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Danışma Kurulu

Yazarları Bilgilendirme

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Başlık sayfasının hemen altına yazarların açık olarak adı-soyadı, ünvanları, çalıştıkları kurum ile çalışmanın yapıldığı kurum belirtilmelidir. İletişim kurulacak yazarın posta adresi ile telefon numarası ve e-posta adresleri yazılmalıdır. Ayrıca derginin ön yüzünde kullanılmak üzere Türkçe ve İngilizce kısa başlık yazılmalıdır.

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Başlık sayfasından sonra ayrı bir sayfada araştırma ve derlemeler için en az 200, en fazla 250, olgu bildirileri için en az 100, en fazla 150 kelimeden oluşan bir özet bulunmalıdır.

Araştırma Makaleleri için yazılacak özet amaç, gereç ve yöntem, bulgular, sonuç olmak üzere yazılmalıdır. Türkçe özetin altında aynı düzende yazılmış İngilizce özet yer almalıdır.

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belirtilmelidir. Mikroskopik resimlerde büyütülme oranı ve boyama tekniği açıklanmalıdır. Resim, şekil, grafik ve tabloların çözünürlükleri en az 300 dpi olmalıdır. Yazar başka kaynaktan aldığı resim, şekil, grafik ve tablolar için telif hakkı sahibi kişi ve kuruluşlardan izin almalı ve yazı içinde bunu belirtmelidir. Yazı içinde ilaçların veya aletlerin özel isimleri kullanılamaz.

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  Comfort A. A good age. London: Mitchell Beazley; 1997.

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- Wharton N. Health and safety in outdoor activity centres. J Adventure Ed Outdoor Lead. 1996;12(4):8–9.

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Bildiriler, Konferans Notları

Chasman J, Kaplan RF. The effects of occupation on preserved cognitive functioning in dementia. Poster session presented at: Excellence in clinical practice, 4th Annual Conference of the American Academy of Clinical Neuropsychology; 2006 Jun 15–17; Philadelphia, PA.

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Adli Raporların Yaşamsal Tehlike Kriteri Açısından Değerlendirilmesi

Evaluation of Forensic Reports in Terms of Life-Threatening Criteria

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Özet

Adli raporda, yaralanmanın "yaşamsal tehlikeye" neden olup olmadığı yargılama için önem taşır. Bu çalışmada, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na yansıyan, adli travmatoloji ile ilgili olaylarda, yaşamsal tehlike durumunun değerlendirilmesi ve verilerin literatürle paylaşılması amaçlanmıştır. 2013 ile 2017 yılları arasındaki 5 yıllık dönemde, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na başvuran olgulardan yaşamsal tehlikesi olan olgular retrospektif olarak incelendi. Olguların rapor içerikleri ve demografik verileri değerlendirildi. Çalışma kapsamında değerlendirilen 3009 adli olgunun 355'inde (%12) yaşamsal tehlike olduğu belirlendi. Yaşamsal tehlikesi olan olguların % 79,7'sinin erkek olduğu, en sık 21-30 yaş grubunda oldukları, olgulardan % 45,1'inin trafik kazası nedeniyle yaralandığı, yaşamsal tehlikeye neden olan yaralanmanın en sık (n=130, % 36,6) baş bölgesinde olduğu belirlendi.Çalışmada elde edilen veriler literatürle uyumlu bulundu. Özellikle acil servis hekimlerinin, adli rapor düzenleme konusunda daha özenli davranmaları ve bu konudaki hizmet içi eğitimlerin önemli olduğu düşünüldü.

Anahtar Kelimeler: Adli rapor, Adli tıp, Yaşamsal tehlike,

Abstract

In the forensic report, it is important for the judgment whether the injury is "life-threatening" or not. In this study, it is aimed to evaluate the life-threatening situation in events related to forensic traumatology that reflected in the Department of Forensic Medicine, Eskişehir Osmangazi University Faculty of Medicine and to share the data with the literature. In the 5-year period between 2013 and 2017, among the cases who applied to Eskişehir Osmangazi University Faculty of Medicine Department of Forensic Medicine, life-threatening cases were analyzed retrospectively. Report contents and demographic data of the cases were evaluated. It was determined that 355 (12%) of the 3009 forensic cases evaluated within the scope of the study were life-threatening. 79.7% of the life-threatening cases were male, they were mostly in the 21-30 age group, 45.1% of the cases were injured due to a traffic accident, and the most life-threatening injury (n = 130, 36.6%) was determined to be in the head area.The data obtained in the study were found to be compatible with the literature. It was thought that especially emergency physicians should be more attentive in preparing forensic reports and in-service trainings on this issue were important.

Keywords: Forensic report, Forensic medicine, Life-threatening

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1. Giriş

Hekimlerin hastaları tedavi etmek dışında, adli olguları tespit etmek, gerekli bildirimi yapmak ve adli raporunu hazırlamak gibi hukuki sorumlulukları da vardır (1). Bir dış etken sonucu meydana gelen tüm yaralanmalar adli olgu olarak değerlendirilmektedir (1,2). Adli olgular, genellikle yaralanma sonrasında ilk olarak acil servise başvurular. Dolayısıyla bu olaydan ilk olarak hekimlerin bilgisi olur. Hekimlerin adli olguyu tanıma ve uygun şekilde raporunu düzenleme sorumluluğu bulunmaktadır (2).

Adli travmatolojiyi ilgilendiren olaylarda, düzenlenecek adli raporlar, Türk Ceza Kanunu'nda (TCK) ilgili maddelere cevap verir nitelikte olmalıdır (2,3). Bu konuda "Türk Ceza Kanunu'nda Tanımlanan Yaralama Suçlarının Adlî Tıp Açısından Değerlendirilmesi" şeklinde bir kılavuz hazırlanmıştır. Bu kılavuzda vücutta oluşan lezyonlar ve bulgular ayrıntılı olarak değerlendirilmiş ve kanun maddelerine uygun olarak kriterler belirlenmiştir (1-3). TCK'nın 87. maddesinin d fıkrasında, yaralanmanın yaşamsal tehlikeye neden olması ile ilgili hüküm yer almaktadır (1-4). Kılavuza göre, yaşamsal tehlike oluşturan yaralanmalar genel olarak; kafatası kırıkları, beyin kanamaları, kafa içi değişimler, ilk üç servikal vertebra kırığı, Glasgow Koma Skoru'nun 8 ve altında olduğu bilinç kapalılığı durumları, iç organ yaralanmaları, iç kanamalar, büyük damar yaralanmaları, medulla spinalis lezyonları, batın ve göğüse penetre yaralanmalar, % 20'den fazla ikinci derece, % 10'dan fazla üçüncü derece yanıklar, giriş ve çıkış lezyonu bulunan elektrik yaralanmaları, kuduz hayvan ısırıkları, ağır toksikoloji tablolar olarak sıralanabilir (2,5). Adli raporda, yaralanmanın "yaşamsal tehlikeye" neden olup olmadığı yargılama için önem taşır. Karşı tarafın, gözaltına alınıp alınmaması gibi hukuki süreçte önemli rol oynar. Bu nedenle "yaşamsal tehlike" durumunun olabildiğince hızlı belirlenmesi gerekmektedir.

Bu çalışmada, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na yansıyan, adli travmatoloji ile ilgili olaylarda, yaşamsal tehlike durumunun değerlendirilmesi ve verilerin literatürle paylaşılması amaçlanmıştır.

2. Gereç ve Yöntem

2013 ile 2017 yılları arasındaki 5 yıllık dönemde, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na başvuran olgulardan yaşamsal tehlikesi olan olgular çalışma kapsamına alındı. Çalışmada kati rapor düzenlenen oldular değerlendirildi. Cinsel suç olguları, hukuki ehliyet, akıl sağlığı değerlendirmeleri gibi adli psikiyatrik değerlendirmeler ve maluliyet oranı istenilen olgular çalışma kapsamına alındı.

Çalışma Adli Tıp Anabilim Dalı'nda dosyaların retrospektif olarak incelenmesi yöntemi ile yapıldı. Olguların, yaş, cinsiyet gibi demografik verileri incelendi. Olayın olduğu mevsim, olayın türü, orijini, yaralanan vücut bölgesi ve organ, yaşamsal tehlikenin nedeni değerlendirildi. Olguların alkol durumları incelendi.

Anabilim Dalımızda adli raporlar genellikle dosya üzerinden yazılmaktadır. Dolayısıyla tarafımıza sunulan hastane evraklarındaki eksiklikler nedeniyle bazı bilgilere ulaşılamamıştır. Bu durum çalışmamızın kısıtlılığıdır.

Veriler SPSS istatistik paket programına yüklenerek değerlendirildi ki-kare ve yüzde analizleri yapıldı.

Çalışma T.C. Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurul Başkanlığı'nın 26.06.2018 Tarih ve 17 sayılı kararı ile onaylandı ve yapıldı.

3. Bulgular

Çalışmanın kapsadığı 2013 ile 2017 yılları arasındaki 5 yıllık dönemde, Anabilim dalımızca hakkında adli rapor düzenlenen adli travmatolojiyi ilgilendiren 3009 olgudan 355'inde (%12) yaşamsal tehlike olduğu belirlenmiştir.

Yaşamsal tehlikesi olduğu belirlenen olguların en küçüğünün 1, en büyüğünün 87 yaşında

olduğu, olguların en sık 21-30 yaş aralığında olduğu (n=84, % 23,7) yaş ortalamasının 36,2±1,9 olduğu saptanmıştır. Olguların % 79,7'sinin erkek (n=283), % 20,3'ünün (n=72) kadın olduğu belirlenmiştir.

Olguların yaş grubunun cinsiyete göre dağılımı tablo 1'de sunulmuştur. Yaş grubu ile cinsiyet arasında bir ilişki olduğu belirlenmiştir. (P=0,032). 11 yaş ve üzerindeki yaş gruplarında erkek/kadın oranının yaklaşık olarak dört kat olduğu ancak 0-10 yaş grubunda, erkek, kadın sayılarının birbirlerine yakın olduğu görülmüştür (erkek=16, kadın=12). 0-10 yaş grubunda yaşamsal tehlike açısından cinsiyetin çok belirleyici olmadığı, ancak diğer yaş gruplarında belirgin olarak erkelerin yaşamsal tehlikeye maruz kalma oranlarının daha fazla olduğu belirlenmiştir.

Tablo 1. Olguların yaş gruplarının cinsiyete göre dağılımı

Yaş Grubu	Cinsiyet				Toplam
	Erkek		Kadın		
	n	%	n	%	n
0-10	16	57,1	12	42,9	28
11-20	39	79,6	10	20,4	49
21-30	74	88,1	10	11,9	84
31-40	44	80,0	11	20,0	55
41-50	50	83,3	10	16,7	60
51-60	28	77,8	8	22,2	36
61 ve üzeri	32	74,4	11	25,6	43
Toplam	283	79,7	72	20,3	355

$\chi^2=13,791$ $P=0,032$

Yaşamsal tehlikesi olan olguların olay türlerine göre dağılımı grafik 1'de sunulmuştur. Olguların en sık trafik kazası nedeniyle yaşamsal tehlike geçirdikleri belirlenmiştir (n=160, %45,1). Trafik kazasını kesici-delici alet yaralanması (n=87, % 24,5) ve darp-cebir (n=51, % 14,4) izlemiştir.

Grafik 1. Olguların, olay türlerine göre dağılımı (* 2 olgu besin zehirlenmesi, 1 olgu ilaç zehirlenmesi)

Olguların orijinlerine göre değerlendirildiğinde, 192 olgunun (% 54,1) kaza, 161 olgunun (% 45,4) travmatik etkili eylem, 2 olgunun (% 0,5) intihar girişimi olduğu belirlenmiştir (Grafik 2).
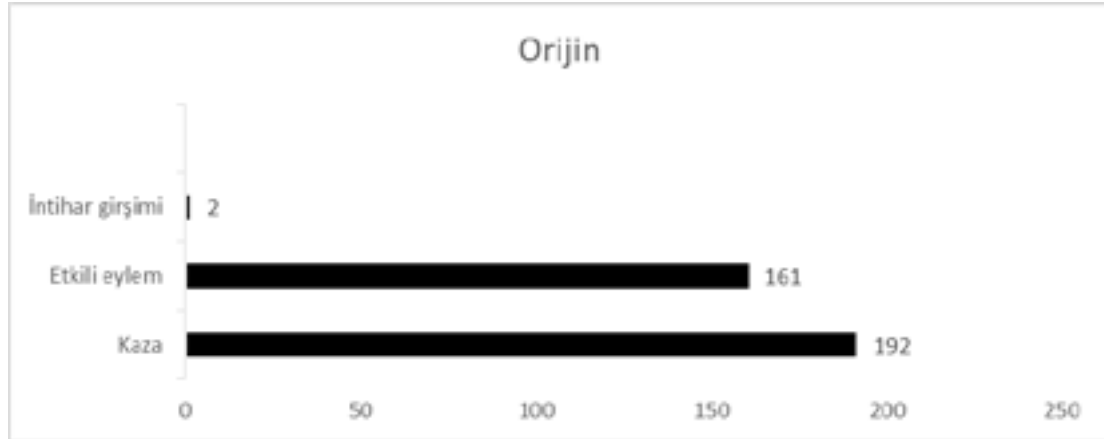
Grafik 2. Olguların orijine göre dağılımı

Orijin ile cinsiyet arasında anlamlı bir ilişki olduğu tespit edildi (Tablo 2). Erkek olguların %50,5 'inin (n=143), %0,7'sinin (n=2) intihar girişimi, %48,8'inin (n=138) kaza olduğu, kadın olguların %25'inin (n=18) etkili eylem, %75'inin (n=54) kaza olduğu, kadın olgularda intihar girişimi orijinine rastlanılmadığı belirlendi.

Tablo 2. Orijinin cinsiyete göre dağılımı

Cinsiyet	Orijin				Toplam	
	Kaza		Etkili eylem / İntihar girişimi*			
	n	%	n	%	n	%
Erkek	138	48,8	145	51,2	283	100,0
Kadın	54	75,0	18	25,0	72	100,0
Toplam	192	54,1	163	45,9	355	100,0

$\chi 2$=15,910   P<0,0001 *(İstatiksel anlamlılık için Etkili eylem ile intihar girişimi birleştirildi.)

Yaş grupları ile orijin arasında anlamlı bir ilişki saptandı (Tablo 3, P<0,0001). 20 yaşından küçük ve 40 yaşından büyük olgularda, yaşamsal tehlikeye kazaların daha sık neden olduğu, 20 ile 40 yaş arasında ise etkili eylemlerin yoğunluk kazandığı görülmektedir. İntihar girişimi olgularının ikisinin de erkek olduğu olguların 21 ve 30 yaşlarında olduğu, bir olgunun ekstremite bölgesine ateşli silah, diğer olgunun da ilaç içme şeklinde olduğu belirlendi.

Tablo 3. Yaş gruplarının, orijine göre dağılımı

Yaş grubu	Orijin				Toplam	
	Kaza		Etkili eylem / İntihar girişimi*			
	n	%	n	%	n	%
0-10	26	92,9	2	7,1	28	100,0
11-20	30	61,2	19	38,8	49	100,0
21-30	25	29,8	59	70,2	84	100,0
31-40	25	45,5	30	54,5	55	100,0
41-50	31	51,7	29	48,3	60	100,0
51-60	27	75,0	9	25,0	36	100,0
61 ve üzeri	28	65,1	15	34,9	43	100,0
Toplam	192	54,1	163	45,9	355	100,0

$\chi 2$=48,207   P<0,0001 *(İstatiksel anlamlılık için Etkili eylem ile intihar girişimi birleştirildi.)

Olguların en sık sonbahar ayında yaşamsal tehlike geçirdiği belirlendi (n=106, % 29,9). Sonbaharı, yaz mevsiminin izlediği (n=97, % 27,3) belirlendi. Orijin ile mevsim arasında

anlamlı bir ilişki görülmedi (Tablo 4, P>0,05). Tüm olay türlerinin en az kış aylarında meydana geldiği, diğer mevsimler arasında belirgin bir farklılık olmadığı görüldü.

Tablo 4. Orijinlerin mevsimlere göre dağılımı

| Mevsim | Orijin | | | | Toplam | |
| | Kaza | | Etkili eylem/İntihar Girişimi | | | |
	n	%	n	%	n	%
Sonbahar	54	28,1	52	31,7	106	29,9
Kış	35	18,2	27	16,1	62	17,4
İlkbahar	43	24,5	43	26,7	90	25,4
Yaz	56	29,2	41	25,5	97	27,3
Toplam	192	100,0	163	100	355	100,0

$\chi 2=3,749$ P>0,05

Olguların, yaralanma bölgelerinin dağılımı tablo 5'te sunulmuştur. İzole olarak en sık baş bölgesinin yaralandığı (n=102, % 28,7), birden fazla bölge yaralanmaları da değerlendirildiğinde ise en sık göğüs bölgesinin yaralandığı (n=142, % 40) belirlenmiştir. 292 olguda (% 82,3) tek vücut bölgesi yaralanırken, 61 olguda ((% 17,2)

birden fazla vücut bölgesi yaralanmıştır. 2 olguda (% 0,5) yaşamsal tehlike nedeni GKS düşüklüğü gibi parametrelerdir. Toplamda 130 (% 36,6) olguda baş, 77 (% 21,7) olguda batın, 44 (% 12,4) olguda ekstremiteler, 21 (% 5,9) olguda boyun bölgesinin yaralandığı görüldü.

Tablo 5. Olguların yaralanma bölgelerine göre dağılımı

Yaralanan Vücut Bölgesi	n	%
Baş	102	28,7
Boyun	15	4,2
Göğüs	94	26,5
Batın	48	13,5
Ekstremiteler	33	9,3
GKS düşüklüğü gibi parametreler*	2	0,6
Baş, boyun	3	0,8
Baş, göğüs	20	5,6
Baş, ekstremiteler	1	0,3
Boyun, göğüs	1	0,3
Batın, göğüs	23	6,5
Göğüs, ekstremiteler	5	1,4
Batın, ekstremiteler	3	0,8
Baş, boyun, göğüs	1	0,3
Baş, boyun, ekstremiteler	1	0,3
Baş, göğüs, batın	2	0,6
Göğüs, batın, ekstremiteler	1	0,3
Toplam	355	100,0

Olguların 178'inde (% 50,1), bir yaşam tehlike nedeni olduğu, 177 olguda (% 49,9) birden fazla yaşamsal tehlike nedeni olduğu belirlendi. Tüm olgular değerlendirildiğinde,

yaşamsal tehlikeye neden olan en sık sebebin 108 olgu ile (% 30,4) beyin kanaması olduğu belirlendi. Olguların yaşamsal tehlike nedenleri tablo 6'da sunulmuştur.

Tablo 6. Yaşamsal tehlike nedenlerinin dağılımı

Yaşamsal tehlike nedeni	n	%
Kafa kemiklerinde kırık	14	3,9
Beyin kanaması	33	9,3
Akciğer kontüzyonu	32	9,0
Batına nafiz yaralanma	11	3,1
Göğüse nafiz yaralanma	3	0,8
İlk üç vertebra kırığı	8	2,3
Damar yaralanması	35	9,9
Hemopnömotoraks	29	8,2
Diğer iç organ yaralanmaları	28	7,9
Kafa kemiklerinde kırık ve beyin kanaması	51	14,4
Kafa kemiklerinde kırık, beyin kanaması, hemopnömotoraks ve akciğer kontüzyonu	18	5,0
Kafa kemiklerinde kırığı, beyin kanaması, ilk 3 vertebra kırığı, damar yaralanması	3	0,8
Beyin kanaması, hemopnömotoraks	3	0,8
Akciğer kontüzyonu, hemopnömotoraks, damar yaralanması	13	3,7
Göğüse ve batına nafiz yaralanma ve hemopnömotoraks	17	4,8
Beyin kanaması, diğer iç organ yaralanmaları	1	,3
Akciğer kontüzyonu, diğer iç organ yaralanmaları	5	1,4
Akciğer kontüzyonu, ilk 3 vertebra kırığı, hemopnömotoraks	1	,3
Akciğer kontüzyonu, medulla spinalis yaralanması, hemopnömotoraks	2	,6
Batına nafiz yaralanma ve diğer iç organ yaralanmaları	16	4,5
Batına, göğüse nafiz yaralanma, damar yaralanması ve hemopnömotoraks	5	1,4
Göğüse nafiz yaralanma, hemopnömotoraks ve diğer iç organ yaralanmaları	5	1,4
Damar yaralanması ve diğer iç organ yaralanmaları	3	,8
Kafa kemik kırığı, beyin kanaması, göğüse nafiz yaralanama ve hemopnömotoraks	2	0,6
Kafa kemik kırığı, beyin kanaması, ilk 3 vertebra kırığı, hemopnömotoraks	1	,3
Akciğer kontüzyonu, hemopnömotoraks, diğer iç organ yaralanmaları	4	1,1
Batına nafiz, göğüse nafiz, damar yaralanması diğer iç organ yaralanmaları	3	0,8
Göğüse nafiz yaralanma, hemopnömotoraks ve diğer iç organ yaralanmaları	1	,3
Kafa kemik kırığı, beyin kanaması, akciğer ve diğer iç organ yaralanmaları	1	,3
Kafa kemik kırığı, beyin kanaması, akciğer kontüzyonu, ilk 3 vertebra kırığı	1	,3
Batına ve göğüse nafiz, hemopnömotoraks ve diğer iç organ yaralanmaları	6	1,7
Toplam	**355**	**100,0**

Olguların 229'unda (% 64,5) alkol ile ilgili bilgi olmadığı, 87 olguda (% 24,5) yapılan testlerde alkol saptanmadığı, 39 olguda (% 11,0) alkol tespit edildiği belirlendi (Grafik 3). Alkol tespit edilen olguların en sık 201 mg/dl ve üzeri miktarda alkollü olduğu (n=11, % 28,2) belirlendi. Hastane evraklarından 152 trafik kazası olgusunun 94'ünde (% 61,8) alkol ile ilgili bilgi olmadığı görüldü. Darp, cebir, kesici delici alet yaralanması ve diğer yaralanma türlerini içeren 161 etkili eylem

olgusunun 108'inde (% 67,1) alkol ile ilgili   bilgi olmadığı görülmüştür.
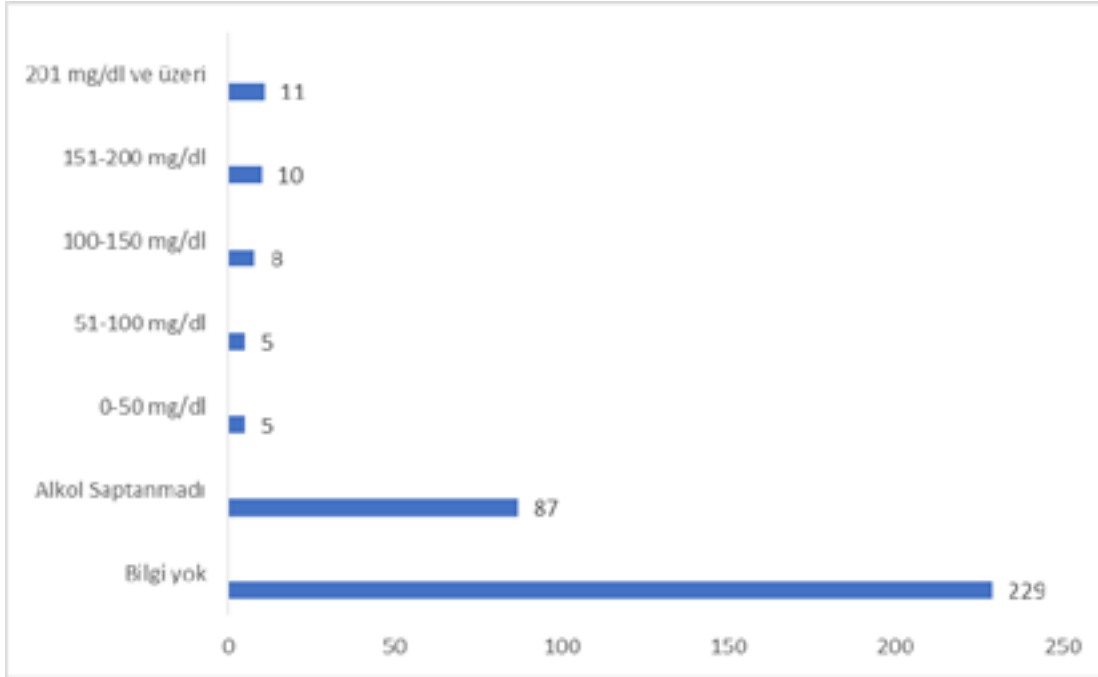
Grafik 3. Olguların alkol durumunun dağılımı

4. Tartışma

Adli nitelikli olaylarda hekimler, yaralanan kişiyle ilk karşılaşan kişilerdendir. İlk muayene ve düzenlenecek adli rapor, yaralanmaya neden olan tarafın olay sonrası gözaltına alınıp alınmayacağını belirleyebilir. Bu raporlarda yapılacak hatalar adli sürecin uzamasına ve kimi zaman haksızlıklara neden olabilmektedir. Adli nitelikli her olguda yaşamsal tehlikenin olup olmadığı araştırılmalıdır (4). Denizli'de yapılan bir çalışmada, acil hekimlerinin adli raporlarda yer alan hayati tehlike durumunu %13 oranında yanlış değerlendirdikleri belirlenmiştir (6). Çoltu ve arkadaşlarının Bursa'da yaptıkları çalışmada bu oranın % 6,5 olduğu bildirilmiştir (7). Adana'da acil servise başvuran 5870 adli olgunun olgunun değerlendirildiği bir çalışmada, olguların geçici raporlarında 3336 (% 56.8) olgunun yaşamsal tehlikenin olduğunun bildirildiği, ancak adli tıp uzmanlarınca değerlendirildiğinde, bu hastaların % 78.9'unun (2632 olgu) yaşamsal tehlikesinin olmadığı bildirilmiştir (8). Sunulan çalışmada olgulara ait adli raporlar tarafımızca düzenlendiği için acil hekimlerinin adli raporları değerlendirilememiştir. Hekimlerin

adli rapor düzenleme konusundaki eksikliklerinin giderilmesi için hizmet içi eğitimler yararlı olabilir. Demirci ve arkadaşlarının yaptığı çalışmada hizmet içi eğitimlerin, hekimlerin adli olgulara karşı yaklaşımında olumlu sonuçlar verdiği bildirilmiştir (9).

Kafadar'ın yaptığı çalışmada yaşamsal tehlikeye maruz kalan 78 olgunun 12'sinin (%15,38) kadın, 66'sının (%84,61) erkek olduğunu saptanmıştır (4). Sivas'ta Cumhuriyet Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na başvuran adli nitelikli olguların % 76,8'inin erkek olduğu bildirilmiştir (10). Çalışmamızda da yaşamsal tehlikeye maruz kalan 355 olgunun 283'ünün (%79,7) erkek, 72'sinin (%20,3) kadın olduğu saptanmıştır. Bu durumda ülkemizde sosyal yaşam ve iş yaşamında erkeklerin daha aktif olması, kadınların çalışma hayatından uzak olmasının etkili olduğu düşünülmüştür.

Adli travmatoloji ilgilendiren çalışmalarda, olguların genellikle 20-40 yaş arasında oldukları bildirilmiştir (4,8-19). Sivas'ta yapılan çalışmada adli olguların % 56,9'unun

20-29 yaş arasında olduğu bildirilmiştir (10). Isparta'da adli olguların değerlendirildiği bir çalışmada, olguların % 64,86'sının erkek olduğu ve tüm olguların yaş ortalamasının 28,7 olduğu bildirilmiştir (15). Çalışmamızda da 163 etkili eylem sonucu yaşamsal tehlikeye maruz kalan olgudan 59'unun(%36) 21-30 yaş aralığında olduğu, 30'unun (%18) 31-40 yaş aralığında olduğu tespit edilmiştir. Adli olayların genç yaş grubunda sık görülmesi; trafikte daha fazla bulunmaları, yüksek riskli işlerde çalışmaları, sosyal ortamda daha fazla vakit geçirmeleri, saldırgan yapıları ve alkol kullanımı oranlarının yüksek olmasına bağlı olabilir. Bu bulgu ile ilgili olarak çalışmamızda, yaş grupları ile orijin arasında anlamlı bir ilişki saptandı (Tablo 3, P<0,0001). 20 yaşından küçük ve 40 yaşından büyük olgularda, yaşamsal tehlikeye kazaların daha sık neden olduğu, 20 ile 40 yaş arasında ise etkili eylemlerin yoğunluk kazandığı görülmektedir.

Trafik kazaları adli tıp pratiğinde sık görülen olgulardır. Serinken ve arkadaşlarının Denizli'de yaptığı çalışmada, acil servise başvuran adli nitelikli olguların % 68,3'ünün trafik kazaları olduğu belirlenmiştir (6). Sivas ilinde yapılan çalışmada bu oran % 56,9 olarak belirtilmiştir (10). Literatür ile uyumlu olarak çalışmamızda yaşamsal tehlikeye maruz kalan 355 olgunun 160'ının (%45,1) trafik kazası nedeniyle yaralandığı belirlenmiştir.

Kesici-delici alet yaralanmaları, adli tıp pratiğinde sık görülen ve ölümcül yaralanmalara neden olan olaylardandır (14). Elazığ'da yapılan adli raporların değerlendirildiği bir çalışmada yaşamsal tehlikeye maruz kalan olguların en sık (% 35,89) kesici-delici alet ile yaralandıkları bildirilmiştir (4). Sunulan çalışmada, yaşamsal tehlikeye neden olan en sık ikinci olayın kesici-delici alet yaralanması olduğu belirlenmiştir (n=87, % 24,5). Sunulan çalışma ile Elazığ'da yapılan çalışma arasındaki bu farkın, sosyokültürel ve coğrafik şartlara bağlı olduğu düşünülmektedir.

Adli olguların değerlendirildiği çalışmalarda, yaralanmanın en sık baş bölgesinde olduğu bildirilmiştir (8,10,14-17). Sivas'ta yapılan çalışmada, adli nitelikli olguların % 44,6'sında yaralanmanın baş bölgesinde olduğu belirtilmiştir (10). Kafa travması ve buna bağlı olarak, beyin kanaması, kafa kemiklerinde kırıklar ve diğer kafa içi patolojik değişimlerin adli travmatoloji pratiğinde sık rastlanılan olayla olduğu literatürde paylaşılmıştır (20-23). Sunulan çalışmada da literatüre uygun olarak en sık baş (% 36,6, n=130) bölgesinde yaşamsal tehlikeye neden olan yaralanma olduğu belirlenmiştir.

Alkolün etkili olduğu adli travmatoloji ilişkili olaylarda özellikle acil serviste çalışan hekimlere alkol seviyesinin ilk anda belirlenmesi ve raporlanması görevi düşmektedir. Kişinin kan alkol seviyesi adli veya idari soruşturmanın seyrini etkileyecek bir parametredir (24). Sunulan çalışmada olguların çok büyük bir kısmında alkol ile ilgili bilgi olmadığı görülmektedir. Olguların 229'unda (% 64,5) alkol ile ilgili bilgi olmadığı, 87 olguda (% 24,5) yapılan testlerde alkol saptanmadığı, 39 olguda (% 11,0) alkol tespit edildiği belirlendi (Grafik 3). Alkol tespit edilen olguların en sık 201 mg/dl ve üzeri miktarda alkollü olduğu (n=11, % 28,2) belirlendi. Acil hekimlerinin bu konuda yeterli bilgiye sahip olmadığı görülmektedir. Acil servislerde çalışan hekimlerin adli hekimlik görevi olduğu tartışmasızdır. Bu konuda gerekli özenin gösterilmemesi durumunda yasal sorumluluk ortaya çıkabilir. Acil servise başvuran tüm adli nitelikli olgularda, adli rapora alkol değerinin yazılması ile ilgili acil servis hekimlerinde farkındalık oluşturulmalıdır. Bu konuda verilecek hizmet içi eğitimlerin yararlı olacağı düşünülmektedir.

Adli olgularda, ayrıntılı bir şekilde muayene, gerekli tetkiklerinin yapılması ve elde edilen bulgular sonucunda anlaşılabilir, kılavuza uygun bir adli rapor yazılması, adalet sisteminin hızlı ve doğru işlenmesi açısından önemlidir. Yaşamsal tehlike oluşturan adli olaylarda, hızlı ve doğru bir şekilde düzenlenmesi, kişilerin en temel hakları olan adil yargılanmanın öneli bir parçasını oluşturmaktadır.

Acil servis ve birinci basamak sağlık kuruluşlarında çalışan hekimlerin, adli olguyu tanıma, uygun şekilde bildirimini yapma ve adli raporlarının doğru şekilde düzenleme ile ilgili yeterli eğitimi almış olmalıdır.

Yaşamsal tehlike durumunun belirlenmesi için, kimi zaman ileri tetkikler gerekebilir. Periferde bulunan sağlık merkezlerinde toksikolojik analiz ve görüntüleme yöntemleri açısından kısıtlılıklar olabilir. Bu durumlarda hekimler yaşamsal tehlike kararını, tetkiklerin yapılacağı ileri birimlere veya tüm hastane evraklarını inceleyecek adli tıp uzmanlarına bırakmalıdır. Bu durumu da raporlarında açıkça belirtmelidirler. Adli nitelikli olaylarda, tam bir muayene yapılması, gerekli konsültasyon ve tetkiklerin yapılması, gerekli durumlarda sevklerin sağlanması, tüm bilgi ve bulguların kaydedilmesi, uygun olan hastaların gerekli süre kadar gözlenmeleri ve gerekirse tekrar muayene çağırılmaları gerekir.

Adli olgulardaki yaşamsal tehlike nedenleri bölgesel olarak farklılık göstermektedir. Adli Tıp ve Acil Tıp uzmanlarının göreve başlamadan önce ve görev süresince çalıştıkları bölge hakkındaki bilimsel çalışmaları incelemeleri mesleki becerilerinin artmasına ve tecrübe kazanmalarına yardımcı olacaktır.

Tüm adli nitelikli olgularda mutlaka alkol testi istenilmesi gerekmektedir. Çalışmamızdaki verilerden, ilimizdeki acil servis hekimlerinin bu konuda yeterli hassasiyeti göstermedikleri anlaşılmaktadır. Adli yaptırımlara maruz kalmamak adına hekimlerin adli olgularda alkol tetkikini rutin olarak yapmaları gerekmektedir.

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Research Article / Araştırma Makalesi

Effects of COVID-19 Pandemic on Childhood Epilepsy Management; A Survey Study

COVID-19 Pandemisinin Çocukluk Çağı Epilepsi Yönetimi Üzerindeki Etkileri; Anket Çalışması

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Abstract

The World Health Organization (WHO) declared the new coronavirus disease (COVID-19) pandemic on March 11, 2020. The pandemic has significantly impacted health systems worldwide, forcing them to reconsider the management of chronic diseases. Reorganization of health systems has inevitably prioritized the management of patients with COVID-19 infection, reducing hospital access for patients with other chronic diseases. Epilepsy is one of the most common chronic diseases of childhood, and pediatric neurologists have reviewed the methods they use in the management and treatment of epilepsy during pandemics. We organized a survey to evaluate the attitudes of pediatric neurologists in epilepsy management during the pandemic period. The 24-item questionnaire, created with Microsoft Forms, was sent to child neurologists via social communication platforms. Data were collected over two weeks. Variables were evaluated with Pearson chi-square and Student's t-test. Mann-Whitney U test and Student's t-test were used to compare the averages between the two groups. p <0.05 value was considered statistically significant. 118 participants (79 women and 39 men) who answered all the questions were included in the study. The mean age of the participants was 41.46±7.49 years, and the median child neurology experience was 6 years (3 months-36 years). The participants mostly postponed the outpatient clinic appointments of patients whose seizures were under control (77.5%). Most participants preferred to reduce the number or postpone electroencephalographies (EEG) during this period. The outpatient clinic visits of patients with well-controlled epileptic seizures can be postponed during the pandemic. In cases where face-to-face communication is not possible during the pandemic period, the patients' medical history and video images may help diagnose. The telemedicine method can also be useful in the post-pandemic period in the follow-up and management of patients with controlled epileptic seizures.

Keywords: children, epilepsy, treatment, EEG, covid 19 pandemic

Özet

Dünya Sağlık Örgütü (DSÖ), 11 Mart 2020'de yeni koronavirüs hastalığını (COVID-19) pandemi olarak ilan etti. Bu durum dünya çapında sağlık sistemlerini önemli ölçüde etkiledi ve kronik hastalıkların yönetimini yeniden gözden geçirmeye zorladı. Sağlık sisteminin salgın döneminde yeniden düzenlenmesi, kaçınılmaz olarak COVID-19 enfeksiyonlu hastaların yönetimine öncelik vererek, diğer kronik hastalıkları olan hastalar için hastaneye erişimi azalttı. Epilepsi, çocukluk çağının en yaygın kronik hastalıklarından biridir ve pediatrik nörologlar, pandemiler sırasında epilepsi yönetimi ve tedavisinde kullandıkları yöntemleri gözden geçirmek zorunda kalmıştır. Biz de pandemi döneminde epilepsi yönetiminde pediatrik nörologların tutumlarını değerlendirmek amacıyla bir anket düzenledik. Microsoft Forms ile oluşturulan 24 maddelik anket sosyal iletişim platformları aracılığıyla çocuk nörologlarına gönderildi. Veriler iki hafta boyunca toplandı. Değişkenler Pearson ki-kare ve Student's t-testi ile değerlendirildi. İki grup arasındaki ortalamaları karşılaştırmak için Mann-Whitney U testi ve Student's t-testi kullanıldı. p <0.05 değeri istatistiksel olarak anlamlı kabul edildi. Tüm soruları cevaplayan 118 katılımcı (79 kadın ve 39 erkek) çalışmaya dahil edildi. Katılımcıların ortalama yaşı 41,46 ± 7,49 yıl ve ortanca çocuk nöroloji deneyimi 6 yıl (3 ay-36 yıl) idi. Katılımcılar çoğunlukla nöbetleri kontrol altında olan hastaların poliklinik randevularını (% 77,5) ertelemişlerdir. Katılımcıların çoğu bu dönemde elektroensefalografilerin (EEG) sayısını azaltmayı veya ertelemeyi tercih ettiler. İyi kontrollü epileptik nöbetleri olan hastaların poliklinik ziyaretleri pandemi sırasında ertelenebilir. Pandemi döneminde yüz yüze iletişimin mümkün olmadığı durumlarda hastaların tıbbi geçmişi ve video görüntüleri tanıya yardımcı olabilir. Teletıp yöntemi, pandemi sonrası dönemde, kontrollü epileptik nöbetleri olan hastaların takip ve yönetiminde de faydalı olabilir.

Anahtar Kelimeler: Çocuk, karaciğer nakli, canlı aşılama

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1. Introduction

In March 2020, the WHO declared the COVID-19 pandemic. As a result, governments have introduced some control measures to reduce transmission and ease the health systems' burden. The COVID 19 pandemic has reshaped the management of chronic diseases. The reorganization of health systems has inevitably prioritized patients with COVID-19 infection, reducing hospital access for patients with other chronic diseases.[1] Epilepsy is one of the most common chronic diseases affecting 60 million people worldwide.[2,3] The prevalence of epilepsy in childhood in our country is 0.8%, and epilepsy patients constitute most of the patient burden of pediatric neurologists.[4]

In the management of epilepsy, regular outpatient visits are carried out to regulate the antiepileptic treatment and manage behavioral or psychological problems related to epilepsy. The precautions and limitations brought due to the pandemic have affected the outpatient services.[1] For this reason, pediatric neurologists have reviewed the methods they use to manage and treat epilepsy, both by the government and hospital policy and with their preferences. Besides, patients did not prefer to go to the hospital, except in emergencies, due to infection risk. During this period, patients with epilepsy started to be evaluated by phone and video calls.[5] Since the pandemic's duration is not known, and patient evaluations cannot be postponed indefinitely, the use of telemedicine services has become particularly important during this period.[1] The physicians who could not benefit from telemedicine services communicated with their patients through various social communication networks, telephone and video calls, and short message services.[1]

The telemedicine method provides a real-time interactive conversation between the patient and the physician. There are 33750 articles about telemedicine in medical search engines until May 2020, of which about 1300 are related to COVID-19.[6,7] However, these publications do not mention the changes caused by the pandemic in the management of epilepsy. This survey study aimed to reveal how pediatric neurologists manage epilepsy patients during the pandemic period.

2. Methods

This study is a descriptive, cross-sectional survey study. A 24-item questionnaire was drafted using Microsoft Forms and distributed among pediatric neurologists via Turkey's social communications services. All participants were informed about the purpose and the anonymity of the study before starting the survey. The study was kept open for two weeks, and data were collected in two weeks period. The study protocol was approved by Republic of Turkey Ministry of Health (approval no: 2020-05-17T21_02_14). Ethics approval was obtained by the ethics committee of the health sciences University Behcet Uz Pediatric Hospital with the number 2020 / 18-04. The questionnaire included questions about the participants' socio-demographic characteristics and workplace of the measures taken during the pandemic period, how these measures affect patient management, and the methods used while applying these measures. (Figure 1)

Statistics

Measurements such as mean, median, frequency, standard deviation (SD) from statistical analyzes were made with Statistical Package for Social Sciences (SPSS) software for Windows, version 23.0 program, and the results were given as mean $\pm$ SD, percentage values and median values . Variables were evaluated with Pearson chi-square and Student's t-test. Student's t-test were used to compare the averages between the two groups. $p < 0.05$ value was considered statistically significant.

3. Results

Among 121 participants, 118 participants who answered all the questions were included in the study. Seventy-nine women and 39 men completed the questionnaire. Eighty-four of the participants were pediatric neurologists and 39 were pediatric neurology residents. The mean age of the participants was 41.46 ± 7.49 years, and the median child neurology experience was 6 years (3 months-36 years).

One hundred thirteen participants (96%) stated that they made changes in epilepsy management during the pandemic. There was a decrease in the number of outpatient clinic patients except for one participant. Only 35% of participants were involved in deciding hospital policy for the COVID-19 pandemic.

