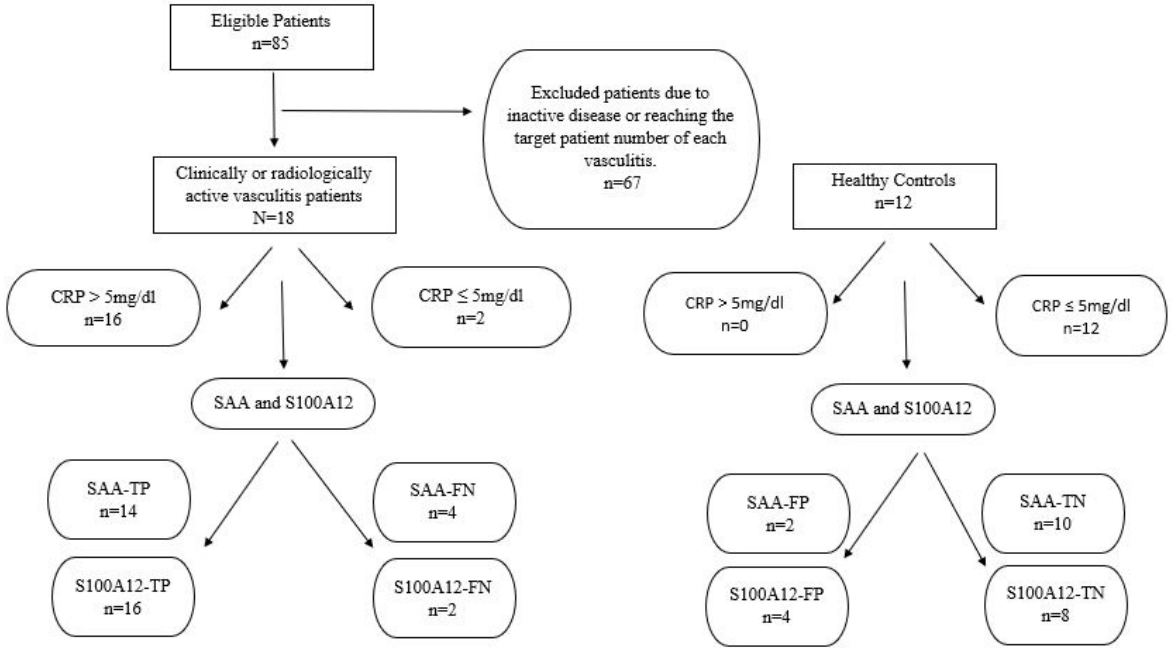

Figure 1. Flowchart of the study
CRP: C-reactive protein, FN: False negative, FP: False positive, SAA: Serum amyloid A, TN: True negative, TP: True positive

Table 1. Demographics and biomarker levels of active vasculitis patients and the control group

Variable	Patients (n=18)	Healthy controls (n=12)	p-value
Age, years	52 (28-80)	36 (26-56)	0.01
Female, %	56%	50%	0.76
BMI, kg/m^2	24.8 (18.2-33.2)	27.7 (18.0-37.8)	0.16
CRP (mg/L)	61.4 (3-306)	2.2 (1.24-4.15)	<0.001
SAA (mg/L)	26.0 (0.07-42)	2.0 (0.49-15.62)	0.004
S100A12 (ng/mL)	60.8 (17.1-125.3)	21.4 (16.1-82.2)	0.013
NLR	5.1 (1.3-20.8)	1.6 (1.2-4.5)	<0.001
PLR	304.5 (72.2-1322.5)	107.0 (67.8-230.8)	<0.001

BMI: Body mass index, CRP: C-reactive protein, SAA: Serum amyloid A, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio. p<0.05 is considered as significant. Numerical data was showed as median (min-max)

There was no correlation between biomarkers in the HCs (p>0.05, data not shown). SAA has a high positive correlation with CRP, whereas NLR and PLR have a moderate positive correlations (Table 3, r=0.8, p<0.001; r=0.5, p=0.035; and r=0.49, p=0.038, respectively). S100A12 was highly correlated with CRP only in GCA patients (r=0.83, p<0.05,). Moreover, CRP, SAA and NLR were moderately correlated with BVAS for all patients (r=0.57, p=0.013; r=0.63, p=0.005; and r=0.52 p=0.028 respectively). There was no correlation between BVAS and S100A12.

