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İletişim
Editör Sekreteri:
Yeşim ÇELİKKANAT
Adres: Osmangazi Tıp Dergisi, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, 26480 Eskişehir, Türkiye
Tel: +90 222 239 29 79 / 4489
Fax: +90 222 239 37 72
e-Posta: otd@ogu.edu.tr

Dergi web sayfası:
http://dergipark.gov.tr/otd/

Basımevi
Eskişehir Osmangazi Üniversitesi Basımevi
Adres: Eskişehir Osmangazi Üniversitesi Meşelik Yerleşkesi, Eskişehir
Tel: +90 222 239 37 50 / 3105
Fax: +90 222 229 30 47
e-mail: esogugrafik@gmail.com

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Araştırma Makaleleri /Research Articles

Osmangazi Tıp Dergisi
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Research Article / Araştırma Makalesi

Yarık Damak-Yarık Dudaklı Çocuk Hastalarda Orta ve İç Kulak Etkilenmesinin Geniş Band Timpanometri, Hava ve Kemik Yolu İşitsel Beyin Sapı Potansiyel Ölçümleri ile Değerlendirilmesi

Assessment of Affected Middle and Inner Ear of Children with Cleft Lips/Palates with Wide Band Tympanometry and Brainstem Auditory Response Measurements.

Şükrü Turan, Armağan İncesulu, Birgül Gümüş, Ercan Kaya, Mehmet Özgür Pınarbaşlı, Melek Kezban Gürbüz, Hamdi Çaklı, Cemal Cingi, Erkan Özüdoğru

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Kulak Burun Boğaz Hastalıkları Anabilim Dalı, Eskişehir, Türkiye

Özet

Bu çalışmada, yarık dudak patolojisinin eşlik ettiği veya etmediği yarık damak tanısı ile opere edilmiş çocuk olgularda; objektif test yöntemleri ile orta ve iç kulak fonksiyonlarını değerlendirmeyi ve kontrol grubundaki sağlıklı bireylerle karşılaştırmayı amaçladık. Ek olarak, opere edilmiş yarık damak ± yarık dudaklı hasta grubunun orta kulak parametrelerinin yeni bir test yöntemi olan Geniş Bant Timpanometre testi ile belirlenmesi amaçlanmıştır. Bu amaç doğrultusunda, daha önce yarık damak tanısı ile opere edilen ve başarılı damak onarımı yapılmış, yaşları 1-5 yıl arasında olan 23 olgu (46 kulak) hasta grubuna dahil edildi. Bilinen sağlık problemi olmayan, yaşları 1-5 yıl arasında olan 23 olgu (46 kulak) ise kontrol grubunu oluşturdu. Her iki gruba da tanısal hava ve kemik yolu İşitsel Beyinsapı Uyarılmış Potansiyelleri testi ve Geniş Bant Timpanometre testi yapıldı. Hasta grubunda hava yolu İşitsel Beyinsapı Uyarılmış Potansiyelleri testinde V. dalganın gözlendiği eşik uyaran şiddeti kontrol grubuna göre anlamlı olarak yüksek bulunurken, kemik yolu İşitsel Beyinsapı Uyarılmış Potansiyelleri testinde her iki grup arasında anlamlı farklılık saptanmadı. Geniş Bant Timpanometre testinde hasta grubunda kontrol grubuna göre; basınçlı absorbans değerleri ve timpanogram tepe basınçlarında anlamlı farklılık gözlenirken, kulak kanalı hacmi ve rezonans frekans değerlerinde her iki grup arasında anlamlı farklılık saptanmadı. Yapılan testler sonucunda hasta grubunda toplam 19 (%41.3) kulakta efüzyonlu otitis media, 2 (%4.3) kulakta da çok ileri derecede sensörinöral tip işitme kaybı gözlenmiştir. Yirmi beş (%54.4) kulak ise sağlıklı olarak saptanmıştır. Yarık damak onarım operasyonu sonrasında bile %41 gibi yüksek oranlarda efüzyonlu otitis media sıklığı olması, bu olguların odyolojik testler ve fizik muayene eşliğinde düzenli aralıklarla uzun dönem takibinin gerekliliğini ortaya koymaktadır.
Anahtar Kelimeler: Efüzyonlu otitis media, Geniş bant, İmpanometri, işitme kaybı, İşitsel beyinsapı uyarılmış potansiyelleri, Yarık damak

Abstract

In this study, we aimed to evaluate the middle and inner ear function of children operated for diagnosis of cleft palate with or without cleft lip using objective test methods and to compare them with healthy individuals group. In addition, it was also aimed to determine the middle ear parameters of the Wide Band Tympanometer test, which is a new test method. For this purpose, 23 patients (46 ears) between 1 and 5 years of age, who had been previously treated with a cleft palate and successfully repaired, were included in the patient group. Twenty-three cases (46 ears) with no known health problems and ages between 1 and 5 years constituted the control group. Both groups were applied diagnostic air and bone conducted brainstem auditory evoked potentials test and Wide Band Tympanometer test. In the patient group, in the air conducted brainstem auditory evoked potentials test, the threshold of wave V was significantly higher than the control group, and there was no significant difference between two groups in the bone conducted brainstem auditory evoked potentials test. In the Wide Band Tympanometer test in the patient group, there was a significant difference in pressure absorbance values and tympanogram peak pressures compared to the control group, but no significant difference was found between two groups in the ear canal volume and resonance frequency values. As a result of the tests conducted in the patient group, a total of 19 (41.3%) ears was found with otitis media with effusion and 2 (4.3%) ears had profound sensorineural hearing loss. Twenty-five (54.4%) ears were found to be healthy. The fact that the otitis media with effusion frequency is as high as 41% even after repairmen of cleft palate, reveals the necessity of long-term follow-up at regular intervals by using audiological tests and physical examination.
Keywords: Brainstem auditory evoked potentials, Eleft palate, Hearing loss, Otitis media with effusion, Wideband tympanometry