Participants stated that the main reason (68.6%) for the decrease in the number of outpatient visits was parents' preferences and concern about COVID-19 transmission (Figure 2). The most challenging part of outpatient follow-up during the pandemic was close contact with the patient during physical examination (Figure 3). While 42 participants (35.6%) stated no change in the diagnostic methods, the same number of participants stated that they postponed the electrophysiological examinations.
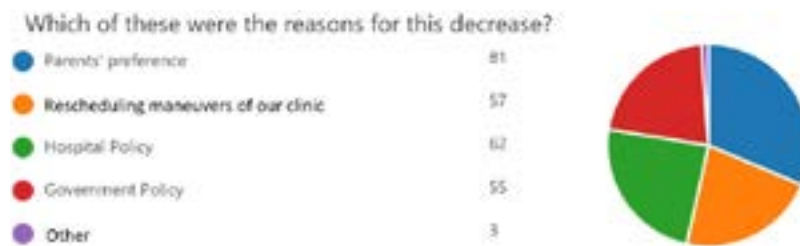
Figure 2. The reasons for the decrease in the number of patients
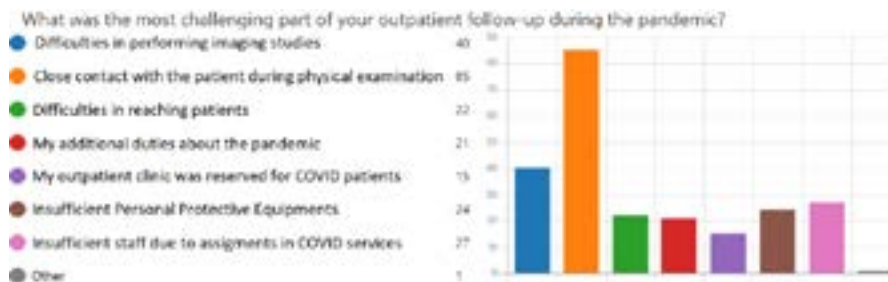
Figure 3. Difficult parts of the pandemic when doctors manage the out-patient

All participants stated that they used technological devices to solve their patients' seizure-related complaints at least once during the pandemic. There was no significant increase in the use of remote communication before and after the pandemic (Student's t-test). However, there was an increase, although not significant, among those using telemedicine. Most of the patients (77.5%) whose appointments were delayed were patients with well-controlled seizures. Of the 66 (56%) participants, there was an increase in the number of seizures in a very few number of patients whose appointments were delayed. There was no increase in the number of seizures in any of the 46 (39%) participants. Half of the participants avoided antiepileptic medication dose reduction during this period.

Many participants (62%) have reduced the number of relatives admitted to the patient's room. A considerable number of postponed EEG appointments or reduced the number of EEG appointments, but some preferred to take protective measures during EEG examinations (Figure 4). While evaluating the patient who presented with the first seizure, participants stated that they preferred different practices than the methods they used before. The most common method was the evaluation of the patient's history and video images together. (Figure 5).

When age groups were evaluated, there was no difference in out-of-hospital

communication rates with the patient (Pearson chi-square).
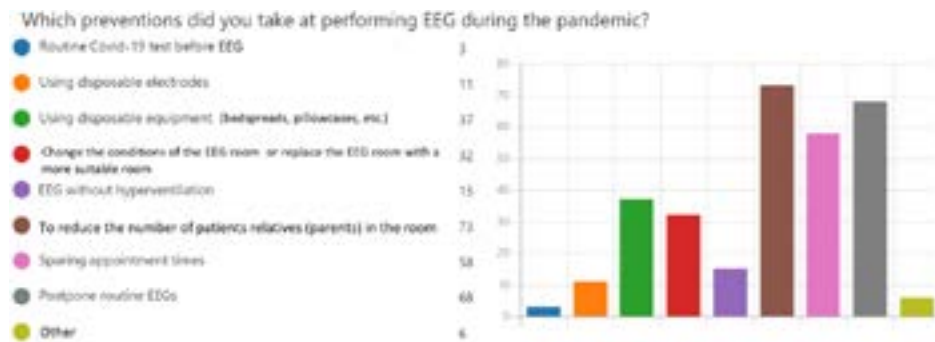
Figure 4. Which preventations did the doctors take at performing EEG during pandemic
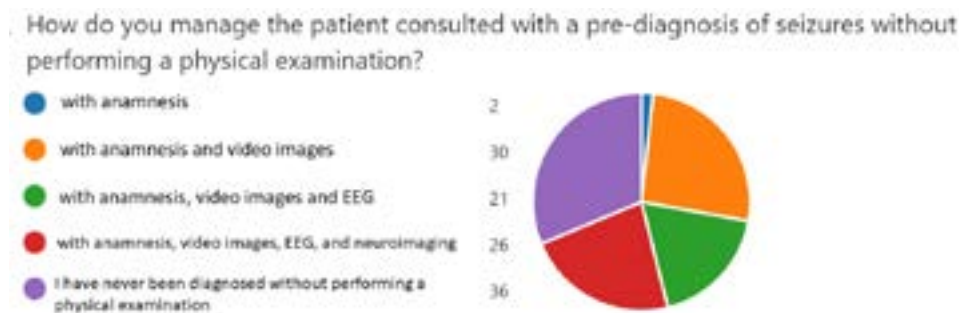
Figure 5. How the doctors manage the paient with a seizure without examination

4. Discussion

The COVID 19 pandemic has significantly impacted people, national economies, and health systems worldwide. In this period, physicians had to take some precautions to protect themselves and their patients with chronic diseases. Although guidelines have been published to manage chronic diseases during the pandemic period, each physician has created their protective measures, especially in the early period of the pandemic. Measures by Governments such as maintaining social distance and ensuring that people stay at home have reduced patients' hospital admissions other than emergencies. However, this may have caused epilepsy patients to have anxiety about reaching their physicians in an emergency. A recent study showed that patients with epilepsy during the COVID-19 outbreak have significantly higher psychological distress than the general population.[8] Anxiety reduces the quality of life in patients with epilepsy.[9] Therefore, even if the routine outpatient clinic visits of epilepsy patients were postponed, it should be ensured that they communicate with their physicians through methods other than face-to-face interviews. In our study, 96 participants (81.3%) postponed the routine outpatient visits. Instead, they stated that they used remote communication like social communication networks, telephone, video interviews, or telemedicine, at least once during the pandemic to evaluate their patients. Most of the patients (77.5%) whose appointments were delayed were patients with well-controlled seizures. No increase in seizures was observed in most patients whose outpatient visits were postponed (p <0.05). Some participants (13%) stated that due to various hospital and government policies, they

had to postpone all their patients regardless of the patient's condition, and some of the participants (8%) did not postpone any of their outpatient visits. Among the participants who postponed outpatient visits, 40% did not observe seizures in any patient, and 57% of them observed seizures in only a few patients. This result suggests that patients with well-controlled epileptic seizures can be managed without a hospital application. In the literature, no statistically significant difference was found between epilepsy patients evaluated by telemedicine methods and face-to-face communication in terms of seizure frequency.[10]

All participants stated that they had used at least one national or international 'epilepsy management in pandemic' guideline during the pandemic period. Guidelines do not recommend hospital admissions except for the first seizure, status epilepticus, and seizures that cause physical injury[1,11,12] They state that a careful medical history and video images can be used to evaluate new patients, and physical examinations and examinations can be delayed.[12] In our study, only 26% of the participants preferred to diagnose epileptic seizures with the history of and video images of the patient. However, %30 of the participants did not diagnose the patient without examining the patient, and %41 did not give up electrophysiological methods or neuroimaging. This can be partially explained by the inadequate legal regulations regarding remote communication methods in health systems in our country. It may have been difficult for physicians to leave their old habits during the diagnostic process.

It was observed that the participants who did not communicate with out-of-hospital patients in any way before the pandemic or who only communicated via e-mail were working at the university hospital and were over 50 years old. One reason for this may be that these participants are mentors of the center where they work, and that out-of-hospital communication can be achieved with their assistants. However, this determination is not significant when we compare the participants over the age of 50 and those under 50 in the whole group. Because the participants who do not use any fast communication method are in a very minority (5%).

While nearly all participants used an easily accessible communication method for their out-of-hospital patients. The official professional telemedicine usage before the pandemic was 5%. These participants' common characteristics are that they work in a private office or hospital and are between 35 and 55 years old. Although it was not statistically significant, an increase in the use of telemedicine was observed than the pre-pandemic in our study. That may indicate that it will be used more in the future. Legal regulations are needed to use the telemedicine method, which has been applied globally for years. In a study, a program to diagnose epilepsy in children could detect epilepsy with a sensitivity of 91.5% and a specificity of 88.6%.[13] In another study, an application with 11 questions diagnosed epilepsy with 88% sensitivity and 100% specificity in adult patients.[14] Therefore, in cases where the patient cannot easily reach the physician, such as the pandemic period, telemedicine or other remote communication methods might help prevent delays in diagnosis and treatment

The major limitation of our study is that it is a survey study based on the statements of the participants.

In conclusion, the outpatient clinic visits of patients with well-controlled epileptic seizures can be postponed during the pandemic period. In cases where face-to-face communication is not possible during the pandemic period, the patients' medical history and video images may help in diagnosis. Telemedicine can be useful in the long-term management of these patients, even after pandemics. Remote management of patients with epilepsy may also be useful for patients living in rural areas, distant to tertiary centers. It is necessary to establish the technical structure and make the legal regulations for the wide use of telemedicine.

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Research Article / Araştırma Makalesi

Do Angle Measurements on Two Different Projections on Hip Ultrasonography Alter the Diagnosis in Patients Being Screened for DDH?

GKD için Taranan Bebeklerde Kalça Ultrasonografisinde İki Farklı Projeksiyondaki Açı Ölçümleri Teşhisi Değiştirir mi?

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Abstract

Hip ultrasonography with the Graf method is used worldwide. Four different projections can be used for the evaluation of sonographic images. The best projection with the lowest rate of wrong interpretation is the "standing-up right"-projection and the worst is the ''horizontal-cranial left'' projection. The aim of this study was to show the concordance of two researchers using these two different projections. Hip sonographic evaluation according to the Graf method was applied to 166 infants (332 hips) comprising 84 males (50.6%) and 82 females (49.4%). The hip sonographic images were obtained in both the standing-up right and horizontal-cranial left projections. Two researchers independently measured the alpha and beta angles manually with a goniometer and classified the hip type. The alpha, beta angle measurement values, comparisons of the angles in both projections and for both researchers are presented in detail in Tables 1 and 2. The inter-observer agreement of the Graf types of hips was as follows; Graf types between researcher 1 and 2, Right hip- (standing-up right) Kappa value 0.84, Left hip- (standing-up right) Kappa value 0.77, Right hip- (horizontal-cranial left) Kappa value 0.67, Left hip- (horizontal-cranial left) Kappa value 0.64. The intraclass correlation coefficient (ICC) values of the agreement between the two researchers for all the measured hip angles were as follows; right ∝ angle ICC: 0.96, right β angle ICC: 0.91, left ∝ angle ICC: 0.93, and left β angle ICC: 0.59. Although the standing-up right projection is known to be the best projection with the lowest rate of wrong interpretation according to the Graf guidelines, the results of this study showed the evaluation of similar Graf hip types on the two projections. Therefore, the horizontal cranial left projection, which is considered to be the worst of the four projections, can be used safely for hip evaluation if the Graf checklist is followed appropriately.

Keywords: DDH, Graf-technique, Hip ultrasonography, Diagnosis, Interobserver reliability, Infant

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Özet

Graf yöntemi ile kalça ultrasonografisi dünya çapında kullanılmaktadır. Sonografik görüntülerin değerlendirilmesinde dört farklı projeksiyon kullanılabilmektedir. En az yanlış yorumlama oranı ile ''dik-sağ'' projeksiyon en iyi ve ''yatay-baş sol'' projeksiyon ise en kötü olanıdır. Bu çalışmanın amacı, iki araştırmacının bu iki değişik projeksiyondaki uyumunu göstermektir. Graf metoduna göre kalça sonografik değerlendirmesi 84 erkek (%50.6) ve 82 kız (%49.4) dan oluşan 166 (332 kalça) bebeğe uygulanmıştır. Sonografik görüntüler hem dik-sağ hemde yatay-baş sol projeksiyonda elde edilmiştir. İki araştırmacı birbirinden bağımsız olarak gonyometre ile elle alfa ve beta açılarını ölçmüş ve kalça tiplendirmesini yapmışlardır. Tablo 1 ve 2 de ayrıntılı olarak, alfa beta açı ölçüm değerleri, ve açıların her iki projeksiyonda ve her iki araştırmacıya göre karşılaştırması sunulmuştur. Kalçaların Graf tiplerinin gözlemciler arası uyumu şöyleydi; araştırmacı 1 ve 2 arasındaki Graf tipleri, Sağ kalça (dik-sağ) Kappa değeri 0.84, sol kalça (dik-sağ) Kappa değeri 0.77, sağ kalça (yatay-baş sol) Kappa değeri 0.67, sol kalça (yatay-baş sol) Kappa değeri 0.64 dür. Tüm ölçülmüş kalça açıları için iki araştırmacı arasındaki Intraclass Korelasyon Katsayısı (IKK) değerlerinin uyumu şöyleydi; sağ alfa açısı IKK: 0.96, sağ beta açısı IKK: 0.91, sol alfa açısı IKK: 0.93, ve sol beta açısı IKK: 0.59. Dik-sağ projeksiyon, Graf' ın yönergelerine göre en az yanlış yorumlama oranlarına sahip olsa da, bu çalışmanın sonuçları iki projeksiyonda da Graf kalça tiplerinin değerlendirmesinin benzer olduğunu gösterdi. Bu nedenle, dört projeksiyon içinden en kötüsü olan yatay-baş sol projeksiyon, eğer Graf'ın kontrol listesine doğru bir şekilde uyulursa kalça değerlendirmesinde güvenli bir şekilde kullanılabilir.

Anahtar Kelimeler: GKD, Graf teknik, Kalça Ultrasonografisi, Teşhis, Gözlemciler arası güvenilirlik, Bebek

1. Introduction

Hip ultrasonography started to be used for patients with Developmental Dysplasia of the hip (DDH) with the Graf technique described by Prof. Reinhard Graf in 1985. It is now widely accepted as the primary method for screening, diagnosis and follow-up of treatment of DDH in newborns (1). Since the acceptance of its utility, hip ultrasonography (USG) has come into widespread use in daily practice in many countries. Before hip USG, the most common physical examination manoeuvres used for detecting DDH were the Barlow and Ortolani manoeuvres (1). In addition to these physical examination tests, the most frequently used imaging method for both diagnosis and treatment of DDH was pelvis radiography. However, there are disadvantages to radiography for the evaluation of DDH, including the risk of radiation and that only bony structures can be seen. In the first months of life, most bony parts of the femoral head and acetabulum remain cartilaginous, which limits the use of plain radiographs for the diagnosis in infants younger than 6 months (2). Therefore, hip sonography has become important in diagnosis, especially in the first six months of an infant's life. The advantages of USG in the detection of DDH include the absence of radiation and the ability to visualise soft tissue structures such as the labrum, hyaline cartilage, and hip capsule. Hip sonography is performed in many centres by orthopaedic surgeons, radiologists, and paediatricians. Generally, orthopaedic surgeons and radiologists take the sonographic images in different ways. Radiologists usually take sonographic views in the horizontal-cranial left-sided position, and state that the images are taken in the anatomic position of the infant lying in the cradle. Orthopaedic surgeons generally take images in both the standing-up right and horizontal-cranial right-sided positions. Graf reported four different projections and stated that the best projection with the lowest rate of wrong interpretation was the "standing-up right" projection (3).

The aim of this study was to investigate whether there is a difference in both classification and angle measurements according to the Graf method between two different sonographic projections. The study hypothesis was that the evaluations made on two different projections (standing-up right and horizontal cranial-left) would be reliable and consistent with each other.

2. Materials and Methods

This retrospective study was approved by the hospital Institutional Review Board Ethics Committee. Informed consent was obtained from all the parents of the children included in the study. USG screening of the hip for DDH according to the Graf method was performed at our centre. Paediatricians referred the infants to the Radiology Department for evaluation of the hip joints especially between 4-6 weeks of life. All hip sonographies in this study were performed by the second author (AMA). For the evaluations, a 7.5 MHz linear probe was used with the two different projections of horizontal-cranial left (Fig.1a,1c) and standing-up-right position (Fig.1b,1d) and at least two sonographic views obtained for each hip joint. Two researchers then independently measured the alpha (α) and beta (β) angles with a goniometer (1) on the sonographic print-outs. The researchers measured 4 sonographic views for both the right and left hip for both projections. Three lines were drawn on the sonograms as follows; the first line was drawn parallel to the iliac wing, the second line was drawn from the lower point of the os ilium to the turning point of the bony roof (from concavity to convexity), and the third line was drawn from the turning point to the labrum. The alpha angle was calculated between the first and second lines, and the β angle was calculated between the first and third lines. After calculating the angle values, the Graf types of the hips were determined according to the Graf classification. The measured angles from the two different projections were recorded separately for each patient and the results of the two researchers were compared with each other.
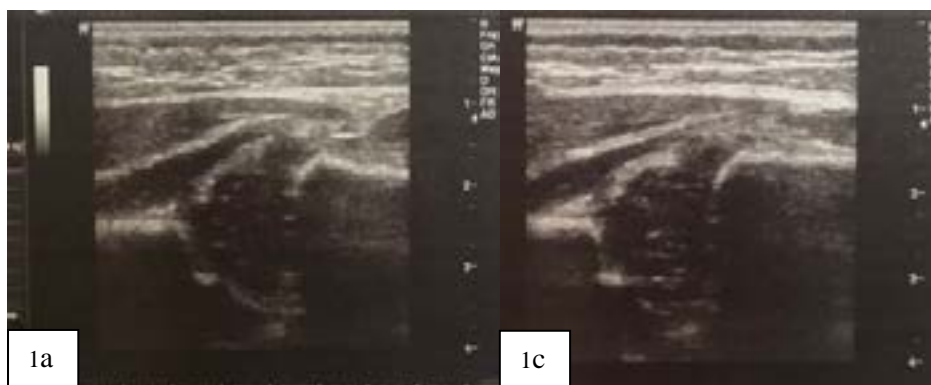
Figure 1a. Right Hip ultrasonography in Horizontal-cranial left position (Graf type 1 hip)
Figure 1c. Left Hip ultrasonography in Horizontal-cranial left position (Graf type 1 hip)
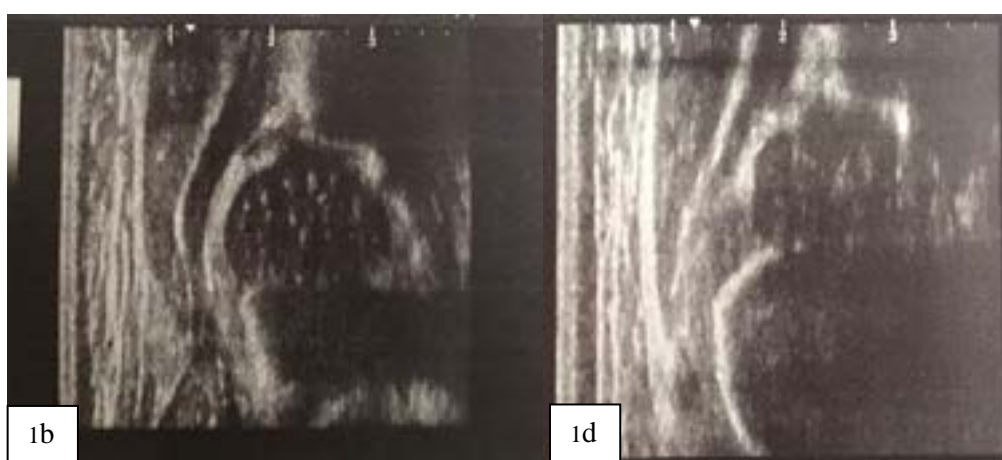
Figure 1b. Right Hip ultrasonography in Standing-up right position (Graf type 1 hip)
Figure 1d. Left Hip ultrasonography in Standing-up right position (Graf type 1 hip)

Statistical analysis

Data obtained in the study were analyzed statistically using IBM SPSS statistics vn 22 software. For the α and β angle value comparisons, ANOVA analysis was used. The Sidak test was applied to pairwise comparisons of the angle measurements. The Kappa test was used for both intra and inter-observational agreement analysis of the Graf types of the hips. The Intraclass Correlation Coefficients (ICC) were calculated in evaluation of the agreement of hip angles. A value of $p<0.05$ was considered statistically significant.

3. Results

Retrospective evaluation was made of 166 infants (332 hips), comprising 84 males (50.6%) and 82 females (49.4%) with a mean age at presentation of 46.10 days (range: 4-125 days). A total of 332 hips were evaluated by two raters and classified according to Graf type. The mean± standard deviation (SD) values of the α and β angles on the two different projections according to researchers (R) 1 and 2 are presented in detail in Table 1. The pairwise comparisons of the measured α and β angles on both projections are presented in Table 2. The mean differences between angle values and the p values of all the comparisons between the measured angles are shown in Table 2. The statistically significant p values are presented in italic and bold style format in Table 2. The numbers of hip Graf types on both projections identified by the two researchers are presented in Table 3. The results of the agreement of Graf types of hip

in the intra-observer evaluation were as follows; Researcher 1- right hip (standing-up right- horizontal cranial left) Kappa value 0.86, Researcher 1- left hip (standing-up right- horizontal cranial left) Kappa value 0.93, Researcher 2- right hip (standing-up right- horizontal cranial left) Kappa value 0.84, Researcher 2- left hip (standing-up right- horizontal cranial left) Kappa value 0.88. The inter-observer agreement of the hip Graf types was as follows; Graf types between Researchers 1 and 2, Right hip- (standing-up right) Kappa value 0.84, Left hip- (standing-up right) Kappa value 0.77, Right hip- (horizontal cranial left) Kappa value 0.67, Left hip- (horizontal cranial left) Kappa value 0.64. The intraclass correlation coefficient (ICC) values of the reliability of all the measured hip angles of the two researchers were as follows; Right α angle ICC: 0.96 (95% Confidence Interval (CI): 0.95-0.97), right β angle ICC: 0.91 (95% CI: 0.88-0.93), left α angle ICC: 0.93 (95% CI: 0.91-0.94), left β angle ICC: 0.59 (95% CI: 0.48-0.68).

Table 1. The Mean± Std. Deviation values of alpha (α) and beta (β) angles on two different projections according to Raters (R) 1 and 2

	SU-R-α	SU-R-β	SU-L-α	SU-L-β	HC-R-α	HC-R-β	HC-L-α	HC-L-β
R1	62.58±4.45	64.08±4.13	62.64±4.38	63.94±4.06	63.21±4.66	65.23±4.11	63.06±4.67	66.19±2.71
R2	63.68±4.67	65.63±3.87	62.98±4.81	66.70±4.35	63.74±4.43	65.98±3.69	62.89±4.33	66.36±5.81

Standing up-right/Right hip-α: SU-R-α
Standing up-right/Right hip-β: SU-R-β
Standing up-right/Left hip-α: SU-L-α
Standing up-right/Left hip-β: SU-L-β
Horizontal cranial-left/Right hip-α: HC-R-α
Horizontal cranial-left/Right hip-β: HC-R-β
Horizontal cranial-left/Left hip-α: HC-L-α
Horizontal cranial-left/Left hip-β: HC-L-β

Table 2. Pairwise comparisons of the measured alpha (α) and beta (β) angles on both projections by the two raters

	Mean Difference (Degrees)	p value
R1-SR-Right α/R1-HL-Right α	0.6	*0.04*
R1-SR-Right α/R2-SR-Right α	1	*0.001*
R1-SR-Right α/R2-HL-Right α	1.1	*0.001*
R1-HL-Right α/R2-SR-Right α	0.4	0.983
R1-HL-Right α/R2-HL-Right α	0.5	0.863
R2-SR-Right α/R2-HL-Right α	0	1
R1-SR-Right β/R1-HL-Right β	1.1	*0.001*
R1-SR-Right β/R2-SR-Right β	1.5	*0.001*
R1-SR-Right β/R2-HL-Right β	1.9	*0.001*
R1-HL-Right β/R2-SR-Right β	0.3	1
R1-HL-Right β/R2-HL-Right β	0.7	0.734
R2-SR-Right β/R2-HL-Right β	0.3	0.873
R1-SR-Left α/R1-HL-Left α	0.4	0.987
R1-SR-Left α/R2-SR-Left α	0.3	1
R1-SR-Left α/R2-HL-Left α	0.2	1
R1-HL-Left α/R2-SR-Left α	0	1
R1-HL-Left α/R2-HL-Left α	0.1	1
R2-SR-Left α/R2-HL-Left α	0	1
R1-SR-Left β/R1-HL-Left β	2.2	*0.001*
R1-SR-Left β/R2-SR-Left β	2.7	*0.001*
R1-SR-Left β-R2-HL-Left β	2.4	*0.001*
R1-HL-Left β-R2-SR-Left β	0.5	1

R1-HL-Left β-R2-HL-Left β			0.1	1
R2-SR-Left β-R2-HL-Left β			0.3	1

Table 3. Distribution of the Graf hip types on both projections according to the two raters

	Type 1	Type 2a	Type 2b	Type 2c
R-1 SU-Graf-R	142	20	0	4
R-1 SU-Graf-L	140	22	1	3
R-1 HC-Graf-R	140	22	0	4
R-1 HC-Graf-L	139	23	1	3
R-2 SU-Graf-R	145	18	0	3
R-2 SU-Graf-L	142	20	1	3
R-2 HC-Graf-R	143	20	0	3
R-2 HC-Graf-L	141	21	1	3

Standing up-right/Graf type-Right hip: SU-Graf-R
Standing up-right/Graf type-Left hip: SU-Graf-L
Horizontal cranial-left/Graf type-Right hip: HC-Graf-R
Horizontal cranial-left/Graf type-Left hip: HC-Graf-L

4. Discussion

Developmental dysplasia of the hip (DDH) is one of the most common musculoskeletal problems in newborns (3). DDH is characterized by an abnormal relationship between the femoral head and the acetabulum. These problems range from dysplasia, where the anatomy of the developing articulation surfaces is abnormal, to potential partial or complete dislocation of the hip joint over time. Hip ultrasonography, which was first described by Graf, has been used for the diagnosis and follow-up of DDH in children since the early 1980s (4). Since then, the use of hip sonography has spread worldwide (5). Hip sonography using this technique has reduced the conservative treatment rate and avoided over-treatment as well as operations and consequently, femoral head necrosis (3). In the Graf static method, a coronal plane image is obtained and qualitative evaluation is made of the hip bone and cartilage of acetabular components, and then classification is made based on the quantitative measurements between these components and the os ilium. The α angle represents the bony roof of the acetabulum and the β angle represents the cartilage roof (1). Graf reported that only ultrasonographic images in the standard plane are acceptable for measurement (3). In accurately defined anatomic sonographic examination, appropriate interpretation, and measurement techniques are carefully followed, and hip disorders in newborns can be easily managed using this method. If anatomical identification cannot be visualized or the standard plane is missing in a sonographic image, it is of no value and should not be used for diagnosis. In completely dislocated hips (Graf Type 3–4), non-standard sonograms can be used for the evaluation because the displacement of the femoral head avoids the visualization of the femoral head and the center of the acetabulum in the same frontal section (1).

Graf's technique of evaluation is based on a coronal image of the hip obtained from the lateral approach with the femur in anatomic position. This method emphasizes the angular measurements of acetabular landmarks, in addition to the assessment of hip position (6). All the anatomical structures previously stated by Prof. Graf (3), should be seen on the sonographic image. If the checklist is ignored, the interpretation of the image may be incorrect. A usability check (lower limb, plane, labrum) should also be kept in mind to be able to obtain more accurate results in hip sonography evaluation. Only sonograms in the standard plane are accepted for measurement (3). The Graf checklist (Fig. 2) should be checked when performing the hip sonography procedure. The Graf checklist contains the following anatomical structures; 1: Chondro-osseous border, 2: Femoral head, 3: Synovial

fold, 4: Joint capsule, 5: Labrum, 6: Cartilaginous roof, 7: Bony roof, and 8: Bony rim (concavity-convexity). If hip sonography is applied using this checklists, misdiagnosis can be prevented (3). Gunay et al. reported that except in special circumstances as previously mentioned by Professor Graf, Type 1 mature hips which have worsened over time are related to an initial incorrect diagnosis. It was concluded that if a Graf Type 1 hip was determined appropriately according to the Graf checklist, it will never worsen later in normal circumstances (7). In the current study, all the sonographic images met the Graf checklist criteria, and therefore the measurement results of the two raters were consistent with each other.

Figure 2. Standard sonogram and Graf checklist (1) (Figure 3, with the permission of Medical Ultrasonography Journal 2013, Vol. 15, no. 4, 299-303).

Graf described four view projections when performing hip sonography, and reported that the sonographic projections from best to worst were as follows; standing-up right position, horizontal-cranial right position, standing-up left position, and horizontal-cranial left position (3). Therefore in this study, the two sonographic views evaluated were the best projection and the worst projection according to Graf (3). However, it was thought that if the Graf usability and checklist rules were strictly followed, the angle measurements and the Graf classifications of the hips would show concordance even if the views were taken in different projections. The results of this study showed there were no statistically significant differences between the two projections in terms of angle measurements and Graf classifications even though the sonograms were evaluated and measured by an orthopaedic surgeon and a radiologist independently of each other. Another issue is that the amount of experience and training in hip ultrasonography has an important influence on the agreement of assessment of the hip joint. Both the raters in this study had more than 15 years of experience in hip ultrasonography. Previous studies have demonstrated that both the performance of USG and its interpretation influence the results and potential treatment (8). It has been reported that α angle measurements are more reliable and have more concordance than the measured β angles with both digital and manual measurement techniques. However, the same study showed that both measurement methods were reliable and concordant (9). The current study results were also in concordance with each other in terms of both angle measurements in different projections, although the β angles of the left hips had lower ICC (0.59) values compared to the others. Nevertheless, those β angle results did not influence the hip classification.

The diagnosis of DDH in the infant hip cannot be made solely by evaluation of the ultrasound images obtained in the standard plane without the bony roof and the cartilage roof measurements. In the Graf method, the diagnosis, classification, and follow-up treatment of infantile DDH strictly depends on the bony roof (α) angle and cartilage roof (β) angle measurements (1,10). Roovers et al. reported average standard deviations of 3.2° and 6° for the α and β angles, respectively (11). Graf stated deviations for both angle values of $\pm$ 4° (12). In another study, the angle values were compared by four groups of observers. The variability for the α angle was between 0° and 16°, and for the β angle it was between 0° and 26°. The standard deviation for the observers was lower for the α angle than for the β angle. It was stated that the study had produced similar results and could be regarded as comparably good according to literature (13). In the same study, although the variability of the α and β angles when measured on the same sonogram was high between observers, it did not lead to any false negative assessments since there was a tendency to classify hips as more severely affected than they actually were in cases of uncertainty (13). In the current study, both researchers made the hip classification of Graf type 2a instead of Graf type 1 on the right hips of 2 infants and on the left hip of 1 infant. However, the Graf type 2a hips, which were physiologically immature, returned to Graf type 1 mature hips in the latest follow-up. Therefore, these classifications did not change the final results in terms of defining type 1 mature hips. It was thought that these incorrect measurements made by both raters for three hips in this study was caused by the horizontal-cranial left position, which was previously defined by Graf as the worst projection. Nevertheless, with the exception of those three hips, all the other results were the same on the two projections.

In a study by Simon et al., the inter-observer agreement of ultrasonography measurements was investigated, and it was concluded that if the hip was immature there was no increase in the discrepancy in assessment between observers (13). Similarly, in the current study, it was thought that inter-rater agreement could be more difficult in hips which are borderline such as Graf type 2a, 2b and sometimes 2c, than fully dislocated hips such as Graf type D, 3 and 4.

This study had some limitations, primarily the low number of cases. Furthermore, each rater only measured the sonograms once, so despite inter-observer agreement, there was no evaluation of intra-observer agreement.

5. Conclusions

All the images in this study were taken according to the Graf checklist, and despite the use of two different sonographic projections to determine the angles and hip types, no major differences were determined between the two images according to the results of two independent raters. The standing-up right projection showed more agreement values between the raters than the horizontal-cranial left projection. Although Graf stated that the best projection with the lowest rate of wrong interpretation was the standing-up right projection, the results of the current study showed similar Graf hip types on both the standing-up right and the horizontal-cranial left projections. Thus, if the checklists are strictly followed, the horizontal-cranial left projection can also be safely used for the evaluation of hip joints in infants.

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Research Article / Araştırma Makalesi

Investigation of Clinical, Laboratory and Radiological Results of Novel Coronavirus Disease (Covid-19)

Yeni Koronavirüs Hastalığının (Covid-19) Klinik, Laboratuvar ve Radyolojik Sonuçlarının İncelenmesi

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Abstract

Covid-19, which emerged in China in December 2019 and spread to the whole world in a short time, has been a serious public health problem threatening humanity. In this study, we aimed to reveal demographic, clinical, laboratory and radiological features of patients diagnosed with Covid-19. The study is a retrospective cross-sectional study consisting of patients who were hospitalized in health institutions in Bolu, Turkey between 11.03.2020 and 19.04.2020 with a definitive or probable diagnosis of Covid-19. The number of patients in the study was 262. The mean age of the patients participating in the study was 57.39 ± 19.85, the youngest patient was 19 and the oldest was 94 years old. Of the patients, 40.1% was between the ages of 18-50, 59.9% were over 50 years old. 55.3% of the patients were women and 44.7% were men. Most common symptoms were fever (75.6%), cough (71.8%) and dyspnea (46.9%). Elevated CRP (in 71.3%), elevated LDH (in 56.9%), elevated D-DIMER (in 56.4%) and lymphopenia (in 30.5) were most detected laboratory abnormalities. The result of the real-time reverse-transcription polymerase chain reaction (RT-PCR) test was positive in 35.5% of 262 patients. 88.5% of the patients had chest CT findings compatible with Covid-19. Additionally, 24% had both positive RT-PCR results and CT findings compatible with Covid-19. Expected findings were found to be in older patients more than younger ones. We suggest that clinical features, laboratory abnormalities and radiological findings can be used to provide an early diagnosis and treatment of Covid-19.

Keywords: Covid-19, clinical features, radiological findings, laboratory findings.

Özet

Aralık 2019'da Çin'de ortaya çıkan ve kısa sürede tüm dünyaya yayılan Covid-19, insanlığı tehdit eden ciddi bir halk sağlığı sorunu olmuştur. Bu çalışmada Covid-19 tanısı alan hastaların demografik, klinik, laboratuvar ve radyolojik özelliklerini ortaya çıkarmayı amaçladık. Çalışma, 11.03.2020 ile 19.04.2020 tarihleri arasında Bolu ilindeki sağlık kuruluşlarında kesin veya olası Covid-19 tanısı ile hastaneye yatırılan hastalardan oluşan retrospektif kesitsel bir çalışmadır. Çalışmaya katılan hasta sayısı 262 idi. Çalışmaya katılan hastaların yaş ortalaması 57.39 ± 19.85, en genç hasta 19 ve en yaşlı hasta 94 idi. Hastaların% 40.1'i 18-50 yaş aralığında,% 59.9'u 50 yaşın üzerindeydi. Hastaların% 55,3'ü kadın,% 44,7'si erkekti. En sık görülen semptomlar ateş (% 75,6), öksürük (% 71,8) ve nefes darlığı (% 46,9) idi. Yüksek CRP (% 71.3'te), yüksek LDH (% 56.9'da), yükselmiş D-DIMER (% 56.4'te) ve lenfopeni (30.5'te) saptanan laboratuar anormallikleriydi. Gerçek zamanlı ters transkripsiyon polimeraz zincir reaksiyonu (RT-PCR) testinin sonucu 262 hastanın% 35,5'inde pozitifti. Hastaların% 88,5'inde Covid-19 ile uyumlu göğüs BT bulguları vardı. Ek olarak,% 24'ü hem pozitif RT-PCR sonuçlarına hem de Covid-19 ile uyumlu BT bulgularına sahipti. Beklenen bulguların, gençlere göre yaşlı hastalarda daha fazla olduğu bulundu. Covid-19'un erken tanı ve tedavisi için klinik özelliklerin, laboratuvar anormalliklerinin ve radyolojik bulguların kullanılabileceğini önermekteyiz.

Anahtar Kelimeler: covid-19, klinik özellikler, radyolojik bulgular, laboratuvar bulguları

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1. Introduction

In December 2019, a group of pneumonia cases with unknown etiology were detected in Wuhan, China. After investigating these cases, it was concluded that there might a common agent. Thereafter, it was found to be a new type in the coronavirus family (1). On February 11 2020, this disease caused by novel coronavirus was named Covid-19 by the World Health Organization (WHO) (2). The first death due to Covid-19 occurred in China on January 9, 2020 and within weeks following, deaths were reported in Thailand, Japan and Europe. Since Covid-19 started to be seen all over the world, WHO defined it as a pandemic on March 11, 2020 and determined its center as Europe (3,4).

Before December 2019, 6 subtypes of coronavirus were known to infect humans, causing respiratory diseases. 4 of those are HCoV - 229E, HCoV - OC43, HCoV - NL63 and HKU1 and they mostly cause mild upper respiratory tract infections. However, despite occurring rarely, they can cause serious respiratory system infections in infants, children and the elderly (5). SARS-CoV and MERS-CoV, other types of coronavirus, cause more serious and dangerous infections (6). It is thought that the nucleotide structure of SARS-CoV2, which is the cause of Covid-19, is similar to that of bats and the origin of the disease may be bats (7).

The course of Covid-19 is defined in 5 groups according to its clinical severity. As for these groups; asymptomatic cases are patients who do not show any clinical symptoms and are positive for the SARSCoV-2 RT-PCR test. In mild clinical cases, there are signs of acute upper respiratory tract infection such as fatigue, muscle pain, cough, sore throat, sneezing and runny nose. In the group with moderate clinical course, the clinical presentation is pneumonia accompanied by fever, cough and sometimes wheezing, but dyspnea and noticeable hypoxemia aren't expected. In severe clinical cases, there are signs and symptoms such as dyspnea, central cyanosis, oxygen saturation less than 92% and hypoxemia which progress rapidly in one week. In critical cases, clinical pictures such as acute respiratory distress syndrome (ARDS), respiratory failure, shock, and multiple organ disorders may appear. [8, 9]

In previous studies, it is not known how long SARS-CoV-2 can survive on the surfaces, but it is thought it may remain alive for a few hours on inanimate surfaces. (10) According to the studies, it is estimated that the incubation period is considered as 5.2 days (1-12.5), but it can last up to 14 days. (11) In our study, clinical, laboratory and radiological results of both definitive and probable cases of Covid-19 were compiled. Those who have a positive RT-PCR test were defined as definitive cases. Some cases had very typical clinical and particularly radiological findings although their RT-PCR results weren't positive, they were assumed as probable case.

Our aim in this study is to show that assessment of clinical, laboratory and radiological findings together may help for providing an early diagnosis and treatment of Covid-19.

2. Materials and Methods

This is a retrospective, cross-sectional study consisting of patients who were hospitalized in health institutions affiliated to City Health Administrative of Bolu, Turkey between 11.03.2020 and 19.04.2020 with a definitive or probable diagnosis of Covid-19. Ethical approval of the study was obtained from Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (Date: 12.05.2020, Number: 2020/93).

The number of participants in the study was 262. Written informed consent was obtained from all the patients. Data was collected by scanning the patients retrospectively from the Public Health Management System of City Health Administrative and Hospital Information Management System. Data concerning the patients consisted of age, gender, results of RT-PCR samples, results of laboratory parameters such as white blood cell (WBC), red blood cell (RBC), lymphocyte (LYM), hemoglobin (HGB),

basophile (BASO), platelet (PLT), plateletcrit (PCT), neutrophil (NEU), monocyte (MONO), D-DIMER, C-reactive protein (CPR) and lactate dehydrogenase (LDH), chest computerized tomography (CT) results and clinical findings including fever, cough, dyspnea, anosmia, diarrhea, headache, joint pain, anorexia and sore throat. Tables were made using data. Patients under the age of 18 and those who did not want to participate in the study were not included.

The analysis of the data obtained as a result of the research was carried out in SPSS 23 statistical package program. Descriptive statistical methods (frequency, arithmetic mean, standard deviation, cross tables) were used. The appropriateness of the distribution of the data to the normal distribution was checked by skewness and kurtosis coefficients, and ± 1 interval was taken as reference (12). All of the laboratory data did not show normal distribution. Mann-Whitney U test and Kruskal Wallis tests were used for data which was not suitable for normal distribution. For data which fits a normal distribution, Scheffe test was used in case of homogeneity of variances from post-hoc tests. Chi-square test was used in the analysis of categorical data.

3. Results

Table 1. Demographic characteristics, RT-PCR and Chest CT Results

Demographic Features		$\overline{x}$ ±SS	min-max
Mean Age		57,39± 19,85	19-94
		N	%
Age Groups	18-50	105	40,1
	51 and above	157	59,9
Gender	Woman	145	55,3
	Man	117	44,7
RT-PCR Results	Positive (+)	93	35,5
	Negative (-)	169	64,5
Absence or presence of chest CT findings	Present	232	88,5
	Absent	5	1,9
	Didn't undergo	25	9,5
Location of chest CT findings	Right lung	43	16,4
	Left lung	30	11,5
	Bilateral	159	60,7
PCR+ CT+		63	24,0
PCR+ CT-		25	9,5
PCR+ CT (without a CT scan)		5	1,96
PCR- CT+		169	64,5

It was determined that the mean age of the patients participating in the study was 57.39 ± 19.85, the youngest patient was 19 and the oldest was 94 years old. Of the patients, 40.1% was between the ages of 18-50, 59.9% was over 50 years old. 55.3% of the patients were women and 44.7% were men. The result of RT-PCR test was positive in 35.5% of 262 patients. 88.5% of the patients had chest CT findings compatible with Covid-19.

Additionally, 24% had both positive RT-PCR results and chest CT findings compatible with Covid-19. Among patients who had CT findings of Covid-19, 60.7% had bilateral findings, 27.9% had unilateral findings. Among those who showed unilateral findings 16.4% were found to be in the right lung and 11.5% in the left (Table 1).

Moreover, among 232 patients who had CT findings compatible with Covid-19, there was a statistically significant relationship between the age groups (p = 0.002 <0.05). Of 232 patients, 84 (36.2%) were between the ages of 18-50 and 148 (63.8%) were 51 years old and above.