The area under the curve (AUC) of CRP, SAA, S100A12, NLR and PLR was found to be significantly greater than the reference line [p<0.05, AUC (95% CI): 0.95 (0.88-0.99), 0.82 (0.65-0.98), 0.77 (0.60-0.95), 0.90 (0.79-0.99) and 0.89 (0.76-0.99), respectively]. A level of 7.5 mg/L (sensitivity 78%, specificity 83%) for SAA and 24 ng/mL (sensitivity 89%, specificity 67%) for S100A12 were found as the optimum cut-off points for diagnosing vasculitis (Figure 2). There were two patients with active vasculitis who had normal CRP levels. Both of them had GCA and their BVAS was found 2 and 3. SAA was higher than the defined cut off limit in one patient (25.44 mg/L) while S100A12 was higher than the defined cut off limit (81.44 and 37.22 ng/mL) in both patients.

Discussion

In view of challenges in the management of vasculitis and not having an ideal biomarker to diagnose, and to determine the disease activity and relapses, it is important to study new biomarkers. Especially, biomarkers, which can assess

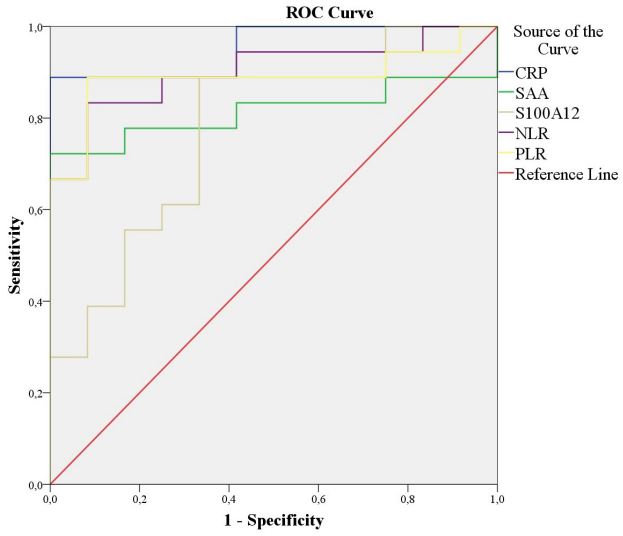

Figure 2. Receiver operating characteristic curves for tested biomarkers for the diagnosis of vasculitis
CRP: C-reactive protein, FN: False negative, FP: False positive, ROC: Receiver operating characteristic, SAA: Serum amyloid A, TN: True negative, TP: True positive

Table 2. Demographics, biomarker levels and disease activity of groups

	GCA (n=6)	Takayasu (n=6)	GPA (n=6)	Healthy (n=12)	p-value
Age, years	66 (52-80)	41 (28-52)	51.6 (32-76)	36 (26-56)	0.004
Female, %	17%	100%	50%	50%	0.04
CRP (mg/L)	80.3 (8.9-191.0)	7.5 (3-53.8)	129.5 (51.2-306.0)	2.2 (1.24-4.15)	0.001
SAA (mg/L)	21.8 (0.42-32.0)	10.1 (0.07-39.1)	30.5 (25.1-42.0)	2.0 (0.49-15.62)	0.004
S100A12 (ng/mL)	49.8 (17.1-87.3)	77.9 (17.6-114.8)	55.7 (27.6-97.7)	21.4 (16.1-82.2)	0.08
NLR	3.0 (1.3-20.8)	5.2 (1.6-20.8)	9.5 (4.6-16.1)	1.6 (1.2-4.5)	0.001
PLR	246.1 (72.2-1117.5)	285.5 (99.6-1322.5)	536.9 (169.2-844.4)	107.0 (67.8-230.8)	0.002
BVAS	3.5 (2-5)	3 (1-6)	7 (5-14)	NA	0.006