Correspondence:
Şükrü TURAN
Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Kulak Burun Boğaz Hastalıkları Anabilim Dalı, Eskişehir, Türkiye
e-mail: drsukruturan@gmail.com

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1. Giriş

Yarık damak yarık dudak en yaygın görülen doğumsal anomaliler arasında olup insidansı 1:500-1000 canlı doğumdur (1,2). Yarık damaklı çocuklarda işitme kaybı ilk olarak Alt tarafından 1878 yılında tanımlanmıştır. Günümüzde iki patoloji arasındaki ilişki evrensel olarak bilinmektedir (3,4). Yarık damak ve/veya yarık dudakla doğan çocuklarda, efüzyonlu otitis media (EOM) prevelansı sağlıklı çocuklara göre daha yüksektir ve bebeklerin % 92-99'unda efüzyonlu otitis media görülmektedir (1,5,6). Bu yüksek prevelansın nedeni bu doğumsal anomaliye bağlı tensör veli palatini ve levator veli palatini kaslarının işlevinin bozulması sonucunda Eustachi tüpünün yeterli fonksiyon gösterememesidir (2,5,7,). Ortaya çıkan efüzyonlu otitis media, tekrarlayan nitelikte veya kalıcı olabilir, tek kulağı veya her iki kulağı etkileyebilir ve şiddeti efüzyon derecesi ile değişkenlik gösterir (2). Ayıca efüzyon sağlıklı çocuklara göre daha erken, hayatın ilk 6 ayında başlar ve daha ileri yaşlara kadar devam eder (2).

Orta kulakta gelişen efüzyona bağlı ortaya çıkan iletim tipi işitme kaybının, çocuğun eğitim, dil, bilişsel ve psikososyal gelişiminde önemli bir etkisi olduğu bilinmektedir (4). Yarık damaklı olgularda miks veya sensörinöral tip işitme kaybı daha az oranda görülür. Özellikle sendromun eşlik ettiği olgularda sensörinöral tip işitme kaybı görülme oranı % 5'lere kadar çıkabilir (8).

Odyolojik testler içinde objektif testlerden biri olan immitansmetrik değerlendirme orta kulak yapılarının işlevi hakkında bilgi verir. Tek frekansta timpanogram sonucu sağlayan klasik immitansmetrenin aksine geniş band akustik immitansmetrede klik uyaran kullanılarak, birçok frekansta (226-8000 Hz) timpanogram elde edilmektedir. Bu yeni nesil immitansmetrenin bir sonucu olan Geniş bant timpanometri (GBT) sayesinde orta kulak hakkında daha fazla bilgi sağlanmaktadır (9). Objektif odyolojik testlerden biri olan uyarılmış işitsel beyin sapı cevapları (ABR) testi ise klik, tone burst ve chirp uyaranları kullanılarak, kemik ve hava yolu işitme eşikleri konusunda objektif bilgi sağlamaktadır.

Bu çalışmada opere olmuş yarık damaklı çocuk olguların işitme durumu ve orta kulak yapılarının fonksiyonu ABR ve GBT testleri kullanılarak değerlendirilmiştir. Elde edilen sonuçlar sağlıklı çocuk ile karşılaştırılıp farklılıklar belirlenmiştir.

2. Gereç ve Yöntem

Bu çalışma prospektif, kontrollü, klinik çalışma olarak planlanmıştır. Çalışma Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Kulak Burun Boğaz Hastalıkları Anabilim Dalı ve Odyoloji Bilim Dalında gerçekleştirildi.

Çalışma için Eskişehir Osmangazi Üniversitesi Klinik Araştırmalar Etik Kurulu Başkanlığı'nın 29.01.2015 tarihli ve 05 sayılı ve Etik Kurul protokol numarası ile onay alındı. Çalışmaya 1-5 yaş aralığındaki 46 gönüllü dahil edildi. Çalışmada hasta grubu (Grup 1) yarık dudağın eşlik ettiği veya etmediği yarık damak tanısı ile opere olmuş, operasyon sonrası damak yarığı düzelmiş, dış kulak anomalisi bulunmayan, 1-5 yaş aralığındaki 23 gönüllüden oluşturuldu. Kontrol grubu (Grup 2) ise özgeçmişinde bilinen sağlık problemi olmayan, yapılan ayrıntılı kulak burun boğaz muayenesinde patoloji saptanmayan, 1-5 yaş aralığındaki 23 sağlıklı gönüllüden oluşturuldu. Her iki grupta 46 kulaktan elde edilen sonuçlar değerlendirildi.

Gönüllülerin yaşları, cinsiyetleri, yarık damak yarık dudak tipleri, operasyon yaşları, eşlik eden hastalıkları, geçirilmiş operasyon öyküleri, geçirilmiş kulak hastalıklarının varlığı, soygeçmiş özelliği, gebelik süresince annenin radyasyon maruziyeti, geçirdiği enfeksiyonlar, kullandığı ilaçlar, girişimsel işlem yapılıp yapılmadığı, oligohidramnios öyküsü olup olmadığı, gebelik öncesi üç ay ve gebeliğin ilk üç ayında annenin folik asit kullanım öyküsü sorgulandı.

Gönüllülerin tamamına ayrıntılı kulak burun boğaz muayenesi yapıldı. Her bir gönüllüye aynı gün içerisinde tanısal kemik ve hava yolu ABR Testi ve GBT testi yapıldı. Tüm testler aynı odyoloji uzmanı tarafından, aynı cihazlarla, aynı ortam koşullarında (çift kapı

ile sesten yalıtılmış, sıcaklığı 24-26 °C aralığında bulunan loş ışıklı odada) ve doğal uyku esnasında yapıldı.