Table 2. Clinical features of the patients

Symptoms	Presence of symptoms	Absence of symptoms	p-value
Fever	198 (%75,6)	64 (%24,4)	**0,020***
Cough	188 (%71,8)	74 (%28,2)	**0,005***
Dyspnea	123 (%46,9)	139 (%53,1)	**0,025***
Diarrhea	50 (%19,1)	212 (%80,9)	0,566
Headache	32 (%12,2)	230 (%87,8)	0,298
Joint Pain	27 (%10,3)	235 (%89,7)	0,061
Anorexia	16 (%6,1)	246 (%93,9)	0,365
Sore throat	35 (%13,4)	227 (%86,6)	0,328
Anosmia	12 (%4,6)	250 (%95,4)	0,163
* a value of p<0,05 was taken as significant ** Chi-Square test			

To evaluate the relationship between the presence of symptoms in 262 patients; fever, cough and dyspnea were statistically significant (p = <0.05). Among patients with a definitive or probable diagnosis of Covid-19; fever (75,6%), cough (71.8%) and dyspnea (46.9%) were the most frequent symptoms. Diarrhea (19.1%), headache (12.2%), joint pain (10.3%), anorexia (6.1%), sore throat (13,4%) and anosmia (4.6%) were the other symptoms (Table 2).

Table 3. Analysis of laboratory parameters according to the age groups

Analysis of laboratory parameters according to the age groups			
	''18-50'' age group	''51 and above'' age group	p-value
	Median (Min-Max)**		
WBC	7 (2,1-19,8)	7,69 (1,25-26)	0,129
RBC	4,89 (3,47-6,53)	4,44 (1,08-5,78)	**0,000***
LYM	1,78 (0,484-4,75)	1,2 (0,3-4,86)	**0,000***
HGB	14,4 (7,3-18,2)	13 (3,69-17,2)	**0,000***
BASO	0,051 (0-0,6)	0,046 (0-0,9)	0,742
PLT	211 (76-603)	213 (20,5-712)	0,804
PCT	0,178 (0,058-0,396)	0,177 (0,02-0,547)	0,929
NEU	4,4 (0,7-16,5)	5,51 (0-21,7)	**0,005***
MONO	0,567 (0,187-1,89)	0,535 (0,064-2,52)	0,262
D_DİMER	0,39 (0,03-8,36)	1,16 (0,1-19,93)	**0,000***
LDH	221,5 (80-863)	264,5 (54,9-1491)	**0,000***
CRP	8,545 (0-282,7)	36,5 (0-355)	**0,000***
* a value of p<0,05 was taken as significant ** Mann-Whitney U test			

Mean RBC, LYM, HGB, D-DIMER, NEU, LDH and CRP values differed significantly between the age groups (p <0.05). Mean RBC, LYM and HGB values in the ''18-50 ''age group were higher. On the other hand, mean D-DIMER, NEU, LDH and CRP values were higher in the ''51 and above'' age group (Table 3).

Table 4. Analysis of laboratory parameters according to RT-PCR results

Analysis of laboratory parameters according to RT-PCR results			
Parameters	**PCR (+)**	**PCR (-)**	**p-value**
	Median (Min-Max)**		
WBC	5,5 (2,1-15)	9,04 (1,25-26)	**0,000***
RBC	4,72 (1,08-6,24)	4,54 (1,17-6,53)	**0,001***
LYM	1,49 (0,4-4,75)	1,4 (0,3-4,86)	0,386
HGB	13,9 (3,69-17,2)	13,3 (5,5-18,2)	**0,004***
BASO	0,035 (0-0,6)	0,061 (0-0,9)	**0,000***
PLT	199 (96-444)	229 (20,5-712)	**0,001***
PCT	0,165 (0,089-0,33)	0,186 (0,02-0,547)	**0,001***
NEU	3,45 (0,7-12,7)	6,61 (0-21,7)	**0,000***
MONO	0,497 (0,1-1,38)	0,6 (0,064-2,52)	**0,004***
D_DİMER	0,42 (0,03-11,7)	0,97 (0,032-19,93)	**0,000***
LDH	232 (80-644)	261,5 (54,9-1491)	**0,013***
CRP	7,25 (0-162,8)	36,5 (0-355)	**0,000***
* a value of p<0,05 was taken as significant ** Mann-Whitney U test			

The relationship between the results of RT-PCR test and laboratory findings were as follows; The mean WBC, BASO, PLT, PCT, NEU, MONO, D-DIMER, LDH and CRP values were found to be higher in patients with negative RT-PCR results (p <0.05). However, it was found that those with positive RT-PCR results had significantly higher mean RBC and HGB values (Table 4).

The relationship between CT findings and laboratory results of patients with positive RT-PCR results was also analyzed; the mean WBC and NEU values were found to be significantly higher in those who had no findings consistent with Covid-19 in chest CT, while the mean LDH and CRP values were significantly higher in those who had findings consistent with Covid-19 in chest CT.

Table 5: Analysis of laboratory parameters according to their reference ranges

	Low	**Normal**	**High**
WBC	39 (% 14,9)	169 (% 64,5)	54 (% 20,6)
RBC	37 (%14,1)	212 (%80,9)	13 (% 5)
HGB	40 (%15,3)	221 (%84,4)	1 (%0,4)
PLT	22 (%8,4)	232 (%88,5)	8 (%3,1)
NEU	9 (%3,4)	177 (%67,6)	76 (%29)
LDH	3 (%1,1)	76 (% 29)	149 (%56,9)
LYM	80 (%30,5)	182 (%64,5)	-
CRP	-	75 (%28,7)	186 (%71,3)
D_DİMER	-	96 (% 43,6)	124 (% 56,4)
MONO	-	224 (%85,5)	38 (%14,5)
PCT	-	262 (%100)	-
BASO	-	229 (%87,4)	33 (%12,6)

Among 262 patients who had a definitive or probable diagnosis of Covid-19; the WBC count was below the normal range in 39 (14.9%) patients and above the normal range in 54 (20.6%) patients; the RBC count was lower than the normal range in 37 (14.1%)

patients and higher than the normal range in 13 (5%) patients; HGB level was below the normal range in 40 (15.3%) patients and above the normal range in 1 (0.4%) patient; 22 (8.4%) patients had the PLT count lower than the normal range in and 8 (3.1%) patients had higher levels than the normal range; the NEU count was lower than the normal range in 9 (3.4%) patients and higher than the normal range in 76 (29%) patients; LDH was found to be decreased in 3 (1.1%) patients and increased in 149 (56.9%)patients; the LYM count was below the normal range in 80 (30.5%) patients; CRP increased in 186 (71.3%) patients; there were 124 (56.4%) patients with an increased level of D-DİMER; the BASO count was higher than the normal range in 33 (%12,6); the MONO count was above the normal range in 38 (%14,5) patients.

4. Discussion

Our study was performed cross-sectionally and retrospectively. It consisted of 262 patients with a definitive or probable diagnosis of Covid-19. Demographic characteristics, clinical features, laboratory abnormalities and chest CT imaging results of the patients were evaluated.

Fever, cough, dyspnea, sore throat, weakness and muscle pain are the most common symptoms of Covid-19. Besides, symptoms such as anorexia, nausea and diarrhea can be seen. (13,14). In a meta-analysis study performed with 656 patients, fever was found in 88.7%, cough in 57.6% and dyspnea in 45.6%. Other common symptoms were recorded as weakness (29.4%), sputum (28.5%), sore throat (11%), headache (8%) and diarrhea (6.1%) (15). In our study, the most common symptoms were fever (75.6%), cough (71.8%) and dyspnea (46.9%). The other symptoms were diarrhea (19.1%), headache (12.2%), joint pain (10.3%), anorexia (6.1%), sore throat (13.4%) and anosmia (4.6%). The percentages of fever, cough and dyspnea were found to be significantly higher (p = <0.05).

In a study conducted by Zhou et al, patients' clinical, laboratory and radiological findings were evaluated. The most common symptoms in the study were fever (94%), cough (79%), weakness (23%), myalgia (15%), diarrhea (5%) and nausea (4%). Lymphopenia was found in 40% of the patients, leukopenia in 17%, leukocytosis in 21%, anemia in 15% and thrombocytopenia in 7%. The other findings were elevated ALT (31%), elevated troponin (17%), elevated D-DIMER (42%) and elevated ferritin (80%). The most detected radiological finding in the study was ground glass opacity (71%). Pulmonary infiltration was found to be bilateral in 75% of the patients (16). In our study, radiological findings compatible with Covid-19 were detected in 88.5% of the patients who underwent a chest CT scan. Detected CT findings were bilateral in 60.7% of patients and were unilateral in 27.9% (16.4% in the right lung, 11.5% in the left lung). Among 232 patients possessing radiological findings, 84 (36.2%) were in the"18-50" age group and 148 (63.8%) were in the ''51 and above '' age group. The older patients were found to have more radiological findings than the younger ones had and the difference was statistically significant.

In a study, laboratory parameters of patients diagnosed with Covid-19 were studied, 63% had lymphopenia, 25% had leukopenia and CK, procalcitonin, HGB and PLT were measured as normal (17). In our study, elevated CRP (71.3%), elevated LDH (56.9%), elevated D-DIMER (56.4%), lymphopenia (30.5), neutrophilia (29%), leukocytosis (20.6%), anemia (15.3%), leukopenia (14.9%), basophilia (12.6%), monocytopenia (14.5%) thrombocytopenia (8.4%) and neutropenia (3,4%) were detected laboratory abnormalities. Laboratory parameters of RT-PCR positive patients were also analyzed according to chest CT findings; the mean LDH and CRP values were significantly higher in patients with compatible CT findings compared to those without any CT findings associated with Covid-19. Additionally, the mean WBC, BASO, PLT, PCT, NEU, MONO, D-DIMER, LDH and CRP values were found to be higher in patients with negative RT-PCR results. On the other hand, patients with positive RT-PCR results had significantly higher mean RBC

and HGB values. The fact that mean WBC, BASO, PLT, PCT, NEU, MONO, D-DIMER, LDH and CRP results were significantly higher in those with negative RT-PCR results can be explained by inadequate sensitivity of PCR method and high sensitivity of CT scan. All the mentioned patients had chest CT findings consistent with Covid-19 in spite of not having positive RT-PCR results.

In a study evaluating the hematological parameters of patients diagnosed with Covid-19, leukopenia was found in 29.2% of the patients, lymphopenia in 36.9% and thrombocytopenia in 20%. In the study, only 1 patient had severe leukopenia and none had severe thrombocytopenia. Severe lymphopenia was observed in 5 patients (18). In a meta-analysis study, it was suggested that thrombocytopenia might be associated with severity of covid-19 (19). As mentioned above, in our study, findings such as lymphopenia, leukopenia and thrombocytopenia were 30.5%, 14.9% and 8.4%, respectively and were found to be similar to previous studies.

In our study, in accordance with our expectation, laboratory abnormalities were mostly seen in elderly patients. The mean D-DIMER, LDH and CRP values were found to be higher in patients aged 51 years and older. The difference was statistically significant. However, the mean LYM value was lower in the older patients.

In a study researching the role of chest CT imaging for early diagnosis of Covid-19, the initial chest CT reports made a correct interpretation in 49 of 51 patients before the diagnosis was confirmed by RT-PCR test and only an error of 3.9% appeared (20). RT-PCR test was positive for 93 patients in our study. Of 93 patients, 63 (67.7%) had radiological findings compatible with Covid-19 on their initial chest CT. Among all 262 patients included in our study, the rate of presence of CT findings was 88.5%, while the rate of positive RT-PCR results was only 35.4%. Because of low sensitivity (45-60%) of some RT-PCR kits (21), and high sensitivity of chest CT imaging compared to RT-PCR test (22), we suggest CT imaging can be

considered as a diagnostic tool for Covid-19. Moreover, although RT-PCR is accepted as gold standard for diagnosis of Covid-19, it can't be performed in every health institution. Furthermore, results may be false negative because of various factors like the usage of RT-PCR kits with low sensitivity.

In a retrospective study conducted by Shi et al., radiological findings of 81 patients were evaluated. In the study, ground glass opacity was detected in 65% of the patients (23). In another study, ground glass opacity was the most detected radiological finding, similarly. In that study, a single lesion was detected on the initial CT in some patients. It was revealed that the lesions were mostly seen in the lower and middle zones (24). In our study, chest CT was ordered to 237 patients. CT findings compatible with Covid-19 were found to be in 88.5% of the patients who underwent a chest CT scan. CT findings were bilateral in 60.7% and unilateral in 27.9%. The most common finding was ground glass opacity. Consolidation was also detected in some patients. In our study, similar to previous studies, it was shown that radiological findings were frequent and mostly bilateral in Covid-19. The most common finding was recorded as ground glass opacity. Although some of our patients were detected with filiation method at the asymptomatic stage, the frequency of radiological findings was quite high.

We suggest that an evaluation of clinical and laboratory findings together with radiological findings may help to make a pre-diagnosis. Thus, isolation and treatment of the patients can be provided at an early stage before confirming the definitive diagnosis. Through this method, it would be easier to prevent the spread of the disease and the deterioration of the prognosis of the patients.

5. Conclusion

Covid-19 infection has emerged as an important public health problem affecting our country and our world. Recognizing the disease and starting a treatment at an early stage would help to reduce the destruction caused by the disease. RT-PCR is accepted as

the gold standard for the diagnosis of Covid-19. However, due to the fact that PCR tests could not be carried out in every health center and the results can be affected by various factors such as some PCR kits with low sensitivity, requirement of using other diagnostic tools shows up for early diagnosis. For this purpose, evaluation of clinical and laboratory features together with radiological findings would be an alternative diagnostic method. In this way, it would be possible to provide a treatment for Covid-19 without waiting for RT-PCR results. Our study and some previous studies support that kind of diagnostic approach. Since the patients in our study are limited to a certain region, comprehensive studies with more patients in more than one center will be more informative.

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Reliability and validity of the Turkish version of the Lasa Physical Activity Questionnaire (LAPAQ)

Lasa Fiziksel Aktivite Anketi'nin (LAFAA) Türkçe Versiyonunun Güvenirliği ve Geçerliği

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Abstract

LASA Physical Activity Questionnaire (LAPAQ) is frequently used for the elderly population in the literatüre, and its validity-reliability studies have been carried out. There are also comparative studies with other physical activity questionnaires. This study's aim is to investigate the reliability and validity of the Turkish version of the LAPAQ (LAPAQ-T) for elderly individuals. One hundred and seven elderly were included in the study. LAPAQ-T and Physical Activity Scale for the Elderly (PASE) were administered to the individuals participating in the study on the first day. LAPAQ-T was re-applied by the same physiotherapist 1 week after the first evaluation to measure test-retest reliability. The test-retest took place with the participation of 27 people. The intra-class correlation coefficient (ICC) was used to evaluate test-retest reliability. The ICC value for test-retest reliability was found to be 0.977, which suggests excellent test-retest reliability. A high correlation was found between the LAPAQ-T total score and the PASE total score (r=0.703, p<0.001). The results of our study show that the LAPAQ-T is a reproducible, reliable and valid questionnaire that evaluates the level of physical activity for elderly individuals. Therefore the questionnaire will be useful for clinicians in evaluating physical activity.

Keywords: Elderly, physical activity, reliability, validity

Özet

LASA Fiziksel Aktivite Anketi' nin (LAFAA) literatürde yaşlı popülasyonda sıklıkla kullanılmakta ve geçerlik-güvenirlik çalışmaları yapılmış olup, diğer fiziksel aktivite anketleri ile karşılaştırmalı çalışmaları da bulunmaktadır. Bu çalışmanın amacı LAFAA'nın Türkçe Versiyonunun yaşlı yetişkinlerde güvenirliğini ve geçerliğini araştırmaktı. Çalışmaya yüz yedi yaşlı yetişkin dahil edildi. Çalışmaya katılan bireylere ilk gün LAFAA-T ve Yaşlılar için Fiziksel Aktivite Ölçeği (PASE) uygulandı. Test-tekrar test güvenilirliğini ölçmek için ilk değerlendirmeden 1 hafta sonra LAFAA-T aynı fizyoterapist tarafından tekrar uygulandı. Test-tekrar test 27 kişinin katılımı ile gerçekleşmiştir. Test-tekrar test güvenilirliğini değerlendirmek için sınıf içi korelasyon katsayısı (ICC) kullanıldı. Test-tekrar test güvenilirliği için ICC değeri 0,977 olarak bulundu, bu durum mükemmel test-tekrar test güvenilirliğini gösterdi. LAFAA-T toplam puanı ile PASE toplam puanı arasında yüksek ilişki bulundu (r = 0.703, p <0.001). Çalışmamızın sonuçları, LAFAA-T'nin yaşlı yetişkinlerde fiziksel aktivite düzeyini değerlendiren tekrarlanabilir, güvenilir ve geçerli bir anket olduğunu göstermektedir. LAFAA-T'nin fiziksel aktiviteyi değerlendirmede klinisyenler için faydalı bir anket olacağını düşünüyoruz.

Anahtar Kelimeler: Yaşlı, fiziksel aktivite, güvenirlik, geçerlik

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1. Introduction

In recent years, the importance of physical activity has started to be further emphasized to remind that individuals are a productive part of society in old age, to eliminate the shortcomings, activity limitations and the limitations in social participation that occur with aging, and to ensure that they maintain their lives independently (1). Physical activity is considered as one of the most important components of physical and mental well-being in elderly individuals (2). Regular physical activity in the elderly is important to maintain health and functional ability. Furthermore, it has been shown in the studies that regular physical activity in elderly individuals has many beneficial effects on health and physical fitness. In addition to its effects on cardiovascular, neurophysiological, and musculoskeletal system health, it also has many proven benefits for body composition and metabolism (3). The complex structure of physical activity makes it difficult to evaluate it in all its aspects and investigate its effect on outcome parameters (e.g., energy expenditure). Due to this complex structure, there is no absolute gold standard in the evaluation of physical activity (4). Demographic features such as culture, sex and age, diseases, and motivation and cognitive functions are effective in determining physical activity. It is difficult and complex to determine the level of physical activity, especially in elderly individuals (5). Specific physical activity questionnaires have been developed for old individuals because they often have memory problems, faster fatigue response, and difficulty in following up their physical activity, and because they are less active than young people (6). These questionnaires are advantageous compared to other methods because they are cheap to use and provide ease of use in comprehensive studies. However, many of the questionnaires used to assess physical activity have been developed to assess young and middle-aged individuals (7-9). Physical activity questionnaires used in Turkey are limited. One of the questionnaires of which the Turkish version study has been carried out among physical activity questionnaires is the International Physical Activity Questionnaire (IPAQ). Another one is the Physical Activity Assessment Questionnaire (PAAQ) developed and frequently used in our country. However, these questionnaires have been applied only to the young and middle-aged population and have not been applied to elderly individuals (10). The physical activity questionnaires frequently used in old individuals in the literature are the Community Health Activities Model Program for Seniors physical activity questionnaire (CHAMPS) (11), Yale Physical Activity Scale (YPAS) (6), and the Physical Activity Scale for the Elderly (PASE) (12). Among physical activity questionnaires for the elderly, PASE is the only questionnaire, the Turkish version study of which has been carried out (7). The LASA physical activity questionnaire (LAPAQ) for old individuals is one of these questionnaires. The LAPAQ for elderly individuals does not have a Turkish cultural adaptation and validity-reliability study, as other questionnaires frequently used in studies. The LAPAQ is frequently used for elderly population in the literature and its validity-reliability studies have been carried out, and there are also comparative studies with other physical activity questionnaires (9). Since its Turkish version and cultural adaptation studies have not been carried out, it cannot be used in studies conducted on elderly individuals in our country. The advantages of this questionnaire over others are its short application time, easy scoring, and applicability by letter or phone. Especially since there are not enough international questionnaires used in elderly population with proven validity and reliability, it is difficult to make an evaluation in elderly individuals due to the physical and mental problems in them. Therefore, an international questionnaire with the proven validity and reliability in our country has become an important deficiency and need in the evaluation of elderly individuals.

This study's aim is to investigate the reliability and validity of the Turkish Version of the LAPAQ (LAPAQ-T) in elderly individuals.

2. Materials and Methods

Patients and Setting

Volunteers over 65 years of age who applied to the Physiotherapy and Rehabilitation Department were included in the study.

The individuals who volunteered to participate in the study were signed the informed consent form. This study was approved by the Non-Interventional Research Ethics Committee of Hacettepe University (Decision No: GO 18/261-37). The socio-demographic data (age, height, weight, educational level, marital status, etc.), background, family history, and history of fall of all the individuals who participated in the study were recorded. The Mini-Mental State Examination (MMSE) was used to determine the general cognitive status of elderly individuals. Volunteer individuals over 65 years of age, with a good cognitive level (13) (MMSE of 24 and above), who could be mobilized independently were included in the study. Elderly individuals who had severe chronic diseases (cardiovascular disease, chronic obstructive pulmonary disease, uncontrollable hypertension, diabetes, etc.) that might be contraindicated for moderate and intense physical activity, were diagnosed with cognitive disorder and had undergone surgery in the last six months were not included in the study.

LAPAQ-T and PASE were administered to the individuals participating in the study on the first day. LAPAQ-T was re-applied by the same physiotherapist 1 week after the first evaluation to measure the test-retest reliability.

Instruments

LASA Physical Activity Questionnaire

The LAPAQ is a face-to-face questionnaire that covers outdoor walking, cycling, gardening, light home activities, heavy household activities, sports and maximum living conditions. The activities carried out in the last two weeks are questioned. It includes a total of 31 questions. Scoring in the LAPAQ is performed according to the duration of activities: the activity durations are classified as 0, 1-15, 16-30, 31-60 and 61-120 min and > 120 min per day and are scored as 0, 1, 2, 3, 4, and 5, respectively. For each activity, the total score of the LAPAQ within two weeks is calculated by multiplying the frequency of the activity and the time score. For example, if an individual walked for 45 min 8 times in the last two weeks, the total score is 3x8=24. If he walked more than once in a day, the total time in two weeks is calculated, and the average time in one day is calculated by dividing it by 14. The point equivalent of this time is multiplied by 14. For example, if an individual walked for 10 min 45 times in two weeks (45x10)/14=32 minutes= 3 points, and the total score= 3x14=42. The total activity score is calculated by summing the scores of all activities over two weeks (9). High scores show better physical activity levels.

Scoring of the Physical Activity Scale for the Elderly

The validity of a measuring instrument can be determined by comparing that measuring instrument with other known and accepted measurements. To this end, PASE, of which validity and reliability studies in Turkish have been carried out, was used to test its validity in the study (7). PASE was developed in 1993 to evaluate the leisure, work, and household physical activity components. The PASE can be applied by personal interview, telephone, or post. The PASE questions participants' walking, mild, moderate and intense sports and recreation activities, muscle strength and endurance exercises, work-related activities including walking and standing, lawn and garden maintenance, care of another person, home repair, the intensity, frequency, and duration of heavy and light household activities within the last week. The PASE score is calculated based on the weight of a PASE assigned for each of the different activities that the participants took part in within the last week. Activity frequencies and activity weights are multiplied to obtain the PASE scores of activities. The PASE scoring

is done without including the question of sitting activities, which is the first one of leisure time activity questions, in the evaluation (12).

Translation and Cross-Cultural Adaptation

First of all, to study the validity and reliability of the LAPAQ, permission was obtained from the owner of the scale, Vianda S Stel, and the guidelines of Beaton et al. were used for transcultural compatibility during the translation process (14). The original questionnaire was independently translated into Turkish. In the first stage, it was translated into Turkish by two independent experts who knew English at a good level. Two separate Turkish translations were compared by the researchers for inconsistencies. After comparison, a Turkish version was obtained. These text were again translated into English by two independent people, who were English native speakers and who knew Turkish at a good level and were far from medicine The Turkish version was compared with the original English version to detect possible interpretation errors and nuances that might have been overlooked. The Turkish version was then jointly evaluated by four translators, domain expert researchers to assess the need for cultural adaptation. After a pilot study was performed on 20 elderly individuals, the LAPAQ was finalized into Turkish without cultural adaptations.

Statistical Analysis

Reliability

Test-retest reliability is one of the most commonly used reliability analysis methods. Test-retest reliability is found by giving a measuring instrument to the same group, with two different applications under the same conditions and then by calculating the correlation of the scores obtained in these two applications. To determine the test-retest reliability in the study, the Turkish version of the LAPAQ was applied again after one week considering this parameter. The test-retest took place with the participation of 27 people. The intra-class correlation coefficient (ICC) was used to evaluate test-retest reliability. The ICC varies between 0.00 and 1.00. Values between 0.50 and 0.75 indicate modarete reliability, between 0.75 and 0.90 indicate good reliability and values above 0.90 indicate excellent reliability (15). Cronbach's alpha coefficient (α) was calculated for internal consistency. Cronbach's alpha value is ≥ 0.9 excellent, $0.7 \leq \alpha < 0.9$ good, $0.6 \leq \alpha < 0.7$ acceptable, $0.5 \leq \alpha < 0.6$ weak, $\alpha < 0.5$ unacceptable (16).

Validity

In this study, construct validity was evaluated by comparing the results of the LAPAQ and PASE. The construct validity coefficients (r) were accepted as 0.81-1.0 excellent, 0.61-0.80 very good, 0.41-0.60 good, 0.21-0.40 moderate, and 0-0.20 weak. Construct validity was measured with the Spearman correlation coefficient (17).

3. Results

Demographic Characteristics

One hundred and seven elderly individuals (41 females and 66 males) were included in the study. The test-retest was completed with 27 people. The socio-demographic data of individuals are shown in Table 1.

Table 1. Socio-Demographic Characteristics and Clinic Data of the Elderly individuals (n: 107)

		Min-Maks
Age, years, mean ± SD	71.66±3.87	66-79
Height, cm, mean ± SD	165.40±8.27	145-183
Weight, kg, mean ± SD	75.75±12.03	52-115
Body mass index, kg/m^2, mean ± SD	27.81±4.70	18.52-42.22

Gender		
Female, n (%)	41(38.3)	
Male, n (%)	66(61.7)	
LAPAQ, mean± SD (n=107)	45.62±36.67	0-156
PASE, mean± SD (n=107)	64.60±45.24	0-183.50

LAPAQ: LASA Physical Activity Questionnaire; PASE: Physical Activity Scale for the Elderly; SD: standart deviation

Test-Retest Reliability

There was a very high correlation between the LAPAQ-T 1st and 2nd measurement values (r=0.940, p<0.001) (Table 2). The ICC value for test-retest reliability was found to be 0.977 (0.948–0.990) at the confidence interval of 95%, which suggests excellent test-retest reliability. Cronbach's alpha coefficient was found to be 0.663 (acceptable).

Table 2. Test-retest reliability subheadings and the total score with respect to the Turkish version of the LAPAQ.

n=27	r	p
walking	0.759	p<0.001*
gardening	0.805	p<0.001*
bicycling	-	-
Light household	0.912	p<0.001*
Heavy household	0.911	p<0.001*
Sports	0.789	p<0.001*
Total LASA PAQ	0.940	p<0.001*

*p<0.001; Spearman's correlation analysis, LAPAQ: LASA Physical Activity Questionnaire

Construct Validity: A high correlation was found between the LAPAQ-T total score and the PASE total score (r=0.703, p<0.001) (Table 3). A good correlation was found between the LAPAQ-T light household score and heavy household score and the PASE household activities score (r=0.621, p<0.001 and r=0.445, p<0.001 respectively)

Table 3. Correlation Coefficients Between the subscale scores of LAPAQ-T and PASE

LASA subheadings	PASE Leisure time activities	PASE Household activities	PASE Work-related activities	PASE Total
walking	r=0.362 p=0.001	r=0.121 p=0.218	r=-0.129 p=0.189	r=0.302 p=0.002*
gardening	r=0.173 p=0.078	r=0.182 p=0.063	r=-0.043 p=0.664	r=0.223 p=0.022*
bicycling	r=0.058 p=0.555	r=-0.127 p=0.197	r=-0.010 p=0.922	r=-0.076 p=0.441
Light household	r=0.122 p=0.215	r=0.621 p=0.001*	r=-0.105 p=0.284	r=0.532 p=0.001*
Heavy household	r=0.271 p=0.005*	r=0.445 p=0.001*	r=-0.058 p=0.555	r=0.497 p=0.001*
Sports	r=0.272 p=0.005*	r=0.203 p=0.039*	r=0.217 p=0.027	r=0.309 p=0.001
Total LAPAQ-T	r=0.427 p=0.001*	r=0.625 p=0.001*	r=-0.084 p=0.398	r=0.703 p=0.001*

*p<0.05; Spearman's correlation analysis, LAPAQ-T: LASA Physical Activity Questionnaire Turkish Version; PASE: Physical Activity Scale for the Elderly

4. Discussion

In this study, the psychometric properties of the LAPAQ-T were compared with the PASE commonly used in the clinic. The results of our study show that the LAPAQ-T is a reproducible, reliable and valid questionnaire that evaluates the level of physical activity in elderly individuals.

Measurements that objectively evaluate the physical activity, such as accelerometer and pedometer, are widely used. It is stated that self-reported surveys play an essential role in determining the level of physical activity in terms of reaching larger samples. At the same time, in terms of cost, it is emphasized that self-reported surveys are more advantageous than objective measurements (6). Recently, there has been an increasing interest in the evaluation of physical activity in older individuals in the literature. However, the important thing is the selection of an appropriate physical activity questionnaire for society. As far as we know, physical activity questionnaires specific to elderly individuals are very limited in Turkish society.

The LAPAQ is a scale created to determine the level of physical activity in older individuals. The LAPAQ is also frequently used in the literature (19, 20). However, upon examining the LAPAQ version studies, the number of the studies conducted is observed to be limited (21,22). It draws attention that the validity of the LAPAQ has been assessed with the accelerometer and pedometer in previous studies, and a low relationship was found between the accelerometer and LAPAQ. For this reason, unlike the studies in the literature, PASE, which is used frequently in the clinic and whose validity and reliability has been made in the elderly with different cultures, was preferred to test the Turkish validity of this questionnaire (12).

The answers to some subheadings of the LAPAQ-T version draw attention. The number of people who answered yes to the cycling subheading in the questionnaire is only one. Most of the elderly individuals in our country do not have a habit of cycling. Furthermore, riding a bicycle is generally not preferred as a form of transportation in our society. Only 19 people answered questions about gardening activities. Conducting the study with individuals living in apartment buildings in large cities has brought along this result. From among 107 people, only 29 people stated that they did heavy housework, and 16 people did sports. It is reported that educational level, sex, and environmental factors such as seasons and residential areas may affect the physical activity level of individuals (8). The last two weeks are taken into account when evaluating the physical activity level in the LAPAQ. Our study was conducted between January-December 2019, and it is thought that the low physical activity level of people may have been adversely affected by the winter season. These factors should be taken into account in future studies.

A high positive correlation was found between the LAPAQ-T and PASE total scores. When reviewed in general, the fact that the two questionnaires contain similar activities explains this result. It was observed that the relationship levels between the LAPAQ-T and PASE subgroups were low. However, when the activities in its sub-categories are examined, it is seen that LAPAQ questions the physical activities in more detail. For this reason, it was thought that there might be a low relationship between the sub-categories. When we compare the questionnaire content, the LAPAQ consists of six subheadings, and the PASE consists of three subheadings. For example, while walking, gardening, cycling, and sports are evaluated separately in the LAPAQ, these are calculated in a single subgroup as leisure activities in the PASE. In the LAPAQ, housework is scored separately as light and

heavy housework. In the PASE, the total score is given to housework. It was seen that the housework subtitles of both questionnaires, had moderate relations with each other.

In their study, Stel et al. (9) used the pedometer for the LAPAQ validity and the log of activities they did during the last seven days. The activity log contains activities similar to the LAPAQ. They found a high correlation (r = 0.68) between the LAPAQ and the 7-day log and a moderate correlation (r = 0.56) with the pedometer. The repeatability of the LAPAQ was reasonably good (weighted kappa: 0.65–0.75).

In another study, it was observed that there was a low relationship between the LAPAQ and accelerometer, and there were large differences in the duration of physical activity calculated between the LAPAQ and the wrist-mounted accelerometer. The researchers stated that the difference between the methods was related to body mass index, disability level, and the presence of depressive symptoms. They indicated to researchers that they should take into account these differences when using questionnaires and/or accelerometers in future studies (23).

In a study conducted on elderly individuals in the Netherlands, the researchers compared the LAPAQ with the accelerometers and reported that the reproducibility of the LAPAQ was moderate, but there was a low relationship when they compared it with the accelerometer. Although the authors did not consider the LAPAQ suitable for the precise measurement of physical activity levels in elderly individuals they stated that it was a quick and practical self-administered questionnaire that could be used in practice and studies to determine whether a person's activity level is above the time recommended by the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) (21).

As a result, although their methods are different, studies on the original LAPAQ support the results of our study (9). The LAPAQ appears to be a valid and reliable questionnaire that assesses the level of physical activity in elderly individuals. It is important because it evaluates all six components of physical activity separately. There was no question that the participants said they did not understand and that did not fit the lifestyle when they were responding to the LAPAQ questions. This situation makes us think that the questionnaire is suitable for the lifestyle of Turkish elderly individuals. At the same time, the questionnaire is easy to score and answered in a short time, and there is no need for special training for practitioners. It is a questionnaire that can also be applied by telephone call. When analyzing it from these aspects, we think that the LAPAQ Turkish version will be a useful questionnaire for clinicians in evaluating physical activity.

Declaration of interest

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Research Article / Araştırma Makalesi

Otolog Hematopoetik Kök Hücre Nakli Yapılan Hastalarda Komorbidite İndekslerinin Sağkalım ile İlişkisinin Değerlendirilmesi

Evaluation of the Relationship Between Comorbidity İndexes and Survival in Autologous Hematopoietic Stem Cell Transplant Patients

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Özet

Bu çalışmanın amacı hematopoetik kök hücre nakli yapılan hastalarda komorbidite indekslerinin sağkalımı öngörmede prediktif değerlerini saptamaktı. Ağustos 2009–Mart 2014 tarihleri arasında otolog hematopoetik kök hücre nakli (OHKHN) yapılan hematolojik maligniteli 110 hastanın verileri retrospektif olarak incelendi. Komorbidite indeksleri ve sağkalım süreleri arasındaki ilişki Kaplan-Meier testi kullanılarak incelendi. OHKHN yapılan 110 hastanın 58'ini (%53) kadın, 52'sini (%47) erkek hastalar oluşturmaktaydı. Hastaların ortanca yaşı 54 (22-72)'tü. OHKHN yapılan hastaların 84'ü (%76) Multipl miyelom (MM), 18'i (%17) Non-hodgkin lenfoma (NHL), 8'i (%7) Hodgkin lenfoma (HL) tanılıydı. 2 yıllık takiplerinde hastaların 57'si (%52) nüks olmuştu, 53'ü (%48) remisyondaydı, 40'ı (%36) hayatını kaybetmişti. Hayatta olan 70 (%64) hasta vardı. En sık komorbiditeler pulmoner hastalıklar (%33), psikiyatrik hastalıklar (%29) ve enfeksiyon hastalıklarıydı (%20). Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Flexible Hematopoietic Cell Transplantation Comorbidity Index (Flexible HCT-CI) ve Charlson Comorbidity Index (CCI) skoru ile progresyonsuz sağkalım ve genel sağkalım arasındaki ilişki incelendiğinde istatistiksel anlamlı bir ilişki bulunamadı (p>0.05). Yapılan çalışmalarda genel sağkalımı en iyi öngören komorbidite skoru HCT-CI olmakla birlikte bizim çalışmamızda daha sık 65 yaş altı, perfomans durumu iyi olan, komorbid hastalığı az olan hastalara nakil yapılması nedeni ile HCT-CI komorbidite skorunun bu grup hastalarda kullanımı ve sağkalımı öngörmedeki etkisi kısıtlıdır. Komorbidite indekslerindeki parametre sayıları arttıkça sağkalımı öngörmedeki duyarlılıkları artmaktadır. Nakil öncesi rutin kullanıma girmeleriyle birlikte bu konuyla ilgili tecrübelerimiz artacaktır.

Anahtar Kelimeler: hematopoetik kök hücre nakli, komorbidite indeksleri, genel sağkalım, progresyonsuz sağkalım

Abstract

The aim of this study was to determine the predictive value of comorbidity indexes for survival in hematopoietic stem cell transplant patients. Data of 110 hematologic malignant patients who underwent autologous hematopoietic stem cell transplantation (OHKHN) between August 2009 and March 2014 were retrospectively reviewed. Comorbidity indexes and survival times were analyzed using the associated Kaplan-Meier test. Of the 110 patients who underwent OHKHN, 58 (53%) were female and 52 (47%) were male patients. The median age of the patients was 54 years. Multiple myeloma (MM), 18 (17%) Non-hodgkin's lymphoma (NHL) and 8 (7%) Hodgkin's lymphoma (HL) were found in 84 patients (76%). In 2 years follow-up of 110 patients with autologous transplantation, 57 (52%) had recurrences. 53 patients (48%) were in remission. Patients had lost 40 (36%) of their lives for 2 years. There were 70 (64%) patients in life. There was no statistically significant relationship between the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Flexible Hematopoietic Cell Transplantation Comorbidity Index (Flexible HCT-CI) and Charlson Comorbidity Index (CCI) scores and disease free survival and total survival (p> 0.05). Although HCT-CI is the best predictor of overall survival in studies, the use of the HCT-CI comorbidity score in this group of patients and its effect in predicting survival is limited in our study because of transplantation to patients under 65 years of age, with good performance and low comorbid disease. As the number of parameters in the comorbidity indices increases, their sensitivity in predicting survival increases. Our experience on this subject will increase as they enter into routine use before transplantation.

Keywords: hematopoietic stem cell transplantation, comorbidity indexes, overall survival, progression free survival

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1. Giriş

Hematopoetik kök hücre nakli (HKHN) lösemi, lenfoma, multipl miyelom gibi malign hematolojik hastalıkların yanında aplastik anemi, bazı solid tümörler, gibi birçok hastalığın tedavisinde kullanılmaktadır (1). HKHN ile önemli bir oranda hastalık kontrolü ve kür sağlama başarısı yakalanmıştır. Hematopoetik kök hücre (HKH); kemik iliğinde, bebek kordon kanında, periferik kanda bulunan kan hücrelerine dönüşebilen kök hücreleridir (2). HKHN kemik iliği veya periferik kandan HKH'lerin toplanması ve hastaya infüzyon yolu ile verilmesi işlemidir. Otolog HKHN (OHKHN) ise hastanın kendi hücrelerinin infüzyonla kendine verilmesi işlemidir (3,4).

HKHN birçok ciddi hastalık için kür şansı sağlayan tek tedavi yöntemi olmasına karşın önemli oranda mortalite ve morbiditeyi de beraberinde taşımaktadır. Hastalık evresi, yaşı, HLA uyumu, alıcı ve verici arasındaki cinsiyet uyumu, komorbid hastalıklar nakil ilişkili komplikasyon ve mortaliteyi belirlemektedir (5).

Yapılan çalışmalarda hastaların komorbid hastalıklarının sağkalım süresini azalttığı gösterilmiştir (6). Hastalara HKHN yapılmadan önce risk durumlarını belirlemek için çeşitli komorbidite indekslerinden yararlanılmıştır. Nakil öncesi komorbid hastalıklarının ciddiyeti ve laboratuvar değerlerine göre her komorbidite indeksi için farklı parametreler ve farklı skorlama sistemleri geliştirilmiştir. Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Flexible Hemotopoietic Cell Transplantation Comorbidity Index (Flexible HCT-CI), Charlson Comorbidity Index (CCI) bu komorbidite indekslerinden en sık kullanılanlarıdır (7-10).

Yapılan çalışmalarda yaş arttıkça komorbiditelerin yükünü artırdığı gösterilmiştir. Bu nedenle HCT-CI revize edilerek hasta yaşı eklenmiştir. Flexible HCT-CI hesaplanırken yaş> 40 olan hastalara 1 puan ilave edilir (9). Retrospektif olarak yapılan bu çalışmada hesaplanan komorbidite indekslerini karşılaştırılarak 2 yıllık progresyonsuz sağkalım ve genel sağkalımı öngörmede prediktif değerlerini saptamayı amaçladık.

Tablo 1. Charlson Komorbidite İndeksi Skorlama Sistemi (11)

SKOR	DURUM
1	Miyokard infarktüsü (geçirilmiş, sadece EKG değişiklikleri hariç)
	Konjestif kalp yetmezliği
	Periferik vasküler hastalık (≥6 cm aort anevrizması dahil)
	Serebrovasküler hastalık (SVO, TIA)
	Demans
	Kronik akciğer hastalığı
	Bağ doku hastalığı
	Peptik ülser
	Hafif karaciğer hastalığı (kronik hepatitler dahil)
	Diyabet organ komplikasyonsuz (sadece diyetle kontrol edilenler hariç)
2	Hemipleji
	Orta veya ağır böbrek hastalığı
	Diyabet organ komplikasyonu ile birlikte
	Tümör metastatik olmayan (tanıdan itibaren 5 yıl geçmişse dahil edilmez)
	Lösemi (akut veya kronik)
	Lenfoma
3	Orta veya ağır karaciğer hastalığı
6	Metastatik solid tümör
	AIDS (sadece HIV pozitif hastalara puan verilmez)
	40 yaşından sonraki her dekad için total skora 1 puan eklenir.