BVAS: Birmingham vasculitis activity score, CRP: C-reactive protein, GCA: Giant cell arteritis, GPA: Granulomatosis with polyangiitis, NA: not applicable, NLR=Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SAA: Serum amyloid A, p<0.05 is considered as significant. Numerical data was showed as median (min-max)

Table 3. Correlations between biomarkers and disease activity

	CRP	SAA	S100A12	NLR	PLR
BVAS	**0.57***	**0.63***	0.21	**0.52***	0.44
CRP	1	**0.80**	0.33	**0.50**	**0.49**
SAA	**0.80**	1	0.41	**0.66**	**0.60**
S100A12	0.33	0.41	1	0.22	0.38

BVAS: Birmingham vasculitis activity score, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SAA: Serum amyloid A.
Bold indicating significance of correlation at the 0.05 level (2-tailed)

disease activity reliably and detect relapse, are urgently needed in clinical practice. S100A12 and SAA have not been fully analyzed for this purpose. In particular, this is the first study that compares SAA and S100A12. Here, we report a preliminary study, which analyzed the utility of SAA and S100A12 on discriminating patients with active vasculitis, whether at initial presentation or relapse, from healthy controls, and investigated the correlation between disease activity and S100A12 and SAA.

S100A12 did not correlate with disease activity and had a significant but a lower capability of discriminating active vasculitis from HCs among all biomarkers. This is noteworthy since S100 proteins have received much attention recently. The S100 protein family is a unique class of calcium-binding proteins which are expressed and released at local sites of inflammation.[7-9] Besides S100A12 and S100A8/9 proteins have been shown to be useful biomarkers of disease activity in some rheumatic diseases in many studies.[20-25] However, there are some conflicts about S100A12. On one hand, S100A12 was found to be elevated in patients with active MPO-ANCA-associated glomerulonephritis, Behçet's disease and GCA compared to vasculitis patients or/and HCs. Moreover, S100A12 was correlated with disease activity and pathologic activity scores[26] and was strongly expressed in the pathological examination of GCA, and Behçet's disease.[26-28] On the second hand, S100A12 was found similar in active and inactive Takayasu patients.[29] Above all, S100A12 was found to be related to aortic aneurysms and wall repair itself, irrespective of inflammatory diseases.[30,31] The major concern is the association between S100A12 and vessel wall damage itself, since this makes it impossible to discriminate between the active and inactive patients, which is an urgent need in clinical practice

Both the discriminative capability of active vasculitis from HCs and the correlation with disease activity of SAA was more significant than S100A12. SAA may be a reliable biomarker than S100A12 for assessing patients with vasculitis. This is somehow expected since all available data about SAA, even very few, supported our results; SAA might be related to the pathogenesis of GCA[32] and was a more reliable biomarker than CRP in patients with active GCA and MPO-ANCA associated vasculitis.[33,34] Moreover, SAA was elevated in Takayasu patients[35] and decreased in treatment responders,[36] unlike S100A12. Moreover, this study supported the knowledge that CRP can be quite normal in some clinically active Takayasu and histopathologically active GCA patients,[4-6] as our two clinically active GCA patients had normal CRP levels. Though SAA was highly correlated with CRP, SAA effectively differentiated one of these patients from healthy controls. Although the knowledge regarding SAA and vasculitis is more enlightening and precise then S100A12, SAA fell out of favor. However, according to our results, this should be reconsidered and further research should be conducted.

Study Limitations

A small sample size and lack of follow-up assessment were the major limitations of our study. The main limitations were the lack of diseased controls (mimickers) and inactive vasculitis patients. Moreover, BVAS is not the perfect-activity assessment measure for patients with GCA and Takayasu arteritis.

Conclusion

Consequently, this is the first study that compares SAA and S100A12 as biomarkers in vasculitis patients and has results to widen the research fields. Both discriminative capability of active vasculitis and correlation with disease activity of SAA were more significant than S100A12. Our results draw attention to the SAA as a biomarker of vasculitis and point to the need of further longitudinal research regarding the diagnostic and assessment utility of SAA and SAA-like proteins for vasculitis.