Gönüllülerin araştırmaya alınma kriterleri;

1. Yarık dudağın eşlik ettiği veya etmediği yarık damak nedenli opere olmuş olgular,
2. Operasyon sonrasında yarık damak defekti tamamen düzelen olgular,
3. Dış kulak anomalisi bulunmayan ve herhangi bir kulak girişimi bulunmayan olgular,
4. Kontrol grubu için tanı konmuş hastalığı olmayan sağlıklı bireyler

Gönüllülerin araştırmadan çıkarılma kriterleri;

1. Tanısal hava ve kemik yolu ABR ve GBT testleri yapılamayan gönüllüler
2. Test döneminde üst solunum yolları enfeksiyonu geçiren gönüllüler
3. İzole yarık dudak varlığı
4. Yarık damak nedenli opere olmamış olgular veya yarık damak nedenli opere olmasına rağmen damak defekti tamamen düzelmeyen olgular
5. Özgeçmişinde bilinen kronik hastalık öyküsü olan sağlıklı bireyler

Çalışmada gönüllülerin bilateral işitsel uyarılmış beyin sapı değerlendirilmesinde *ECLİPS EP25 Klinik ABR®* cihazı kullanıldı. ABR değerlendirilmesinde iletken jel emdirilmiş yüzeyel elektrotlar temizlenen cilde yerleştirildi. Kayıt sırasında elektrotların impedansı 5 kΩ altında tutuldu. Referans elektrotlar A1 (sol mastoid) ve A2 (sağ mastoid) bölgesine, aktif elektrod Fz (alın orta hat) bölgesine, toprak elektrod ise Fpz (alın proksimali) bölgesine yerleştirildi. Hava yolu ABR değerlendirilmesinde uyaran dış kulak yoluna uygun prob yerleştirilerek insert kulaklık ile sunuldu. Kemik yolu ABR değerlendirmesinde uyaran mastoid kemik üzerine taçla tutturulan kemik vibratör (B-71) ile sunuldu. Kemik yolu eşiklerin belirlenmesinde CE Chirp LS (level spesifik) uyaran kullanıldı. Hava yolu işitme eşikleri üç uyaran kullanılarak ayrı ayrı belirlenmiştir. Hava yolu değerlendirmesinde kullanılan uyaranlar; CE Chirp LS, 1 kHz CE Chirp LS, 4 kHz CE Chirp LS dir. Hem hava yolu hem de kemik yolu değerlendirmelerinde alternate polaritede, 33.1/s uyaran sıklığında, 33-3000 Hz kayıtlama filtre bandında ve 1500-2000 averajlama kullanılarak dalga kaydı alındı.

Çalışma grubundaki bireylerin bilateral GBT ölçümü *Interacoustics TITAN® Geniş Bant Timpanometre* cihazı ile 200-(-400) daPa aralığında yapıldı. Ölçümler 226-8000 Hz frekans aralığını kapsayan, 2 milisaniye durasyonlu, 96 dB peSPL da SBS (Ses basınç seviyesi) şiddet düzeyinde ve 21.5 Hz frekansıyla verilen klik uyaranla gerçekleştirildi. GBT ölçümü sırasında dış kulak yoluna yerleştirilen uygun prob vasıtasıyla elde edilen veriler analiz için *Interacoustics* firması tarafından oluşturulan, verilerin sayısal dökümü ve grafiksel sunumunu sağlayan özel bir *Microsoft Office Excel* dosyasına aktarıldı.

Verilerin değerlendirilmesinde IBM SPSS Statistics 21.00 paket programı kullanıldı. Sürekli değişkenlerin gruplara göre normal dağılıma uygunluğu *Shapiro - Wilk* testi ile değerlendirildi. Normal dağılım gösteren değişkenlerin gruplara göre karşılaştırılmasında *Student t* testi kullanıldı. Normal dağılıma uygunluk göstermeyen değişkenlerin gruplar arasındaki karşılaştırlmasında *Mann - Whitney U* testi kullanıldı. Kategorik değişkenlerin (cinsiyet) gruplara göre karşılaştırılmasında *Ki-kare* analizi kullanıldı. İstatistiksel anlamlılık düzeyi $p<0.05$ olarak kabul edildi.

3. Bulgular

Hasta grubunda 12 (%52.2) erkek, 11 (%47.8) kadın olmak üzere 23 yarık damak ve/veya yarık dudaklı olgu mevcuttu. Kontrol grubunda ise 12 (%52.2) erkek, 11 (%47.8) kadın olmak üzere 23 sağlıklı gönüllü mevcuttu. Her iki grubunu cinsiyet dağılımlarının homojen olduğu gözlenmektedir ($p=1$). Hasta grubunda en küçük 14 ay, en büyük 60 ay olmak üzere ortalama yaş 34.69 ± 16.07 ay saptandı. Kontrol grubunda ise en küçük yaş 13 ay, en büyük yaş 53 ay olmak üzere ortalama yaş 35.34±12.17 ay saptandı. Hasta grubundaki

olgularda yarık damak tiplerine göre 15 olguda izole yarık damak (%65.2), 6 olguda tek taraflı yarık dudak ve damak (%26.1), 2 olguda ise iki taraflı yarık dudak ve damak (%8.7) gözlendi. Olguların 21'inde (%91.3) geçmişte bir veya birden fazla otitis media geçirme öyküsü mevcuttu. İzole yarık damağı olan iki olgunun birinde Pierre Robin sendromu tanısı diğerinde ise DiGeorge sendromu tanısı konulmuştu. Dört (%17.4) olguda ek olarak kardiyovasküler, üriner, nörolojik ve solunum sistemi ile ilgili problemler de mevcuttu. Olguların ebeveynlerinin hiçbirinde akraba evliliği öyküsü saptanmadı. Beş (%21.7) olgunun soygeçmişlerinde yarık damak ve/veya yarık dudak öyküsü mevcuttu.

Gebelik öncesi 3 aylık dönemde folik asit kullanımının yarık damak oluşum oranını azalttığı bilinmektedir. Hasta grubundaki olguların annelerinden 18 (%78.3) inin gebelik öncesi dönemde düzenli olarak folik asit kullandığı, 5 (%21.7) inin folik asit kullanmadığı saptanmıştır. Gebelik döneminde toplam 9 (%39.1) annenin yarık damak ve yarık dudak etiyolojisinden sorumlu olma ihtimali olan bir ya da daha fazla sağlık sorunu yaşadığı saptanmış ve olası etiyolojik nedenleri Tablo 1'de gösterilmiştir.