EKG: Elektrokardiyografi, SVO: Serebrovasküler Olay, TIA: Transiskemik Atak, AIDS: Edinsel İmmun Yetmezlik Sendromu, HIV: Human İmmundeficiency Virus

Tablo 2. Hematopoietic Cell Transplantation- Komorbidite İndeksi (7)

Komorbiditeler	Tanımlar	Skor
Aritmi	Atriyal fibrilasyon, Atriyal flutter	1
	Hasta sinüs sendromu, Ventriküler aritmi	
Kardiyovasküler	Koroner arter hastalığı, Miyokard enfarktüsü	1
	Konjestif kalp yetmezliği, EF≤50	
İnfalamatuar Barsak Hastalığı	Crohn hastalığı, Ülseratif kolit	1
Diyabet	OAD veya insülin kullanan hastalar	1
Serebrovasküler Hastalıklar	TIA, Serebral emboli, tromboz, hemoraji, SAK	1
Psikiyatrik hastalıklar	Depresyon, anksiyete tedavi alanlar	1
Karaciğer hastalığı - orta	Kronik hepatit	1
	bilirubin≥NÜS-1,5*NÜS, AST/ALT≥NÜS-2,5*NÜS	
Obezite	BMI≥35 erişkinlerde	1
	Yaşa göre BMI≥95. Percantil (çocuklarda)	
Enfeksiyon	Dokümente enfeksiyon, Nedeni bilinmeyen ateş	1
	Fungal pnömoni şüpheli pulmoner nodüller	
	Tbc profilaksisi gerektiren PPD pozitifliği	
Romatolojik hastalıklar	SLE, RA, Polimyozit, MKDH, Polimiyalji romatika	2
Peptik ülser	Gastik ülser, duodenal ülser	2
	Endoskopiyle doğrulanmış ve Tedavi gerektiren	
Böbrek hastalıkları –orta/ağır	Serum Kreatin>2 mg/dl	2
	Diyaliz alan, Böbrek nakli yapılmış	
Akciğer hastalıkları -orta	DLCO ve/veya FEV1 %66-%80 arasında	2
	Dispne hafif aktiviteyle	
Akciğer hastalıkları -ağır	DLCO ve/veya FEV1 ≤ %65	3
	Dispne istirahatte, Oksijen tedavisi alan	
Kalp kapak hastalıkları	Asemptomatik MVP hariç	3
Solid maligniteler	Tedavi almış olan	3
	Non- melanom cilt kanserleri hariç	
Karaciğer hastalıkları orta/ağır	Siroz	3
	Bilirubin> 1,5*NÜS, AST/ALT>2,5*NÜS	

*EF: Ejeksiyon fraksiyonu, **OAD:** Oral antidiyabetik, **TIA:** Transiskemik atak, **SAK:** Subaraknoid kanama, **AST:** Aspartat aminotransferaz, **ALT:** Alanin aminotransferaz, **NÜS:** Normalin üst sınırı, **BMI:** Vücut kitle indeksi, **Tbc:** Tüberküloz, **PPD:** Pürifiye protein derivesi, **SLE:** Sistemik lupus eritematozus, **RA:** Romatoid artrit, **AS:** Ankilozan spondilit, **DLCO:** Karbonmononksit difüzyon kapasitesi, **FEV:** Zorlu ekspiratuvar volüm, **MVP:** Mitral valv prolapsusu **MKDH**: Mikst konnektif doku hastalığı*

2. Gereç ve Yöntemler

Uludağ Üniversitesi İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı, Kemik İliği Nakil Ünitesinde Ağustos 2009–Mart 2014 tarihleri arasında otolog hematopoetik kök hücre nakli yapılan hematolojik maligniteli 110 hastanın verileri retrospektif olarak incelendi. Hasta verileri ''International Classification of Disease (ICD)'' tanı kodları ile medikal kayıtlarımızdan elde edildi. Uludağ Üniversitersi Tıp Fakültesi Girişimsel Olmayan Klinik Çalışmalar Etik Kurulundan 15.03.2016 tarihinde 2016-4/6 sayı numarası ile etik kurul onayı alındı.

İstatiksel Analiz

Verilerin istatistik analizi için SPSS versiyon 21.0 yazılımı kullanıldı. Değişkenlerin normal dağılım gösterip göstermediğini değerlendirmek için Kolmogorov-Smirnov testi kullanıldı. Kategorik veriler sıklık ve yüzde (%) olarak verildi. Normal dağılım göstermeyen değişkenler median (minimum-maksimum) olarak ifade edildi. OHKHN yapılan hastalarda HCT-CI, Flexible HCT-CI, CCI indeksleri hesaplandı. Hesaplanan komorbidite skorları HCT-CI için düşük (0), orta (1-2), yüksek (>2); Flexible HCT-CI için düşük (0-3), orta (4-5), yüksek (>5); CCI için düşük (0), orta (1-2), yüksek (>2) risk olmak üzere 3 gruba ayrıldı. Komorbidite indeksleri ve sağkalım süreleri arasındaki ilişkili Kaplan-Meier testi kullanılarak incelendi. Hesaplanan her komorbidite indeksinin 2 yıllık progresyonsuz sağkalım ve genel sağkalım ile ilişkisi incelendi. Anlamlılık düzeyi p<0.05 olarak belirlenmiştir.

3. Bulgular

OHKHN yapılan 110 hastanın 52'sini (%47) erkek hastalar oluşturmaktaydı. Hastaların ortanca yaşı 54'tü (22-72). Hastaların demografik özellikleri tablo 3'te verilmiştir.

Hastalar tanılarına göre gruplandığında OHKHN yapılan en sık hasta grubu %76 (n=84) ile multipl miyelom (MM)'du. OHKHN yapılan diğer hastalıklar ve alt tipleri Tablo-4'de verilmiştir.

Tablo 3. OHKHN yapılan hastaların özellikleri

	n=110	(%)
Ortanca yaş	54 (22-72)	
Cinsiyet		
• Kadın	58	(53)
• Erkek	52	(47)
Tanı		
• MM	84	(76)
• NHL	18	(17)
• HL	8	(7)

***MM:** Multipl Miyelom, **NHL:** Non Hodgkin Lenfoma, **HL:** Hodgkin Lenfoma **OHKHN:** Otolog Hematopoetik Kök Hücre Nakli*

Tablo 4. Hastalık tanılarının alt tiplere göre dağılımı

MM	**(%76)**
• IgG kappa/lambda	46 (%41,8)
• IgA kappa/lambda	15 (%13,6)
• Kappa hafif zincir	12 (%10,9)
• Lambda hafif zincir	8 (%7,3)
• IgD hafif zincir	1 (%0,9)
• Nonsekretuar	1 (%0,9)
• Plazmositom	1 (%0,9)
NHL	**(%17)**
• DBBHL	10 (%9)
• Mantle cell lenfoma	4 (%3,6)
• Büyük hücreli anaplastik lenfoma	3 (%2,7)
• Periferal T hücreli lenfoma	1 (%0,9)
HL	**(%7)**
• Klasik tip	4 (%3,6)
• Nodüler sklerozan	4 (%3,6)

***MM:** Multipl Miyelom, **NHL:** Non Hodgkin Lenfoma, **HL:** Hodgkin Lenfoma **DBBHL:** Diffüz Büyük B Hücreli Lenfoma, **Ig:** İmmunglobulin*

MM tanılı 84 hastanın 4'ü (%5) International Staging System (ISS)'ye göre evre 1, 30'u (%35) evre 2, 50'si (%60) evre 3'tü. Lenfoma tanılı hastalarda ise Ann-Arbor Evrelendirme Sistemine göre evre 1 olan 1 hasta (%3); evre 2, 7 hasta (%26); evre 3, 10 hasta (%38); evre 4, 8 hasta (%30) vardı.

MM hastalarında 200mg/m2 melfelan kullanıldı. Lenfoma tanılı hastalara ise busulfan 3.2 mg/kgx4 gün ve siklofosfamid 60 mg/kgx2 gün verildi. MM tanılı 4 hasta kronik böbrek yetmezliği nedeniyle hemodiyaliz tedavisi alıyordu. Bu hastalara melfelan 140 mg/m2 verildi. Hemodiyaliz alan hastalarda ek hastalıklar nedeniyle komorbidite skorları yüksekti (CCI:5-6, HCT-CI:5-8, F-HCT-CI:6-9). Hepatik komorbiditesi olan hastaların 7'si HBV, 1'i HCV tanılıydı. 11 hastada hafif derecede AST/ALT yüksekliği mevcuttu. Bu hastalarda hazırlık rejimlerinde doz modifikasyonu yapılmadı.

OHKHN yapılan hastaların 37'sinde (%33) hastada pulmoner komorbidite, 32 (%29) hastada psikiyatrik hastalık, 23 (%20) hastada enfeksiyon hastalıkları, 19 (%17) hastada hepatik komorbidite, 16 (%14) hastada diyabet mellitus (DM), 13'ünde (%11) kardiyak hastalık, 6 (%5) hastada renal komorbidite, 6 (%5) hastada gastrointestinal hastalık, 6 (%5) hastada periferik vasküler hastalık, 6 (%5) hastada obezite, 4 (%3) hastada serebrovasküler hastalık, 1 (%0,9) hastada romatolojik hastalık mevcuttu. İnflamatuar barsak hastalığı ve malignite tanılı hasta yoktu.

Otolog nakil yapılan 110 hastanın 2 yıllık takiplerinde 57'si (%52) nüks olmuştu. Hastaların 53'ü (%48) remisyondaydı. Hastaların 2 yıllık takipte 40'ı (%36) hayatını kaybetmişti. Hayatta olan 70 (%64) hasta vardı.

HCT-CI skoru düşük olan 18 hasta vardı. Takiplerinde 2 yılda 10 (%55) hastada nüks gelişmişti. Remisyonda olan 8 (%45) hasta vardı. Hastaların 6'sı (%33) 2 yıllık takipte hayatını kaybetmişti. Orta riskli olan 57 hastanın 34'ünde (%59) nüks gelişmişti. Remisyonda olan 23 (%41) hasta, ölen 21 (%36) hasta vardı. Yüksek riskli olan 35 hastanın 13'ü (%37) nüks olmuştu. Remisyonda 22 (%63) hasta ve ölen 13 (%37) hasta mevcuttu. HCT-CI skoru ile progresyonsuz sağkalım ve genel sağkalım arasındaki ilişki incelendiğinde istatistiksel anlamlı bir ilişki bulunmadı. (p=0.068 ve p=0.897)

Flexible HCT-CI skoru düşük olan 77 hasta vardı. Hastaların 45'inde (%58) nüks gelişmişti. Remisyonda 32 (%42) hasta ve ölen 28 (%36) hasta vardı. Orta riskli 22 hastanın 10'unda (%45) nüks olmuştu. Remisyonda 12 hasta (%55) ve ölen 5 (%22) hasta vardı. Yüksek riskli 11 hastanın 2'sinde (%18) nüks olmuştu. Remisyonda 9 (%82) hasta, ölen 7 (%63) hasta mevcuttu. Flexible HCT-CI skoru ile progresyonsuz sağkalım ve genel sağkalım arasında istatistiksel anlamlı bir ilişki saptanmadı (p=0.085 ve p=0.071).

CCI skoru düşük olan 23 hastanın 15'i (%65) nüks olmuştu. Remisyonda 8 (%34) hasta ve ölen 8 (%34) hasta mevcuttu. Orta riskli olan 57 hastanın 30'u (%52) nüks olmuştu. Remisyonda 27 (%48) hasta ve ölen 20 (%35) hasta vardı. Yüksek riskli 30 hastanın 12'sinde (%40) nüks olmuştu. Remisyonda 18 (%60) hasta ve ölen 12 (%40) hasta vardı. CCI skoru ile progresyonsuz sağkalım ve genel sağkalım arasında istatistiksel anlamlı bir ilişki saptanmadı (p=0.279 ve p=0.705). Komorbidite indeksleri ile genel sağkalım ve progresyonsuz sağkalım arasındaki ilişki Tablo-5'de özetlenmiştir.

Tablo 5. OHKHN yapılan hastalarda komorbidite indeksleri ile sağkalım arasındaki ilişkinin değerlendirilmesi.

	Hasta sayısı	Progresyonsuz Sağkalım			p
	n=110	Nüks n=57 (%52)	Remisyonda n=53 (%48)	Nüks yüzdesi	
HCT-CI					0.068
*Düşük (0)	18	10	8	%55	
*Orta (1-2)	57	34	23	%59	
*Yüksek (>2)	35	13	22	%37	
F-HCT-CI					0.085
*Düşük (0-3)	77	45	32	%58	
*Orta (4-5)	22	10	12	%45	
*Yüksek (>5)	11	2	9	%18	
CCI					0.279
*Düşük (0)	23	15	8	%65	
*Orta (1-2)	57	30	27	%52	
*Yüksek (>2)	30	12	18	%40	
	Hasta sayısı	Genel Sağkalım			p
	n=110	Ölü n=40 (%36)	Yaşıyor n=70 (%64)	Ölüm yüzdesi	
HCT-CI					0.897
*Düşük (0)	18	6	12	%33	
*Orta (1-2)	57	21	36	%36	
*Yüksek (>2)	35	13	22	%37	
F-HCT-CI					0.071
*Düşük (0-3)	77	28	49	%36	
*Orta (4-5)	22	5	17	%22	
*Yüksek (>5)	11	7	4	%63	
CCI					0.705
*Düşük (0)	23	8	15	%34	
*Orta (1-2)	57	20	37	%35	
*Yüksek (>2)	30	12	18	%40	

HCT-CI:*Hematopoietic Cell Transplantation Comorbidity Index* **F-HCT-CI:***Flexible Hematopoietic Cell Transplantation Comorbidity Index* **CCI:** *Charlson Komorbidite İndeksi* **OHKHN:** *Otolog Hematopoetik Kök Hücre Nakli*

4. Tartışma ve Sonuç

HKHN hematolojik maligniteli hastaların tedavisinde gün geçtikçe daha yaygın halde kullanılmaya başlanmıştır. Artan nakil sayısı ve 65 yaş üstü hastalara da nakil yapılmaya başlanmasıyla birlikte hastaların komorbid hastalıkları önemli bir sorun haline gelmiştir. Nakil hastalarında eşlik eden komorbid hastalıklar mortalite ve morbiditede artışa neden olmaktadır (12-14). Komorbid hastalıkların morbidite ve mortalite üzerine etkisini öngörmek üzere çeşitli komorbidite indeksleri geliştirilmiştir. Literatürde bu komorbidite indeksleriyle ilgili yapılmış az sayıda çalışma vardır (15-17). Yaptığımız bu tek merkezli çalışmamızda OHKHN yapılan hematolojik maligniteli hastalarda komorbidite indekslerinin progresyonsuz sağkalım ve genel sağkalım üzerine etkisini belirlemeye çalıştık.

OHKHN yapılan 110 hastanın median yaşı, cinsiyeti, hastalık tanılarının dağılımı literatür ile uyumluydu. Bizim çalışmamızda OHKHN yapılan 110 hastadan nüks olan 57 (%52) ve ölen 40 (%36) hasta mevcuttu. OHKHN yapılan hastaların 84'ü (%76) Multipl miyelom (MM), 18'i (%17) Non-hodgkin lenfoma (NHL), 8'i (%7) Hodgkin lenfoma (HL) tanılıydı. En sık görülen komorbiditeler pulmoner hastalıklar, psikiyatrik hastalıklar, enfeksiyon, hepatik komorbiditeler, diyabet ve kardiyak komorbiditelerdi.

M Kleber ve arkadaşlarının 2011 yılında yayınladığı bir çalışmada 127 MM tanılı hasta incelenmiş HCT-CI genel sağkalım ile ilişkili bulunurken CCI skoru mortalite ile ilişkili saptanmamış (18). Ayman Saad ve arkadaşları tarafından 2014 yılında yapılan 1156 MM tanılı OHKHN yapılan hastanın dâhil edildiği

çok merkezli bir çalışmada ise HCT-CI skorunun mortaliteyle ilişkisi incelenmiştir. HCT-CI skoru 0, 1, 2, 3 ve >3 olan %42, %18, %13, %13 ve %14 hasta olduğu saptanmıştır. En sık görülen komorbiditelerin pulmoner, diyabet, obezite, psikiyatrik, kardiak ve renal komorbiditeler olduğu bulunmuştur. Yüksek HCT-CI skorları relaps dışı mortalite ile ilişkili bulunmamış, fakat genel sağkalımı azalttığı görülmüştür. Hasta yaşının relaps dışı mortalite ve genel sağkalım üzerine ilişkisi gösterilememiştir (19). Bizim çalışmamızda her üç komorbidite indeksi de (HCT-CI, Flexible HCT-CI, CCI) progresyonsuz sağkalım ve mortalite ile ilişkili bulunamadı. Çalışmamızda anlamlı ilişki bulunamamasının sebebi 65 yaş altı, perfomans durumu iyi olan, komorbid hastalığı az olan hastalara nakil yapılması; yaşlı ve komorbiditesi fazla olan hastalarda naklin tercih edilmemesi; çalışmaya dahil edilen hasta sayısının az olması, farklı tanıları olan heterojen bir hasta grubunun olması olabilir.

Komorbidite indeksleriyle yapılan çalışmalarda farklı sonuçlar elde edilmiştir. Bu sonuçlara göre genel sağkalımı en iyi öngören komorbidite skoru HCT-CI olarak gözükmektedir. HCT-CI skoru ile sağkalım arasında ilişki kurulamayan çalışmalarda farklı tanılara sahip hasta gruplarının bir arada değerlendirilmesinin buna neden olduğu

düşünülmüştür. EKO, SFT ve DLCO parametrelerinin eklenmesiyle pulmoner ve kardiyak komorbiditeler daha objektif olarak değerlendirilmiştir (6,7). Bizim çalışmamızda ve mevcut çalışmaların hepsinde en sık saptanan komorbid hastalık pulmoner hastalıklardır. SFT ve DLCO testlerinin parametrelere eklenmesi HCT-CI skorunun duyarlılığını artırmış, HCT-CI skorunu diğer diğer komorbidite indekslerine göre daha ön plana geçirmiştir.

Komorbidite indeksleri sıklıkla AHKHN yapılan hastalarda kullanılmaktadır. Her ne kadar OHKHN sırasında uzun dönemde progresyonsuz sağkalımı predikte ettikleri bazı çalışmalarda gösterilse de kısa dönemde etkinlikleri tartışmalıdır (18,19). OHKHN uygulanan hastalarla ilgili daha fazla çalışmaya ihtiyaç vardır. HCT-CI skoruyla genel sağkalım arasındaki ilişkiyi inceleyen çalışmaların metaanalizi ve çalışmamıza ait sonuçlar Tablo-6'da verilmiştir.

Sonuç olarak komorbidite indekslerindeki parametre sayıları arttıkça sağkalımı öngörmedeki duyarlılıkları artmaktadır. Yapılan metaanalizlerde komorbidite indeksleri kullanılarak genel sağkalım ve progresyonsuz sağkalım öngörülebilmektedir. Komorbidite indekslerinin HKHN öncesi rutin kullanma girmesiyle birlikte bu konuyla ilgili tecrübelerimiz artacaktır.

Tablo 6. HCT-CI skoru ile yapılan önceki çalışmaların analizi

Çalışma (Kaynak)	Yıl	Hasta sayısı	Tanı	2 yıllık toplam sağkalım HCT-CI skoruna göre (%)			p değeri
				Düşük	Orta	Yüksek	
Sorror ve ark (7)	2005	364	AML, KML, MDS	71	60	34	**0.001**
Sorror ve ark (15)	2007	244	AML	80	48	33	**<0.001**
Sorror ve ark (20)	2007	577	AML, MDS	64		35	**<0.001**
Majhail ve ark (21)	2008	373	AML, NHL, ALL	72	59	48	**<0.01**
Gulfoyle ve ark (22)	2008	187	AML, MDS, KML	45	55	42	0,76
Farina ve ark (23)	2009	203	NHL, MM	87	51	49	**<0.001**
Defor ve ark (24)	2009	444	AML, NHL, ALL	62	58	50	0.08
Terwey ve ark (25)	2010	151	ALL	58	50	46	0.2
Kataoka ve ark (26)	2010	187	AML, ALL, KML	70	60	39	**<0.01**
Barba ve ark (10)	2010	194	AML, MDS, NHL	54	59	49	0.43
Castagna ve ark (27)	2010	63	AML,MM(>60 yaş)	64	68	69	0.9
Patel ve ark (28)	2010	52	AML, ALL	86	59	50	0.1
Smith ve ark (29)	2011	252	ALL, İmmün yetmezlik (<20 yaş)	88	67	62	**<0.01**

Kleber ve ark (18)	2011	127	MM (OKHN)	61		38	<0.002
Birninger ve ark (17)	2011	340	AML	29	40	44	0.7
Raimondi ve ark (30)	2012	1937	AML, ALL, KLL	*			<0.0001
Nakaya ve ark (31)	2014	243	AML, ALL, MDS	*			0.44
Saad ve ark (19)	2014	1156	MM (OKHN)	83		79	0.04
Mevcut çalışma	2016	110	MM,NHL (OKHN)	67	64	63	0.897

*Belirtilmemiş

HCT-CI: *Hematopoietic Cell Transplantation Comorbidity İndex,* **AML:** *Akut myeloid lösemi,* **ALL:** *Akut lenfoid lösemi,* **MDS:** *Miyelodisplastik sendrom,* **MM:** *Multipl myelom,* **OHKHN:** *Otolog hematopoetik kök hücre nakli,* **AHKHN:** *Allojenik hematopoetik kök hücre nakli* **NHL:** *Non Hodgkin Lenfoma* **HL:** *Hodgkin Lenfoma*

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Our Experience with Esophageal Atresia and Tracheoesophageal Fistula

Özefagus Atrezisi ve Trakeoözefageal Fistül Deneyimlerimiz

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Abstract

To evaluate the treatment results of patients who were operated with the diagnosis of esophageal atresia and tracheoesophageal fistula (EA and TEF) in our clinic. The results of patients who were operated with the diagnosis of esophageal atresia and tracheaesophageal fistula between April 2017 and November 2019 were retrospectively evaluated. The patients were evaluated in terms of gestational age, birth weight, gender, atresia type, surgical approach, and duration of treatment. Postoperative mechanical ventilator follow-up was examined in terms of the transition time to nasogastric tube and oral feeding, and complications. A total of 24 patients, 20 (83%) boys and 4 (17%) girls, were included in the study. The mean age at surgery was 3.9 days. The gestational age of the patients was 35 weeks and the mean birth weight was 2391 grams. Distal tracheaesophageal fistula + proximal atresia were detected in 22 (92%) patients. Congenital heart disease was detected in 14 (58%) patients. The follow-up time in the ventilator was 27 hours, and the average oral feeding time was 11 days. Three (12.5%) patients died. Hospital stay was 16 days. During their follow-up, anastomotic stenosis was observed in 5 (21%) patients, and anastomotic leakage was observed in one (4%) patient. EA and TEF are anomalies that can be highly cured with surgical treatment. The follow-up of patients with EA by the neonatal team is important for the follow-up and treatment of additional anomalies. Therefore, these patients should be followed up with a multidisciplinary approach. Families should be informed about the frequent postoperative anastomotic stenosis.

Keywords: Esophageal atresia; tracheoesophageal fistula; treatment; complications

Özet

Kliniğimizde özefagus atrezisi ve trakeaözefageal fistül (ÖA ve TÖF) tanısı ile ameliyat edilen hastaların tedavi sonuçlarını değerlendirmek. Nisan 2017 - Kasım 2019 tarihleri arasında özefagus atrezisi ve trakeaözefageal fistül tanısıyla ameliyat edilen hastaların sonuçları retrospektif olarak değerlendirildi. Hastaların gestasyonel yaş, doğum ağırlığı, cinsiyet, atrezi tipi, cerrahi yaklaşım, tedavi süresi açısından değerlendirildi. Postoperatif mekanik ventilatör takibi, nazogastrik tüp ve oral beslenmeye geçiş süresi ve komplikasyonlar açısından incelendi. Çalışmaya 20 (% 83) erkek ve 4 (% 17) kız toplam 24 hasta dahil edildi. Ortalama ameliyat yaşı 3,9 gün idi. Hastaların gestasyonel yaşı 35 hafta ve ortalama doğum ağırlığı 2391 gramdı. Distal trakeaözefageal fistül + proksimal atrezi 22 (% 92) hastada tespit edildi. Ondört (% 58) hastada konjenital kalp hastalığı tespit edildi. Ventilatörde takip süresi 27 saat, ortalama oral beslenme süresi 11 gündü. Üç (%12.5) hasta öldü. Hastanede kalış süresi 16 gündü. Takiplerinde 5 (% 21) hastada anastomoz darlığı, bir (% 4) hastada anastomoz kaçağı görüldü. ÖA ve TÖF cerrahi tedavi ile yüksek oranda iyileştirilebilen anomalilerdir. ÖA hastalarının yenidoğan ekibi tarafından izlenmesi, ek anomalilerin takibi ve tedavisi için önemlidir. Bu nedenle bu hastalar multidisipliner bir yaklaşımla takip edilmelidir. Ameliyat sonrası sık karşılaşılan anastomoz darlığı açısından aileler bilgilendirilmelidir.

Anahtar Kelimeler: Özefagus atrezisi; trakeaözefageal fistül; tedavi ; komplikasyonlar

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1. Introduction

Esophageal atresia (EA) and tracheoesophageal fistula (TEF) are serious, life-threatening diseases in pediatric surgery. EA is seen in 1 / 3000-5000 live births. As a result of developments in neonatal intensive care unit (NICU) and surgical advances in recent years, the chance of survival of these patients has increased. However, there has been a parallel increase in complications of these patients. Early complications that can be seen after surgery include anastomotic leak, anastomotic stenosis and recurrent TEF (1,2). Gastroesophageal reflux (GER) and esophageal dysmotility are frequent postoperative late complications. These complications affect the nutritional intake, growth and development of the infant. As EA often accompanies multiple anomalies, a multidisciplinary approach is important. Additional problems, such as additional anomalies, low birthweight and prematurity of the patient affect morbidity and mortality (3-5)

The aim of this study was to evaluate the treatment results of patients who underwent surgery for a diagnosis of EA and TEF in our clinic and to present our clinical experience on this subject.

2. Material and Methods

The study was approved by the Local Ethics Committee (Date, no: 21.12.2020/03). A retrospective review was made of the outcomes of patients who were operated on because of EA and TEF between April 2017 and November 2019.The diagnosis of EA was made by nasogastric tube or pouch radiography (Figure 1). All patients were hospitalized in the NICU before and after surgery and were followed up by neonatologist. If the patient had no pathology requiring emergency surgery, surgery was performed under semi-elective conditions. If the patient was not stable, stabilization was achieved first. The patients were evaluated in terms of gestational age at birth, birthweight, gender, atresia type, surgical approach, duration of postoperative mechanical ventilator follow-up, complications.

Figure 1. Pouch radiograpy

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn.17.0 software (IBM Statistics for Windows version 17, IBM Corporation, Armonk, NY, USA). Conformity of continuous data to normal distribution was tested with the Kolmogorov - Smirnov test. Categorical data were stated as n (number) and percentage (%), and quantitative data as mean ± standard deviation (SD).

3. Results

Evaluation was made of a total of 24 patients, comprising 20 (83%) males and 4 (17%) females, average age of surgery 3.9 days. The average gestational age at birth was 35 weeks, and average birthweight was 2391 grams. Distal TEF + proximal atresia was determined in 22 (92%), isolated esophageal atresia in one (4%) and isolated TEF in one (4%) patients. Congenital anomalies were determined in 18 of 24 (75%) patients. In some patients, it was detected more than one congenital anomaly; congenital heart disease was determined in 14 (58%) patients, urinary system anomaly in seven (29%), total situs inversus in one (4%), duodenal atresia in one (4%), and small for gestational age in one (4%) (Figure2). Thoracotomy was performed in 23 (96%) patients. The primary esophageal anastomosis was performed in one of these patients who isolated esophageal atresia six months after gastrostomy. Right thoracotomy was performed in 16 (70%) of 23 patients who underwent thoracotomy, and muscle-sparing right thoracotomy was performed in seven (30%). The patient with isolated tracheoesophageal fistula was repaired by approaching from the neck. The mean follow-up on the ventilator was 27 hours, mean nasogastric feding time was 1.5 days and the mean oral feeding time was 11 days. Mortality developed in two patients due to heart disease and in one patient due to prematurity. The mean hospital stay of the patients was 16 days. There were no complications in 18 (75%) patients during follow-up. Anastomotic stenosis was observed in five (21%), and anastomotic leakage was observed in one (4%) patient (Table 1).

Figure 2. Esophagogram: stenosis in the patient with situs inversus

Table 1. Demographic data and results of patients

Gender (M/F)		20 (83%) / 4 (17%)
Surgery age (day)		3.95±6.85
Gestational age		35±3.1
Birth weight (gr)		2391±687
Atresia type	Distal TEF + proximal atresia	22 (92%)
	Isolated TEF	1 (4%)
	Isolated Atresia	1 (4%)
Additional Anomalies	Congenital heart diseases	14 (58%)
	Urinary System Anomalies	7 (29%)
Totaly 18/24 (75%)	Gastrointestinal anomalies	1(4%)
	Small for gestational age	1(4%)
Surgical Method	Right thoracotomy	16 (67%)
	Right thoracotomy + muscle sparing	7 (29%)
	Gastrostomy	1(4%)
Nasogastric feeding time (day)		1.5(1-2)
Oral feeding time (day)		11.36±10.50
Ventilator follow-up time (hour)		27.13±25.89
Discharge time (day)		16
Mortality		3 (13%)
Complication	No	18 (75%)
	Stenosis	5 (21%)
	Anastomosis leak	1 (4%)

M:Male, F:Female

4. Discussion

Preoperative risk assessment is important for patients. Developments in anesthesia procedures, intensive care conditions, and nutritional support for these patients have increased the survival of these patients. Low birthweight, prematurity, and concomitant cardiac anomalies are the most important risk factors. Therefore, these risks must be managed well (4). In this study, all patients were followed up in the NICU. Additional anomalies were investigated and pathologies requiring early intervention were investigated. After the operation, the newborn was followed up in the intensive care unit (5,6). As there have been rapid developments in neonatal care, the follow-up of these patients before and after surgery by neonatology specialists can be considered to contribute positively to the success of their treatment. Medical follow-up of the patients in this study was conducted by neonatologist.

The incidence of additional anomalies varies between 20% and 50%, and anomalies of the cardiovascular system are the most common (7,8). In the current study, the most common pathologies were found to be of the cardiovascular system, similar to reports in literature.

The most common clinical conditions that may be risk factors before surgery are low birthweight and prematurity (9,10). In the current study, mortality developed due to prematurity in one (4%) patient.

In EA cases, thoracotomy or thoracoscopic surgery can be performed as a surgical method (11). Although the thoracoscopic approach is recommended in the current literature, it has the disadvantages of technical difficulty, the need for much experience, and the difficulty in obtaining the necessary surgical equipment. In the more recent cases in this study, muscle-sparing procedures were performed in patients who underwent thoracotomy. This provides advantages such as faster recovery and a shorter surgical procedure.

The tracheal part of the tracheal fistula can be closed with one by one or with transfix suture (7). The tracheal opening of the fistula was closed with a single suture transfix suture in all patients, and no recurrent fistula was observed in any patient. This method was considered to be useful in fistula ligation.

Tracheomalacia can be seen in some EA cases, and has been reported in literature at a rate of 10-20% (12). In the current study, tracheomalacia was observed in 4 (%16) patients, all of which spontaneously improved over time. Aortopexy was not needed in any patient. Tracheomalacia should be considered and investigated in patients with complaints such as bruising and coughing while feeding.

GIS anomalies accompanying EA should be diagnosed before surgery (4). Duodenal atresia was detected in one patient in our clinic and was operated on simultaneously, with no problems. In the repair of EA, our first choice is to perform primary or delayed primary repair according to anatomic type and distance between the ends (13). In the current study, primary anastomosis was performed in 23 patients and delayed anastomosis in one.

Early oral nutrition in newborns significantly reduces morbidity (14). Feeding was started for all the current study patients from the trans anastomotic tube within the first 24 hours after surgery. This can be considered to have contributed to the early recovery of the patients. In addition, efforts were made not to put intubated patients to sleep as far as possible. Therefore, early extubation was possible in patients with suitable clinical conditions.

Complications such as anastomotic stricture, anastomotic leakage, GER, and esophageal dysmotility are the most common complications in patients with EA. The most common complication is anastomotic stenosis, which is seen at the rate of 6-64% (14). In the current study, anastomotic stenosis was observed at a rate of 20%, which is relatively low compared to the literature. The reason for this is that the GAP in between is close and the proximal and distal esophagus are mobilized as much as possible. A tight anastomosis increases complications such as anastomotic stenosis or leakage. Therefore, efforts were made not to have a tense anastomosis to be able to reduce complications in these patients.

One of the early complications of EA is anastomotic leakage, which has been reported in literature at rates of 10%-34% (15,16). In the current study, only one (4%) patient had anastomotic leakage. The reason for this very low rate compared to the literature was that the esophageal gap was narrowed.

5. Conclusion

EA and TEF are anomalies that can be highly cured with surgical treatment. Monitoring of EA patients by the neonatal team is important for the follow-up and treatment of additional anomalies. Therefore, these patients should be followed up with a multidisciplinary approach. Families should be informed about the frequent postoperative anastomotic stenosis.

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Research Article / Araştırma Makalesi

Hastanede Yatan ve Geçici Üriner Kateterizasyon Uygulanan Hastalarda Kateterde Bakteriyel ve Fungal Kolonizasyonun Araştırılması

Evaluating the Fungal and Bacterial Colonization on Hospitalized Patients with Transient Urinary Catheterization

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Özet

Çalışmamızda geçici üriner kateterizasyon uygulanan hastalarda kateter içi ve eş zamanlı idrar örneği alınarak kateter lümeninde ve idrarda mikroorganizma kolonizasyonunun araştırılması ve olası risk faktörlerinin değerlendirilmesi amaçlandı. Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Eğitim, Araştırma ve Uygulama Hastanesi Genel Cerrahi, Üroloji, Ortopedi ve Travmatoloji, Kadın Hastalıkları ve Doğum kliniklerinde 3 aylık çalışma periyodu boyunca geçici üriner kateterizasyon uygulanan hastalarda kateter içi ve eş zamanlı idrar örneği alınarak kateter lümeninde ve idrarda üreyen mikroorganizmalar ve risk faktörleri değerlendirmeye alındı. Yatış esnasında üriner sistem enfeksiyonu (ÜSE) klinik ve bulguları olan hastalar çalışma kapsamı dışında bırakıldı. Hastaların demografik bilgileri kaydedildi. Kateter lümeni veya idrar kültürlerinde üreyen mikroorganizmalar mini API cihazı yardımıyla tanımlandı. Veriler SPSS 15.0 istatistik programı ile değerlendirildi, p<0.05 değerleri anlamlı olarak kabul edildi. Geçici üriner kateterizasyon uygulanan 129 hasta çalışmaya alındı. Çalışma grubunu oluşturan hastaların 56'sında (%43.4) idrar ve/veya kateterinde mikroorganizma üremiş olup, 73'ünde (%56.6) herhangi bir üreme saptanmadı. Yapılan bivaryet analizlerde kadın cinsiyet, kateterizasyon süresinin uzaması, acil-elektif kateterizasyon uygulanması, üriner kateterizasyonu uygulayan kişi, yakın dönemde üriner girişim öyküsü, diyabet öyküsü gibi bağımsız değişkenlerle idrar ve/veya kateter lümeninden mikroorganizma izolasyonu arasında anlamlı ilişki saptandı (her biri için p< 0.05). Oluşturulan lojistik model sonuçlarına göre de kadın olmak (OR=2.730) ve kateterizasyon süresinin >7 gün olması (OR= 3.232) geçici üriner kateterizasyon uygulanan hastalarda kateter içi ve idrarda mikroorganizmaların kolonizasyonu açısından önemli risk faktörleri olarak saptandı (her biri için p<0.05). Kateter lümeni içinde mikroorganizmaların kolonizasyonu ile nozokomiyal üriner sistem enfeksiyonları (NÜSE) arasındaki ilişki henüz tam olarak aydınlatılamamış olmakla beraber bakteriüri gelişimine öncülük edebilir. Risk faktörlerinin tanımlanması, kolonizasyonun ve diğer komplikasyonların önlenmesinde faydalı olabilir. Kateter ilişkili üriner sistem enfeksiyonu (KİÜSE) tanısı alan ve uygun antimikrobiyal tedaviye rağmen yeterli klinik yanıt alınamayan hastalarda üriner kateter içinde biyofilm gelişmiş olabileceği de göz önüne alınarak üriner kateterizasyonun sonlandırılması veya üriner kateterin değişimi tartışılması gereken konulardır.

Anahtar Kelimeler: Üriner kateterizasyon; bakteriüri; fungüri; kolonizasyon

Abstract

In this cross-sectional study, it's aimed to evaluate fungal and bacterial colonization and related risk factors in patients with transient urinary catheterization. Microorganisms yielded in the catheter lumen and urine those sampled from intra-catheter and simultaneous urine samples and related risk factors were evaluated. Study was conducted in General Surgery, Urology, Orthopedics and Traumatology, Gynecology and Obstetrics wards of Eskişehir Osmangazi University Faculty of Medicine Training, Research and Practice Hospital, in patients who underwent temporary urinary catheterization during the 3-month study period. Patients with clinical signs and symptoms of urinary tract infection during hospitalization were excluded from the study. Demographic data of the patients were recorded. The microorganisms were identified with mini API device. The data were evaluated by SPSS 15.0 statistical program, p <0.05 values were considered significant. One hundred and twenty-nine patients underwent transient urinary catheterization were enrolled in this study. Urine culture and/or intraluminary swab cultures were positive in 56 (%43.4) patients whom enrolled the study. Seventy three (56.6%) of patients were culture negative. Bivariate analysis showed statistically significant relation between female gender, prolonged duration of catheterization, urgent-elective catheterization, person performing catheterization, previously urinary procedures, and presence of diabetes and microorganism isolation in urine and/or intraluminary swab cultures (p < 0.05). Therefore in logistic regression model, female gender (OR=2.730) and duration of catheterization longer than 7 days (OR= 3.232) were found as important risk factors for microorganism isolation in urine and/or intraluminary swab cultures (p< 0.05). Though the relation between intraluminary microorganism colonization and NUTIs is not clearly established, it may lead bacteriuria. Identifying risk factors can be useful in preventing colonization and other complications. In patients with catheter associated urinary tract infection and not responding adequate antimicrobial therapy, it may be considered to discontinue urinary catheterization or change urinary catheter.

Keywords: Urinary catheterization, funguri, funguria, colonization

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1. Giriş

Üriner kateterizasyon, NÜSE gelişiminde önemli bir rol oynar. NÜSE'nin yaklaşık %80'inin üriner kateterizasyon ile ilişkili olduğu gösterilmiştir(1). Üriner kateterde mikrobiyal kolonizasyon genellikle biyofilm oluşumuyla sonuçlanmaktadır. Biyofilm oluşturan mikroorganizmalar sıklıkla antimikrobiyal tedaviye yüksek düzeyde dirençlidirler. Biyofilm içindeki bakteriler oluşturdukları mikro çevre içinde fonksiyonel bir birliktelik oluştururlar. Çeşitli enzimler ve mikroorganizmaların metabolitleri bu mikro çevre içinde yer alır. Bu birliktelikle diğer mikroorganizmaların eliminasyonu, antibiyotiklere karşı direnç ve bakteriyel çoğalmanın potansiyelize edilmesi sonucu ortaya çıkar. Ayrıca biyofilm sayesinde mekanik bir bariyer oluşarak, içeride bulunan bakterilerin doğal savunma sistemleri ve antibiyotiklerin etkisinden korunması sağlanmış olur. Bu nedenle de gelişen enfeksiyonların eradikasyonu sorun teşkil etmektedir(1,2). Kateter lümeninden asendan olarak ilerleyen biyofilm de KİÜSE oluşumu için majör risk faktörü olarak değerlendirilmektedir. Kapalı drenaj sisteminin geliştirilmesiyle bu yolla gelişen enfeksiyonların sıklığı azaltılmıştır(3). KİÜSE patogenezinde biyofilm oluşturan mikroorganizmaların önemi anlaşıldıktan sonra bunu önlemeye yönelik çeşitli stratejiler geliştirilmeye çalışılmıştır. Örneğin antibiyotikle kaplanmış üriner kateterlerin kısa süreli kateterizasyonda KİÜSE gelişimini geciktirdiğini veya engellediğini gösteren umut verici çalışmalar yayınlanmıştır (4). İdrarda anlamlı bakteriürinin gösterilmesi üriner sistem enfeksiyonu (ÜSE) tanısında önemlidir. KİÜSE patogenezi ve tedavisindeki potansiyel önemine rağmen, kateter içinde kolonize olan mikroorganizmaların önemi henüz tam olarak açıklığa kavuşmamıştır. Bu nedenle kateter içi kolonizasyona sebep olan faktörlerin, bakteriüri ve/veya fungüri ile olan ilişkisinin açıklığa kavuşturulması kateter ilişkili enfeksiyonların azaltılmasına yönelik stratejilerin geliştirilmesine yardımcı olacaktır.

Hastaneye yatan hastaların yaklaşık dörtte birine yatış süresi boyunca üriner kateterizasyon uygulanmaktadır. Özellikle yoğun bakım ünitelerinde yatan hastalarda bu oran %100'e kadar ulaşmaktadır. Kateterizasyon süresi hastanın yattığı kliniğe ve hasta popülasyonuna göre değişiklik göstermekte olup, genellikle gereksiz üriner kateterizasyon oranı yüksektir(5). Kateterizasyon süresi, kateter ilişkili mikrobüri için en önemli risk faktörüdür. Otuz güne kadar uygulanan kateterizasyon kısa süreli kateterizasyon olarak tanımlanırken, otuz günü aşan kateterizasyon uygulamaları uzun süreli kateterizasyon olarak tanımlanmaktadır. Üriner kateter uygulanan hastalarda en yaygın görülen komplikasyonlar bakteriüri ve olguların birçoğunda ortaya çıkan üriner sistem enfeksiyonlarıdır. Kısa süreli kateterizasyona bağlı bakteriürilerin çoğu asemptomatiktir. Ateş veya diğer ÜSE semptomları %10-30'a yakın bir oranda görülür. Katetere bağlı bakteriürili hastaların %5'inden daha azında bakteremi gelişmektedir. Bununla birlikte kateterize hasta sayısının fazlalığı nedeniyle nozokomiyal bakteremilerin %15 kadarı KİÜSE'ye bağlıdır. KİÜSE sonucunda ölüm görülebilmesine karşın, atfedilen mortalitenin oranı kesin olarak bilinmemektedir. Katetere bağlı bakteriürili hastalarda yapılan otopsilerde akut piyelonefrit, üriner taşlar veya perinefritik apseler tespit edilmiştir. Kateterle ilişkili üriner sistem enfeksiyonları diğer nozokomiyal enfeksiyonların kaynağı da olabilir.

Bu çalışmada Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Eğitim, Araştırma ve Uygulama Hastanesi Genel Cerrahi, Üroloji, Ortopedi ve Travmatoloji, Kadın Hastalıkları ve Doğum Servisi'nde izlenen ve geçici üriner kateterizasyon uygulanan hastalarda, üriner kateter iç yüzeyinde kolonize olan ve eş zamanlı idrar kültüründe üreyen bakteriyel, fungal mikroorganizmaların araştırılması ve kolonizasyon için risk faktörlerinin saptanması amaçlandı.