Ethics

Ethics Committee Approval: The study was conducted after the ethical approval of the local ethics committee (Gazi University Ethics Committee, approval number: 98, date: 27/01/2020) complied with the declaration of Helsinki.

Informed Consent: Informed consent was obtained from all patients and HCs before the initiation of the study.

Peer-review: Externally and peer reviewed.

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

Financial Disclosure: The author declare that they have no relevant financial disclosures.

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Case Report / Olgu Sunumu

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CPPD-related pseudoneuroarthropathy in a patient with myelodysplastic syndrome

Miyelodisplastik sendromlu bir olguda CPPD ilişkili psödonöroartropati

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Abstract

The calcium pyrophosphate deposition (CPPD) disease is a common form of crystal arthropathy. It usually affects elderly patients. The clinical and radiological features of CPPD vary widely, so CPPD is a great mimicker of other musculoskeletal conditions. Asymptomatic and destructive forms can present at the same time in the same patients. Several diseases have been proposed to be related to CPPD, but hematologic disorders have not been reported to occur concurrently. Charcot arthropathy (CA) is associated with neuropathy and is characterized by erosive joint disease. Here, we report an interesting CPPD case presenting as pseudo-CA in a patient with myelodysplastic syndrome.

Keywords: Chondrocalcinosis, pseudoneuroarthropathy, myelodysplastic syndromes, pyrophosphate arthropathy, pseudogout

Öz

Kalsiyum pirofosfat depozisyon (CPPD) hastalığı kristal artropatilerin yaygın bir formudur. Genellikle yaşlı bireyleri etkiler. CPPD'nin radyolojik ve klinik özellikleri değişken olup bu yüzden kas-iskelet sistemi hastalıklarının iyi bir taklitçisidir. Asemptomatik ve destrüktif formları aynı hastada aynı anda bulunabilir. CPPD ilişkili birçok hastalık tanımlanmış olup hematolojik hastalıklarla ilişkisine dair kanıt yoktur. Charcot artropatisi (CA) nöropatik hastalıklarla ilişkisi olup eklem erozyonları ile karakterizedir. Makalemizde miyelodisplastik sendromlu bir hastada psödo-CA ile prezente olan enteresan bir CPPD olgusunu sunuyoruz.

Anahtar Kelimeler: Kondrokalsinozis, psödonöroartropati, miyelodisplastik sendrom, pirofosfat artropatisi, psödogut

Introduction

The calcium pyrophosphate deposition (CPPD) disease is a crystal arthropathy that is caused by calcium pyrophosphate dihydrate (CPP) crystals. The clinical spectrum varies widely among patients; acute or chronic, monoarticular or polyarticular, and destructive or non-destructive patterns are possible.[1] CPPD prevalence is 4.5% in the adult United Kingdom population and correlates with increasing age (aged 55-59: 3.7%, aged 80-84: 17.5%); the presentation is uncommon in patients younger than 50 years of age. There was no difference in prevalence between men and women.[2] In the literature, the first patient with CPPD is reported by McCarty DJ and coworkers in 1961 by the identification of CPP crystals from arthritic knee joints.[3]

In the following years, the other clinical forms were defined and two characteristic issues stood out for CPPD; it has a heterogeneous clinical spectrum and is a good mimicked for other rheumatic diseases. McCarty DJ classified CPPD into 6 forms; type A: Pseudogout, type B: Pseudorheumatoid arthritis, type C or D: Pseudoosteoarthritis with acute attacks or without inflammation, type E: Asymptomatic CPPD, and type F: Pseudoneuropathic form.[4] In 2011, Europan League Against Rheumatism (EULAR) suggested "asymptomatic CPPD, osteoarthritis with CPPD, acute CPP crystal arthritis, and chronic CPP crystal arthritis" as a definitions because the term "pseudo" may confuse.[5] For example, some patients can have different clinical forms of CPPD simultaneously according to McCarty's classification.[1] Chondrocalcinosis (hyaline cartilage or fibrocartilage) is

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the main hallmark of CPPD and usually appears; synovial/capsule/tendons/ligaments/bursae calcifications, tumoral deposition, joint space narrowing, subchondral sclerosis and cysts, osteophytes, osseous fragmentation, and bone erosions are the other signs of CPPD. The most commonly affected joint is the knee, but the ankle is an uncommon site for CPPD.[6] In this article, we report an intriguing CPPD case who of bilateral ankle/foot arthritis.