Tablo 1. Hasta grubundaki yarık damak yarık dudaklı olguların olası etiyolojik nedenleri

Olası Etiyolojik Nedenler	Olgu sayısı	%
Annenin gebelik öncesi ve gebeliğin ilk üç ayında folik asit kullanmaması	5	21.7
Soygeçmişde yarık damak/dudak öyküsü	5	21.7
Gebelikte annede oligohidramnios gelişme öyküsü	2	8.7
Gebelikte annenin üst solunum yolları enfeksiyonu geçirme öyküsü	2	8.7
Gebelikte annenin sigara kullanım öyküsü	2	8.7
Gebelikte annede preeklamsi gelişme öyküsü	1	4.3
Gebelikte annede Diyabetes mellitus gelişme öyküsü	1	4.3

Yapılan tanısal hava ve kemik yolu ABR ve GBT testlerine göre hasta grubundaki 9 olgunun her iki kulağında, 1 olgunun sadece sağ kulağında efüzyonlu otitis media ile uyumlu bulgular saptanmıştır. Efüzyonlu otitis media saptanan toplam 19 kulağın 8'i çok hafif derecede, 7'si hafif derecede, 4'ünde ise orta derecede iletim tipi işitme kaybı saptandı. Bir olguda ise her iki kulakta çok ileri derecede sensörinöral tip işitme kaybı bulundu. Her iki kulağına işitme cihazı önerilen ve özel eğitime yönlendirilen olguya, takiplerinde işitme cihazından yeterince yarar görmemesi nedeniyle koklear implant operasyonu önerildi. Buna göre hasta grubundaki toplam 46 kulağın 19'unda (%41.3) efüzyonlu otitis media, bir olgunun her iki kulağında (%4.3) çok ileri derecede sensörinöral tip işitme kaybı gözlenmiş olup 25 kulak (%54.4) ise sağlıklı olarak saptanmıştır.

Hasta ve kontrol grubundaki 23'er olgunun her iki kulağındaki tanısal hava ve kemik yolu ABR testinde V. dalgada elde edilen latans değerleri Tablo 2'de gösterilmiştir.

Tablo 2. Hasta ve kontrol grubundaki olguların tanısal hava ve kemik yolu ABR testinde V. dalgada elde edilen latans değerleri.

Uyaranlar		Grup	Kulak sayısı (n)	Minimum latans değeri (ms)	Maksimum latans değeri (ms)	Ortalama latans değerleri (ms)	Standart sapma	P değeri
Kemik		Hasta	46	7.80	11.13	9.19	0.71	0.055
		Kontrol	46	7,87	10,07	8.94	0.51	
		Hasta	46	6.93	10.33	8.78	0.76	**0.017**
	1 kHz	Kontrol	46	6.33	10.07	8.39	0.76	
		Hasta	46	7.87	10.67	8.83	0.59	0.718
Hava	**4 kHz**	Kontrol	46	7.33	9.87	8.78	0.62	
	CE Chirp LS	Hasta	46	7.67	10.33	8.77	0.69	0.424
		Kontrol	46	7.27	9.80	8.67	0.50	

KhZ:kilo Hertz, CE-Chirp: uyaran, LS: Level spesifik

Hasta grubunda kemik yolu ABR testinde V. dalgada elde edilen ortalama latans değerinin kontrol grubuna göre uzadığı gözlenmiş ancak istatiksel olarak iki grup arasında anlamlı farklılık gözlenmemiştir (*p=0.055*). Hasta grubunda hava yolu ABR testinde 1 kHz uyarı ile V. dalgada elde edilen ortalama latans değerinin kontrol grubuna göre uzadığı gözlenmiş ve istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmiştir (*p=0.017*). Hasta grubunda hava yolu ABR testinde 4 kHz ve Chirp uyarımda V. dalgada elde edilen ortalama latans değerinin kontrol grubuna göre uzadığı gözlenmiş ancak istatiksel olarak iki grup arasında anlamlı farklılık gözlenmemiştir (sırasıyla *p=0.718, p=0.424*).

Çalışmamızda tanısal hava ve kemik yolu ABR testinde eşik değerler elde edilirken, uyaran şiddeti yüksekten alçağa doğru düşürüldü. Hasta ve kontrol grubundaki olgularda V. dalganın elde edildiği eşik değerleri Tablo 3'de belirtilmiştir.

Tablo 3. Hasta ve kontrol grubundaki olguların hava ve kemik yolu ABR testinde V. dalganın elde edildiği eşik uyaran değerleri.

Uyaranlar			Grup	Kulak sayısı (n)	Minimum eşik uyaran değeri (dBnHL)	Maksimum eşik uyaran değeri (dBnHL)	Ortalama eşik uyaran değeri (dBnHL)	Standart sapma	P değeri
			Hasta	46	5.0	20.0	14.67	4.52	0.798
Kemik		**Kemik**	Kontrol	46	10.0	20.0	15.0	4.21	
			Hasta	46	10.0	100.0	37.71	22.20	**0.001**
	1 kHz	**Hava 1 kHz**	Kontrol	46	10.0	30.0	23.47	5.25	
Hava									
		Hava 4	Hasta	46	10.0	90.0	31.08	22.33	**0.001**
	4 kHz	**kHz**	Kontrol	46	10.0	30.0	16.08	6.40	
	CE Chirp		Hasta	46	10.0	90.0	28.26	20.60	**0.001**
	LS	**Hava Chirp**	Kontrol	46	10.0	20.0	15.00	4.94	

KhZ:kilo Hertz, CE-Chirp: uyaran, LS: Level spesifik

Hasta grubunda kemik yolu ABR testinde elde edilen eşik uyaran şiddeti ortalaması kontrol grubuna göre daha düşük gözlenmiş ancak istatiksel olarak iki grup arasında anlamlı farklılık gözlenmemiştir (*p=0.798*). Hasta grubunda kullanılan her üç uyaran için hava yolundan elde edilen V. dalga eşiği kontrol grubuna kıyasla daha yüksek olduğu saptanmış olup istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmiştir (*p=0.001*).