2. Gereç ve Yöntemler

a. Hasta Seçimi

Bu kesitsel tip çalışmada Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Eğitim, Araştırma ve Uygulama Hastanesi Genel Cerrahi, Üroloji, Ortopedi ve Travmatoloji, Kadın Hastalıkları ve Doğum kliniklerinde 01.08.2009-01.10.2009 tarihleri arasında geçici üriner kateterizasyon uygulanan hastalarda kateter içi ve eş zamanlı idrar örneği alınarak kateter lümeninde ve idrarda mikroorganizma kolonizasyonunun araştırılması, olası risk faktörlerinin değerlendirilmesi amaçlandı. Geçici üriner kateterizasyon uygulanan 129 hasta çalışmaya alındı. Yatış esnasında üriner system enfeksiyonu klinik ve bulguları olan hastalar çalışma kapsamı dışında bırakıldı. Geçici üriner kateterizasyonun sonlandırılması planlanan hastalar yattığı klinikte ziyaret edildi, hastaların demografik bilgileri kaydedildi.

b. Örneklerin toplanması

Üriner sonda çıkarılırken sondanın proksimali povidonlu iyot çözeltisi ve steril gazlı bez kullanılarak temizlendi. Steril enjektör yardımıyla idrar örneği alındı. İdrar örneği, piyürinin saptanması için Thoma lamında x40 büyütmede incelenip milimetreküpteki lökosit sayısı belirlendi. Sonda çıkarıldıktan sonra steril şartlarda bisturi yardımıyla proksimalde 5 cm'lik uç kesilerek steril idrar kültür kabına alındı. Steril pamuklu çubuk ile sonda parçasında intraluminal olarak mekanik temizlik yapılarak kateter içindeki mikroorganizmaların pamuklu çubuğa geçmesi sağlandı. Pamuklu çubuk steril bir tüp içindeki 5 ml steril serum fizyolojik içine yerleştirildi. 60 saniye boyunca vortekslenerek süspansiyon hazırlandı.

c. Mikrobiyolojik testler

Elde edilen süspansiyon ve daha önce alınan idrar örneği 0.01 ml'lik steril ölçülü öze yardımıyla Kanlı Agar, Eosin Metilen Blue (EMB) Agar ve Sabouraud Dekstroz Agar (SDA) besi yerlerine ekildi. 37oC'de 24 saat etüvde inkübe edildi. 24 saat sonra üremeler değerlendirildi. Besi yerlerinde oluşan üremelerden alınan örnekler Gram boyama metodu ile boyanarak boyanma özelliklerine ve morfolojilerine göre sınıflandırıldı. Eğer birden fazla morfolojik özellik gösteren üreme olmuşsa tek koloni ekimleri yapılarak saf kültür elde edildi. Üreyen mikroorganizmalar mini API cihazı yardımıyla uygun kitler kullanılarak, üretici firmanın talimatlarına uygun olarak tanımlandı.

d. İstatistiksel analiz

Veriler bilgisayar ortamında SPSS 15.0 istatistik programına girilerek değerlendirildi. İstatistiksel analizlerden ki kare testi, student t testi, Pearson korelasyon testi kullanıldı. İki değişkenli analizlerde anlamlı bulunan bağımsız değişkenlerle Backward Wald Lojistik Regresyon modeli oluşturuldu. Hosmer Lemeshov uyum testi ile en uygun sonuçları veren adım 3'ün sonuçları sunulmuştur.

Çalışma, Eskişehir Osmangazi Üniversitesi Etik Kurulu'nun 30.06.2009 tarih ve 65 sayılı kararı ile onay alınarak gerçekleştirildi.

3. Bulgular

Çalışma 129 hastanın katılımıyla tamamlandı. Çalışma grubunu oluşturan 129 hastanın 80'i (%62.0) erkek, 49 (%38.0) kadındı. Hastaların yaş ortalaması 57.24±13.36 yıl olup yaşları 15 ile 86 arasında değişmekteydi.

Hastaların serviste kaldıkları süre boyunca 56'sının (%43.4) idrar ve/veya üriner kateterinde mikroorganizma üremiş olup, 73'ünde (%56.6) hiçbir üreme olmamıştır.

İdrar ve kateter kültüründe üreyen mikroorganizmaların dağılımı Tablo 1'de sunulmuştur. Escherichia coli idrar ve kateter kültürlerinde en sık saptanan mikroorganizma olarak saptandı (Tablo 2, Tablo 3).

Tablo 1. İdrar ve kateter kültürlerinde üreyen mikroorganizmaların dağılımı.

	Gram Pozitif Bakteri	Gram Negatif Bakteri	Maya
İdrar kültürü	13 (%15.1)	15 (%17.4)	4 (%4.6)
Kateter kültürü	22 (%25.6)	27 (%31.4)	5 (%5.9)
Toplam	35 (%40.7)	42 (%48.8)	9 (%10.5)

Tablo 2. İdrar örneklerinde bakteri ve mayaların dağılımı.

Mikroorganizma	Üreme(n)	Oran(%)
Escherichia coli	12	37.6
Enterococcus faecium	5	15.7
Staphylococcus epidermidis	3	9.3
Candida glabrata	2	6.3
Candida albicans	2	6.3
Staphylococcus hominis	1	3.1
Staphylococcus warneri	1	3.1
Staphylococcus haemolyticus	1	3.1
Staphylococcus cohnii	1	3.1
Pseudomonas aeruginosa	1	3.1
Acinetobacter baumannii	1	3.1
Proteus mirabilis	1	3.1
Brevibacillus brevis	1	3.1
Toplam	32	100

Tablo 3. Kateter kültüründe üreyen mikroorganizmalar.

Mikroorganizma	Üreme (n)	Oran(%)
Escherichia coli	13	24.0
Pseudomonas aeruginosa	6	11.0
Staphylococcus epidermidis	5	9.2
Enterococcus faecium	4	7.4
Enterococcus faecalis	4	7.4
Acinetobacter baumannii	3	5.5
Candida glabrata	3	5.5
Staphylococcus aureus	2	3.7
Staphylococcus haemolyticus	2	3.7
Klebsiella pneumoniae	2	3.7
Candida albicans	2	3.7
Staphylococcus hominis	1	1.9
Proteus stuarti	1	1.9

Micrococcus luteus	1	**1.9**
Corynobacterium striatum	1	**1.9**
Moraxellalacunata	1	**1.9**
Enterococcus hirae	1	**1.9**
Listeria monocytogenes	1	**1.9**
Aeromonas salmonicida	1	**1.9**
Toplam	**54**	**100.0**

Hastaların 66'sı (%51.2) Genel Cerrahi, 41'i (%31.8) Üroloji, 14'ü (%10.9) Beyin Cerrahisi, 4'ü (%3.1) Ortopedi, 4'ü (%3.1) Kadın Hastalıkları ve Doğum Servisi'nde izlenmekteydi. Yapılan ki-kare testinde hastaların izlendiği servislere göre idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme arasında istatistiksel olarak anlamlı bir fark saptanmadı (p= 0.695).

Hastaların 49'u (%38.0) kadın, 80'i (%62.0) erkekti. Kadın hastaların 29'unda (%59.2), erkek hastaların 27'sinde (%33.8) idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptandı. Yapılan ki-kare testiyle çalışmaya alınan kadın hasta grubunda idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptanmasının erkek hasta grubuna göre istatistiksel olarak anlamlı şekilde yüksek olduğu saptanmıştır (p=0.005). İdrar ve/veya kateter lümeni içinden alınan örneklerdeki üremelerin hastaların cinsiyetlerine göre dağılımı Tablo 4'de sunulmuştur.

Tablo 4. İdrar ve/veya kateter lümeni içinden alınan örneklerdeki üremelerin hastaların cinsiyetlerine göre dağılımı.

	Üreme olmayan hastalar n (%)	Üreme olan hastalar n (%)	Toplam
Kadın	20 (40.8)	29 (59.2)	**49 (100.0)**
Erkek	53 (66.3)	27 (33.8)	**80 (100.0)**
Toplam	73 (56.7)	56 (43.3)	**129 (100.0)**

*p< 0.05

Çalışmaya alınan hastalarda üriner kateterizasyon süresi 1-17 gün arasında değişmekte olup, ortalama 4.84±3.43 gündü. Hastaların 107'sinde (%82.9) kateterizasyon 0-7 gün sürerken, 22'sinde (%17.1) 7-17 gün arasında sürmüştür. Kateterizasyonun 0-7 gün sürdüğü hastaların 40'ında (%37.4), 7-17 gün süren hastaların 16'sında (%72.7) idrar ve/veya kateter lümeni içinden alınan

örneklerde üreme saptandı. Yapılan ki-kare testiyle üriner kateterizasyonun 7-17 gün arasında sürdüğü hasta grubunda idrar ve/veya kateter lümeni içinden alınan örneklerde üreme saptanmasının üriner kateterizasyonun 0-7 gün sürdüğü hasta grubuna göre istatistiksel olarak anlamlı şekilde yüksek olduğu saptanmıştır (p=0.002). İdrar ve/veya kateter lümeni içinden alınan örneklerdeki üremelerin hastaların kateterizasyon süresine göre dağılımı Tablo 5'de sunulmuştur.

Tablo 5 . İdrar ve/veya kateter lümeni içinden alınan kültürlerde üremelerle hastaların kateterizasyon süresine göre dağılımı.

Kateterizasyon Süresi	Üreme olmayan hastalar n (%)	Üreme olan hastalar n (%)	Toplam
0-7 gün	67 (62.6)	40 (37.4)	107 (100.0)
7-17 gün	6 (27.3)	16 (72.7)	22 (100.0)
Toplam	73 (56.6)	56 (43.4)	129 (100.0)
*p=0.002			

Hastaların 31'ine (%24.0) acil şartlarda üriner kateterizasyon uygulandığı, 98'ine (%76.0) elektif şartlarda üriner kateterizasyon uygulandığı saptanmıştır. Acil üriner kateterizasyon uygulanan hastaların 20'sinde (%64.5), elektif üriner kateterizasyon uygulanan hastaların 36'sında (%36.7) idrar ve/veya kateter lümeni içinden alınan örneklerde üreme saptandı. Yapılan ki-kare testiyle acil üriner kateterizasyon uygulanan hasta grubunda idrar ve/veya kateter lümeni içinden alınan örneklerde üreme saptanmasının elektif üriner kateterizasyon uygulanan hasta grubuna göre istatistiksel olarak anlamlı şekilde yüksek olduğu saptanmıştır (p=0.007).

Hastaların 56'sında (%43.4) üriner kateterizasyonun sonlandırılması sırasında alınan idrar örneğinde piyüri saptandı. Üreme olmayan hastalarda idrarda ortalama beyaz küre sayısı 3.8±9.52, üreme olan hastalarda, 57.1±133.2 olarak saptandı. Yapılan Pearson korelasyon testi ile idrarda ve/veya katterde üreme olması ile idrardaki beyaz küre sayısı arasında istatistiksel olarak anlamlı zayıf pozitif bir ilişki bulundu (p<0.05).

İdrar kateter çapı ile idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır (p=0.503).

Hastaların 47'sine (%36.4) üriner kateterizasyonun hemşireler tarafından, 82'sine (%63.6) doktorlar tarafından uygulandığı saptanmıştır. Üriner kateterizasyonun hemşireler tarafından uygulandığı hastaların 27'sinde (%57.4), doktorlar tarafından uygulandığı hastaların 29'unda (%35.4) idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptandı. Hemşireler tarafından üriner kateterizasyon uygulanan hasta grubunda idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptanmasının doktorlar tarafından üriner kateterizasyon uygulanan hasta grubuna göre istatistiksel olarak anlamlı şekilde yüksek olduğu saptanmıştır (p=0.015).

Hastaların 20'sinde (%15.5) yakın dönemde üriner sisteme girişim öyküsü bulunmaktayken, 109'unda (%84.5) böyle bir öykü saptanmadı. Üriner girişim öyküsü olan hastaların 13'ünde (%65.0), üriner girişim öyküsü olmayan hastaların 43'ünde (%39.4) idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptandı. Üriner girişim öyküsü olan hasta grubunda idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptanmasının üriner girişim öyküsü olmayan hasta grubuna göre istatistiksel olarak anlamlı şekilde yüksek olduğu saptanmıştır (p=0.034).

Hastaların 11'inde (%8.5) diyabet öyküsü bulunmaktayken, 118'inde (%91.5) böyle bir öykü saptanmadı. Diyabet öyküsü olan hastaların 8'inde (%72.7), diyabet öyküsü olmayan hastaların 48'inde (%40.7) idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptandı. Yapılan ki-kare testiyle diyabet öyküsü olan hasta grubunda idrar ve/veya kateter lümeni içinden alınan kültürlerde üreme saptanmasının diyabet öyküsü olmayan hasta grubuna göre istatistiksel olarak anlamlı şekilde yüksek olduğu saptanmıştır (p=0.040).

İdrar ve/veya kateter lümeni içinden alınan kültürlerde üremelerle hastalarda üriner obstrüksiyon öyküsüne, taş öyküsüne, üriner kateterizasyonun uygulandığı zamana, üriner kateterizasyon sebebine, uygun endikasyonda üriner kateterizasyon uygulanmasına, üriner girişim öyküsüne, malignite öyküsüne, kronik renal yetmezlik öyküsüne, cerrahi operasyon uygulanmasına, cerrahi operasyon bölgesine, antibiyotik kullanımına göre dağılımlara bakılmış ve herhangi bir ilişki saptanamamıştır (her biri için p>0.05).

Nötropeni, transplantasyon öyküsü, immunsupresyon, diyaliz öyküsü, üriner sistemde sık enfeksiyon öyküsü ve silikon sonda kullanımının idrar ve/veya üriner kateter kültüründe üreme varlığı üzerine istatistiksel olarak anlamlı bir etkisi olmadığı saptanmıştır(her biri için p>0.05).

İki değişkenli analizlerde anlamlı bulunan bağımsız değişkenlerle (cinsiyet, kateterizasyon süresi, acil-elektif kateterizasyon, üriner kateterizasyonu uygulayan kişi, yakın dönemde üriner girişim öyküsü, diyabet öyküsü) oluşturulan lojistik model sonuçları Tablo 6'da verilmiştir. Lojistik model sonuçlarına göre, kadın olmak (OR=2.730) ve kateter süresinin >7 gün olması (OR= 3.232) geçici üriner kateterizasyon uygulanan hastalarda idrar ve/veya üriner kateter kültüründe mikroorganizma üremesi için bağımsız risk faktörleriydi (her biri için p<0.05).Üriner kateter kullanımında mikroorganizma üremesi ile anlamlı ilişkili bağımsız değişkenlerle oluşturulan lojistik model sonuçları Tablo 6'da sunulmuştur.

Tablo 6 . Üriner kateter kullanımında mikroorganizma üremesi ile anlamlı ilişkili bağımsız değişkenlerle oluşturulan lojistik model sonuçları.

Adım 3	B	Standard hata	Wald	sd*	P	OR**	%95GA*** (enaz– ençok)
Cinsiyet (referans=erkek)							
Kadın	1.004	0.393	6.524	1	**0.011**	2.730	**1.263 – 5.899**
Kateter süresi (referans=0-7gün)							
>7gün	1.173	0.546	4.613	1	**0.032**	3.232	**1.108 – 9.429**
Constant	**0.992**	**0.271**	**13.435**	**1**	**0.000**	**0.371**	

Hosmer and Lemeshow Test X^2 =0.199;p=0.978
*sd= Serbestlik derecesi, ** OR= Odds Oranı, *** GA= GüvenAralığı

4. Tartışma ve Sonuç

Kateter ilişkili üriner sistem enfeksiyonları farklı hasta gruplarında sıklıkla karşılaşılan ve önemli morbiditeye sebep olan enfeksiyonlardır(5). Nozokomiyal üriner sistem enfeksiyonları, hastane enfeksiyonlarının önemli bir kısmını oluşturur ve sıklıkla üriner sistem kateterizasyonu sonrası gelişir(6). Ülkemizden yapılan bir çalışmada nozokomiyal üriner sistem enfeksiyonlarının %97.3'ünün üriner kateterizasyonla ilişkili olduğu bildirilmiştir(7). European Society of Clinical Microbiology and Infectious Diseases

(ESCMID) çalışma grubu bu oranı %63 olarak bildirmiştir(8).

Üriner kateterler en eski ve en sık kullanılan medikal araçlardan biridir(9). Üriner kateterler, spinal kord yaralanması olan hastalarda, bakım evleri, hastaneler gibi yerlerde sıklıkla kullanılmakta, ilişkili olarak gelişen enfeksiyonlar sağlık bakım giderlerinde de büyük maliyet artışlarına neden olmaktadır(5). Ayrıca üriner sistem enfeksiyonları, hasta konforunda bozulma, mobilitenin sınırlanması gibi olumsuz sonuçlara sebep olabilir(10). NÜSE ile üriner kateterizasyon arasındaki ilişki, çeşitli hasta gruplarında, çeşitli kliniklerde risk

faktörlerinin belirlenmesi açısından geniş kapsamlı olarak araştırılmıştır. Birçok çalışmada üriner kateterizasyon süresinin uzaması, kadın cinsiyet, kateter bakımında yapılan hatalar, ileri yaş, sistemik antimikrobiyallerin kullanılmaması, diyabet öyküsü gibi değişkenler KİÜSE gelişiminde risk faktörü olarak tanımlanmıştır(5,11,12).

Çalışmamızda iki değişkenli analizlerde; kadın cinsiyet, üriner kateterizasyon süresinin >7 gün olması, acil şartlarda üriner kateterizasyon uygulanması, üriner kateterizasyon uygulayan kişi, yakın dönemde üriner girişim öyküsü, diyabet öyküsü gibi parametrelerle geçici üriner kateterizasyon uygulanan hastalarda idrar ve/veya kateter lümeni içinden alınan içinden alınan örneklerde üreme saptanması açısından anlamlı farklılık saptandı. Ancak lojistik model sonuçlarına göre; bağımsız değişkenlerden sadece kadın olmak ve kateter süresinin >7 gün olması geçici üriner kateterizasyon uygulanan hastalarda idrar ve/veya üriner kateter kültüründe mikroorganizma üremesi için bağımsız risk faktörleri olarak saptandı.

Uygunsuz endikasyonda ve gerektiğinden uzun süreli üriner kateterizasyon uygulanması, hastane enfeksiyonları ve mortalitede artışlara sebep olmaktadır(13).Bu konuda yapılan çalışmalarda uygunsuz üriner kateterizasyon oranını Munasinghe ve ark. %38 (14), Gokula ve ark. %54 (15), Hazelett ve ark. %45.8 (16) olarak saptamışlardır. Avrupa'da 25 ülkede 141 hastanede NÜSE'lerin araştırıldığı bir çalışmada, hastaların %7.6'sında üriner kateterizasyonun uygun endikasyonda uygulanmadığı saptanmıştır(8). Bizim çalışmamızda hastaların 23'ünde (%17.8) uygunsuz endikasyonda üriner kateterizasyon uygulaması saptanmıştır. Uygunsuz üriner kateterizasyon oranlarımız literatürdeki verilerden düşük olmakla birlikte, Avrupa ortalamasından yüksektir. Bu oranların düşürülmesi başta KİÜSE ve diğer komplikasyonların azaltılmasına katkı sağlayacaktır.

Yapılan çalışmalar üriner kateterizasyon süresinin KİÜSE gelişiminde en önemli risk faktörü olduğunu göstermiştir. Tissot ve ark.

(17) ise kateterizasyon süresinin >11 gün olmasının bu riski 20 kat arttırdığını göstermişlerdir. Wald ve ark. (18) majör cerrahi operasyon yapılan 35 904 hasta üzerinde yaptıkları çalışmada üriner kateterizasyon süresinin 2 günden uzun olduğu hasta grubunda KİÜSE gelişimi riskinin diğer hastalara oranla anlamlı olarak yüksek olduğunu göstermişlerdir. Colau ve ark.(19) transüretral prostat rezeksiyonu uygulanan 101 hastada yaptıkları çalışmada, üriner kateterizasyon süresinin 3 günü geçmesini bakteriüri gelişimi açısından anlamlı risk faktörü olarak tanımlamışlardır. Apisarnthanarak ve ark.(10) 450 yataklı bir hastanede üriner kateterizasyon uygulanan hastaları değerlendirdikleri bir çalışmada kateterizasyon süresinin uzadığı hastalarda nozokomiyal üriner sistem enfeksiyonlarının daha sık geliştiğini belirlemişlerdir. Bu hastalarda hastanede yatış süresinin anlamlı oranda uzadığını göstermişlerdir. Bizim çalışmamızda da üriner kateterizasyon süresinin >7 gün olmasının (p=0.002) geçici üriner kateterizasyon uygulanan hastalarda idrar ve/veya üriner kateter lümeni içinden alınan kültürde mikroorganizmaların üreme riskini 3.2 kat arttırdığı saptanmıştır. Çalışmamızın sonuçları bu açıdan literatürle uyumludur. Üriner kateterizasyonun mümkün olan en kısa sürede sonlandırılmasıyla bakteriüri/fungüri ve ÜSE gelişme riski asgariye indirilebilir.

Pek çok çalışmada bakteriüri gelişimi ile cinsiyetin rolü değerlendirilmiş, erkeklerle karşılaştırıldığında kadınlarda KİÜSE'nin daha sık geliştiği gösterilmiştir. Tambyah ve ark.(11) 1497 kateterize hastada yaptıkları bir çalışmada KİÜSE gelişen hastaların %66'sının kadın olduğunu bildirmiştir. Leone ve ark. (20) altı yataklı bir yoğun bakımda yaptıkları çalışmada kadın cinsiyeti KİÜSE gelişimi için bağımsız bir risk faktörü olarak bulmuşlardır. Puri ve ark.(21), Laupland ve ark.(22), Johnson ve ark.(23) da çeşitli hasta grupları üzerinde yaptıkları çalışmalarda kadın cinsiyet ile KİÜSE gelişimi arasındaki ilişkiyi göstermişlerdir. Çalışmamızda geçici üriner kateterizasyon uygulanan kadın hastaların %59.2'sinde idrar ve/veya kateter lümeni içinden alınan örneklerde üreme saptandı. Literatürle benzer şekilde kadın

cinsiyetin geçici üriner kateterizasyon uygulanan hastalarda idrar ve/veya üriner kateterde mikroorganizmaların üreme riskini 2.7 kat arttırdığı saptanmıştır.

Araştırmamızda geçici üriner kateterizasyon uygulanan hastaların %43.4'ünde idrar ve/veya kateter lümeni içinden alınan örneklerin kültürlerinde mikroorganizma varlığı saptanmıştır. Ayrıca, idrar ve/veya üriner kateter lümeni içinden alınan örneklerde üreme olması için, kadınlarda riskin erkeklere oranla 2.7 kat, üriner kateterizasyon süresinin >7 gün olanların, <7

gün olanlara göre 3.2 kat fazla olduğu saptandı. KİÜSE tanısı alan ve uygun antimikrobiyal tedaviye rağmen yeterli klinik yanıt alınamayan hastalarda üriner kateter içinde biyofilm gelişmiş olabileceği de göz önüne alınarak üriner kateterizasyonun sonlandırılması veya üriner kateterin değişimi mutlaka değerlendirilmelidir.

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Research Article / Araştırma Makalesi

Analysis of Serum Nickel, Silicium, Arsenic and Boron in Smoking Individuals

Sigara İçenlerde Serum Nikel, Silisyum, Arsenik ve Bor Analizi

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Abstract

Smoking induces inflammation and oxidative stress via radical production from chemicals resulting in cardiocerebrovascular and respiratory diseases, cancers, stroke and sudden death. Elements found in tobacco plant and tobacco smoke are absorbed into blood circulation and transferred into blood and peripheral tissues. The aim of the present study is to evaluate the alterations of serum nickel (Ni), silicium (Si), arsenic (As) and boron (B) levels in smokers. The study groups were categorized as individuals who quitted smoking (Group 1; n: 35; 15 female/20 male), who were smoking (Group 2; n:35; 13 female, 22 male) and who never-smoked (Group 3; n; 40; 20 female/20 male). Biochemical parameters were analyzed in Biochemistry Laboratory of Haseki Traning and Research Hospital. Serum element levels were measured using Inductively Coupled Plasma Atomic Emission Spectroscopy in Trace Element Laboratory of Biophysics Department of Cerrahpasa Medical Faculty at Istanbul University-Cerrahpasa. ANOVA test and Pearson's correlation tests were used for statistical analysis and p < 0.05 was evaluated as statistically significant. Serum Ni levels of Group 2 were higher than the other study groups with no significance. Group 2 had statistically higher serum Si and As levels than Group 1 and Group 3 (p < 0.01, p < 0.05, respectively). There was no statistical significance by means of serum B levels among study groups. Increased serum levels of Si and As in smokers might induce atherosclerosis via inflammation, dyslipidemia and burden oxidative stress. Besides, higher serum Ni levels of smokers might reflect its toxic effects. However, serum B was lower in smokers probably related with its consumption in biological defence mechanisms. Monitorization of serum nickel, silicium, arsenic and boron levels should be considered as biomarkers for smokers.

Keywords: Nickel; silicium; arsenic; boron; smoking

Özet

Sigara içimiyle oluşan radikaller, inflamasyon ile oksidatif stresi uyararak kardiyoserebrovasküler ve solunum sistemi hastalıklar, kanserler, felç ve ani ölüme sebep olmaktadır. Tütün bitkisinde ve sigara dumanında bulunan elementler kan dolaşımı aracılığıyla perifer dokulara geçmektedir. Bu çalışmanın amacı, kronik obstrüktif akciğer hastalığı (KOAH) tanısı olmayan sigara içenlerde serum nikel (Ni), silisyum (Si), arsenik (As) ve bor (B) düzeylerindeki değişiklikleri değerlendirmektir.Gereç ve Yöntemler: Çalışma grupları sigarayı bırakanlar (Grup 1; n: 35; 15 kadın / 20 erkek), sigara içenler (Grup 2; n: 35; 13 kadın, 22 erkek) ve sigara içmeyenlerden (Grup 3; n; 40; 20 kadın / 20 erkek) oluşturuldu. Biyokimyasal parametreler Haseki Eğitim ve Araştırma Hastanesi Biyokimya Laboratuvarında ölçüldü. Serum element düzeyleri İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi Biyofizik Anabilim Dalı Eser Element Laboratuvarı'nda İndüktif Eşleşmiş Plazma Atomik Emisyon Spektroskopisi kullanılarak ölçüldü. İstatistiksel analiz için ANOVA testi ve Pearson's korelasyon testleri kullanıldı. p <0.05 istatistiksel olarak anlamlı olarak değerlendirildi. Grup 2'nin serum Ni düzeyleri diğer çalışma gruplarına daha yüksek olmasına rağmen, istatistiksel anlamlılık yoktu. Grup 2'nin serum Si ve As düzeyleri, Grup 1 ve Grup 3'ten istatistiksel olarak daha yüksekti (p <0.01, p <0.05, sırasıyla). Çalışma grupları arasında serum B düzeyleri açısından istatistiksel anlamlılık yoktu. Sigara içenlerde artmış serum Si ve As düzeyleri, inflamasyon, dislipidemi ve oksidatif stres aracılığıyla ateroskleroza neden olabilir. Ayrıca, sigara içenlerde serum Ni düzeylerinin yüksek olması, Ni'in toksik etkilerini yansıtabilir. Bununla birlikte, sigara içenlerde serum B düzeyinin daha düşük olması, muhtemelen biyolojik savunma mekanizmalarında tüketilmesinden kaynaklanmaktadır. Serum nikel, silisyum, arsenik ve bor düzeylerinin takibi sigara içenler için biyolojik belirteçler olarak kullanılabilir.

Anahtar Kelimeler: Nikel; silisyum; arsenik; bor; sigara içimi

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1. Introduction

Smoking-related diseases have increased the number of deaths in developing countries, reported by The World Health Organization (1). Smoking is not only hazardous for smokers, it also induces other healthy individuals in many ways. Smoking acts as a pathologic initiative factor that produces oxidant status including reactive oxygen species (ROS), damage for biomolecules like DNA, RNA, proteins and enzymes, and inflammation (2,3). Smoking not only establishes a risk factor for cardiocerebrovascular diseases (CCVD), but also induces respiratory diseases and many cancers especially lung cancer, stroke and sudden death (4).

Cigarette includes many toxic elements and metabolites like carbon monoxide and cyanide. Toxic elements inhaled from the tobacco smoke are transferred to blood circulation and are accumulated in special organs like lungs, liver, kidney. Smoking and exposure to smoking disturb blood circulation and peripheral tissue oxygenation both directly or indirectly (5,6). Smoking is also known to have a close relationship with trace elements, which are essential inorganic compunds for biological organism. Their levels in the body and body fluids are effected by nutritional, environmental and habitual factors like smoking and alcohol abuse (7).

In the present study, we focused on serum nickel (Ni), silicium (Si) and arsenic (As) toxic elements and boron (B) as a protective element for human health in smokers. Ni is not an essential element for nutrition in human metabolism. Its functional metabolism could not be explained for humans and animals. Humans are exposed to Ni by orally, by inhalation and by cutaneously producing inflammation and oxidative status within the organism. One of the exposure of human body to Ni is by smoking. Most of Ni in cigarette smoke is volatile and its chemical composition has not been explained yet (8,9). Silicium (Si) that is one of the most abundant elements in the world can be inhaled into the respiratory system in different forms of silicium oxide. Silica particles are transported into the lungs via tobacco smoke inhalation (10,11). Choux et al., reported that alveolar macrophages of a patient diagnosed with pulmonary fibrosis associated with tobacco was stated to contain many silica particles (12). Heckman and Lehman presented that rats had inclusions of Si in their lung epithelial cells after being exposed to chronic tobacco smoke (10). Individuals who do not have smoking habit may just be exposed to Si occupationally. Few data related with Si might be due to the difficulties of its analysis (13). Arsenic (As) is an element frequently found especially in water, soil and air within the environment. As toxicity can effect millions of people causing pathologic conditions in many body systems such as gastrointestinal, cardiovascular, respiratory, hematopetic and cutaneous region (14,15). The biological and positive effects of boron (B) have been discussed in several researches related humans and animals. B has important roles for mineral status, hormone, lipid and energy metabolisms, bone structure, cell wall metabolism and enzymatic reactions, anti-oxidant defence by elimination of reactive oxygen species and immune system (16-18).

Smoking is an initiative factor for pathological conditions like chronic obstructive pulmonary disease (COPD) inducing oxidative stress via ROS production from chemicals and additives. Despite the fact that Ni, Si and Ar are known to be inhaled by respiratory system, their specifity of being toxic even with very minor concentrations and their negative effects on biological organism could not have been elucidated yet. The aim of the present study was to evaluate the effects of smoking on alterations of serum nickel, silicium, arsenic and boron levels in smoking individuals.

Materıals and Methods

Study groups

The individuals who admitted to Outpatient Clinic of Department of Respiratory Medicine at Haseki Traning and Research Hospital, accepted to join the present study with their written consent included the study. The ethical approval was taken from Istanbul University-Cerrahpasa/Cerrahpasa Medical Faculty Ethics Committee. Serum levels of Ni, Si, Ar and B were analyzed for the all

individuals included in the study (n: 110). The study groups were establihed as individuals who quitted smoking (Group 1; n: 35; 15 female/20 male), who were smoking (Group 2; n:35; 13 female, 22 male) and who never-smoked (Group 3; n; 40; 20 female/20 male) (19).

Demographic variables of the individuals included in the study such as age, gender and body mass index, and systolic/diastolic blood pressures were recorded.

Individuals who were diagnosed with COPD (n: 2), diabetes mellitus (n: 4), metabolic diseases (n: 1), cancer (n: 2) and autoimmune diseases (n: 1), and who had pathologic values for blood parameters (n: 2) were excluded from the study. The blood samples of the individuals were collected in the morning after a night fasting interval into plastic blood test tubes without any preservative in order to prevent any metal or element interaction. Whole blood samples were centrifugated utilizing a Hettich Universal centrifuge at 3000 rpm for 20 minutes to obtain serum for biochemical and element analysis. Biochemical analysis were held in Biochemistry Laboratory of Haseki Traning and Research Hospital. All blood samples with hemolysis were excluded from the study.

Centrifugated seum samples were collected in Eppendorf tubes at -80 ºC until the analysis of serum elements.

Analytical method

Element analysis for serum levels of Ni, Si, Ar and B was conducted using Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-OES) (iCAP 6000-Thermo) in Trace Element Laboratory of Biophysics Department of Cerrahpasa Medical Faculty at Istanbul University-Cerrahpasa. Each serum element analysis was measured triplicate and their average was evaluated. Standard solutions were prepared for each analyzed element (Ni, Si, Ar, B) from each of their 1000 µg/dL stock solutions. Calibration graphs were drawn for every element using these standard solutions and deionized water as a blank solution. The analysis of serum samples were done on the same day using the same calibration method in order to prevent any interaction from medium features like temperature and moisture. Element analysis was performed in both axial and radial mode for each element. Serum levels of analyzed elements were expressed in micrograms per milliliter (µg/mL) (2). The technical data related with ICP-OES system are summarized in Table 1.

Table 1. Technical and Analytical Parameters of ICP-OES

Parameters	Ni	B	Si	As
Analysis of replicate number	3	3	3	3
Wavelength (nm)	206.200	249.775	251.611	189.040
Power (kW)	1.3	1.3	1.3	1.3
Plasma gas flow (L/min)	15	15	15	15
Auxiliary gas flow rate (L/min)	15	15	15	15
Nebuliser gas flow (L/min)	0.7	0.7	0.7	0.7
Sample flow (L/min)	1.51	1.51	1.51	1.51
Pump speed (rpm)	100	100	100	100
Mist chamber	Stumar master	Stumar master	Stumar master	Stumar master
Nebuliser	V-groove	V-groove	V-groove	V-groove
Max curve order	1	1	1	1
Calibration curve limit	0.999	0.999	0.999	0.999

ICP-OES: inductively coupled plasma atomic emission spectroscopy, Ni: nickel, B: boron, Si: silicium, As: arsenic

Statistical analysis

Data obtained from analysis were evaluated utilizing SPSS 21.0. Serum element levels were expressed as means ± standard deviation (SD). ANOVA parametric test was used for variables with normal distribution to evaluate the mean within the three study groups. Non-parametric tests as Kolmogrov and Tamhane tests were used for variables without normal distribution to evaluate the median within the three study groups. The mean and median values were evaluated within 95% confidence interval. Pearson correlation analysis was used for the evaluation of parameters among the study groups and $p < 0.05$ was evaluated as statistically significant.

2. Results

Demographic data and biochemical parameters of study groups were given in Table 2. There was no statistical significance among study groups by means of age, body mass index, systolic blood pressure and diastolic blood pressure (Table 2).

Table 2. Demographic Data and Biochemical Parameters of Study Groups

Elements	Group 1 (n:35) (Ex-smokers)	Group 2 (n:35) (Smokers)	Group 3 (n:40) (Healthy controls)
Age	49±7	40±9	46±6
Gender (F/M)	15/20	13/22	20/10
BMI (kg/m2)	25.36±4.37	24.97±4.23	26.82±4.15
SBP (mmHg)	116.28±16.46	126.82±14.91	124.74±14.81
DBP (mmHg)	72.20±8.15	71.65±7.12	74.45±8.45
WBC (10^3/mL)	7.16±1.02	7.45±1.62	6.85±1.42
Hgb (g/dL)	14.20±1.12	13.68±2.23	14.56±1.42
Hematocrit (%)	42.70±3.77	43.27±4.45	42.85±3.73
Glucose (mg/dL)	95.06±9.01	92.16±4.45	96.87±8.02
FT_3 (ng/dL)	3.24±0.47	3.38±0.56	3.20±0.38
FT_4 (ng/dL)	1.21±0.53	1.19±0.37	1.20±0.32
TSH (mIU/L)	1.67±0.40	1.80±0.87	1.73±0.57
ALT (U/L)	21.83±8.92	25.70±7.60	17.90±5.97 [a**, b**]
AST (U/L)	23.20±6.83	24.35±8.42	19.56±6.62 [a**, b**]
Uric acid (mg/dL)	4.80±0.97	4.70±1.10	4.38±1.43
Creatinin (mg/dL)	0.83±0.12	0.94±0.14	0.70±0.13 [a*, b*]
TC (mg/dL)	173.12±30.30	175.00±27.30	184.26±27.53
TG (mg/dL)	103.65±37.82	121.84±60.45	89.00±25.52 [b*]
LDL (mg/dL)	98.75±34.69	104.45±35.53	92.82±30.20 [b*]
HDL (mg/dL)	46.29±11.15	41.10±13.78	53.12±13.67 [b*]

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, Hgb: hemoglobin, FT_3: free triiodothyronine, FT_4: free thyroxine, TSH: tyhroid stimulating hormone, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TC: total cholesterol, TG: triglyceride, LDL: low density lipoprotein, HDL: high density lipoprotein. Data are shown as the means±SD. [a]Statistical comparison of Group 1 with Group 2 and 3, [b]Statistical comparison of Group 2 with Group 3. ∗$p < 0.05$, ∗∗$p < 0.01$

No statistical significancy was found among study groups in terms of white blood cells (WBC), hemoglobin (Hgb), hematocrit, and levels of serum glucose, free triiodothyronine, free thyroxine levels and thyroid stimulating hormone. Group 1 and Group 2 had significantly higher serum alanine aminotransferase and aspartate aminotransferase levels compared with Group 3 ($p < 0.01$). Serum creatinine levels were statistically higher in Group 1 and Group 2 than Group 3 ($p < 0.05$). Group 1 and Group 2 had higher serum uric acid levels compared with Group 3, however there was no statistical

significancy. Serum levels of total cholesterol (TC) were higher in Group 2 compared with other study groups with no statistical significancy. Serum triglyceride (TG) and low density lipoprotein (LDL) levels were statistically higher in Group 2 than Group 3 (p < 0.05) and Group 1 with no statistical significancy. However, serum high density lipoprotein levels of Group 2 were significantly lower than Group 3 (p < 0.05) and Group 1 with no statistical significancy (Table 2).

Serum Ni levels were higher in Group 2 compared with Group 1 and 3, however there was no statistical significance. Serum Ar levels were measured to be statistically lower in Group 2 compared with Group 3, however no statistical significancy was detected between Group 1 and Group 3. Serum Si levels were statistically higher in Group 2 than in Group 3 (p < 0.01). Group 1 also had lower serum Si levels compared with Group 3, but with no statistical significance. When serum B levels were compared, Group 1 (0.04 ± 0.02 µg/mL) and Group 2 (0.03 ± 0.01 µg/mL) had lower values of serum B levels than Group 3 with no statistical significance (Table 3).

The correlations between changes in variables in Group 1 and Group 2 were given in Table 4 and Table 5, respectively.

Table 3. Serum Levels of Ni, Si, As and B in Study Groups

Elements	Group 1 (n:35) (Ex-smokers)	Group 2 (n:35) (Smokers)	Group 3 (n:40) (Healthy controls)
Ni (µg/mL)	0.55 ± 0.18	0.61±0.20	0.51±0.10
Si (µg/mL)	9.66±1.53	12.75±3.06	9.26±2.40 [b**]
As (µg/mL)	0.08±0.02	0.12±0.03	0.07±0.02 [b*]
B (µg/mL)	0.04±0.02	0.03±0.01	0.05±0.02

*Ni: nickel, Si: silicium, As: arsenic, B: boron. Data are shown as the means±SD. [a]Statistical comparison of Group 1 with Group 2 and 3, [b]Statistical comparison of Group 2 with Group 3. *p < 0.05, **p < 0.01.*

Table 4. Correlations Between Changes in Variables in Group 2

Parameters	r
Ni - TC	0.520**
Si - As	0.542**
Si - B	0.534**
As - B	0.385*
As - TG	0.354*
B - TC	-0.410*
B - LDL	-0.320*

*r: correlation coefficient, Group 2: smokers, Ni: nickel, Si: silicium, As: arsenic, B: boron, TG: triglyceride, TC: total cholesterol, LDL: low density lipoprotein. *p<0.05, **p < 0.01.*

Table 5. Correlations Between Changes in Variables İn Group 1

Parameters	r
Ni - TC	0.530**
Si - WBC	0.626**
Si - Hgb	0.608**
As - Hgb	0.475*
As - Creatinine	-0.433*

*r: correlation coefficient, Group 1: ex-smokers, Ni: nickel, Si: silicium, As: arsenic, TC: total cholesterol, WBC: white blood cell, Hgb: hemoglobin. *p<0.05, **p < 0.01.*

3. Discussion

There is strong evidence related with smoking and its pathological consequences in biological organism invluding CCVD, many cancer types especially lung cancer and COPD (2,13). It has been accepted that serum levels of elements such as Ni, Si and Ar are higher in smokers and individuals who are exposed to smoking than non-smokers, whereas the underlying mechanisms related with these isssue have not explained in detail yet (9,13,15). Many studies related with B reported that B was a protective element functioning in decreasing the risk of CCVD by inhibiting atherosclerosis, inflammation and stroke, and supporting the immune system by scavenging ROS (16,20). Our study groups presented some alterations in their demographical data and biochemical parameters within reference ranges, but these results did not reflect to their clinical situation. In this study, we aimed to investigate particular effects of serum Ni, Si, Ar and B elements in smokers.

Ni and its compounds are toxic for biological organism. The effects of Ni on biological organisms depend on its chemical and physical structure, concentration and exposure time. Ni is a potentially toxic element that has hazardous effects on lungs, kidneys, liver and hematopetic system (8,9,13). There have been also many studies related with healthy individuals exposed to Ni. Gil et al. (21) reported that whole blood Ni levels were higher in smokers compared with non-smokers with no statistical significance. Khlifi et al (22) revealed out that there was a strong correlation between smoking and whole blood Ni levels. In a thesis related with heavy metals, it was stated that smokers had higher whole blood Ni compared with non-smokers (8). Besides, urine Ni levels were also higher in children who had seconhand exposure smoking than un-exposed children (23). Nickel levels of the lung tissue of smokers were reported to be higher than non-smokers (13). Consistent with the previos studies, the present study revealed out that serum Ni levels of smokers and individuals who quitted smoking were higher than healthy controls with no statistical significancy. There was a positive correlation between serum Ni levels and TC both in Group 1 and Group 2 that might indicate the inflammation process in blood vessels triggered by dyslipidemia.