Case Report

In May 2021, a 64 years-old male hematology inpatient with a recent diagnosis of myelodysplastic syndrome (MDS) presented with a two month history of swollen ankles and consulted with our rheumatology department. He was an asymptomatic hepatitis-B virus (HBV) carrier. His family history was unremarkable. He never smoked and did not use alcohol or any illicit drug.

On physical examination, bilateral warm, erythematous, very painful ankle arthritis and pale conjunctiva were examined; there were no other signs or symptoms. Vital signs were normal. Arthritis began acutely and progressed during the two months. There wasn't any history of gastrointestinal or genitourinary tract infection in the last month. Serum laboratory tests were as follows: Glucose, urea, creatinine, electrolytes (including sodium, calcium, potassium, phosphate, and magnesium), procalcitonin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, direct and indirect bilirubin levels were in normal ranges; white blood cell count: 1.390/µL (with 26.6% neutrophils and 71.4% lymphocytes), hemoglobin (Hb): 7.1 g/dL and platelet count: 89.000/µL; uric acid: 3 mg/dL, erythrocyte sedimentation rate: 64 mm/h and C-reactive protein (CRP): 150 mg/L; rheumatoid factor, anti-cyclic citrulline peptide antibody, and antinuclear antibody were negative (which were assessed by ELISA); HBsAg: Positive and HBV-DNA: Negative; other viral serology tests for hepatitis C virus and HIV were negative. Complete urinalysis and plain chest X-ray were normal. The feet's X-rays (Figure 1) showed bilateral destructive and erosive changes suggesting Charcot arthropathy (CA).

To identify the cause of neuroarthropathy, some laboratory tests were performed; the serological test for syphilis was negative and electromyography was normal. Pedal pulses were easily palpable. Anteroposterior radiography of the knees was performed since the knee is the most affected joint for CPPD disease; bilateral (asymptomatic) knee chondrocalcinosis and meniscal calcification were detected (Figure 1). There was no family history of CPPD, and CPPD-associated metabolic diseases such as hemochromatosis, hyperparathyroidism, hypothyroidism, hypomagnesemia, or hypophosphatasia[7] were detected in additional tests. In conclusion, we diagnosed our patient as 'pseudoneuropathic form of CPPD according to McCarthy's definition and as chronic CPP arthritis according to the EULAR definition. In the first-line treatment, methylprednisolone 16 mg/day (P.O.) treatment was initiated for two weeks but the patient had no response to corticosteroid therapy. Therefore, colchicine 1 mg/day (P.O.) was given as a second-line option. After two weeks of colchicine therapy; the arthritis completely resolved and he could walk unaided. The erythrocyte sedimentation rate regressed to 36 mm/h and CRP regressed to 24 mg/L. Written informed consent was obtained from the patient.

Discussion

CA is associated with neuropathy and is characterized by bone and joint erosions, which may cause deformities. The most common etiological disease for CA is diabetes mellitus (DM); syphilis (tabes dorsalis), leprosy, alcoholism, syringomyelia, peripheral nerve injuries, or congenital absence of pain sensation is the other associated factors and joint involvement can vary according to etiology.[8] The absence of other CA-associated factors was the greatest clue in this study and joint involvement was similar to DM, but fasting blood glucose and glycosylated hemoglobin (HbA1C) levels were within normal ranges.