Hasta grubu ve kontrol grubundaki 23'er olgunun her iki kulağına da GBT testleri

yapıldı. Her iki gruptaki toplam 92 kulağın GBT test sonuçları ayrı ayrı değerlendirildi. Grupların GBT testine göre elde edilen eşdeğer kulak kanalı hacmi ve rezonans frekans değerleri Tablo 4'de gösterilmiştir.

Tablo 4. Hasta ve kontrol grubundaki olguların GBT testi ile ölçülen eşdeğer kulak kanalı hacmi ve rezonans frekans değerleri.

	Grup	Kulak sayısı (n)	Minimum	Maksimum	Ortalama	Standart sapma	P değeri
Kulak kanalı hacmi (ml)	Hasta	46	0.020	1.800	0.752	0.277	0.812
	Kontrol	46	0.320	1.400	0.760	0.264	
Rezonans frekansı (Hz)	Hasta	46	238.00	1475.00	811.93	284.03	0.721
	Kontrol	46	272.00	1615.00	836.26	362.19	

Hasta grubundaki 46 kulağın eşdeğer kulak kanalı hacmi ortalama 0.752±0.277 ml, kontrol grubunda ise ortalama 0.760±0.264 ml olarak saptanmıştır. Her iki grupta ortalama eşdeğer kulak kanalı hacminin birbirine yakın olduğu gözlenmiş olup istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmemiştir (*p= 0.812*). Benzer şekilde hasta grubunun rezonans frekans değerlerinin kontrol grubunun rezonans frekans değerlerine göre daha düşük olduğu gözlenmiş ancak istatiksel olarak iki grup arasında anlamlı farklılık gözlenmemiştir (*p=0.721*).

Geniş bant timpanometri testinde elde edilen tepe basınç değerleri Tablo 5'de gösterilmiştir.

Tablo 5. Hasta ve kontrol grubundaki olguların GBT testi ile ölçülen negatif timpanogram tepe basınçları ve pozitif timpanogram tepe basınç değerleri

	Grup	Kulak sayısı (n)	Minimum	Maksimum	Ortalama	Standart sapma	P değeri
Pozitif tepe basıncı (daPa)	Hasta	19	4.0	156	62.84	43.49	**0.001**
	Kontrol	19	1.0	93.0	20.26	22.02	
Negatif tepe basıncı (daPa)	Hasta	27	-299.00	-6.0	-139.70	95.09	**p<0.001**
	Kontrol	27	-85.00	-1.0	-30.48	21.12	

Hasta grubundaki 19 kulağın GBT testi ile ölçülen pozitif timpanogram tepe basınç değerleri ortalama 62.84±43.49 daPa, kontrol grubunda ise ortalama 20.26±22.02 daPa olarak saptanmıştır. Hasta grubunun ortalama pozitif timpanogram tepe basınç değerleri kontrol grubunun ortalama pozitif timpanogram tepe basınç değerlerine göre daha yüksek gözlenmiş olup istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmiştir (*p<0.001*). Hasta grubunun ortalama negatif timpanogram tepe basınç değerleri kontrol grubunun ortalama negatif timpanogram tepe basınç değerlerine göre daha düşük gözlenmiş olup istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmiştir (*p<0.001*).

GBT testinde farklı frekanslarda elde edilen basınçlı absorbans değerleri Tablo 6'da belirtilmiştir.

Tablo 6. Hasta ve kontrol grubundaki olguların GBT testi ile ölçülen basınçlı absorbans değerleri.

Absorbans Frekansı	Grup	Kulak sayısı (n)	Minimum	Maksimum	Ortalama	Standart sapma	P değeri
226 Hz	Hasta	46	0.00	0.18	0.04	0.04	**<0.001**
	Kontrol	46	0.01	0.52	0.15	0.12	
1000 Hz	Hasta	46	0.07	0.84	0.34	0.19	**<0.001**
	Kontrol	46	0.16	0.79	0.52	0.17	
2000 Hz	Hasta	46	0.04	0.96	0.49	0.26	**<0.001**
	Kontrol	46	0.12	0.99	0.69	0.18	
4000 Hz	Hasta	46	0.10	0.99	0.65	0.21	0.343
	Kontrol	46	0.10	0.99	0.67	0.26	
8000 Hz	Hasta	46	0.00	0.46	0.06	0.11	**<0.001**
	Kontrol	46	0.14	0.97	0.41	0.22	

Kontrol grubunda 4000 Hz dışındaki 226 Hz, 1000 Hz, 2000 Hz ve 8000 Hz de elde edilen basınçlı absorbans değerleri, hasta grubundaki aynı absorbans frekansında elde edilen basınçlı absorbans değerlerine göre daha yüksek olduğu gözlenmiş ve her frekansta istatiksel olarak da iki grup arasında anlamlı farklılık olduğu gözlenmiştir ($p<0.001$). Kontrol grubunda 4000 Hz de elde edilen basınçlı absorbans değerleri ile hasta grubunda 4000 Hz de elde edilen basınçlı absorbans değerlerinin benzer olduğu gözlenmiş ve istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmemiştir ($p=0.343$).

4. Tartışma

Yarık damak ve otitis media arasındaki ilişki 1800'lü yıllardan beri bilinmektedir (3,4). Yarık damak ve/veya dudakla doğan çocuklarda, Eustachi tüpünün işlev bozukluğundan dolayı efüzyonlu otitis media prevelansı yüksektir (5). Damak yarığı onarımı öncesinde yarık damak yarık dudaklı bebeklerin %88-99' unda efüzyonlu otitis media (EOM) görülmektedir (5,6). Yarık damak onarımı sonrasında olguların %50'sinin östaki tüpü disfonksiyonu normale dönmekte (1) ve yarık damak onarımı sonrasında EOM bir miktar iyileşmektedir (10). Çalışmamızda opere yarık damaklı 23 olgudan oluşan hasta grubunda efüzyonlu otitis media sıklığı %41.3 olarak saptanmıştır.