Si and its chemical compounds are reported to present on both the surface section and interior components of tobacco leaves (11). Thus, Si analyzed in cigarettes and its smoke have a strong correlation with the concentration of these Si compounds. Si is distributed from inhalation into blood flow leading to atherosclerosis via inflammation in vital organs like lung, brain, liver and kidneys. It has been widely accepted that Si exposure induced inclusion particles formation in macrophages found in bronchiolar, alveolar and interstitial space of lungs in smokers (10,11,24). The difference of the present study was that serum Si levels were analyzed in study groups and our results were consistent with the previous studies by means of Si accumulation in biological tissues. The higher serum Si levels in smokers compared with healthy controls might report the bioaccumulation of Si in blood tissue. The positive correlation of serum Si with WBC and Hgb in Group 1 indicated that defence mechanisms to compensate burden of ROS and to improve oxygen status in biological organism have just started.

Exposure to As for humans is not only by water sources, also As is taken into the organism via smoking and is excreted by urine with a mean half-life of three or four hours (25). While As is transfered through alveolocapillary membrane, it is readily distibuted to the whole body by blood flow. Kucukkurt et al. (26) used As diluted drinking water in rats to induce oxidative stress in blood and vital tissues such as kidney, liver, brain and heart. According to the results of this work, Group 2 had significantly higher serum As levels than Group 3 indicating the accumulation of Si in blood tissue. Even the half-life of As is about three to four hours and its analytical determination is difficult, As levels of the smokers in our study could be detectable due to the fact that smokers had the habit of smoking regularly. Besides, there was a positive correlation between Si and As in

smokers supporting their synergistic hazardous effects for organism. The higher serum levels of TG and the positive correlation between As and TG in Group 2 might indicate the deteriorating effect of As on lipid profile. The higher value of creatinine and the negative correlation between serum As levels and creatinine in Group 1 might present that the filtration functions of kidneys started to improve after quitting smoking. Serum As levels were positively corrrelated with Hgb values in Group 1 that might be a consequence of re-distribution of As from organs like kidney, liver and brain. It is known that As is excreted from blood tissue quickly after smoking cessation by its short half-life, so that its re-distribution would start from the organs.

B is accepted as a protective element regulating vital mechanisms for human health, taking an active role in anti-oxidant defence systems and immune system (16-18). Protano et al. (23) reported that children who had seconhand exposure had statistically higher urine B Levels compared with un-exposed children. Kucukkurt et al. (26) reported in As induced oxidative stress in female and male rats that B significantly decreased oxidant status in liver, kidney, heart and brain tissues. Although there is no significancy among study groups by means of serum B levels, the positive correlation of B with Si and As in Group 2 might postulate the defence system of B over the harmful effects of these elements. B has a decreasing effect on lipid molecules by diminishing their clustering and preventing atherosclerosis (20). Consistently, there was a negative correlation of B with TC and LDL in Group 2 that might emphasize the consuption of B due to dyslipidemia.

As a result, the present study postulated the inflammation, dyslipidemia and burden of ROS leading to atherosclerosis associated with disturbed blood flow in smokers. Alterations of serum trace element levels have not reflected to the clinical onset of smokers. Statistically higher serum levels of Si and As in smokers might introduce their synergistically accumulation in blood tissue. Despite there was no statistical significance in terms of serum Ni levels, higher Ni levels in smokers might be a reflection of its toxic effects. The positive correlation of serum B levels with Si and As might be clarified with the protective effect of B via balancing dyslipidemia. The overlooked effect of elements on smoking may be achieved by conducting detailed research covering their underlying mechanisms. In conclusion, we consider that serum nickel, silicium, arsenic and boron levels should be evaluated as biomarkers for smokers.

❖ Nickel and boron elements were presented at Turkish Physical Society 36th International Physics Congress as an oral presentation.
❖ Karis D., Ates Alkan F., Cakmak G., Ercan A.M., "Effects of Smoking on Serum Nickel and Boron Levels", Turkish Physical Society 36th International Physics Congress, Kadir Has University, Istanbul, Turkey, 01 - 05 September 2020, (Abstract Book, 08OP3, pp 134).

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Research Article / Araştırma Makalesi

The Effect of Glycemic Control on Inflammatory Parameters and Vitamin Levels in Patients with Rheumatoid Arthritis and Fibromyalgia

Fibromiyalji ve Romatoid Artritte Glisemik Kontrolün İnflamatuar Parametreler ve Vitamin Değerleri Üzerine Etkisinin İncelenmesi

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Abstract

The aim of this study is to compare the effect of glycemic control on both inflammatory parameters and vitamin levels in both rheumatoid arthritis and fibromyalgia. A total of 76 patients with type 2 diabetes mellitus and rheumatoid arthritis and 76 patients with type 2 diabetes mellitus and fibromyalgia were retrospectively evaluated in terms of the levels of 25 hidroxy vitamin D, vitamin B12, ferritin, folic asit, erythrocyte sedimentation rate, C-reactive protein, fasting blood glucose, hemoglobin A1c and complete blood count. C-reactive protein, ratios of platelet to lymhocyte and neutrophil to lymhocyte (p<0.001) and erythrocyte sedimentation rate (p=0.002) were significantly higher in patients with rheumatoid arthritis. However hemoglobin A1c, fasting glucose level, monocyte to lymhocyte ratio and vitamin levels were similar between patients with rheumatoid arthritis and fibromyalgia. Both groups were divided into two groups according to hemoglobin A1c being higher or lower than 7%. C-reactive protein (p=0.037) and monocyte to lymhocyte ratio (p=0.050) were significantly higher in rheumatoid arthritis patients with hemoglobin A1c≥7% than hemoglobin A1c<7%. However no significant difference was found in any parameter in fibromyalgia patients according to the level of hemoglobin A1c. Our study results showed that the levels of hemoglobin A1c was similar in patients with rheumatoid arthritis and fibromyalgia. And poor glycemic control accelerates inflammation in only rheumatoid arthritis, however it does not seem to effect vitamin levels.

Keywords: Diabetes mellitus, Fibromyalgia, Rheumatoid arthritis, Vitamin D

Özet

Bu çalışmanın amacı, romatoid artrit ve fibromiyaljili hastalarda, glisemik kontrolün hem inflamatuar belirteçler hem de vitamin değerleri üzerine etkisini karşılaştırmaktır. Hem tip 2 diyabeti olan hem de romatoid artriti olan toplam 62 hasta, hem tip 2 diyabeti hem de fibromiyaljisi olan 76 hastanın, 25 hidroksi vitamin D, vitamin B12, ferritin, folik asit, eritrosit sedimentasyon hızı, C-reaktif protein, açlık glukoz düzeyi, hemoglobin A1c ve tam kan sayımı değerleri retrospektif olarak değerlendirildi. Romatoid artritli hastalarda, fibromiyalji hastalarına göre eritrosit sedimentasyon hızı (p=0.002), C-reaktif protein, platelet/lenfosit ve nötrofil/lenfosit oranları (p<0.001) belirgin yüksek saptandı. Ancak hemoglobin A1c, açlık kan glukozu, monosit/lenfosit oranı ve vitamin değerleri her 2 grup arasında benzer bulundu. Her 2 grup da, hemoglobin A1c değerinin %7'den fazla veya düşük olmasına göre iki gruba ayrıldı. C-reaktif protein (p=0.037) ve monosit/lenfosit oranları (p=0.050) romatoid artritli hastalardan hemoglobin A1c değeri ≥%7 olan hastalarda belirgin olarak yüksek saptanırken, fibromiyaljili hastalarda hiçbir parametre, hemoglobin A1c değerine göre farklılık göstermedi. Bu çalışma sonucuna göre, fibromiyalji ve romatoid artritte, hemoglobin A1c değerleri benzerdir. Kötü glisemik kontrol fibromiyaljideki inflamatuar belirteçleri etkilemeyip, romatoid artritte inflamasyonu kötüleştirmekle birlikte, her 2 hastalık grubunda da vitamin değerlerini etkiliyor gibi görünmemektedir.

Anahtar Kelimeler: Diyabet, D vitamini, Fibromiyalji, Romatoid artrit

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1. Introduction

Rheumatoid arthritis (RA) is an inflammatory disease which causes systemic complications (1). There is evidence that fibromiyalgia is also an inflammatory disease (2), however this inflammation is accepted as low grade (3). The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) which are using for monitoring and diagnosis of RA, are classical markers of inflammation (4). And the ratios of monocyte to lymhocyte (M/L), neutrophil to lymphocyte (N/L) and platelet to lymhocyte (P/L) which are also the biomarkers of systemic inflammation (5), have been reported to be a predictors in rheumatoid arthritis (6). There are a few studies which investigates the inflammatory mediators in fibromyalgia. Ilgun et al showed that there were no association between fibromyalgia and both CRP and ESR (7). Karabas and Emre et al. also reported no relation with N/L and P/L. (8,9). Also the pathogenesis of type 2 diabetes mellitus (DM) is associated with inflammation (10). There are contradictory results about the relation between glycemic control and inflammatory parameters. Some of these studies reported a correlation between hemoglobin A1c (HbA1c) and CRP (11) while the others reported no correlation (12).

Moreover, systemic inflamation commonly effects epithelial cells, absorptive areas and villus structures of gastrointestinal tract (13) where almost all vitamins are also absorbed and usually coexists with gastrointestinal dysbiosis and intestinal hyperpermeability (14).

There are studies investigating the relation between poor glycemic control and inflammatory parameters or vitamin levels in diabetics patients. However we could not find any study which investigated the effect of glycemic control on inflammatory parameters and vitamin levels in both inflammatory diseases and low grade inflammatory diseases. In the light of above studies, we aimed to investigate the effect of glycemic control on both inflammatory parameters and vitamin levels in inflammatory diseases.

2. Materials and Methods

This study was a retrospective analysis of patients who had both type 2 diabetes mellitus (ICD-10: E11, E13 and subgroups) and rheumatoid arthritis or fibromyalgia, between January 2019 and April 2020 by searching the patient files and computerized database. The medical records of 76 patients who were diagnosed as rheumatoid arthritis by a specialist according to American College of Rheumatology (ACR) 1987 Criteria (ICD-10: M05, M06 and subgroups) were obtained. And the medical records of 2058 patients with fibromyalgia were obtained. 76 patients who were diagnosed as fibromyalgia by a physical medicine and rehabilitation specialist according to American College of Rheumatology (ACR) 1990 Criteria (ICD-10: M79 and subgroups) were randomly selected from 2058 patients. Randomly selection was performed with "random.org" (online random number generator).

American College of Rheumatology 1990 Fibromyalgia Criteria is widespread pain with tenderness at eleven or more of the eighteen tender points more than three months (15). The diagnosis of type 2 diabetes and rheumatoid arthritis was confirmed from the patient files. Almost all diabetes patients and all rheumatoid arthritis patients were using one or more medication (For type 2 diabetes: insulin / oral anti-diabetic medication, for rheumatoid arthritis: disease modifying anti rheumatic drugs (DMARD) / steroids / anti tumor necrosis factor agents (Anti-TNF)). But the other diabetes patients who took only dietary treatment, had fasting blood glucose values higher than $\geq$ 126 mg/dl or HbA1c values were higher than $\geq 6.5\%$.

Inclusion criteria were: patients with rheumatoid arthritis or fibromyalgia in addition to type 2 diabetes were included to this study. Exclusion criteria were as follows: patients with no confirmation of type 2 diabetes or rheumatoid arthritis, antinuclear antibodies positivity and hematological diseases, infectious diseases, malignancy, patients who had vitamin supplementation and patients who do not have any blood tests in patient files.

The medical records of 152 patients were reviewed for gender, age, antidiabetics medication (oral antidiabetics or insulin), medication of rheumatoid arthritis, complete blood count, ESR, CRP, rheumatoid factor, anti-cyclic citrullinated peptide antibodies (anti CCP), HbA1c, fasting glucose level and vitamin levels (25 hidroxy vitamin D, vitamin B12, ferritin, folic asid). The ratio of neutrophil to lymphocyte (N/L) and platelet to lymphocyte (P/L), monocyte to lymphocyte (M/L) were taken from complete blood count. The level of HbA1c < 7% was accepted as good glycemic control (16).

The study was carried out with the approval of the Council of Ethics of the Faculty of Medicine of Eskisehir Osmangazi University with the decision no 28 dated 03.11.20.

Statistical analysis

The distribution of continuous variables were tested with "Shapiro-Wilk test" and each descriptive statistic was mean ± standart deviation (SD) or median (25%-75%). Non-normally distributed variables were performed using the "Mann Whitney U test". Normally distributed variables were performed with "independent samples t-test". The categorical variables (i.e., insulin and antidiabetics usage) were evaluated with "Chi-square tests" and

also presented as : numbers (n) and percentages (%). A p value <0.05 was considered as statistical significant. All analyses were performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

One hundred and thirty eight (101 female, 37 male) patients with the mean age of 58.69±10.44 (between 24-79 years) who met the criteria were included to the study. 14 patients with rheumatoid arthritis was excluded due to unconfirmed disease.

Information about DM medication of 39 (63%) patients with rheumatoid arthritis and 74 (97%) patients with fibromyalgia was obtained. 50 (80%) patients were using at least one DMARD, 33 (53%) patients were using steroid treatment, 3 (5%) patients were using anti-TNF treatment and 8 (12%) patients were using salazopyrin, only 1 (0.1%) patients were using azotiopurine. CRP, P/L, N/L (p<0.001) and ESH (p=0.002) were significantly higher in patients with rheumatoid arthritis. However HbA1c, fasting glucose level, monocyte to lymhocyte ratio and vitamin levels were similar between patients with rheumatoid arthritis and fibromyalgia (p>0.05) (Table 1).

Table 1. Comparison of parameters between rheumatoid arthritis and fibromyalgia

Patients with Type 2 Diabetes Mellitus (n=138)	Rheumatoid Arthritis (n=62)	Fibromyalgia (n=76)	p value
Age**	58.08 ± 11.21	59.19 ± 9.82	0.534
Gender (female/male) n(%)	43 (69.3%) / 19 (31.7%)	58 (76,3%) / 18 (23.7%)	0.359
Insulin usage (yes/no)	9 (23.1%) / 30 (76.9%)	13 (17.6%) / 61 (82.4%)	0.482
Oral Antidiabetics usage (yes/no)	33 (84.6%) / 6 (15.4%)	58 (78.4%) / 16 (21.6%)	0.426
HbA1c**	7.26 ± 1.92	7.31 ± 1.79	0.891
Fasting blood glucose**	149.23 ± 68.86	150.42 ± 76.35	0.925
CRP**	18.56 ± 24.42	3.67 ± 4.14	**p<0.001**
ESR**	24.22 ± 13.28	15.94 ± 10.66	**0.002**
Neutrophil/lymphocyte rate**	3.17 ± 3.01	1.87 ± 0.73	**p<0.001**
Platelet/lymhocyte rate**	151.08 ± 85.86	112.05 ± 34.87	**p<0.001**
Monocyte/lymhocyte rate**	0.30 ± 0.12	0.25 ± 0.37	0.325
25 hidroxy vitamin D**	21.60 ± 13.02	19.62 ± 10.12	0.392
Vitamin B12**	338.55 ± 146.18	375.39 ± 172.91	0.267

Ferritin*	48.80 (15 - 97.90)	29,0 (18 – 51.50)	0.105
Folic acid**	7.84 ± 4.84	7.48 ± 2.48	0.679

*median (25-75%) **mean ± standard deviation (HbA1c: Hemoglobin A1c, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate)*

55 rheumatoid arthritis patients who had HbA1c records, were divided into two groups according to HbA1c value. CRP (p=0.037) and monocyte to lymhocyte ratio (p=0.050) were significantly higher in patients with HbA1c ≥ 7% (Table 2).

Table 2. Comparison of inflammatory parameters and vitamin levels according to HbA1c in patients with rheumatoid arthritis

Patients with Rheumatoid Arthritis (n=55)	HbA1c < 7% (mean ± standard deviation) (n=32)	HbA1c ≥ 7% (mean ± standard deviation) (n=23)	p value
CRP	12.69 ± 16.84	27.10 ± 31.49	**0.037**
ESR	23.10 ± 12.73	25.05 ± 14.83	0.629
RF	121.83 ± 218.89	181.16 ± 250.52	0.478
Anti-CCP	158.74 ± 114.45	73.14 ± 88.37	0.173
Neutrophil/lymphocyte rate	3.42 ± 3.98	3.02 ± 1.55	0.647
Platelet/lymhocyte rate	155.36 ± 100.10	148.66 ± 74.45	0.787
Monocyte/lymhocyte rate	0.27 ± 0.12	0.34 ± 0.11	**0.050**
25 hidroxy vitamin D	17.78 ± 7.93	26.79 ± 17.36	0.059
Vitamin B12	343.86 ± 147.63	306.67 ± 134.76	0.478
Ferritin*	64.56 (12.17 – 99.25)	98.77 (7,0 – 159,5)	0.897
Folic acid	7.18 ± 4.27	7.76 ± 4.58	0.772

median (25-75%) (CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide antibodies)

Also 73 fibromyalgia patients who had HbA1c records, were divided into two groups according to HbA1c value, however no significant difference was found in any parameter (Table 3).

Table 3. Comparison of inflammatory parameters and vitamin levels according to HbA1c in patients with fibromyalgia

Patients with Fibromyalgia (n=73)	HbA1c < 7% (mean ± standard deviation) (n=43)	HbA1c ≥ 7% (mean ± standard deviation) (n=30)	p value
CRP	3.44 ± 4.53	3.71 ± 3.41	0.864
ESR	16.09 ± 8.11	15.38 ± 14.63	0.856
Neutrophil/lymhocyte rate	1.80 ± 0.73	1.91 ± 0.67	0.525
Platelet/lymhocyte rate	110.61 ± 30.58	113.06 ± 39,0	0.764
Monocyte/lymhocyte rate	0.22 ± 0.05	0.31 ± 0.59	0.324
25 hidroxy vitamin D	19.43 ± 11.12	18.84 ± 7.98	0.817
Vitamin B12	351.85 ± 151.840	401.93 ± 197.76	0.242
Ferritin*	48.38 (19.5 – 53.25)	50.70 (18,0 – 68.25)	0.758
Folic acid	7.78 ± 2.42	7.17 ± 2.57	0.432

median (25-75%) (CRP: C reactive protein, ESR: Erythrocyte sedimentation rate)

4. Discussion

In this study, we investigated the effect of glycemic control on both vitamin levels and inflammatory parameters. Rheumatoid arthritis was selected for first group due to the underlying mechanism "inflammation". Also, in recent studies, it has been reported that fibromyalgia also progresses with a systemic inflammation (2), but this inflammation is low grade (3). Fibromiyalgia was selected for second group due to this "low grade inflammation". Our study results showed that, all inflammatory parameters were higher in RA patients compared to FM patients, as expected. However HbA1c and vitamin levels were similar in both groups. It is already known that rheumatoid arthritis is associated with diabetes mellitus and insulin resistance (17) Also fibromyalgia is associated with diabetes mellitus and high levels of HbA1c. Tishler et al. found that patients with both diabetes and fibromyalgia had significantly higher levels of HbA1c than diabetes patients without fibromyalgia (18).

When we evaluated in terms of glycemic control: the level of inflammatory parameters such as CRP and monocyte to lymphocyte ratios were higher in rheumatoid arthritis patients with poor glycemic control; however in fibromyalgia patients, no inflammatory parameters change according to glycemic control. Inflammation in rheumatoid arthritis is characterised by higher levels of cytokines such as interkeukin-6 and TNF-α which also induce insulin resistance and diabetes mellitus (17). And using glucocorticoid in RA, can disrupt glucose metabolism (19). And also the pathogenesis of diabetes mellitus type 2 is associated with immune system and CRP, interleukin-1β and interleukin-6 has been reported to be elevated (20). Both type 2 diabetes mellitus and rheumatoid arthritis are associated with immune system and inflammation. We believe these two disease may effect each other, poor glycemic control accelerates inflammatory processes in rheumatoid arthritis. We attribute the lack of this effect in fibromyalgia to being inflammation low grade. Similar to our study CRP was found higher in 83 rheumatoid arthritis patients with a poor glycemic control

(HbA1c > 6%) than 213 patients with a good glycemic control, and also it was reported that any relation was not found between usind DMARD and HbA1c. (21). In our study 80% of RA patients were using DMARD. The relationship between DMARD and HbA1c could not be evaluated due to the small number of patients who did not use DMARD.

In the literature, vitamin D has been investigated mostly among the vitamins in patients with diabetes, fibromyalgia and rheumatoid arthritis. In many studies the levels of vitamin D was found lower in both fibromyalgia (22) and rheumatoid arthritis (23). However, there are conflicting results about vitamin D and glycemic control. In some studies it was reported that vitamin D deficiency is associated with poor glycemic control (24) and insulin resistance (25), in others no associaton was reported (26). In our study, any relation was not found between vitamin D deficiency and glycemic control. Also there was not found any relation between HbA1c and other vitamins. Similar to our study results, Karatoprak et al. reported no association between glycemic control and vitamin B12 and folic asid levels (27).

The limitations of our study are its retrospective design, the small sample size and the lack of control group which has only diabetes not rheumatologic disease. Further prospective studies are needed with higher numbers of patients. To the best of our knowledge, it is the first study which compares inflammatory parameters and vitamin levels according to glycemic control in fibromyalgia and rheumatoid artritis, this is the strength of our study.

In conclusion, the levels of HbA1c was similar in patients with rheumatoid arthritis and fibromyalgia. And poor glycemic control accelerates inflammation in rheumatoid arthritis, however glycemic control does not seem to effect vitamin levels. Specialist need to have awareness of rheumatoid arthritis with diabetes mellitus in clinical practise and provide more aggresive intervention for both inflammation and glycemic control.

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Research Article / Araştırma Makalesi

Predictability of Re-rupture After Arthroscopic Repair of Medium Rotator Cuff Tears, a Retrospective Study

Medium Rotator Manşet Yırtıklarının Artroskopik Onarımı Sonrası Yeniden Yırtılmanın Öngörülebilirliği, Retrospektif bir Çalışma

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Abstract

Tears of the rotator cuff (RC), which is one of the shoulder joint stabilizers, are among the most important causes of shoulder pathologies. Patients who do not benefit from conservative treatment usually require surgical treatment, and arthroscopic repair is generally preferred. Re-rupture after RC repair is one of the most common complications. The purpose of this study was to examine the relationship of rotator cuff re-rupture (RCR) with preoperative muscle atrophy and to evaluate whether it is possible to predict its occurrence. Eighty-seven patients who underwent arthroscopic repair due to medium (1–3 cm) full-thickness RC tears and were followed for at least 1 year were evaluated. Demographic data of the patients such as age, gender, affected side, and history of diabetes mellitus, hypertension, hyperlipidemia, and smoking were collected. The repair method (singlerow or doublerow) was recorded. The Constant–Murley Shoulder Score and Oxford Shoulder Score were calculated in preoperative and final controls. In the postoperative 1st year, improvements in the RC and re-rupture were evaluated by ultrasonography (USG). Supraspinatus (SS) atrophies were classified using the modified tangent grading method based on the preoperative magnetic resonance imaging (MRI) results of the patients. On USG, 19 (21.8%) patients had re-rupture and 68 (78.2%) had healing. According to the preoperative MRI results of the patients, 48 (55.2%) patients were found to have first-degree SS muscle atrophy, 29 (33.3%) patients second-degree SS muscle atrophy, and 10 (11.5%) patients third-degree SS muscle atrophy. The atrophy degrees of re-ruptured patients on preoperative MRI were higher than those of healed patients(P<0.001). There was a statistically significant difference in terms of re-rupture according to the preoperative MRI grade of the patients (P<0.001). While re-rupture occurred in all of the third-degree cases by MRI, 24.1% of the second-degree patients and 4.2% of the first-degree patients had re-rupture. The highest rate of re-rupture was seen in third-degree cases and the lowest in first-degree cases. Regarding RCR, we can say that SS muscle atrophy is a risk factor, its probability increases as its degree increases, and it can be predicted preoperatively. We believe that these findings will guide practitioners in determining the most appropriate treatment and predicting the prognosis of patients in the postoperative period.

Keywords: Rotator cuff rupture, rotator cuff re-rupture, supraspinatus muscle atrophy

Özet

Omuz eklemi stabilizatörlerinden olan rotator manşet (RM)' in yırtıkları omuz patolojilerinin en önemli nedenlerinden biridir. Konservatif tedaviden fayda göremeyen hastalara genellikle cerrahi tedavi gerekmektedir ve genelde artroskopik tamir tercih edilir. RM onarımı sonrası yeniden yırtılma en sık karşılaşılan komplikasyonlardandır. Çalışmamızın amacı; rotator manşet yeniden yırtılmanın preoperatif kas atrofisi ile olan ilişkisini incelemek ve yeniden yırtılma oluşumunu tahmin etmenin mümkün olup olmadığını değerlendirmektir. Medium (1-3 cm) boyutunda tam kat rotator manşet yırtıkları nedeni ile artroskopik tamir yapılan, en az 1 yıllık takipte olan 87 hasta değerlendirildi. Hastaların yaş, cinsiyet, etkilenen taraf, diabetes mellitus, hipertansiyon, hiperlipidemi ve sigara kullanımı gibi demografik verileri toplandı. Tamir yöntemi (tek sıra ve çift sıra) kaydedildi. Preoperatif ve son kontrolde Constant Murley Shoulder Score ve Oxford Shoulder Score kullanıldı. Postoperatif 1. yılda rotator manşette iyileşme ve yeniden yırtılma açısından Ultrasonografi (USG) ile değerlendirildi. Hastaların, preoperatif çekilen Manyetik Rezonans (MR) görüntülerinden modifiye tanjant derecelendirme yöntemi ile supraspinatus (SS) atrofileri sınıflandırıldı. USG' de 19 (21,8%) hastada yeniden yırtılma, 68 'inde (78,2%) iyileşme saptandı. Hastaların preoperatif çekilen MR' larında; 48 (55,2%) hasta 1. derece, 29 (33,3%) hasta 2. derece ve 10 (11,5%) hasta 3. derece SS kas atrofisi olduğu saptandı. Preoperatif MR' da yeniden yırtılma olanların sağlam olanlara göre dereceleri daha yüksek saptandı (p<0.001). Hastaların preoperatif MR derecesine göre yeniden yırtılma açısından istatistiksel olarak anlamlı farklılık vardı (p<0.001). MRI 3. derece olanların tamamında tekrar yırtılma yaşanırken 2. derece olanların % 24,1' inde, 1. derece olanların ise % 4,2' sinde yeniden yırtılma oluşmuştur. En çok yırtılma oranı 3. derece, en az 1. derece olgularda görülmüştür. Rotator manşet yeniden yırtılma açısından; SS kas atrofisinin risk faktörü olduğunu, derecesi arttıkça olma ihtimalinin arttığını ve preoperatif tahmin edilebileceğini söyleyebiliriz. Bu durum hastaya en uygun tedavinin belirlenmesinde ve postoperatif dönemde prognozu belirlemek açısından yol gösterici olacağı kanaatindeyiz.

Anahtar Kelimeler: Rotator manşet yırtığı, rotator manşet yeniden yırtığı, supraspinatus kas atrofisi

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1. Introduction

The rotator cuff (RC) consists of four muscles and their tendons that stabilize the humeral head within the shoulder joint and prevent its upward displacement against the deltoid force [1]. Rotator cuff tear (RCT) is one of the most important causes of shoulder problems and its prevalence increases with age [2,3]. Surgical treatment is usually required for patients whose complaints and functional impairments persist despite conservative treatment. Arthroscopic repair has long been considered the standard surgical treatment method for RCT [4,5].

One of the most common complications after RCT arthroscopic repair is rotator cuff re-rupture (RCR), a major concern for shoulder surgeons [6,7]. Studies have reported that patients who developed RCR after RC repair had inferior postoperative clinical outcomes compared to patients who recovered [8–10]. In many studies, the RCR rate varied depending on the patient group selected for the study and the method of evaluation [9–13]. Among the factors that pose a risk for RCR are patient factors such as age and history of smoking, diabetes mellitus (DM), hypertension (HT), and hyperlipidemia (HL); preoperative factors of tissue quality such as supraspinatus (SS) muscle atrophy, fatty degeneration, and tendon mobility; and other factors such as intraoperative surgical technique, postoperative stiffness, and rehabilitation [8,14–19]. Although many risk factors for RCR have been reported, the size of the preoperative tear and fatty infiltration are among the most common and important causes [7,20]. It has been shown that muscle atrophy occurring in the RC is irreversible with surgical repair and is associated with poor outcomes [21,22].

Despite the existence of extensive studies showing that many risk factors are effective for RCR after RCT repair, there is still controversy about whether RCR can be predicted preoperatively. Predicting RCR in the preoperative period would be very useful for both surgeons and patients in determining the surgical treatment method, taking precautions, and determining the postoperative prognosis.

The purpose of our study is to define the RCR rate and associated risk factors after RCT arthroscopic repair by standardizing intraoperative and postoperative factors. In particular, we aim to examine the relation of RCR with muscle atrophy and to evaluate whether it is possible to predict the occurrence of RCR preoperatively. Our hypothesis is that it is possible to predict RCR in patients with RCT in the preoperative period.

2. Materıals and Methods

Study design and participants

We retrospectively reviewed the records of patients who were operated on for RCT at a single center by the same surgeon between July 2015 and September 2019. A total of 281 patients treated surgically with the arthroscopic method were determined.

As per the inclusion criteria of the study, patients were included if they underwent arthroscopic repair due to full-thickness RCT with a size of 1–3 cm (medium) according to the Cofield classification [23] and were followed for at least 1 year. Patients were excluded if they had undergone tenodesis for previous shoulder surgery; if they experienced implant failure or trauma-related RCR, simultaneous adhesive capsulitis, advanced glenohumeral arthritis, or biceps pathology; and if they did not want to be included in the study. Thus, 87 patients who fulfilled the criteria were enrolled in the study.

The study protocol was approved by the Ethics Committee of Ankara City Hospital (Reference Number: E1-21-1482). Written informed consent was obtained from all patients.

Demographic data of the patients such as age, gender, affected side, and history of DM, HT, HL, and smoking were collected. The repair method applied in intraoperative RCT repair was recorded as singlerow (sr) or transosseous equivalent doublerow (dr). The Constant–Murley Shoulder Score (CSS) [24] and the Oxford Shoulder Score (OSS) [25] were calculated to evaluate functional results in the preoperative and final controls.

Imaging plays a vital role in pre- and postoperative evaluation of the shoulder. Ultrasonography (USG) is an excellent modality for evaluating the shoulder postoperatively because of its high spatial resolution and dynamic imaging properties. Although there is a learning curve, USG examination of the shoulder can be focused and is not encumbered by metal anchors or implants. Similar to what is observed in magnetic resonance imaging (MRI), repaired RC tendons may also demonstrate a variable and heterogeneous appearance in USG for years after surgery [26]. All patients were evaluated by USG in terms of healing of the RC and re-rupture in the postoperative 1st year. Dynamic evaluation was performed with a 12L linear probe (9–14 MHz) using a General Electric Healthcare brand Logiq 9 model ultrasound device in our center. SS atrophies were classified using the modified tangent grading method [27] from the first section where the scapula appeared in the Y-shaped sagittal oblique images on preoperative MRIs of all patients. Accordingly, the cases where the SS muscle was above the imaginary line passing through the upper boundaries of the scapular spine and coracoids process were grade 1, those in which it was tangent to the line were grade 2, and those in which it was clearly below the line were determined as grade 3.

Perioperative management

All surgeries were performed in a single center by the same orthopedic surgeon. All patients were situated in the sunbed position with hypotension (systolic blood pressure: 80 to 100 mmHg) under general anesthesia, and a joint pressure pump was operated while maintaining it at about 50 mmHg. Postoperative intravenous analgesic was administered to patients for whom interscalene block could not be performed. Postoperative definitions of tears, repair types, subacromial decompression, additional interventions, intraoperative complications, and operative time were recorded. Anteroposterior lengths of the tears were measured under arthroscopic imaging using a calibrated probe. Considering the tension of the RC, sr or dr repairs were performed.

Postoperative management

Oral analgesic and nonsteroidal antiinflammatory drugs were prescribed at the time of discharge. A shoulder arm sling was used for immobilization for 4 weeks postoperatively.

A similar rehabilitation protocol was applied for all patients after surgery. Pendular exercise was started on the postoperative 1st day. On the 15th day, the sutures were removed and 4-way isometric exercises and passive exercises of up to 90° were started. In addition to isometric exercises, active exercises of up to 90° and passive exercises between 90° and 120° were added at the 1st month controls. After the 6th week, full range of motion active exercise was started. From the 2nd month, strengthening exercises against resistance were started. After 3 months, patients returned to daily activities without any restrictions.

Study measurements

Outcome measurements were collected and scored by one research coordinator. Patient outcome scores were recorded preoperatively and postoperatively.

Constant–Murley Shoulder Score

The CSS is a comprehensive and comparable assessment of shoulder function [24]. This patient- and clinician-completed survey contains four subscales: pain (15 points), activities of daily living (20 points), strength (25 points), and range of motion including forward elevation, external rotation, abduction, and internal rotation of the shoulder (40 points). A higher score represents higher quality of function.

Oxford Shoulder Score

The OSS allows self-assessment of pain and function of the shoulder; it is used in cases of shoulder operations other than stabilization [25]. It contains 12 items: 4 about pain (2 for pain, 2 for interference with pain) and 8 about daily functions. Each item is scored according to 5 Likert-type categories, where 1= no pain/easy to do, 2= mild pain/little difficulty,

3= moderate pain/moderate difficulty, 4= severe pain/extreme difficulty, and 5= unbearable/impossible to do. In the revision study and the online form, the item scoring is from 0 (worst) to 4 (best).

Statistical analysis

Data analyses were performed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov–Smirnov test or Shapiro–Wilk test. The Levene test was used for the evaluation of homogeneity of variances. Continuous data were described as mean ± SD and median (minimum–maximum) for skewed distributions. Categorical data were described as number of cases (%). Differences in statistical analysis among non normally distributed variables between two independent groups were compared by Mann–Whitney U test. Categorical variables were compared using the Pearson chi-square test or Fisher exact test. In addition, the differences in non normally distributed variables between two dependent groups were analyzed by Wilcoxon test. Values of P< 0.05 were accepted as significant in all statistical analysis.

3. Results

The mean age of our patients was 60.97 ± 9.46 years, and 36 were men while 51 were women. The demographic characteristics of the patients are presented in Table 1.

Table 1. Demographic data.

		All cases (n:87)	
Gender	Male	36	(41.4%)
	Female	51	(58.6%)
Age (years)		60.97±9.46	
Average follow-up time (months)		42.99±15.75 44(17–71)	
Side	Right	46	(52.9%)
	Left	41	(47.1%)
Hyperlipidemia		9	(10.3%)
Diabetes mellitus		23	(26.4%)
Hypertension		39	(44.8%)
Smoking		12	(13.8%)

In postoperative USG, 19 (21.8%) patients had RCR and 68 (78.2%) had improvement. When SS atrophies were classified according to the modified tangent grading method based on the preoperative MRI results of the patients, 48 (55.2%) patients were found to have first-degree SS muscle atrophy while 29 (33.3%) patients had second-degree and 10 (11.5%) patients had third-degree. There was a statistically significant difference between the patients with re-rupture and those who were healthy in terms of preoperative MRI grades (P<0.001). Preoperative MRI grades of those with re-rupture were higher than those of healthy patients. There was also a statistically significant difference in RCR according to the preoperative MRI grades of the patients (P<0.001). While all of the third-degree MRI patients experienced re-rupture, 24.1% of the second-degree patients and 4.2% of the first-degree patients did. The highest rate of re-rupture was observed in third-degree cases and the lowest rate was observed in first-degree cases (Table 2).

Table 2. RCR rates according to preoperative MRI (modified tangent) degree.

	Preop. MRI (modified tangent)						P
	1		2		3		
	n	(%)	n	(%)	n	(%)	
Re-rupture	2	(4.2%)	7	(24.1%)	10	100.0%	<0.001
Healthy	46	(95.8%)	22	(75.9%)	-		

Categorical variables are expressed as either frequency or percentage and categorical variables were compared using the Pearson chi-square test or Fisher exact test.

The preoperative mean CSS value of the patients was 36.51 ± 9.50 while the mean postoperative value was 81.13 ± 5.46; postoperative values were thus statistically significantly increased compared to preoperative (P<0.001). The preoperative mean OSS value of the patients was 17.99 ± 4.40, the mean postoperative value was 37.86 ± 3.13, and the postoperative values were statistically significantly increased compared to preoperative (P<0.001). The postoperative CSS and OSS values of the patients with re-rupture were found to be statistically significantly lower than those of patients who recovered (P<0.001) (Table 3).

Table 3. CSS andOSS values.

	Re-rupture		Healthy		P
	$\bar{X}$±SD	Median (min–max)	$\bar{X}$±SD	Median (min–max)	
Preop. CSS	39.95±12.63	35 (28–60)	35.54±8.28	34 (26–64)	0.464
Postop. CSS	73.26±4.58	74 (66–80)	83.32±3.20	83 (72–89)	<0.001
CSS change	33.32±12.5	36 (14–48)	47.78±8.66	8 (21–60)	<0.001
Preop. OSS	19.37±5.47	17(14–28)	17.60±4.02	17 (13–32)	0.466
Postop. OSS	33.68±2.47	34(30–37)	39.03±2.14	39 (32–43)	<0.001
OSS change	14.32±5.38	15 (6–20)	21.43±4.47	21 (7–28)	<0.001

Continuous variables are expressed asmean ± standard deviation (SD) and median (minimum-maximum). Continuous variables were compared with the Mann–Whitney U test.

It was determined that 31 (35.6%) of the patients were treated by dr and 56 (64.4%) by sr RC repair technique. Although the rate of re-rupture was higher in patients who underwent sr repair compared to those who underwent dr, there was no statistically significant difference between the groups in terms of postoperative USG (P> 0.05) (Table 4).

Table 4. Surgery technique.

		Surgery technique				P
		dr (n:31)		sr (n:56)		
		n	(%)	n	(%)	
Postop. USG	Re-rupture	5	16.1%	14	25.0%	0.337
	Healthy	26	83.9%	42	75.0%	

Categorical variables are expressed as either frequency or percentage and categorical variables were compared using the Pearson chi-square test or Fisher exact test.

Although the rates of HL, DM, and HT were higher in patients with re-rupture compared to healthy patients, these differences between the groups did not reach statistical significance (P> 0.05). There was no statistically significant difference between re-rupture or recovery according to smoking habits (P> 0.05). No complications that would require

treatment developed in any of our patients during the postoperative period.

4. Discussion

As the most striking result of our study, SS muscle atrophy was found to be a risk factor for RCR. Accordingly, we can say that RCTs can be predicted in terms of RCR in the preoperative period. We evaluated patients with similarly sized RCTs in this study by standardizing the tear size, which is the most important risk factor for RCR, and thus tried to reduce the confounding effect of this situation.

Jeong et al. [7] stated that RCR can be predicted most effectively when the SS occupation ratio is <43%. Shin et al. [27] concluded that RC repair can positively affect SS muscle atrophy in the postoperative period. Thomazeau et al. [28] reported that SS muscle atrophy on preoperative MRI was a strong predictive factor for RCR. In our study, there was a positive correlation between SS muscle atrophy grade and RCR according to the modified tangent grading method performed on preoperative MRI. As the amount of atrophy increases in the SS muscle, the possibility of RCR increases. We can thus say that a prediction can be made about the possibility of RCR depending on the degree of atrophy in the preoperative SS muscle.

Hein et al. [29] reported that patients who underwent repair with the dr technique had a lower RCR rate than those treated with the sr technique. Millett et al. [19] showed in their meta-analysis that the dr repair technique resulted in a lower RCR rate compared to sr, but they found no difference in clinical outcomes between the two techniques. Zhang et al. [30] showed in their meta-analysis that the dr repair technique had a lower RCR rate than sr, especially in cases of full-thickness RCTs larger than 3 cm. In our study, in contrast to the findings previously reported in the literature, it was observed that there was no statistically significant difference in terms of RCR between patients operated on with dr and sr techniques.

Bishop et al. [31] reported that functional outcomes were significantly worse in patients with RCR. However, a systematic review of 13 studies [32] failed to determine whether functional outcomes of patients with improved RC repairs were permanently superior to those with RCR. Many studies have shown that RCR does not affect pain or clinical function, but some studies have indicated that patients with RCRs have lower clinical function [33–35]. In our study, it was observed that patients with RCR in terms of functional results had lower scores than those who recovered. We think that the lack of consensus on clinical function and pain among those who recovered from RCR in the literature is due to the fact that patient groups and tear sizes were not standardized.

While some authors [36,37] have claimed that DM is associated with RCR, Le et al. [12] reported that there was no significant relationship between them. Jeong et al. [7] also reported that there was no significant relationship between DM, HL, or HT and RCR in their study. In our study, no significant difference was found between patients with and without DM, HT, or HL in terms of RCR.

The limitations of this study were its retrospective nature and the fact that USG is a subjective method of evaluation in terms of RCR. Also, the number of cases could have been higher. The strength of our study was that we standardized the size of rupture, which is the most important risk factor for RCR.

In patients with RCT, we can say that the degree of SS muscle atrophy as examined in preoperative MRI is a risk factor for RCR and RCR can be predicted by evaluating this preoperatively. As the degree of SS muscle atrophy increases, the possibility of RCR increases. Estimating the preoperative RCR will guide practitioners in determining the most appropriate treatment and in predicting the prognosis of patients in the postoperative period.