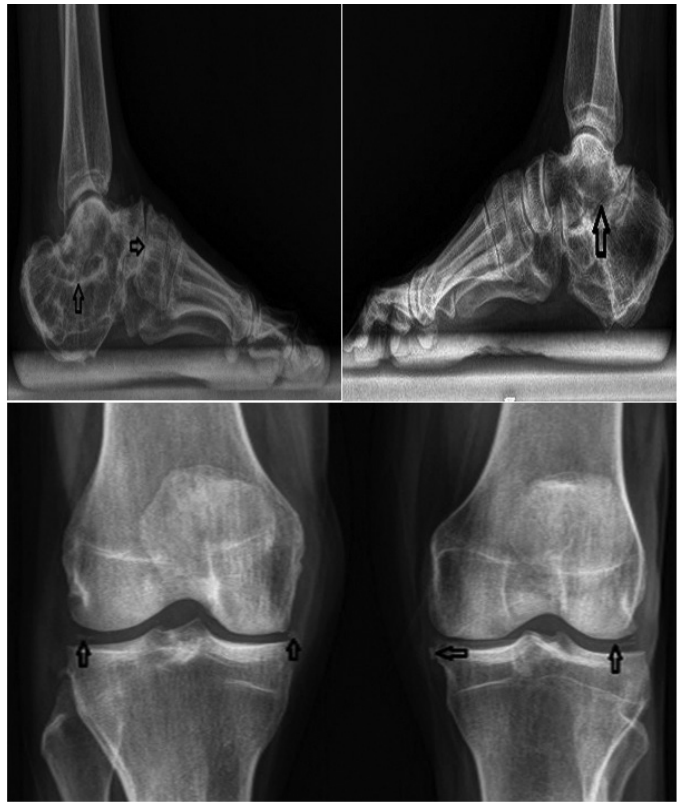

Figure 1. Right food, left foot, and knee radiographies of patient

In a study with 105 patients with CPPD; progressive and destructive joint involvement was present in 15.2% of cases, the hip was the most common site of destructive joint involvement but ankle/foot involvement was not present. Severe destructive changes are common in the knees and especially in women, but our patient did not have any severe damage to knee joints.[1] In another study with 113 patients with CPPD, the destructive arthropathy was 13.5% (n=15) with female predominance and a bilateral symmetrical pattern was observed in only two of 15 cases (other cases are generally polyarticular); knee, shoulder, wrist, and hip were the most common sites in a total of 38 destructive joints, only 5% of them presented in the ankle but hip or shoulder X-rays of our patients did not show destructive feature.[9] The talocalcaneal joint is the most common site for CPPD-related structural changes and CPPD-related joint destruction (especially in the hip, knee, ankle, and cervical spine) can simulate neuropathic arthropathy.[10] In 2015, Lomax et al.[11] reported nine patients (5 female and 4 male, median age: 66) with CPPD-related pseudoneuroarthropathy in foot and ankle joints who were unreported previously; six had bilateral involvement, all cases had multiple joint involvements, and affected joints were talonavicular: 9, tarsometatarsal: 9, subtalar: 6, naviculocuneiform: 6, calcaneocuboid: 3 and ankle: 2. Subtalar, and talonavicular joints of the left foot and subtalar joint of the right foot were affected in our patient.

We found two cases as the coexistence of MDS and CPPD in the literature: Iqbal et al.[12] reported an 83 years-old male patient with radiocarpal joint chondrocalcinosis, knee joint chondrocalcinosis, and degenerative changes in the lumbar spine; Tedeschi et al.[13] reported a 75 years-old male patient with knee, ankle and cervical spine (crowned dens syndrome) involvement. Treatment of CPPD is uncertain; cool packs, temporary rest, non-steroidal anti-inflammatory drugs, colchicine, and intra-articular or oral corticosteroid are recommended for acute attacks; a low-dose corticosteroid, hydroxychloroquine, and methotrexate are recommended for chronic CPPD by the EULAR Task Force.[14] Disease-modifying antirheumatic drugs are not part of the care (such as gout and allopurinol).