Viswanathan ve ark. (8) ortalama yaşın erkek bebeklerde 48.5 gün, kız bebeklerde 43 gün olduğu opere olmamış 90 yarık damaklı ve/veya yarık dudaklı olgu ile yaptıkları çalışmada, 74 (%82) olguda işitme kaybı saptamışlar, bunların 66'sını iletim tipi işitme kaybı, 7'sini mikst tip işitme kaybı ve 1'ini ise sensörinöral tip işitme kaybı olduğunu bildirmişlerdir. Çalışmamızda opere yarık damaklı 23 olgudan oluşan hasta grubunda; 9 olgunun her iki kulağında, 1 olgunun ise sadece sağ kulağında efüzyonlu otitis media saptanmıştır (%41.3). Her iki kulağında EOM saptanan olguların 5'i izole yarık damak, 3'ü iki taraflı yarık damak yarık dudak ve 1'i ise tek taraflı yarık damak yarık dudaktı. Sağ kulağında EOM saptanan olguda ise tek taraflı yarık damak yarık dudaktı. Efüzyonlu otitis media saptanan toplam 19 kulağın 8'i çok hafif derecede, 7'si hafif derecede, 4'ünde ise orta derecede iletim tipi işitme kaybı tanısı konurken yirmi beş (%54.4) kulak ise sağlıklı olarak saptanmıştır.

Yarık damak yarık dudaklı yetişkinlerde kalıcı iletim tipi işitme kaybının tahmini insidansı ise %50'dir (8,10). Goudy ve ark. (1) damak onarım zamanının ortalama 16 ay olduğu, ortalama yaşın 19 yıl olduğu, opere yarık damaklı 101 olgunun uzun dönem sonuçlarını değerlendirdikleri çalışmalarında, iletim tipi işitme kaybının olguların %27.7'sinde devam ettiğini, olguların %47.5'inde hiç görülmediğini ve %27.7'sinde tedaviyle düzeldiğini belirtmişlerdir. Bu bilgilerin ışığında hastaların anne ve babaları uzun dönem takibin gerekliliği ve önemi konusunda bilgilendirilmiştir.

Sundman ve ark. (5) ortalama yaşın 65 gün olduğu, ek hastalıkları olmayan, sensörinöral tip işitme kayıplı olguların çalışma dışı bırakıldığı çalışmalarında 50 yarık damaklı

ve/veya yarık dudaklı opere olmamış olguda tanısal ABR testinde; hava yolu ortalama uyarılma eşik değerleri ortalama 40.1 dBnHL olan iletim tipi işitme kaybı saptanmıştır. Viswanathan ve ark. (8) ortalama yaşın erkeklerde 48.5 gün, kadınlarda 43 gün olduğu 90 yarık damaklı ve/veya yarık dudaklı olguda yaptıkları çalışmada ABR testi ile; hava yolu ortalama uyarılma eşik değerleri sağ kulak için 40 dBnHL, sol kulak için 39.7 dBnHL olarak bulunurken kemik yolu ortalama uyarılma eşik değerlerini sağ kulak için 18.9 dBnHL, sol kulak için 18.1 dBnHL olarak saptanmıştır. Andrews ve ark. (10) ortalama yaşın 3 ay olduğu yarık damaklı 40 olguluk çalışmalarında tanısal ABR testinde; hava yolu ortalama uyarılma eşik değerlerini sağ kulak için 49 dBnHL, sol kulak için 53 dBnHL olarak, kemik yolu ortalama uyarılma eşik değerlerini 26 dBnHL (0-55 dBnHL) olarak bulunmuştur. Çalışmamızda yarık damaklı hasta grubunda 46 kulağın kemik yolu ABR testinde V. dalganın elde edildiği eşik uyaran şiddetleri en düşük 5.0 dBnHL, en yüksek 20.0 dBnHL olmak üzere ortalama 14.67±4.52 dBnHL olarak saptanmıştır. Kontrol grubunda 46 kulağın kemik yolu ABR testinde V. dalganın elde edildiği eşik uyaran şiddetleri ortalaması ise 15.0±4.21 dBnHL olarak saptanmıştır. Hasta grubunda kemik yolu ABR testinde V. dalganın gözlendiği eşik uyaran şiddeti ortalaması kontrol grubuna göre daha düşük gözlenmiş ancak istatiksel olarak iki grup arasında anlamlı farklılık gözlenmemiştir (*p=0.798*). Hasta grubundaki 46 kulağın; hava yolu ABR testinde 1 kHz ile V. dalganın elde edildiği eşik uyaran şiddetleri ortalaması 37.71±22.20 dBnHL (10-100), hava yolu ABR testinde 4 kHz ile V. dalganın elde edildiği eşik uyaran şiddetleri ortalaması 31.08±22.33 dBnHL (10 - 90), hava yolu ABR chirp ile V. dalganın elde edildiği eşik uyaran şiddetleri ortalaması 28.26±20.60 dBnHL (10 - 90) olarak saptanmıştır. Kontrol grubundaki 46 kulağın; hava yolu ABR testinde 1 kHz ile V. dalganın elde edildiği eşik uyaran şiddetleri ortalama 23.47±5.25 dBnHL (10 - 30), hava yolu ABR testinde 4 kHz ile V. dalganın elde edildiği eşik uyaran şiddetleri ortalaması 16.08±6.40 dBnHL (10 - 30), hava yolu ABR testinde chirp ile V. dalganın elde edildiği eşik uyaran şiddetleri ortalaması 15.00±4.94 dBnHL (10 - 20) olarak saptanmıştır. Her iki grubun hava yolu ABR eşikleri karşılaştırıldığında istatiksel olarak anlamlı farklılık gözlenmiştir (*p=0.001*).