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The Effect of Topical Atorvastatin on Viability of Random Pattern Skin Flaps, Experimental Study

Topikal Atorvastatinin Random Paternli Cilt Fleplerinin Yaşayabilirliğine Etkisi, Deneysel Çalışma

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Abstract

Augmentation of viability of random pattern flaps has long been an issue in plastic surgery. Up to date no agents were clinically introduced. Atorvastatins are used clinically for lipid lowering. They are also effective on flap survival with their angiogenic, anti-inflammatory, antioxidant effects with systeic administration. In this study, Atorvastatin is used topically for flap survival alleviation in Mc Farlane flap in rats. Wibstar albino type 20 male rats weighing about 180-230 grams were classified as experiment and control group. Results were evaluated by flap necrosis ratios, lymphocyte cells, neutrophile cells, capillary and granulation tissue density on the 7th postoperative day.. Flap necrosis areas were evaluated with Sasaki's paratemplate method. Tissue biopsies of 1x1 cm at the transition zone between necrotic and healthy tissue, were embedded in parafin blocks after fixation in 10% formalin. Biopsies were sliced by 4 micrometer thickness with a microtome. Cross sections were painted with hematoxylene eosin and evaluated with a light microscope. Whitneyy U test was performed for clinical and histopathological evaluation of groups (p<0,05). Flap viability was alleviated. Average necrosis ratios on flaps were 32.1% in the control group and 14.17% in experimental group. Capillary tissue and neutrophile cell density were found to be higher in atorvastatin group. . Granulation tissue and lymphocyte cell density were not found significantly higher.. Atorvastatins, when applied topically, are effective on flap survival. Further studies should be carried out for human clinical use.

Keywords: Flap, survival, Atorvastatin, topically , angiogenesis

Özet

Random fleplerin yaşayabilirliğinin arttırılması plastik cerrahide,süregelen araştırmalara konu olmuştur. Bir çok ajan denenmiş ancak çoğu klinik kullanıma girememiştir. Atorvastatinler lipid düşürücü olarak kullanılmaktadır. Ayrıca , sistemik uygulama ile flep yaşayabilirliğini , arttırdıkları deneysel olarak gösterilmiştir. Bu çalışmada atorvastatinin , topikal uygulama ile flep yaşayabilirliğine etkisi araştırılmıştır. 180-230 gram ağırlığında wibstor albino tipi , 20 erkek rat kontrol ve deney grubu olarak ayrılmıştır. Her bir grupta , Mc Farlane flebi eleve edilmiş , deney grubunda flep üzerine, hazırlanan atorvastatin krem uygulanırken;kontrol grubu herhangi bir tedavi almamıştır. İşlemden 7 gün sonra flep sağlıklı ve nekrotik doku geçiş zonundan 4 mm' lik kesitler halinde doku örnekleri alınarak ,hematoksilen eozin ile boyanmış ve ışık mikroskobu altında lenfosit hücre yoğunluğu, notrofil hücre yoğunluğu , kapiller dansite ve granulasyon dokusu dansitesi açısından incelenmiştir. Fleplerdeki nekroz alanları sasaki kağıdı metodu ile işaretlenmiş, işaretleme AUTOCAT 2012 programına aktarılarak fleplerdeki nekroz oranları bulunmuştur. Histolojik parametlerin ve fleplerdeki nekroz oranlarının karşılaştırılması için Mann Whitney U testi kullanılmıştır (p<0,05) Çalışmaya göre deney grubunda notrofil hücre yoğunluğu ve kapiller dansite artmış, granulasyon dokusu dansitesi ve lenfosit hücre yoğunluğu ise değişmemiştir. Flep nekroz oranının atorvastatin uygulanan grupta azaldığı gösterilmiştir. Flep nekroz oranı kontrol grubunda 32,1% iken deney grubunda 14,17% olarak bulunmuştur .Ek çalışmalara ihtiyaç olmakla birlikte , atorvastatin topikal olarak kullanım ile flep yaşayabilirliğini arttırmaktadır.

Anahtar Kelimeler: flep;yaşayabilirlik;atorvastatin;topikal;anjiyogenez

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1. Introduction

Augmentaion of viability of random flaps has been researched for a long time. Numerous agents were tried as a better understanding of flap physiology and loss. As there are good results with most of them, no agent was introduced clinically because of the need for systemic administration and possible side effects.

Atorvastatins are used for lowering lipids [1]. After they are proved to lower the risk of cardiac attack free of their lipid lowering effect, attentions are drawn to statins pleiotrophic effects [2]. They are thought to be effective on flap survival after showing their angiogenic effects over VEGF and IL-8 [3-4,5], anti-inflammatory[6,7,8] and antioxidant[9,10,11], endothelial vasodilatation [12,13].

Yang et al have shown that treatment of atorvastatin improved skin flap blood perfusion, vascular density and necrotic area. They have shown that this happens by angioneogenesis and VEGF mRNA expression with the use of atorvastatin [14].

In this study we studied the effect of atorvastatin's topical administration on flap survival by measuring flap necrosis ratios and comparing capillary density and granulation tissue in histopathologic samples. We also studied the effects of atorvastatin's anti-inflammatory effect on flap viability.

2. Materials and Methods

This study was performed in Research and Experiment Laboratory of Plastic Aesthetic and Reconstructive Surgery Clinic in İzmir Atatürk Training and Research Hospital . Study was approved for ethical issues by Ege University Experimental Animals Local Ethical Board. Wibstar albino type 20 male rats weighing about 180-230 grams were classified as experiment and control group. All animals were kept at between 18-20° C with 12 hours shift of light and darkness as standard. Every animal was kept alone at one cage for prevention of mutual damaging. All rats were fed with standard rat food and tap water. Anesthesia was performed with 30 mg/kg ketamine added 0.5 mg/kg basilasin through intramuscular route. Mc Farlane's rectangular 3x9 cm flap model was elevated and sutured back at the original place for both groups. Atorvastatin (Kolestor ®) Sanofi Company, İstanbul, Turkey tablet of 40 mg was dissolved in hot water and mixed with appropiate amount of lanolin and vaselin in order to make topical form[15]. Experimental group was applied 1% topical atorvastatin cream whereas control group received no treatment.

Flap necrosis areas were evaluated with Sasaki's paratemplate method on postoperative 7th day and flap viability rates were calculated. Flap dimensions and necrosis line were copied on transparent acetate paper with an acetate pen. Area of flap and necrosis were placed on milimetric scale and calculated. Their ratios were established as percentage(%). Same calculations were graphically produced with Autocad 2012 program. (figure 1a,b)
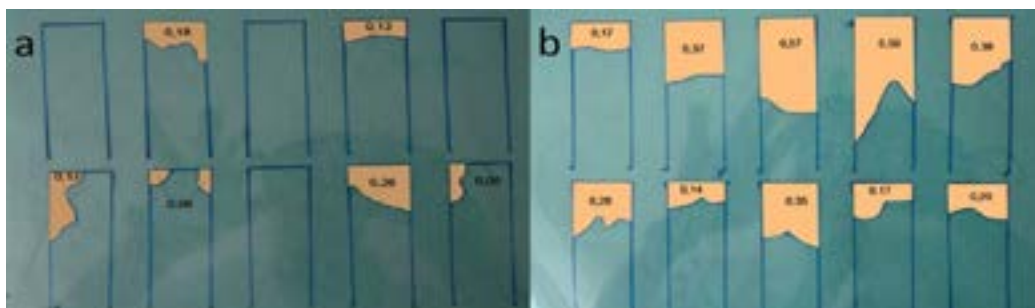

Figure 1.necrotic areas shown in autocad 2012
a)control group b) experiment group

Tissue biopsies of 1x1 cm , on the 7th postoperative day at the transition zone between necrotic and healthy tissue, were embedded in parafin blocks after fixation in 10% formalin. Biopsies were sliced by 4 micrometer thickness with a microtome. Cross sections were painted with hematoxylene eosin and evaluated with a light microscope (figure 2a,b). Evaluation was carried out on four parameters as lymphocyte density, neutrophile density, cappillary and granulation tissue density. Pathologic results were scored. (table 1) Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Descriptive statistics were expressed as mean±SD. Whether the differences in flap necrosis ratio and histopathological density scores between control and study groups were statistically significant or not was evaluated Mann Whitney U test. A p value less than 0.05 was considered statistically significant.
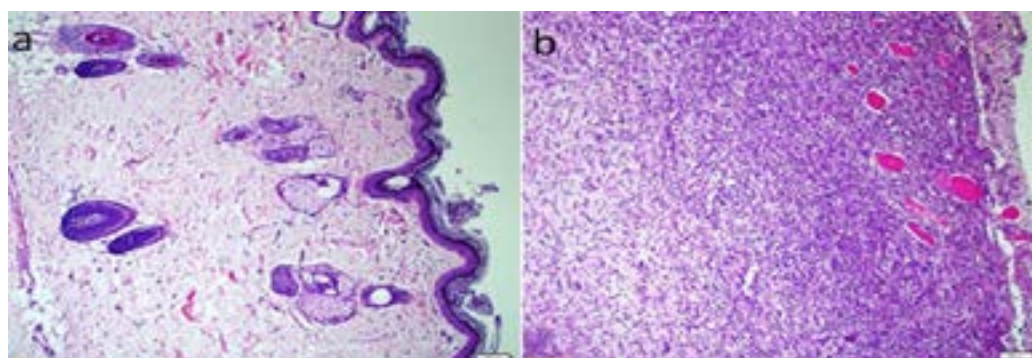
Figure 2.histopathologic tissue samples with light microscobe, hematoxylene eosin, , 40X
a)control group b) experiment group

**Table 1.** The comparisons between control and study groups in terms of histopathological assessment

Density of	Control group	Study group	p-value †
Lymphocyte	1.40±0.52	1.70±0.48	0.189
PMNL	0.00±0.00	1.50±1.27	**0.002**
Capillary	1.10±0.32	1.90±0.74	**0.007**
Granulation	1.10±1.29	2.00±1.05	0.108

† Mann Whitney U test, p<0.05 was considered statistically significant.

3. Results

Average necrosis ratios on flaps were 32.1% in the control group and 14.17% in experimental group. Depending on this data there is statistically significant difference between necrosis ratios in control and experiment group. Flap viability is observed to be alleviated in atorvastatin applied group(p<0,05) (graphic 1)
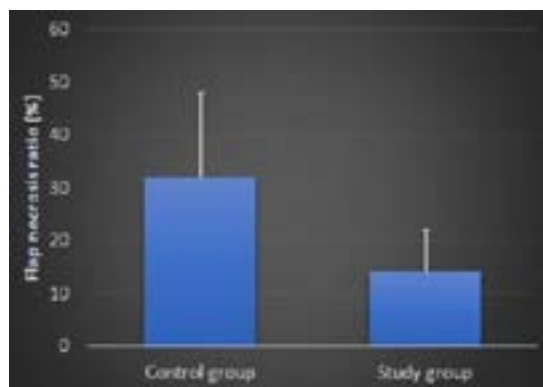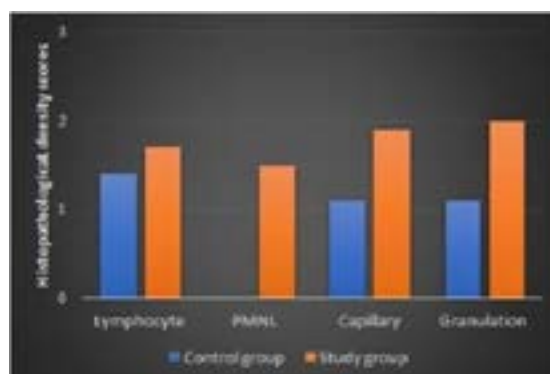
Graphic 1. Comparison of flap necrosis ratio between cases and controls. The top borders of each bar indicate the arithmetic mean of flap necrosis ratio, while the whiskers above of the bar mark plus standard deviation (i.e., +1SD).

Average lymphocyte results were calculated as 1,40±0,52 in control group and 1,70±0,48 in experiment group with scoring values of 0-3 for n=20. These results were not statistically significant(p<0,05). Depending on this, atorvastatin cream is not shown to decrease lymphocyte density (graphic 2).

Average PMNL results were calculated as 0,00±0,00 in control group and 1,50±1,27 in experiment group with scoring values of 0-3 for n=20.These results were statistically significant(p<0,05) (graphic 2). Depending on this, neutrophile cell density in experiment group is found to be higher than control group.

Average capillary density results were calculated as 1,10±0,32 in control group and 1,90±0,74 in experiment group with scoring values of 0-3 for n=20 . These results were statistically significant(p<0,05). Depending on this, capillary density in experiment group is found to be higher than control group (graphic 2).

Average granulation density results were calculated as 1,10±1,29 in control group and 2,00±1,05 in experiment group with scoring values of 0-3 for n=20. These results were not statistically significant(p<0,05). Depending on this, atorvastatin cream is not shown to make a significant difference in granulation density (graphic 2) .

Graphic 2. Comparison of histopathological density scores between cases and controls. The top borders of each bar indicate the arithmetic mean of histopathological density scores.

4. Discussion

Random pattern skin flaps, although use of microsurgery is developing, are still widely used in plastic surgery. But distal flap necrosis is an important problem and causes additional operations, elongated hospital stay, and loss of surgeon and patient motivation.

The major factor in random pattern viability is the blood flow to the flap. With better understanding of flap physiology, experimental agents affecting flap loss in different stages were succesful.

Vasodilatators like sildenafil citrate[16], calcium channel blockers like nifedipin [17] increased blood flow to the flap by dilating the vascular network. Antioxidants [18,19], anti-inflammatory agents[20], hyaluronic acid[21] decreased distal flap necrosis experimentally.

Because of their need for systemic administration and possible side effects, none of the agents could find clinical use.

The most dependable way of flap perfusion augmentation is flap delay but this requires double operations which constitutes its greatest disadvantage.

Hydrodissection [22], tens application[23], microneedling with dermaroller [24] have shown to increase flap perfusion experimentally and they also need no systemic drug use.

Studies with statins have shown that they increased proangiogenetic growth factors. Statins applied in low doses as nanomolar concentrations to human dermovascular cells have shown to increase VEGF. When applied in higher doses this increase was not observed and reported that this effect comes out in biphasic fashion[4].

Yang et al have shown systemic administration of statins have alleviated flap viability[14]. In this study, VEGF mRNA expression was significantly elevated in atorvastatin receiving group. Additionally flap perfusion was found to be higher than control group with doppler ultrasonography on postoperative 30th minute, 4th and 7th days. Capillary density in histopathologic examination was found to be higher in control group.

Significant decrease in flap ischemia with the use of atorvastatin is shown in our study. Flap loss was 32,1% in control group whereas 14,17% in experimental group with atorvastatin(graphic 1). Atorvastatin increases NO emission by direct effect on NOS in early phase and this effect comes out even at ischemic situations[2,12,13]. Elevated NO causes capillary vasodilatation. Statins also increases angiogenic affecting VEGF [3,4,5]. Flap's vascular network is reorganised with capillary dilatation by direct effect of NO and capillary proliferation by VEGF. We observed this effect in our study as increase in capillary density. Capillary density rates with histopathologic examination were found to be significantly higher in experiment group with 1,9 average whereas control group with 1,1 (Table 1) . There is only one study showing the effects of topical statins on capillary density. Toker et al applied topical atorvastatin creams of 1% and 5% concentration on diabetic rat wounds in 2009. They observed that the rates of wound healing were found to be significantly higher in the diabetic rat groups administered 1% and 5% atorvastatin compared with those administered a mixture of lanolin-vaseline and the untreated group. atorvastatin application increases capillary density significantly in both groups compared to control group with no treatment, they also concluded concentrations of 1% and 5% were not significantly different for capillary density[15].

Granulation tissue is a sign, showing that a open wound can be reconstructed, in wound healing. Main ingredients of granulation tissue are fibronectin, hyaluronic acid, macrophages embedded in loose matrix formed by collagen, fibroblasts and dense capillary network. This dense network gives granulation tissue its typical bright red colour. In our study we observed that granulation tissue density was increased in experimental group. Histopathological examination of tissues revealed average density for 1,1 for control group and 2,0 for experiment group although

this was not significantly different(p<0,05) (table 1). Our study showed statins increased vascular component of granulation tissue.

Capillary density rates was found to be higher in experiment group (graphic 2). Extra studies can be performed to observe the effect of statins on other ingredients of extracellular matrix and cellular elements so that effect of statins on granulation tissue can be explained clearly.

Statins have anti-inflammatory effects. Mechanism for anti-inflammatory effect was explained as inhibition of cytokine synhtesis , neutrophile adhesion and ICAM 1 synthesis and shown to be dose dependent[6,7,8]. There are studies showing anti-inflammatory agents increasing flap viability[20]. Main issue is inhibition of cells and mediators responsible for postishemic reperfusion damage. In our study we observed neutrophile cells are significantly higher in experimental group with atorvastatin than the control group(graphic 4). Lymphocyte density was also higher in experiment group but that wasn't significantly different(p<0,05) (table 1)

Atorvastatin's cream form was used for a week in our study. But studies performed for observing anti-inflammatory effects were at least two weeks long[6,7,8]. Additionally in a study with statins at MS disease, it was shown

in order to observe anti-inflammatory effects, doses at least twenty times higher than lipid lowering doses should be administered[25]. In our study we think statins' anti-inflammatory effects have no role in flap viability because of short time and low doses.

Atorvastatin can be applied transdermally beacuse it doesn't need to pass from liver to get activated. Our experiment is a prestudy, in order to get into clinical use absorption differences between species should be noted. Most dependable results for transdermal application can be observed with human experiments. But human transdermal absorbtion varies greatly individually, even between body zones applied on the same individual. This also makes it harder to standardise the process. Rats show less individual differences in transdermal absorption than humans, also rat skin shows similarity to human skin. Both makes rat skin first choice for topical agent experiments[26]. Generally rat skin is twice permeable than human skin. This is explained with membrane lipophilicity, dermal and epidermal thickness, and surface hair follicle density[27].

Doses used on rats can make a prediction for human doses. But individual absorption differences makes unpredicted efficiency, which is a major disadvantage for topical use

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Araştırma Makalesi / Research Article

Is Pathological Assessment Necessary for Excised Sacrococcygeal Pilonidal Sinus Specimens?

Sakrokoksigeal Pilonidal Sinüs Spesmenlerinde Patolojik Değerlendirme Gerekli midir?

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Abstract

In some surgical methods, the cavity of the sacrococcygeal pilonidal sinus remains in the patient. This situation leads us to question the necessity of routine pathological examination. Patients undergoing surgical excision for sacrococcygeal pilonidal sinus between January 2016 and March 2020 at Gaziantep Dr. Ersin Arslan Training and Research Hospital were retrospectively screened. Patients with pilonidal sinus in the non-sacrococcygeal region and patients with minimally invasive treatment and without histopathological examination were excluded. Gender, age, operation notes, and pathology results of the patients were analyzed. For all patients, an excision plus flap (Limberg or Karydakis) procedure was performed and the specimen was sent to routine histopathological examination. Of 1971 patients who underwent surgery for sacrococcygeal pilonidal sinus, 1551 (79%) were male and 420 (21%) were female, with an average age of 24 years (13-66). None of the pathological findings revealed any malignancy. The rate of malignancy reported in the literature is not in concordance with minimally invasive procedures in which pathology samples are not taken. Except in cases of prolonged duration of disease, elderly age, macroscopic suspicion, or recurrence, we believe that routine pathological examination of the pilonidal sinus may be unnecessary.

Keywords: Pilonidal sinus, carcinoma, pathology, squamous cell carcinoma, phenol.

Özet

Pilonidal sinüsün bazı cerrahi yöntemlerinde hastada sakrokoksigeal pilonidal sinüs boşluğu kalmaktadır ve bu durum bizi patolojik incelemenin gerekliliğini sorgulamaya yöneltmiştir. Ocak 2016-Mart 2020 tarihleri arasında Gaziantep Dr. Ersin Arslan Eğitim ve Araştırma Hastanesi'nde sakrokoksigeal pilonidal sinüs için cerrahi eksizyon uygulanan hastalar retrospektif olarak tarandı. Sakrokoksigeal bölge dışındaki pilonidal sinüsü olan hastalar, minimal invaziv tedavi gören ve histopatolojik incelemesi olmayan hastalar çalışma dışı bırakıldı. Hastaların cinsiyeti, yaşı, ameliyat notları ve patoloji sonuçları analiz edildi. Tüm hastalara eksizyon artı flep (Limberg veya Karydakis) prosedürü uygulandı ve spesmenler rutin histopatolojik incelemeye gönderildi. Sakrokoksigeal pilonidal sinüs nedeniyle ameliyat edilen 1971 hastanın 1551'I (% 79) erkek, 420'si (% 21) kadındı ve yaş ortalaması 24 (13-66) idi. Patolojik bulguların hiçbiri malignite göstermedi. Literatürde bildirilen malignite oranı, patoloji örneklerinin alınmadığı minimal invaziv prosedürlerle uyumlu değildir. Uzun süreli hastalık, yaşlılık, makroskopik şüphe veya nüks durumları dışında pilonidal sinüsün rutin patolojik incelemesinin gereksiz olabileceğine inanıyoruz.

Anahtar Kelimeler: Pilonidal sinüs, karsinom, patoloji, skuamöz hücreli karsinom, fenol.

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1. Introduction

Pilonidal sinus is a benign condition, primarily in the sacrococcygeal region, that may cause abscesses, cellulitis, or recurrent sinus tracts. Risk factors include male gender, obesity, and excessive hair growth (1). It is most frequently seen in patients aged 15 to 40 years but is also rarely seen in those over the age of 50 (2). Treatment options include conservative methods such as phenol application, simple incision and drainage, excision, and unroofing, as well as surgical methods such as advancement flaps, cleft lift closure, and Limberg flaps (3).

Histopathological examination of pilonidal sinus specimens detects malignancies only rarely (4, 5); the routine examination is therefore controversial (6-8). Minimally invasive techniques have been successfully used in the pilonidal sinus, such as cleaning the cavity hair, destruction of the cavity of the sinus with silver nitrate and phenol, and destruction of the fistula tract with laser (9-13). These techniques have been used widely and reliably, leading us to question the necessity of histopathological examination. Here, we discuss the pathological findings of the patients who underwent surgery for sacrococcygeal pilonidal sinus in our clinic in the light of the literature.

2. Materials and Methods

This study was approved by the Gaziantep University Ethical Community (2020/177) and registered in an international database (ClinicalTrials.gov NCT 04356768). This study has been conducted in accordance with the Strengthening the Reporting of Cohort Studies In Surgery (STROBE) criteria (14). Patients who were treated for pilonidal sinus between January 2016 and March 2020 at Gaziantep Dr. Ersin Arslan Training and Research Hospital were retrospectively screened. In our clinic, pilonidal sinus specimens are routinely sent to the pathology department for histopathological examination for medico-legal reasons. Patients with pilonidal sinus in the non-sacrococcygeal regions (intermammarian, umbilical, etc.) and patients without histopathological examination who had minimally invasive treatment were excluded from the study. A total of 1971 patients who underwent surgery for sacrococcygeal pilonidal sinus met the inclusion and exclusion criteria and were included in the study. Gender, age, operation grade and pathology results of the patients were analyzed. Statistical analyses were performed using SPSS v22.0 software (IBM, Armonk, NY, USA). Quantitative variables were expressed as mean ± SD, median, min-max, and interval. Qualitative variables were reported as numbers and percentages (%). The Shapiro-Wilk test was used to assess the normality distribution of quantitative variables. While means and standard deviations are used for homogenous distributions, medians and ranges are given for heterogeneous distributions. Fisher's Chi-Square test was used to compare qualitative variables. The Mann-Whitney U test was used for heterogeneous distributions and Student's t-test was used for homogeneous distributions. A p-value below 0.05 was considered statistically significant.

3. Results

Preoperative diagnosis was based on clinical findings. A total of 1971 patients were included in the study and analyzed; 1551 (79%) of the patients were male and 420 (21%) were female. The age distribution of the patients was not homogeneous (Shapiro-Wilk test, $p < 0.05$), and the overall average age was 24 years (13–66). The mean age was 25 (15–66) for male patients and 21 (13–51) for female patients. All patients underwent an excision plus flap (Limberg or Karydakis) operation, and all specimens were sent to routine histopathological examination.

No significant pathological finding was found in 1284 patients (65%). The pathological findings of the remaining 687 patients (35%), listed in order of frequency, included foreign body (n=603), fibrosis (n=54), chronic inflammation (n=24), pseudoepitheliomatous hyperplasia (n=6), epidermoid cyst (n=2), and dermoid cyst (n=1). No malignancy was detected in any patient.

4. Discussion

The most frequent complications of pilonidal sinus are abscesses and cellulitis, but in very rare recurrent cases, it might cause malignancy (0.1%) (15, 16). There is a wide spectrum of treatment for pilonidal sinus, from minimally invasive treatments to surgical excision. In most minimally invasive techniques, specimens are not routinely taken for histopathological examination. Phenol application is a fast and effective treatment for pilonidal sinus without acute or chronic disease and is a minimally invasive method with a strong recommendation based on moderate-quality evidence, 1B. (17). Phenol application is a simple procedure that can be performed with local anesthesia but requires patience for both the surgeon and the patient. Studies have reported successful treatment of the pilonidal sinus at a rate of 70–95% in 14–56 months (18). Pit-picking and sinus cavity destruction with laser or silver nitrate are other minimally invasive methods (12, 19); improvement in pit excision has been reported at a rate of 79% (20), whereas the success rate via laser ablation is reported as 80–90% (11).

The satisfactory results, rapid improvement, possibility of outpatient treatment, and use of only local anesthesia have increased the acceptance of these non-invasive techniques, in all of which the cavity of the sinus remains in the patient. Because the cavity of the sinus remains and no pathological specimens are taken, a malignancy could theoretically be missed. However, to our knowledge, there has been no such reported case.

After surgical excision of pilonidal sinus, specimens are usually sent for pathological examination. Some authors suggest that the pilonidal sinus excision material should be examined after any surgery, whereas some advocate that only suspicious cases (such as prolonged duration of development or patient age over 50 years) should be sent for histopathological examination (6-8). The common feature of cases with malignancy is that they have been treated repeatedly for recurrent pilonidal sinus (21-23). A published review of the development of malignancy in the pilonidal sinus by Eryilmaz et al. identified 83 patients with malignancies (4); a PubMed literature review found three additional reported cases (6, 20, 21). The average age of these 86 patients was 55.3, and the age range was 18–83. Malignancy is more common in men, with a male/female ratio of 4.7:1. Most of the pathology diagnoses in these patients were squamous cell carcinoma, detected in 76 (89.4%). Other diagnoses included epidermoid carcinoma, basal cell carcinoma, and malignant degeneration. Besides, there are also series without malignancy (8, 18). In our clinic, a total excision plus flap (Limberg or Karydakis) operation was performed in all 1971 patients, with routine histopathological examination performed for medico-legal reasons. The average age of our patients was 24 years (13-66), the male/female ratio was 3.7:1, and no malignancy was detected in any patient.

Our study includes a large number of patients who underwent surgery. In patients having minimally invasive procedures, histopathological sampling is not usually performed, and the absence of pathological data from these patients is one of the limitations of this study. In pilonidal sinus patients undergoing minimally invasive treatment, taking a brush or small biopsy from the cavity could help ensure that potential malignancies are not missed. Prospective randomized studies are needed to confirm this approach.

5. Conclusion

The rate of malignancy in the literature is low in spite of minimally invasive procedures in which pathology samples are not taken. Besides, routine histopathological examination causes additional workload and cost. Therefore, except in cases of prolonged duration of disease, advanced age, macroscopic suspicion, or recurrence, we believe that routine pathological examination of the pilonidal sinus may be unnecessary.

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Case Report / Olgu Sunumu

Case of Unusual Foreign Body Insertion in a Gluteal Area in a Schizophrenic Patient: Visual Diagnosis

Şizofreni Hastasında Gluteal Bölgeye Alışılmadık Yabancı Cisim Sokulması

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Abstract

Insertion of a foreign body into the body is frequent in medical literature but multiple insertions are rare. In almost half of cases of foreign body insertion into the body, the cause is for sexual arousal / stimulation. Among other reasons, cognitive disorders ,suicide attempt, psychosis, depression, dementia and delirium, constipation and hemorrhoids treatment, attention-grabbing behavior, as well as abuse should be considered. These insertions can lead to major complications. In this case report, foreign bodies are described in the gluteal area of a 49-year-old psychiatric patient.

Keywords: foreign body, gluteus, schizophrenia

Özet

Yabancı bir cismin vücuda sokulması tıbbi literatürde sıktır, ancak çoklu uygulamalar nadirdir. vücuda yabancı cisim sokulması vakalarının neredeyse yarısında neden cinsel uyarılma / stimülasyon içindir. Diğer nedenler arasında, intihar girişimi, psikoz, depresyon, demans ve deliryum, kabızlık ve hemoroid tedavisi, dikkat çekme davranışı yanı sıra istismar düşünülmelidir. Bu uygulamalar ciddi komplikasyonlara yol açabilir. Bu olgu raporunda gluteal bölgesine yabancı cisim sokan 49 yaşındaki bir psikiyatrik hasta sunulmuştur.

Anahtar Kelimeler: yabancı, cisim, şizofreni

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1. Introduction

Foreign body insertions such as anorectal and urethral holes are frequently presented to emergency department (ED). These insertions can lead to surgical complications and even death [1]. Foreign bodies in children are often accidental and with oral intake, but adults often suffer from concomitant psychiatric diseases [2]. In schizophrenic patients, it may occur as a response to command hallucinations [3]. Foreign bodies can enter the body by swallowing, insertion or by traumatic force. We here report a rare visual diagnosis case of foreign body insertion in the gluteal area in a schizophrenic patient.

Case

A 49- year-old male with previous schizophrenia history about 15 years was admitted to our emergency department with an inability to sit and pain in the gluteal area. He was accompanied by her mother. His medical history included an emotionally unstable personality disorder and an anxious, avoidant personality. Physical examination confirmed edema, ecchymosis and abrasion with mild tenderness in the gluteal area. Digital rectal examination confirmed soft stool. Radiographic evaluation in the form of an acute abdominal series was obtained. His abdomen and pelvic X-ray confirmed multiple linear radiopaque foreign bodies throughout the pelvis (Figure 1,2). Investigation with a CT abdomen and pelvis showed multiple needles, adjacent to the right anus entrance, left and right perirectal area and the posterior rectal wall (figure 3). Our patient was consulted to general surgery, orthopedics and psychiatry departments. He was discharged with conservative treatment after 48 hours of hospitalization.

Figure 1. Abdominal X ray and Foreign bodies

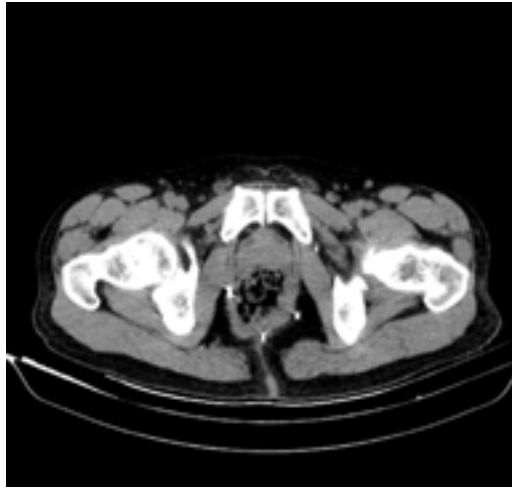

Figure 2. Pelvic X ray and Foreign bodies

Figure 3. Computed tomography and Foreign bodies

2. Discussion

Insertion of a foreign body into the body is frequent in medical literature but multiple insertions are rare. The subject of foreign body removal has wide coverage in the fields of surgery, emergency medicine and paediatry. Self-harm situations such as foreign body insertion are more often indicative of an underlying psychiatric disorder. Diagnosis of these cases, which can be encountered in emergency departments, is sometimes difficult. Because of the underlying psychiatric disorder, patients cannot identify this condition in their anamnesis. It is thought that such behaviors in psychiatric patients occur as a result of delusional beliefs or as a response to hallucinations due to psychotic diseases such as schizophrenia [3]. This is not only seen in schizophrenic patients, but may also occur in patients with substance use, mood disorder, bipolar disorder, and personality disorder [2, 4, 5]. In our patient, a needle was inserted into his body probably as a result of hallucination due to schizophrenia.

Our patient had placed multiple needles intramuscularly in the gluteal region. As in our case, most of these conditions are not fully identified by patients, especially before a life-threatening situation occurs, early recognition and management of the cases are required.

The most prominent cases in the literature about foreign body ingestion/insertion are often related to more than one foreign body. In the literature, psychiatric patients; In addition to oral ingestion, cases of foreign body penetration into the muscle, heart, brain, urethra and bladder have been reported [6-8].

Successful management involves a collaborative approach involving primary care physicians, emergency physicians, surgeons and psychiatrists. It is important to reveal the etiology of foreign body placement, which can help management strategies that target behavioral motivation.

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Case Report / Olgu Sunumu

CADASIL: Clinic and Genetic Corelation

Cadasıl: Klinik-Genetik Korelasyon

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Abstract

CADASIL (Cerebral Autosomal Dominant Arteriopathy, Subcortical Infarcts, Leukoencephalopathy). It is an autosomal dominant familial small vessel disease caused by the mutation of the Notch3 gene in the short arm of the chromosome 19. Clinically it is characterized by recurrent stroke attacks, migraine or migraineous headaches, epileptic seizures and progressive cognitive impairment. In this article, we report four cases of CADASIL that we have clinically evaluated CADASIL and confirmed the diagnosis by moleculer analyses.

Keywords: CADASIL; headache; stroke; dementia, seizure

Özet

CADASIL (Cerebral Autosomal Dominant Arteriopati, Subcortical Infarcts, Leukoencephalopathy) 19. kromozomun kısa kolunda lokalize Notch3 gen mutasyonu sonucu gelişen otozomal dominant geçişli ailesel küçük damar hastalığıdır. Klinik olarak tekrarlayan inme atakları, migren veya migrenöz başağrıları, epileptik nöbetler ve progresif kognitif bozukluk ile karakterizedir. Bu yazıda klinik olarak CADASIL düşündüğümüz, moleküler çalışma ile CADASIL tanısını konfirme ettiğimiz dört olgu klinik ve genetik özellikleri ile sunulmuştur.

Anahtar kelimeler: CADASIL; başağrısı; inme; demans; nöbet

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1. Introduction

Cerebral small vessel diseases (CVD) are an important disease in most developed countries (1). It usually manifests as lacunar infarcts, intracerebral hemorrhage (ICH) and subcortical vascular dementia. Hypertension and diabetes mellitus are known as important risk factors for CVDs. However, many hereditary or idiopathic CVD have also been described (1). Among these, cerebral autosomal dominant arteriopathy, subcortical infarction and leukoencephalopathy (CADASIL) is the most common disease of cerebral small vessels (2). Recurrent stroke, cognitive disorders, migraine, and psychiatric disorders are the main clinical symptoms.

CADASIL was first described by Van Bogaert (1955) in two sisters with a rapidly progressing subcortical encephalopathy of the Binswanger disease type (3). Sourander and Walinder (1977) reported a Swedish family with autosomal dominant inherited cerebral ischemia (4). In this family, clinical findings were characterized by recurrent pyramidal, bulbar and cerebellar symptoms and a gradually developing severe dementia. Multiple small cystic infarctions localized in gray - white matter and pons due to obstruction of small intracerebral and leptomeningeal arteries revealed in autopsy. In the same year, Stevens et al. identified familial vascular dementia with autosomal dominant inheritance in an English family (5). Patients were admitted with temporary motor, sensory and other vascular origin symptoms. In the autopsies of these patients, many small infarct areas were detected in the basal ganglia, thalamus and cerebral white matter. Tournier-Lasserve et al. (1993) used the abbreviation CADASIL for the first time and showed that the disease was localized on the 19q12 chromosome in two French families where they performed linkage analysis (6). Later, Joutel et al. confirmed that the affected gene was Notch3 and identified several mutations related to this gene (7).

Although the prevalence of the disease is not clearly known, it is estimated to be 2-5/100,000 and is more common in men than women. It has been reported in many ethnic groups around the world (8). In this article, 4 cases, which were predicted to be CADASIL in the light of the history and neuroimaging findings accepted to the outpatient clinic with different complaints, were presented to draw attention to the disease (Table 1).

Table 1. Distribution of clinical features of cases

Case	G	A	Complaint	Diagnosis	PH	FH	Notch3 gen mutation
1	F	53	headache	migraine with aura	hypothyroidism	no feature	(C.1903C>T(p.R635C) (p.Arg635Cys)
2	F	24	headache	migraine with aura	no feature	CADASIL	(exon 3- C. 268 C>T/ R90C CM971055)
3	M	46	headache	migraine with aura	aphthae in the mouth	no feature	(p. N944Tfs*328 (c.2829_2829delG)
4	M	41	headache, numbness in the hands and feet	migraine without aura	no feature	no feature	(exon 4 - C.535 C >T/ R153C)

G: gender F: female M: male A: age PH: past history FH: family history

Case 1

A 53-years-old female patient has been suffering from migraine-related headache for the last two years. It was referred to our clinic due to the lesions detected in cerebral Magnetic Resonance Imaging (MRI) performed in an external center where she was evaluated with this complaint. She did not take any other medication except levothyroxine sodium due to Hashimoto's thyroiditis. Her family history was

unremarkable. She did not use alcohol, cigarettes.The physical examination, including the detailed neurological examination, was normal. On laboratory examination; the complete blood cell count, biochemistry panel including lipid profile, kidney, liver and thyroid function tests, collagen tissue tests (including antinuclear antibody, anticardiolipin and antiphospholipid antibodies, anti ds-DNA), and thrombophilia panel were negative. Both Electrocardiography (ECG) and Echocardiogram were normal. Cerebral MRI showed periventricular hyperintense lesions while cerebral MR angiography examination was normal (Image 1a-b). In the light of headache and neuroimaging findings, genetic analysis was requested from the patient who was predicted to be CADASIL, and (C.1903C> T (p.R635C) (p.Arg635Cys) (Heterozygous) mutation was detected in the Notch3 gene. The patient was recognized as CADASIL, genetic counseling provided and family screening recommended (Table1).

Image : a. Normal MR angiography *b.* Hyperintense signal pathologies in the deep white matter adjacent to the posterior horn of the bilateral lateral ventricles prominent on the right in the axial T2 sequence

Case 2

A 24-years-old female patient had migrainous headaches accompanied by the aura for the last 5 years. For this reason, she was diagnosed migraine with aura. Her parents were 3rd degree relatives, her brother and an older sister were diagnosed as CADASIL previously.

On laboratory examination; the complete blood cell count, biochemistry panel including

lipid profile, kidney, liver and thyroid function tests, collagen tissue (romatolojik test desek?) tests (including antinuclear antibody, anticardiolipin and antiphospholipid antibodies, anti ds-DNA), and thrombophilia panel were negative. ECG and Echocardiography were normal. Cerebral MR angiography examination was normal with periventricular hyperintense lesions on cerebral MRI (Image1c-d). Considering her family and past history and findings on neuroimaging, molecular analaysis was performed and detected (exon 3- C. 268 C> T / R90C CM971055) (Heterozygous) mutation in Notch3 gene. Patient was recognized as CADASIL (Table 1).
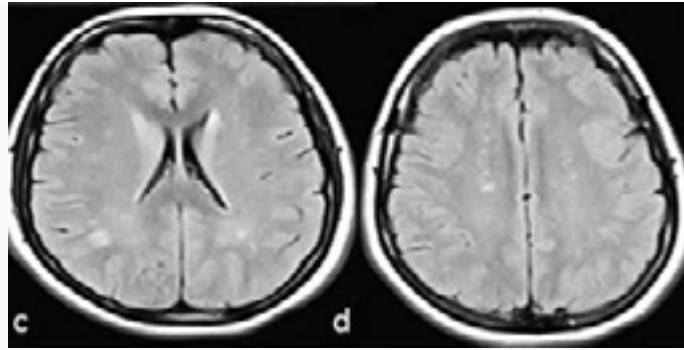
*Image : c. Signal pathologies of bilateral parietal subcortical white matter in T1 sequence **d.** Hyperintense signal pathologies located in the bilateral sentrum semiovale in the T1 sequence*

Case 3

A 46 years-old male patient has had migrainous headaches for the last 10 years. He was admitted to the clinic due to the increase in the frequency and severity of his headache in recent days. Over the past 15 years, he has had recurrent aphthous ulcers in his mouth. There is no feature in the family history.

On laboratory examination; the complete blood cell count, biochemistry panel were normal except homocysteine level. Homocysteine level was slightly high (15 μmol / L; reference range: 5-12). collagen tissue tests and pathergy test were negative. ECG, transthoracic and transesophageal Echocardiography were all normal. Serebral MRI showed periventricular cortical, subcortical hyperintense lesions (Image 1e-f). Moleculer analysis was performed and detected (p. N944Tfs*328 (c.2829_2829delG) (Heterozygous) mutation in Notch3 gene. Thus, he was evaluated as CADASIL (Table1).
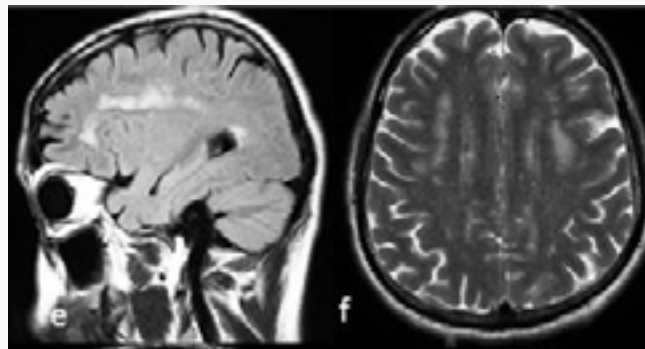

*Image : e. Signal pathologies in periventricular location and tendency to merge in the sagittal section FLAIR sequence **f.** Signal pathologies in bilateral frontoparietal subcortical location in axial T2 sequence at vertex level*

Case 4

A 41 years-old male patient presented with the complaint of headache and numbness in the hands and feet. He reported that had migrainous headaches for the last 5 years and numbness in his hands and feet since the last 1 year.

Neurological examination of the patient, who has no features in his past and family history, was normal. Biochemistry analysis including hemogram, fasting blood sugar, HbA1C, insulin, C-peptide, B12/folate vitamin levels, thrombophilia panel, collagen tissue tests, sugar loading test were normal. ECG was in sinus rhythm and transthoracic and transesophageal Echocardiography were normal. In Electroneuromyography; motor

and sensory nerve conduction velocities and amplitudes were normal.