Currently, we couldn't diagnose our patient as "MDS-related pseudoneuroarthropathy" because of insufficient evidence: First, MDS-related arthritis is typically polyarticular, symmetric, and non-erosive; second, arthritis resolved with only colchicine treatment in this study but increasing evidence suggests that MDS-directed therapy is effective for the paraneoplastic autoimmune complications;[15] third, there is no any proven relationship between MDS and CPPD.[7] We did not consider HBV-related arthropathy since serum HBV-DNA was negative, liver function tests, and bilirubin levels were within normal ranges.

Conclusion

CPPD disease is a common rheumatic disease in the elderly population and a great mimicked for other musculoskeletal diseases. Our case is the first for the coexistence of MDS and destructive CPPD arthropathy in foot joints (like diabetic CA). The absence of neuropathic causes was the major clue for us. Patients with CPPD may not simultaneously have acute attacks at all affected joints simultaneously, so frequently affected joints (especially the knee) should be reviewed in the presence of suspicion. Rheumatologists should keep in mind the many clinical and radiological manifestations of CPPD in daily practice.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.P., G.K., Design: M.P., G.K., Data Collection or Processing: M.P., G.K., Analysis or Interpretation: M.P., G.K., Literature Search: M.P., G.K., Writing: M.P., G.K.

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

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Letter to the Editor / Editöre Mektup

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Anti-Jo-1 associated disease after inactive COVID-19 vaccine

İnaktif COVID-19 aşısı sonrası anti-Jo-1 ilişkili hastalık

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Keywords: Anti-Jo-1, COVID-19, myositis, vaccination
Anahtar Kelimeler: Anti-Jo-1, COVID-19, miyozit, aşı

Dear Editor,

The effect of various environmental factors on the etiopathogenesis of autoimmune diseases has been known for a long time. One of these environmental factors is vaccines. Anti-Jo-1 associated disease is an autoimmune disease of unknown cause presenting with fever, non-erosive arthritis, myositis, Raynaud's phenomenon and mechanic's hand, often accompanied by interstitial lung disease.

A 63-year-old woman with no history of chronic disease, drug use, or past COVID-19 infection presented with weakness and pain in her extremities. The patient also had swelling in both her shoulders, elbows, and hand joints. It was learned that these symptoms started about 3 days after the second dose of her COVID-19 inactivated virus vaccine (Sinovac, Sinovac Biothech Ltd., Beijing, China). She had no fever, Raynaud's phenomenon, rash, or dysphagia but exertional dyspnea after the vaccine. Physical examination revealed 3/5 muscle strength in bilateral lower and upper limb proximal muscles. She had arthritis in her right shoulder, right elbow, both wrists, and both second, third, and fourth metacarpophalangeal joints. She also had a mechanic's hand formation in both of her hands (Figure 1). She had a high erythrocyte sedimentation rate 68 mm/hr (reference range 0-15 mm/hr), serum C-reactive protein level 34 mg/L (reference range 0-5 mg/L), and creatine kinase 3774 U/L (reference range 0-145 U/L) along with a positive antinuclear antibody (3+, speckled) by indirect immunofluorescence assay. In her blood test anti-Jo-1 (3+), anti-Ro52 (3+), and anti-PM/Scl (3+) were found positive. Electromyography and thigh magnetic resonance imaging was consistent with myositis (Figure 2). Bilateral subpleural ground-glass opacities were observed in the lung parenchyma with high resolution computed tomography (Figure 2). The patient was diagnosed with anti-Jo-1 associated disease. The patient was treated with 0.5 mg/kg methylprednisolone and