Literatürdeki çalışmalarda elde edilen işitme eşik değerlerine göre çalışmamızda işitme eşikleri daha iyi bulunmuştur. Bunun nedeni çalışmamıza dahil edilen hastaların daha büyük yaşta olması ve tüm hastaların postoperatif dönemde değerlendirilmiş olmasına bağlı EOM atak sıklığının azalmasıdır. İngilizce literatürde çalışmamızda aldığımız benzer yaş grubunda başarılı yarık damak operasyonu geçirmiş çocuklardaki işitme değerlendirilmesine dair bir literatür bulunamamıştır. Bu konuda yapılan tüm çalışmalar daha büyük yaşta hasta grubunu içermektedir. Flynn ve ark. (11) yaş aralığının 21-30 yıl olduğu, tek taraflı yarık damak ve yarık dudak nedenli opere olmuş 26 olguya, pure tone odyometri testi yaptıkları çalışmalarında; 4 olguda (%15.4) EOM saptamışlardır. Çalışmamızdaki olgularda bulunan işitme eşikleri literatüre göre daha iyi bulunmasına rağmen sensörinöral işitme kaybı saptanan bir hasta dışında diğer hastalarımızda da halen devam eden iletim tipi işitme kaybı ve elde edilen kemik yolu eşiklerine göre kısmen azalan kemik yolu eşikleri bu hastaların dil ve konuşma gelişimi açısında yakın takiplerinin yapılmasını gerekli kılmaktadır.

Yarık damak yarık dudaklı olgularda tek başına veya iletim tipi işitme kaybına eşlik eden sensörinöral tip işitme kayıplarına da rastlanmaktadır (12). Yarık damaklı çocuklarda gözlenen sensörinöral tip işitme kaybı oranları literatürdeki kullanılan tanımlara ve değerlendirme yöntemlerine bağlı olarak %5'e kadar çıkmaktadır (8,10). Jordan ve ark. (13) 89 olguluk çalışmalarında; ek hastalığı olmayan yarık damaklı yenidoğanlarda çok sık iletim tipi işitme kaybı ve çok düşük oranda sensörinöral tip işitme kaybı saptamışlardır. Aynı çalışmada komorbit hastalıkları olmayan yarık damaklı çocukların hiçbirinde kalıcı iletim tipi işitme kaybına rastlamamışlardır. Ayrıca ek hastalığı olmayan yarık damaklı olgularda sensörinöral tip işitme kaybı oranı çok düşük olduğundan orta kulak problemi nedeniyle YDİT'ından kalan bebeklerde tanısal ABR testinin ventilasyon tüpü (VT) tatbik edildikten sonra

yapılabileceğini belirtmişlerdir. Çalışmamızda sensörinöral tip işitme kaybı sadece 1 (%4.3) olguda saptanmış olup bu olguda Pierre Robin Sendromu mevcuttu. Kliniğimizde YDİT düzenli olarak yapılmaktadır. Yarık damaklı olgular, ek orta kulak problemleri nedeniyle, sıklıkla taramadan kalmasına rağmen, biz de çalışmamızın sonucu yanında literatürde belirtildiği gibi bu çocuklarda komorbit hastalık yok ise, tanısal ABR testinin yapılma zamanlamasının ilk 6 ayda olması koşuluyla VT tatbiki sonrasına ertelenmesi fikrine katılmaktayız. Ancak 6 ayı geçen yarık damaklı olgularda orta kulak problemi sebat ediyorsa, dil gelişimi açısından kritik süreç de dikkate alınarak, genel anestezi altında miringotomi ve/veya VT tatbiki uygulanmalı ve aynı seansta tanısal ABR testi de yapılmalıdır. Bu sayede tanının erken konularak tedavinin de erken dönemde başlanması sağlanmalıdır.

Geniş bant timpanometri, orta kulağın değerlendirilmesi için yeni bir yöntemdir. Geniş frekans aralığında klik uyarı ile ölçüm yapan GBT testi tek ölçümde orta kulak fonksiyonu hakkında klasik timpanometriye göre klinisyene daha fazla bilgi sağlamakta ve farklı orta kulak patolojilerinin tanısına yardımcı olmaktadır. Ayrıca bu test, klasik timpanometriye kıyasla, iletim tipi işitme kaybında daha hassas sonuçlar verebilir (14). GBT yetişkinlerde 10 kHz, bebeklerde 20 kHz'lik bir frekansa kadar immitansa dayalı değerlendirme yapabilmektedir (15). Geniş Bant Timpanometri testi ile eşdeğer kulak kanal hacmi değerlendirilebilir. Çalışmamızda ortalama yaşın 34.6±16.07 ay olduğu hasta grubunda eşdeğer kulak kanalı hacmi ortalama 0.752±0.277 ml, ortalama yaşın 35.34±12.17 ay olduğu kontrol grubunda ise 0.760±0.264 ml olarak saptanmıştır. Yaş ve cinsiyet dağılımları benzer olan her iki grupta ortalama eşdeğer kulak kanalı hacminin birbirine yakın olduğu gözlenmiş olup, istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmemiştir ($p=0.812$). İki grup arasında farklılık olmaması çalışmadaki hiçbir çocuğun kulak zarında ileri derecede retraksiyon veya perforasyon olmamasına bağlı olabilir. Kontrol grubundan elde edilen normatif değerler kullanılarak yarık damaklı çocukların kulak zarı değişikliklerinin takibi yapılabilir. Bu sayede kulak zarında ileri derecede retraksiyon veya adezyon gelişmeden GBT testi ile tanı konulabilir.