There was significant periventricular hyperintense lesions in the posterior horns on cerebral MRI. Cerebral MR angiography was normal (Image 1g-h). In the molecular studies, mutation in the Notch3 gene (exon 4 - C.535 C> T / R153C) was detected and the patient was recognized as CADASIL.
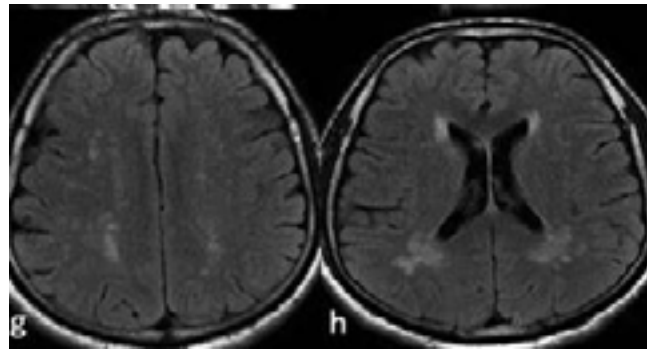

Image: g. *Signal pathologies in bilateral parietal localization at the vertex level in FLAIR sequence* *h.* *Hyperintense signal pathologies in the deep white matter adjacent to the posterior horn of the bilateral lateral ventricles in FLAIR sequence*

2. Discussion

CADASIL characterized by different neurological symptoms such as ischemic stroke, dementia, migraine, psychiatric complaints and epileptic seizures. Ischemic stroke is the most common clinical manifestation of CADASIL and occurs in approximately 60-84% of patients. (3,9). Stroke is usually presented with lacunar syndromes such as pure motor, pure sensory, dysarthria or clumsy hand syndrome, and ataxic hemiparesis and occurs at a young age (mean 41-49 years). It is sometimes progressive and large cerebral artery involvement is detected in 20-30% of patients. But symptomatic arterial stenosis are rare (10). Some cases may be asymptomatic and the presence of cerebral ischemic lesions detected incidentally on cerebral MRI should suggest CADASIL (11). Lesions that are presented with nonspecific or periventricular ischemia in the early period, spread to the external capsule, the anterior of the temporal lobe and subcortical regions, which are characteristic for the disease in a few years (12). In addition to ischemic stroke, spontaneous intracerebral hemorrhages (ICH) due to increased vascular fragility may also be seen. Hemorrhages are often localized to the thalamus, basal ganglion, cerebellum and cerebral lobes. In studies conducted on the subject in Korea and Taiwan, ICH have been reported in 25% of symptomatic cases (13,14). In approximately 70% of patients who have had a stroke, recurrent strokes cause subcortical infarcts, resulting in vascular parkinsonism and pseudobulbar palsy (14). In our series, the strongest evidence suggesting CADASIL in all four cases was the presence of subcortical ischemia in the cerebral MRI examination.

Cognitive impairment is the second most common symptom. It occurs in approximately 60% of cases and causes dementia in almost a quarter or half of cases (15). In these cases, frontal lobe dysfunction is remarkable and it is characterized by findings such as executive function, working memory and impaired verbal fluency. Patients with episodic memory impairment have difficulty recalling rather than coding. As the disease progresses, typical signs of subcortical vascular dementia develop. Cognitive dysfunction is closely related to the number of lacunar infarcts in the brain MRI (16).

Migraine is one of the common symptoms (22-77%) in CADASIL patients. Migrainous headaches usually begin around the age of 20. 80% of migraine has aura. The mechanism of migraine is not fully known in patients with

CADASIL. In terms of clinical features, there is no difference between patients with and without migraine (17). In all of our cases, the symptom of admission was headache, and three of them described the aura.

Psychiatric complaints such as conversion, anxiety, behavior and personality disorders, psychosis and delusion, drug addiction and alcoholism occur in 20-41% of patients. These complaints rarely occur at the beginning of the disease, most of them are temporary. Most patients with psychotic symptoms have an underlying dementia. Apathy is one of the remarkable findings and it occurs in approximately 41% of cases with cognitive impairment (9). A detailed psychiatric history was taken from our cases and no symptoms suggesting any disease were detected.

In 5-10% of patients, epileptic seizures occur in the late period, and most of these cases have a history of stroke and dementia. Seizures are generalized tonic-clonic features rather than focal. A few patients may have acute reversible encephalopathy, which lasts for several days, accompanied by fever, confusion, coma, and seizures. In approximately half of these cases, right-to-left shunt was detected in the Transcranial Doppler. However, the clinical significance of this condition is uncertain because there was no difference in clinical or MRI findings between patients with and without shunting (18). No seizures were detected in any of our cases.

The clinical course of the disease is quite variable, even among family members; The age of onset of stroke, dementia and migraine can cover a fairly long time, such as 20 years, among family members (9). This suggests a weak correlation between genotype and phenotype.

Diagnosis of CADASIL is important for several reasons. First, the clinical course and prognosis are different in CADASIL and other stroke patients. Second; proven treatments for ischemic stroke, including thrombolytic, antithrombotic, antihypertensive agents, and statins have not been validated for CADASIL patients. Migraine, recurrent subcortical stroke, psychiatric complaints and family history associated with these diseases are more common in CADASIL, contributing to its differentiation from other cerebrovascular diseases (19). The diagnosis is made by the presence of subcortical multiple lacunar infarcts in cerebral MRI, presence of NOTCH 3 gene mutation, as well as granular osmophilic material (GOM) accumulation in the skin and muscle vessels. There is no specific treatment in CADASIL. Genetic counseling includes supportive care, depression, and symptomatic treatments for comorbid diseases such as migraine, as well as treatment for secondary prevention from ischemic stroke. Some studies have shown that acetazolamide is effective in migrainous headaches (20). Although the risk of ICH is higher from the society, acetylsalicylic acid can be given to patients who have an ischemic stroke, there are opinions suggesting the use of donepezil to reduce cognitive destruction. Life expectancy is lower than the normal population. The most common causes of death are pneumonia, cardiac arrhythmia and myocardial infarction.

Consequently, due to the limitations in clinical, neuroradiological and genetic diagnosis in day conditions, CADASIL seems to be low in incidence and prevalence, but the number of notifications about the disease is increasing day by day. CADASIL, which is the most common hereditary cerebrovascular disease, should be considered in the differential diagnosis in patients who present to the neurology outpatient clinics with different complaints and findings in favor of ischemia in neuroimaging.

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A Case Report of Familial HDR Syndrome

Ailesel HDR Sendromu: Bir Olgu Sunumu

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Abstract

HDR Syndrome is a rare disease that is inherited autosomal dominantly characterized by a triad of hypoparathyroidism, sensorineural hearing impairment and renal dysplasia. This syndrome is caused by haploinsufficiency of GATA3 gene. We report a family in which two sisters and the father diagnosed with HDR Syndrome because of having hypoparathyroidism and sensorineural deafness. One of these patients had an arachnoid cyst in the left temporal region and cerebellar tonsillar ectopy. The father had horseshoe kidney. A heterozygous GATA3 gene variant (NM_001002295.1 c.1099C>T (p.R367X)) were showed in the sisters. By presenting this case, the clinical and genetic features of HDR Syndrome are reviewed.

Keywords: Hypoparathyroidism; deafness, renal dysplasia; HDR Syndrome

Özet

HDR Sendromu, hipoparatiroidizm, sensörinöral işitme bozukluğu ve böbrek displazisi triadı ile karakterize, nadir görülen otozomal dominant geçişli bir hastalıktır. Bu sendrom, GATA3 geninin haplo yetersizliğinden kaynaklanır. Burada iki kız kardeşte ve babalarında hipoparatiroidizm ve sensörinöral sağırlık saptanması nedeniyle HDR Sendromu tanısı konulan bir aile sunulmuştur. Kardeşlerden birinde sol temporal bölgede araknoid kist ve serebellar tonsiller ektopi, babada at nalı böbrek vardı. Her iki kız kardeşte heterozigot GATA3 gene varyantı (NM_001002295.1 c.1099C> T (p.R367X)) saptandı. Bu olgu sunularak HDR Sendromunun klinik ve genetik özellikleri gözden geçirilmiştir.

Anahtar Kelimeler: Hipoparatiroidi; sağırlık; renal displazi; HDR Sendromu

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1. Introduction

HDR Syndrome (OMIM 146255), a rare disease that is inherited autosomal dominantly, characterized by a triad of hypoparathyroidism (HP), sensorineural hearing impairment and renal dysplasia (1-13). Barakat et al (1) first defined the HDR Syndrome in two male siblings who had nephrosis, HP and hearing impairment in 1977. It is also called as Barakat Syndrome. The patients with HDR syndrome reported by Barakat et al. (1) died from kidney failure in early childhood. At autopsy, the parathyroid glands were absent in one of whom, and hypoplastic in the other these patients.

HDR Syndrome is caused by haploinsufficiency of *GATA3* gene located on chromosome 10p14-10pter. *GATA3* gene encodes GATA binding zinc finger transcription factors that are essential in the development of mainly parathyroid glands, the inner ear and kidneys and also central nervous system and thymus during the embryonic period. This gene variants are resulted in many malformations in different systems. HDR Syndrome is a genetically and clinically heterogenous disorder. HDR Syndrome is caused by many different *GATA3* intragenic variants and distal 10p deletions involving *GATA3* gen*e* region (2-9,10,11).

We report a family with HDR Syndrome in which we demonstrated a heterozygous *GATA3* gen*e* NM_001002295.1 c.1099C>T (p.R367X) variant.

2. Case Presentation

A 12-year-old girl (Case 1) had been referred to our clinic because her serum calcium level was 7.1 mg/dl during the complaint of tetanic spasms and numbness in the hands. She was born with a birth weight of 4000 g at 40 gestational weeks by a normal vaginal delivery after an unremarkable pregnancy. The patient had a history of convulsion when she was 2.5 years old. Her serum calcium level was normal at that time and magnetic resonance imaging had been revealed a 4x4 cm arachnoid cyst in the left temporal region and cerebellar tonsillar ectopy. She had received phenobarbital therapy for four years after that convulsion. She has been using hearing aids since the age of 3 years.

Physical examination of the patient revealed that body weight: 45 kg (25-50 p.), height: 157 cm (50-75 p.), no facial dysmorphism. Systemic examinations and neuromotor development were in normal limits.

In the laboratory analysis, serum calcium: 5.93 (8.6-10.2) mg/dl, phosphorus: 5.7 (2.7-4.5) mg/dl, alkaline phosphatase: 517 (0-270) U/L, magnesium: 0.9 (0.65-1.05) mmol/l, parathormone: 47 (15-65) pg/ml, BUN: 3.8 mg/dl, creatinine: 0.4 mg/dl. Urinalysis was normal. Echocardiography was normal. Any structural renal abnormalities were not detected with ultrasonography (USG). Oral calcitriol and calcium treatment were started for HP.

In her family history, there was no consanguinity between father and mother. Her 16-year-old sister (Case 2) was being followed up with a diagnosis of HP in our clinic since she was 8 years old. She had admitted with the complaint of tetanic spasms in the hands. She had been suffering from intermittent muscle aches. This sister was born 4100 g at term by an uncomplicated vaginal delivery. She had also hearing impairment and had been using hearing aids since the age of 2. She had no facial dysmorphism. Her growth and neuromotor development were normal. Her renal function tests and urinalysis were within normal limits. Echocardiography and renal USG was normal. She was using oral calcium and calcitriol therapy for HP since the diagnosis.

The father had hearing impairment and was also using hearing aids since childhood. Due to the similar clinical presentations of both siblings and the father, underlying genetic causes were reviewed and HDR Syndrome was considered. The both parents were investigated for HDR Syndrome. HP and horseshoe kidney were determined in the father. Treatment for HP was started to him. The mother did not have any sign of HDR Syndrome.

Informed consent from the children and parents was obtained prior to the genetic analysis. Targeted next generation sequencing of the related *GATA3* gene (INTERGEN Laboratory) showed that previously defined a heterozygous *GATA3* gene pathogenic variant NM_001002295.1 C.1099C>T (p.R367X) in these both sisters (Figure 1). Genetic analysis was not done in the father.
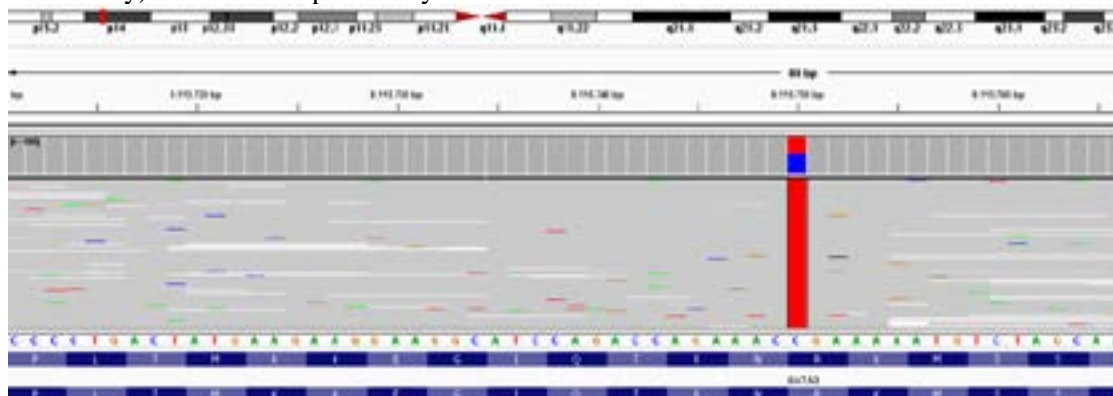

Figure 1. Picture of genetic analysis of Case 1

One of the sisters has been following and receiving treatment of HP for 6 years and one for 14 years. Despite receiving treatment, the drug dose had been adjusted because asymptomatic hypocalcemia varying between 6.6-7.4 mg/dl was found in some routine controls in Case 2 and no additional pathology was observed during their routine controls.

3. Discussion

HDR Syndrome is characterized by HP, sensory neural deafness and renal dysplasia (1-12). This triad of the syndrome is determined in the most patients with HDR Syndrome. The father of our patients had all three phenotypic characteristics. On the other hand, a wide spectrum of genotypic and phenotypic variations has been reported in this syndrome. HP and hearing impairment were identified in our two patients. Some cases who had only two main findings of the syndrome have been also reported as in our two patients (2,4,5).

The age of onset of HP is variable. History of tetanic spasms and convulsions due to hypocalcemia present in the most of the patients. There are reports of severe hypocalcemia observed during the neonatal period (2). Asymptomatic hypocalcemia is also determined in children (2,5,6). Both of our patients presented with the complaint of tetanic spasms in the hands in early childhood.

Asymptomatic HP was diagnosed in the father.

Bilaterally, mild to-moderate-severe sensorineural hearing impairment have been observed in the most of patients with HDR Syndrome (1-3,5-12). Fukami et al. (2) reported a four-year-old case of HDR Syndrome with HP and renal pelvic duplication. But he did not have hearing loss. A frame ship mutation in the *GATA 3* gene was determined in this patient. The case with HDR Syndrome reported by Döneray et al. (4) had a p.R367X variant in the *GATA3* gene and showed no deafness. All of our patients had hearing impairment.

Quite variable renal pathologies have been reported in patients with HDR Syndrome such as renal agenesis, renal hypoplasia and dysplasia, , renal ectopy, proteinuria, hematuria, nephrosis, renal tubular acidosis, renal cyst, pelvic duplication, pelvic and horseshoe kidney (1,2,4-9, 11). Horseshoe kidney was detected in our patient's father. However, there are some patients with HDR Syndrome without any both structural and functional renal abnormalities as in our sisters (5,10). These patients should be monitored for impaired renal function that may develop in the future.

Some developmental anomalies of the other systems have been reported in this syndrome

such as dysmorphic facial features, vagina and uterus abnormalities, VSD, pyloric stenosis, clinodactyly, pectus excavatum, scoliosis, central nervous system abnormalities; autism, delayed, psychomotor development, extrapyramidal signs, hemimegalencephaly (8-11). One of our patients had cerebellar tonsillar ectopy and an arachnoid cyst in the left temporal region.

The HDR Syndrome is genetically heterogenous disorder. *GATA3* gene encodes GATA binding zinc finger transcription factors that are essential in the development of mainly parathyroid glands, the inner ear and kidneys and also central nervous system and thymus during the embryonic period (3). Many different intragenic *GATA3* mutations and deletions of 10p have been reported in patients with HDR Syndrome (2-9,10,11). DiGeorge Syndrome is one of the main causes of congenital HP caused by the deletions at chromosome 22q11.2. On the other hand, distal 10p deletions (10p13-10p14) involving *GATA3* gene defined as second DiGeorge region result in the HDR Syndrome and as well as congenital heart defects, immune deficiency, facial dysmorphism. This clinical picture is called as DiGeorge like Syndrome (2,3). Fukami et al. (2) had reported a case with 10p15 deletion presenting all characteristics of the HDR Syndrome and as well as congenital cardiac defects, facial dysmorphism and T-cell immune deficiency. On the other hand, Fukai et al. (12) identified a de novo 10p deletion in a case of

DiGeorge Syndrome with facial dysmorphisim, severe progressive renal failure, intellectual disabilities and also findings of HDR Syndrome (HP and deafness) and a deletion in the 22q11 region had been demonstrated in this patient previously. These authors pointed out that 22qdeletion and HDR Syndrome could be found together in a patient. Our patients had no facial dysmorphism and congenital cardiac defect. Genetic analysis revealed a previously defined heterozygous *GATA3* gene NM_001002295.1 c.1099C>T (p.R367X) variant in our both patients.

Murayo et al. (6) reported a case of HDR syndrome that developed type 1 diabetes. They stated that *GATA3* haploinsufficiency has been shown to have a role in lymphocyte development and functions before. So they suggested that there might be a relationship between the development of diabetes and *GATA3* haploinsufficiency in the HDR Syndrome. Our patients did not have any immunological abnormalities or history or clinical finding of any autoimmune disease. The earliest finding observed in all of our patients was deafness. Patients with familial congenital deafness should be investigated for asymptomatic hypocalcemia/HP as in HDR Syndrome. The patients with HDR Syndrome also should be monitored for some other clinical abnormalities may develop later during their treatment and follow-up.

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Derleme / Review

Glioblastome Multiforme 'de Güncel Durum ve Uzun Yaşam

Current Situation and Long Life in Glioblastome Multiforme

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Özet

Glioblastome Multiforme (GBM) özellikle orta ve ileri yaş grubunda sık görülen, en kötü huylu primer beyin tümörüdür. Cerrahi rezeksiyon, radyoterapi ve kemoterapiyi içeren üçlü tedaviye rağmen sağ kalım süresi ortalama bir yıl civarındadır. Bu tanıyı almış, üç yıl veya daha uzun süre yaşamda kalmış hastaların uzun yaşadığı düşünülür. GBM hastalarının çok düşük bir yüzdesi bu gruba girer. Uzun yaşadığı gözlenen GBM'li olgularda histopatolojik tanının tekrar gözden geçirilmesi gerekir. Uzun yaşamla ilişkili faktörler kesin olarak bilinmemektedir. Genç yaş, Karnofsky skoru yüksekliği ve Metil Guanin MetilTransferaz(MGMT) metilas-yonunun GBM'li hastalarda daha iyi bir prognoz ve daha uzun sağ kalımla ilişkili olduğu öne sürülmüştür.

Anahtar kelimeler: Beyin tümörü; Glioblastome multiforme; Kemoterapi; Radyoterapi;Cerrahi

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Abstract

Glioblastome multiforme (GBM) is the most frequent and most malignant primary brain tumor seen especially in the middle and elderly age group. Survival, despite therapy including surgical extirpation, postoperative radiotherapy and chemotherapy is one year on average. Survival of three years or more is considered long survival. A very low percentage of GBM patients fall into this category. In such cases histopathologic diagnosis has to be reconfirmed. Factors associated with this condition are unknown. Young age, preoperative high Karnofsky score and methyl guanine methyl transferase (MGMT) methylation have been proposed to be associated with better prognosis and longer survival in GBM patients.

Keywords: Brain tumor; Glioblastome multiforme; Chemotherapy; Radiotherapy; Surgery

1. Giriş

Diffüz infiltratif gliomlar meningiomlardan sonra en sık görülen primer santral sinir sistemi tümörleridir. Tüm santral sinir sistemi(SSS) tümörlerinin % 22'sini oluşturur. Ek olarak GBM ise, en sık görülen malign santral sinir sistemi tümörleridir ve SSS tümörlerinin % 14,6'sını, malign santral sinir sistemi tümörlerinin % 48,3'ünü oluşturur(1). Ayrıca GBM, tüm kanserlerin %1,4'ün da, kansere bağlı ölümlerin % 2,9'unda rastlanır(2). Tedavi edilmeyen GBM hastalarında, ortalama sağkalım süresi sadece 3 ay olup agresif bir neoplazmdır(3). Tedaviye rağmen tanıdan sonra ortalama sağ kalım süresi genellikle 12 ila 18 ay arasındadır. Beş yıllık yaşam süresi tanıdaki yaş ve cinsiyete göre değişmekle birlikte ortalama % 6,8'dir. On yıldan fazla yaşayanlar % 1'den daha azdır(4). GBM tedavisinde cerrahi önemli bir seçenektir. Cerrahi, klinik tanının histolojik olarak doğrulanmasını sağlar ve ayrıca tam rezeksiyonla sağkalım süresini artırır, dekompresif ve sitoredüktif etkiye sahiptir. Rezektif cerrahinin ana kontrendikasyonları, kötü performans durumu (70'in altında Karnofsky), ileri yaş ve önemli yerleşim yeridir(3). Rekürens, hastalığın seyri boyunca kaçınılmaz bir sonuç olup, rekürens görüldükten sonra ortalama sağ kalım süresi 5-7 ay arasındadır.

GBM,frontal (% 43), temporal (% 28), parietal (% 25) ve oksipital (% 4) loblarda olmak üzere daha çok supratentoriyal kompartmanda görülür. Serebellumda ve çocuklarda görülmesi seyrektir. Erkeklerde kadınlara göre 1,6 kat, beyaz ırkta Afrikalı ve Afrika kökenli Amerikalılarda iki kat fazla görülür. Amerika Birleşik Devletlerinde görülme oranı 3,19/ 100,000 nüfus ve ortalama görülme yaşı 64 olarak saptanmıştır (3). Bu makalede, GBM'li olgularda uzun yaşamla ilgili literatur incelemesi ve GBM serimizde üç yılı aşkın yaşayan altı olgudan üçünde yapılan genetik çalışma sonuçları sunuldu.

2. Tartışma

Glioblastomların oluşum ve yayılmasında; astrositlerin, nöroglial kök veya progenitor hücreler, oligodendrosit prekürsör hücreler ve glioblastoma kök hücrelerin rol oynadığı düşünülmekle beraber kesinlik kazanmamıştır. Bu tümörler moleküler heterojenite gösterirler.

Bilinen risk faktörleri GBM tanısı almış olguların çok düşük yüzdesinde geçerlidir. Baş ve boyuna iyonize radyasyon risk faktörü olarak belirlenmiştir. Cep telefonu kullanımının beyin tümörü oluşumuna yol açma potansiyeli ile ilgili yoğun araştırmalar yapılmış, fakat kanıtlanabilen bir ilişki saptanmamıştır(5). Glioblastomalı hastaların büyük çoğunluğunda aile kanser öyküsü yoktur. Tüm gliomların % 5'i ailevidir.

Malign gelişme ile ilgili olarak iki tür glioblastoma vardır. De novo oluşanlar, primer tip GBM dir. yetişkinlerde görülen diffüz infiltratif gliomların en kötü prognoz gösteren tipidir. Bu tümörler ileri yaşlı ve beyaz ırkta daha sık görülür, klinik öykü kısa sürelidir ve yaşam süresi sınırlıdır. Düşük grade'li gliomların evrilmesiyle oluşanlar ise sekonder tip GBM olarak isimlendirilir. sekonder gliomlar daha genç yetişkinlerde görülür. İki tip arasında cinsiyet farklılığı, hormonal değişiklikler ve genetik özellikler ile açıklanmaktadır.

Dünya Sağlık Örgütü (DSÖ), 2016 yılında Santral Sinir Sistemi (SSS) tümörleri sınıflamasını güncellemiştir. Güncellemede en önemli nokta; mikroskopik bulgulara dayanarak yapılan alışılmış patolojik değerlendirme ve tanılara belirli moleküler özelliklerin eklenmesi olmuştur. Tedavi şemalarının belirlenmesinde de; histogenetik sınıflandırma ve derecelendirme sisteminin prognozla kabaca ilişkili olmasının yarar sağladığı, uzun süre uygulama alanı bulduğu belirtilmiştir. Ancak son yıllarda genetik ve epigenetik konularındaki buluşlar, histogenetik sınıflamanın sorgulanmasına yol açmıştır. Bu sorgulamanın belli başlı üç ana nedeni vardır. Öncelikle bir tümörün içinde değişik farklılaşmaların birlikte olması mümkündür, ayrıca DSÖ sınıflamasında; tümör derecelendirmesi ile prognoz arasındaki ilişki, ana moleküler belirleyicilerle prognoz

arasındaki ilişkiye kıyasla daha zayıfdır. Son olarak moleküler testler, mikroskopik değerlendirmeye oranla çok daha objektifdir ve tekrarlayabilme özelliği vardır.

Klasik hematoksilen-eozin boyası ile elde edilen histolojik sonuç tümör için ilk tabakalandırmayı oluşturmaktadır. Tanıya göre tümörün ait olduğu ana grup belirlenmektedir. Daha sonra moleküler değerlendirme ile alınan sonuçlar tanıya eklenir ve böylece tümörün alt tabakalandırması yapılmış olur. DSÖ,2016 yılı SSS tümörleri güncellemesinde, fenotipik ve genotipik sınıflandırmaların birlikte kullanılmasını öngörmektedir. Bir başka yeni kavram,tabloları olabilecek en dar şekliyle tanımlamak amacıyla NOS (not otherwise specified) kavramının öne sürülmüş olmasıdır. Buna göre NOS'un üç durumda kullanılması önerilmiştir: a) genetik testlerin yapılmadığı durumlar, b) genetik test sonuçlarının histolojik bulgularla uyumlu genetik değişiklikler göstermemesi hali, c) yetersiz doku örneği veya doku artefaktına bağlı olarak tümörün yapısı veya sitolojik özellikleri hakkında şüphe varlığı.

Glioblastom, malign infiltratif bir astrositom olup tanı açısından nekroz ve/veya mikrovasküler proliferasyonun değerlendirilmesi esastır. Histolojik özellikleri açısından glioblastoma çok değişkenlik göstermektedir. Tanısal ve prognostik öneme sahip paternler, psödopalizatlaşma gösteren nekroz, konfluan nekroz, mikrovasküler proliferasyon, intravasküler tromboz, değişik yönlere farklılaşma gösteren tümör hücrelerinin varlığıdır. Astrositik orijinli olduğu için glioblastomların büyük çoğunluğu GFAP(Glial Fibriler Asidik Protein) eksprese eder. Başta CAM 5.2 olmak üzere keratin boyaları metastatik karsinom, glioblastoma ayrımında GFAP ile birlikte kullanılır. Glioblastom, malign melanom ayrımında S100 proteini ile glioblastomda da immünreaksiyon görüleceği için öncelikle HMB45(Human Melanoma Black),MITF(Microphthalmia Transcription Factor), Melan A ve tirozinaz gibi melanositik belirteçlerin değerlendirilmesi önemlidir(6).

Gliomagenesiste ilk görülen gen değişmeleri, izositrat dehidrojenaz (IDH) mutasyonudur. Daha sonra TP53 ve ATRX mutasyonları izler. IDH mutasyonu, beyin tümörleri için daha iyi tanımlanmış bir genetik değişimdir ve yeni DSÖ sınıflandırmasına entegre edilmiştir. Bu yenilikler kapsamında ; glioblastomalar, IDH wild tip (IDH wt) ve IDH mutant tip(IDH 1,2) olarak iki ana gruba ayrılmıştır(7). IDH 1 ve IDH 2 gen değişimleri ve kromozom 1P , 19q kod kaybı varlığına veya yokluğuna bağlı olarak, yetişkinlerde primer glioblastom IDH wt olarak tanımlanır. Yine sekonder glioblastomlar da IDH gen değişimi ve 1P / 19q kod kaybı olabilir ya da olmayabilir. IDH 1 de olan gen değişimleri daha çok 132 kodlu gende olur. Vakaların % 90 da gen değişimi R132H genindedir. IDH 2 gen değişimleri daha az sıklıkla 172 kodlu gende olur, en sık R172K da görülür (4).

IDH 1 ve 2 mutasyonları genetik ve klinik olarak ayrı bir glioma tipini oluşturur. Bu tür tümörün görüldüğü hastalar histopatolojiden bağımsız olarak daha iyi prognoz gösterir, kemoterapi ve radyoterapiye daha olumlu yanıt verir. Ancak IDH mutasyonunun tümör supresor fonksiyonunun moleküler temeli aydınlanmamıştır. Bunun aksine IDH wt, GBM hücrelerinin metabolik adaptasyonunu kolaylaştırarak agresif büyümeye yol açar. Böylece wt ve mutant IDH 1/2 arasındaki fonksiyonel dengenin klinik gidiş, kemoterapi ve radyoterapiye duyarlılığı belirlediği öne sürülmüştür(8). Gliom oluşumunda, MGMT metilasyonu testinin yapılamadığı durumlarda IDH mutasyonuna bakılabilir

GBM' e ait spesifik klinik semptom yoktur. Yeni ortaya çıkan epileptik nöbetler, ilerleyici baş ağrısı,

 mental durum değişiklikleri, fokal nörolojik semptomlar, artmış intrakranial basınç belirtileri başlıca şikayetlerdir. Radyolojik tanıda öncelikli seçenek, kontrastlı manyetik rezonans (MR)'dır. Bu tümörler, nekrotik alanlar içeren, kontrast madde tutan, çevresinde ödem olan görüntü verirler. Ayırıcı tanıda düşük grade'li gliomlar, metastazlar ve bazen lenfoma düşünülmelidir. Apse ve

demyelinizan lezyonlar da ayırıcı tanıda akılda tutulmalıdır.

Dinamik kontrastlı perfüzyon ağırlıklı MR kesitler(DSC-MRI)de serebral kan akımını ölçmek mümkündür. Serebral kan akımı, mikrodamar dansitesi ve alanı ile ilişkilidir(9).Tümörün indüklediği anjiyogenezise bağlı oluşan mikrovasküler proliferasyon GBM için önemli bir göstergedir.(10). Serebral kan akımı GBM'in diğer tümör tiplerinden ve histolojik gradelerinden ayırt edilmesine de katkı sağlar(11).

MR spektroskopi, tümör içinde metabolitlere ait yoğunluk değişikliklerini belirler. Glioblastomlarda tipik olarak artan hücre proliferasyonuna bağlı olarak oldukça yüksek kolin değerleri ve nöron kaybı nedeniyle azalana N-asetil aspartat değerleri gözlenir(12). Ancak benzer değişikliklere diğer neoplastik patolojilerde ve inflamatuar hastalıklarda da rastlanır(13).Beynin özellikli lokalizasyonlarında görülen tümörlerde fonksiyonel MR cerrahi planlama ve güvenlik sınırları içinde maksimum rezeksiyonun yapılabilmesi için yarar sağlar.

Pozitron emisyon tomografi (PET), tümör biyolojisi ve yaygınlığı hakkında fikir vermesinin yanısıra ayırıcı tanıda, radyoterapi planlamasında, tedavi sonrası izlemde tümör ilerlemesi veya yalancı tümör ilerlemesi hakkında da bilgi sağlar(14).

GBM'in genetik taranmasında ortak kayıp bölgeleri olarak 1p, 6q, 9p, 10p, 10q, 13 q, 14q, 15q, 17p, 18q, 19q, 22q ve Y saptanmıştır. Bu genetik kayıpların çoğu spesifik tümör supresor gen kaybını temsil eder, bu da direkt olarak gliomagenez üzerine etkilidir. GBM'li hastalarda % 60-80 oranında görüldüğü için en sık rastlanan genetik değişiklik 10. kromozomdaki heterozigotluğun kaybıdır. GBM'de genomik düzeyde genetik değişikliklere bağlı olarak gen ifadesi kazançları gösterilmiştir. Bu şekildeki artmış gen ifadesi, gen ifadesi kayıplarına göre çok seyrek görülür. En sık gözlemlenen olay 7. kromozomdaki EGFR geninin amplifikasyonudur(15).

Günümüzde GBM'in standart tedavisi güvenlik sınırları içinde maksimum cerrahi rezeksiyon sağlandıktan sonra radyoterapi ve eş zamanlı kemoterapidir. 5- aminolevulinik asitten türetilen tümör floresansı, kontrast tutan tümörün, en geniş rezeksiyonunu mümkün kılarak GBM'li hastalarda ilerlemesiz sağkalımın artmasına yol açtı(3). Radyoterapinin en sık kullanılan uygulaması günlük 2 Gy olmak üzere 30 fraksiyon halinde toplam 60 Gy'dir. Radyoterapi planlaması ameliyat sonrası çok erken dönemde çekilen MR'da saptanan hedefler gözetilerek yapılmaktadır(16). Yaşlı olgularda üç haftada tamamlanan günlük 2.6 Gy'nin 15 fraksiyon halinde toplam 40 Gy olarak verilen hipofraksiyon şeklindeki tedavinin standart protokol ile eşdeğer etkiye sahip olduğuna ait kanıt bulunmaktadır(17).

Kemoterapötik ajan olarak Temezolamid(TMZ), 75 mg/m2/gün x 6 hafta olarak başlanır. İdame dozu 150-200 mg/m2/gün x 5 gün olmak üzere 28 günlük altı siklus şeklindedir(18). MGMT metile olmayan tümörlerde temezolamid etkisi minimaldir, dolayısıyla bu özelliği gösteren seçilmiş olgularda temezolamid verilmeyebilir(19). Radyoterapi ve TMZ kemoterapisinin kombinasyonu, birincil rezeksiyonu takiben sağkalımı uzattığı gösterilen en etkili adjuvan tedavidir. Radyoterapi ve ardından TMZ, tek başına radyoterapi ile karşılaştırıldığında önemli ölçüde uzun süreli sağkalım sağlar(3).

Üçlü tedaviye rağmen günümüzde GBM'in prognozunu anlamlı şekilde iyileştiren, kür sağlayan sonuçlar elde edilememiştir. Bu durum tamamen yeni tedavi modalitelerinin araştırılmasını gerekli kılmıştır. Bu seçenekler hedeflenmiş moleküler tedavi, immunoterapi ve viral tedavidir. GBM tedavisinde karşılaşılan önemli bir sorun ileri derecede intratümöral ve tümörler arası heterojenite göstermesidir. Aynı tümörün farklı bölgelerinde değişik genetik kompozisyona sahip hücreler, transkripsiyonel alt gruplar ve proliferasyon kinetikleri görülebilir. GBM'li hastada ilk spesimenle rekürens görüldüğünde alınan spesimen kıyaslandığında EGFRvIII (epidermal growth factor receptor variant III) mutasyonu gibi belirli genetik değişikliklerle

geçici heterojenite görülebileceği bildirilmiştir(20).

Krex ve ark. 55 olguluk uzun yaşamlı GBM olgularını değişik parametreler kullanarak incelemişlerdir. Yapılan moleküler analizde %74 olguda MGMT hipermetilasyonu, % 29 olguda TP 53 mutasyonu ve % 26 olguda EGFR amplifikasyonu saptamışlardır. Sadece % 6 tümörde 1p ve 19q delesyonu kombinasyonu görülmüştür Glioblastomdaki TP53 mutasyonlarının tanıya olan etkinliği EGFR amplifikasyonuna benzer şekilde, tam aydınlatılamıştır.Bazı çalışmalarda TP53 mutant tümörlü hastaların daha iyi prognozu bildirilmiştir (21).EGFR amplifikasyonu tüm glioblastomlarda %30-40 olup genellikle primer glioblastoma sınırlıdır. EGFR amplifikasyonu olan olguların yaklaşık %50'sinde tirozin kinaz aktivitesine neden olan EGFRvIII rearanjmanı ile sonuçlanır. Liu ve ark. EGFR amplifikasyonunun veya EGFRvIII transcript varlığının klasik yöntemlerle tedavi gören GBM'li hastalarda prognozu etkilemediği sonucuna varmışlardır. Buna karşın nadir de olsa astrositik astrositomlarda EGFR aberrasyonlarının daha kısa sağ kalımla ilişkili olabileceğini öngörmüşlerdir(22).

Hegi ve ark. intratümöral MGMT (06-metilguanin-DNA- metiltransferaz) sessizliği ile sağ kalım arasındaki olası ilişkiyi araştırmışlardır. Çalışmaya randomize olarak sadece radyoterapi alan GBM hastaları ile radyoterapi ile birlikte temozolomid alan hastalar alınmıştır. Sonuçta metile MGMT promoter gösteren olguların temozolomid'den yarar gördüğü gözlenmiş, aynı etki metile MGMT promoter göstermeyen olgularda görülmemiştir. Böylece MGMT DNA onarım geninin promoter metilasyonu ile epigenetik susturulmasının alkile edici ajan tedavisi alan GBM hastalarda sağ kalımı uzattığı sonucuna varılmıştır. MGMT epigenetik sessizleşmesine % 20-40 oranında rastlanır(23).

Nörodejeneratif hastalıklarla ilişkili olan MAPT (Microtubule- Associated Protein) ve TAU geni epigenetik olarak insan gliomlarında wt ve mutant IDH 1/2 arasındaki denge tarafından kontrol edilmektedir.

Gargini ve ark. IDH 1/2 mutant tümörlerde TAU genini yüksek bulmuşlardır. Tümörün ilerlemesiyle TAU geni azalmıştır. EGFR (epidermal growth factor receptor) mutasyonu olan tümörlerde MAPT'ın hemen hemen hiç olmadığı, TAU'nun aşırı ifadesinin mikrotübül stabilizasyonu sağlayarak EGFR'ı bloke ettiği gösterilmiştir. Çalışmanın sonucu gliomlarda TAU'nun EGFR sinyalinin önemli bir inhibitörü olduğunu ortaya koymuştur. Bazı kanserlerde yazarlar, TAU proteininin anjiyogenezisi engellediği, normal damarlaşmaya yol açtığı, gliomun agresifliğini azalttığı ve kemoterapiye duyarlılığını arttırdığını göstermişlerdir(24).

Mikrotübül fonksiyonunu etkileyen ilaçlar, hücrelerin mitozdan korunmasını sağlayabilir ve hücre döngüsü durmasına veya apoptoza neden olabilir. Stabilize ve inhibe edici bir çok mikrotübül hedefleyen ajan kanser tedavisinde kullanılmıştır. Bazı kanserlerde mikrotübül fonksiyonu ile zıtlaşan ilaçların EGFR inaktivasyonu ile ilişkili olduğu görülmüştür(25).

GBM serimizde üç yılı aşkın yaşayan altı olgudan üçünde genetik çalışma yapılmıştır. Üç yıldan fazla yaşam sürdükleri için 1. ve 3. olguların tekrarlayan ameliyatlarında GBM tanısı almışlardır. İlk ameliyat preparatları yeniden değerlendirilmiş ve GBM tanısı sabit kalmıştır. İkinci olgu bir kez ameliyat edildiği için patolojik tanısı yeniden değerlendirilmiş ve tanı GBM olarak kalmıştır. Bu olguların genetik çalışma sonuçları şu şekildedir:

Olgu 1

45 yaşında erkek hasta. Üç kez tümör için, bir kez BOS kaçağı tamiri için duraplasti ameliyatı yapıldı. Radyoterapi ve kemoterapi aldı. İlk cerrahi sonrası 65 aydır hayatta.

aCGH analizi Xp22.33-21.1, 1p13.1-p36.32, 3q13.33-q26.31, 6q13 - q27, 8p23.3 - p11.21,13q11 - q31, 17 p13.3 - p12,18 p11.32-p11.21, 19q12- q13.43, 20p13-p11.21, 22q12.1-q13.33 kromozomlarında kısmi kopya kayıpları ve 1q, 4p, 9p, 19p kromozomlarında kısmi kopya kazanımları saptandı.2,5,11,12 ve 17'ci kromozomlarda tam kromozom kazanımı görülürken 10,15 ve

16'cı kromozomların monosomik olduğu anlaşıldı.

Olgu 2

69 yaşında kadın hasta. Sağ oksipital yerleşimli GBM. Cerrahi sonrası radyoterapi ve yurtdışında kemoterapi aldı. Ameliyatdan 78 ay sonra kaybedildi

aCGH analizi 1p36.11-p35.2, 2p23.3, 3q26.33-q27.3, 5q31.2-q31.3,8q24.3,9q31.3-q32, 12 q24.31, 22q11.21-q11.22 kromozomlarında kısmi kopya kayıpları ve 1p21.1 - p13.3, 2p12 - p11.2, 7p12.1 –

p11.2 kromozomlarında kısmi kopya kazanımları gösterdi. Tüm kromozom kaybı veya kazancı gözlenmedi.

Olgu 3

40 yaşında erkek hasta, temporo-oksipital yerleşimli GBM. İki kez ameliyat edildi. Radyoterapi ve kemoterapi aldı.111 aydır hayatta.

aCGH analizi 3q11.1q13.31, 9p24.3p13.1, 15q14q15.1, 6p12.1p11.1, 16q23.2q24.3, 18p11.32p11.21, 19q13.31q13.41 kromozomlarında kısmi kopya kayıpları ve 6p21.1p12.3, 19p12, 19q11q13.12

kromozomlarında kısmi kopya kazanımları ortaya koydu. 7 ve 8'ci kromozomlarda tam kromozom kazanımı görülmesine karşın 10 ve 22'ci kromozomların monosomik olduğu anlaşıldı.

3. Sonuç

GBM'in moleküler patogenez ve biyolojisinin anlaşılmasında önemli gelişmeler kaydedilmesine karşın bunun klinik yansımaları ve dolayısıyla hastalığın küratif anlamda tedavisini sağlayacak yöntemler henüz rutin uygulamaya konulamamıştır. Tamamen yeni tedavi seçeneklerinin geliştirilmesinin yanısıra bunların değerlendirebileceği klinik çalışmaların da yapılması gerekmektedir. Araştırmaların yoğunlaşacağı alanlar kan-beyin bariyerinin aşılması sorunu, moleküler görüntüleme, kan ve BOS'da moleküler işaretleyicilerin daha geniş anlamda kullanılması, moleküler işaretleyicilerin klinik çalışmalara uyarlanması ve daha etkin klinik çalışma modellerinin geliştirilmesi üzerine olacağı ve bunlardan elde edilecek olumlu sonuçlarla GBM patolojisine tam bir tedavi modalitesinin geliştirileceği düşünülmektedir.

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