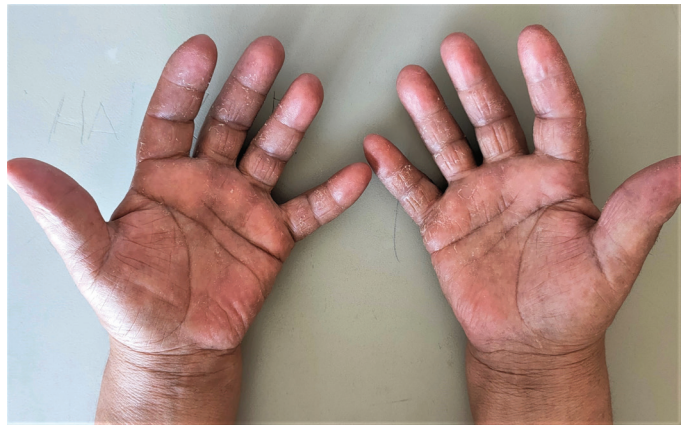

Figure 1. Mechanic's hands

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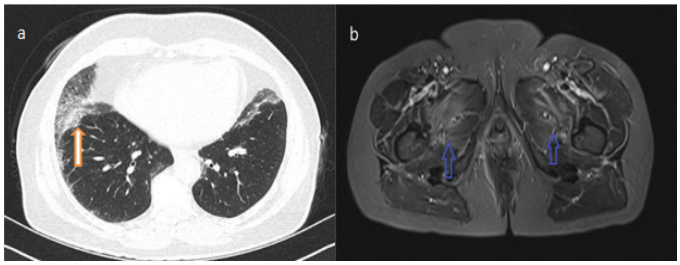

Figure 2. Subpleural ground glass opacities (arrow) (a) in high resolution computed tomography in a patient with anti-Jo-1 associated disease after COVID-19 vaccine. TIRM-hyperintense lesions in adductor muscles was compatible with myositis (blue arrow) (b)

azathioprine (150 mg/day). Her symptoms regressed during follow-up. She is still being followed up with low dose methylprednisolone (4 mg/day) and azathioprine (150 mg/day) without any symptoms.

Vaccines, as infectious agents, can cause immune system activation and autoantibody production. The broad homology between viral and bacterial elements in vaccines and human peptides may facilitate pathological autoimmune processes. Cross-reaction because of molecular mimicry, especially in genetically susceptible individuals, are suggested as a prototype mechanism of such processes.[1] Autoimmune disease may occur by rearrangement of memory T cells, activation of superantigens, or release of autoantigens because of cross-reaction. Cases such as Gullian-Barre syndrome and arthritis have previously been reported after various vaccines.[2]

While cases of autoimmune reactions after COVID-19 infection have been defined over time, information on immunological outcomes after COVID-19 vaccines is insufficient.[3] It is predicted that m-RNA vaccines, a vaccine developed against COVID-19, may lead to abnormal activation of the immune system related to a strong immune response.[4] However, these outcomes may also be observed with inactivated COVID-19 vaccine.

Reports of autoimmune diseases such as immune thrombocytopenic purpura after COVID-19 vaccination suggest that these vaccines may trigger autoimmune diseases, possibly through immune system activation, in susceptible individuals.[5] Some studies suggest that vaccines may trigger inflammatory myositis, but a complete link has not been demonstrated yet.[6] However, it has been suggested that anti-Ro-52 antibodies may play a possible role in susceptibility to vaccine-caused myositis.[7] In this study, there was a strong anti-Ro-52 antibody positivity. cases of polymyositis and local deltoid muscle myositis were previously reported after COVID-19 vaccine.[7,8] While a case of anti-Jo-1 associated disease after influenza vaccination was previously described,[9] to the best of our knowledge, this is the first such case after COVID-19 vaccination. In conclusion, although the relationship between autoimmune diseases such as inflammatory myopathies after vaccination has not yet been fully understood in various studies and case reports, the causal relationship cannot be denied. In this period of intensive vaccination against the COVID-19 virus, such post-vaccination autoimmune diseases should be kept in mind. Comprehensive and accurate immunological studies are needed to understand such autoimmune clinical manifestations after vaccination.

Ethic

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.A., K.E.K., U.İ., H.E., Concept: Z.A., K.E.K., H.E., Design: Z.A., K.E.K., H.E.,Data Collection or Processing: Z.A., K.E.K., H.E., Analysis or Interpretation: Z.A., U.İ., H.E., Literature Search: Z.A., K.E.K., U.İ., H.E., Writing: Z.A., U.İ., H.E.

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