Çalışmamızda hasta grubundaki 19 kulağın GBT testi ile ölçülen pozitif timpanogram tepe basınç değerleri ortalaması 62.84±43.49 daPa, kontrol grubundaki 19 kulağın GBT testi ile ölçülen pozitif timpanogram tepe basınç değerleri ortalaması 20.26±22.02 daPa olarak saptanmıştır. Çalışmamızda hasta grubundaki 27 kulağın GBT testi ile ölçülen negatif timpanogram tepe basınç değerleri ortalaması -139.70±95.09 daPa, kontrol grubundaki 27 kulağın GBT testi ile ölçülen negatif timpanogram tepe basınç değerleri ortalaması ise -0.48±21.12 daPa olarak saptanmıştır. Her iki grup arasında timpanogram tepe basınç değerleri istatistiksel olarak da farklı saptanmıştır ($p<0.001$). Literatürde yarık damak-yarık dudaklı hasta grubunda GBT ile yapılmış çalışma sayısı çok azdır (6). Hunter ve ark. (6) yaş aralığının 9 hafta ila 2 yıl olduğu, 17 yarık damak yarık dudaklı olguda yaptıkları çalışmada GBT'nin Otoakustik Emisyon (OAE) ile birlikte kullanılmasının YDİT'nda daha yararlı olduğunu belirtmişlerdir. Çalışmamızda da elde edilen sonuçlar dikkate alındığında yarık damaklı çocukların YDİT'nda OAE ve klasik timpanometri yanında GBT'nin de rutine girmesini önermekteyiz.

Rezonans Frekansındaki değişiklikler işitme sisteminin iletim mekanizmasındaki değişikliklerle paraleldir (14). Rezonans Frekansı EOM, atelektazik kulak zarı, kemikçik zincir devam bozukluğu, geniş vestibuler aquaduktta azalırken; otoskleroz, kemikçik fiksasyonu, romatoid artrit, juvenil romatoid artritte artmaktadır (16). Özgür ve ark. (14) Türk toplumunda farklı yaş gruplarında sağlıklı bireylerde GBT normatif verilerini çıkarmayı amaçladıkları çalışmalarında; 1 ay-2 yaş grubunda ortalama RF değerleri sağ kulak için 706.6 Hz (240-1677), sol kulak için 784.0 Hz (252-2986) olarak bildirilmiştir. Aynı çalışmada 2-20 yaş grubunda ise ortalama RF değerleri; sağ kulak için 1036.0 Hz (178-3566), sol kulak için 1184.0 Hz (558-3451) olarak bildirilmiştir. Çalışmamızda RF değerleri hasta grubunda

ortalama 811.93±284.03 Hz (238.0-1475.0 Hz) olarak, kontrol grubunda ise ortalama 836.26±362.19 Hz (272.0-1615.0 Hz) olarak saptanmıştır. Hasta grubunun rezonans frekans değerlerinin kontrol grubunun rezonans frekans değerlerine göre daha düşük olduğu gözlenmiş ancak istatiksel olarak iki grup arasında anlamlı farklılık gözlenmemiştir (*p=0.721*). Çalışmamızda Rezonans frekansındaki azalma yarık damağın başarılı şekilde rekonstrükte edilmesine rağmen kulak zarı ve orta kulaktaki rezidüel patolojilere bağlı olabilir. Bu sonuca göre yarık damak/yarık dudaklı çocuklar esas patolojileri (yarık damak yarık dudak) açısından takipten çıksalar dahi kulak zarı ve orta kulak patolojileri açısından uzun dönem takip edilmelidir.

Ayrıca tedavi edilmemiş EOM'nın uzun dönem komplikasyonları arasında adezyon ve kolesteatom da mevcuttur (10). Goudy ve ark. (1) ortalama yaşın 19 olduğu opere edilmiş yarık damaklı 101 vakalık serilerinde %5.9 oranında kolesteatoma bildirmişlerdir. Möller 113 olguluk çalışmasında kolesteatom oranını %1 olarak bildirmiştir (17). Imbery ve ark. (18) 352 olguluk çalışmalarında kolesteatom oranını %1.1 olarak bildirmiştir. Aynı çalışmada kolesteatom insidansı ile uygulanan VT sayısı arasında istatistiksel olarak anlamsız sonuç saptanmış. Çalışmamızda hiçbir olguda kolesteatom saptanmamıştır. Bunun en önemli nedeni olguların henüz takip sürelerinin kısa olmasıdır. Literatürdeki kolesteatom riski oranları nedeniyle yarık damak ve/veya yarık dudaklı olgularda yaşam boyu otolojik takibin gerekli olduğunu düşünmekteyiz ve bu konuda aile bilgilendirilmesi yapılmalıdır.

Geniş Bant Timpanometri testinde 226 Hz, 1000 Hz, 2000 Hz ve 8000 Hz de elde edilen basınçlı absorbans değerlerinde istatiksel olarak da iki grup arasında anlamlı farklılık olduğu gözlenmiştir (*p<0.001*). Buna karşın 4000 Hz de elde edilen basınçlı absorbans değerlerinin ise her iki grupta benzer olduğu gözlenmiş ve istatiksel olarak da iki grup arasında anlamlı farklılık gözlenmemiştir (*p=0.343*). Hunter ve ark. (6) yaş aralığının 9 hafta-2 yıl olduğu, daha önceden hiç VT tatbiki yapılmamış 17 yarık damaklı olgudan oluşan çalışmalarında; %82 kulakta (28/34) geniş bant reflektans değerlerini anormal olarak bildirmişlerdir. Ancak çalışmamız yarık damak/yarık dudak tamir edilmesinden sonra yapıldığı için anormal absorbans değeri olguların sadece %41'inde saptanmıştır.

Bu çalışmada yarık damak/yarık dudak patolojisi başarılı şekilde rekonstrükte edilmiş çocuklarda yapılmış olmasına rağmen tanısal ABR testi ile iletim tipi işitme kaybı yanında geniş band timpanogram tepe basıncı ve basınçlı absorbans frekans parametrelerinde aynı yaş grubundaki kontrol grubuna göre patolojik bulgular saptanmış, efüzyonlu otitis media saptanan toplam 19 kulağın 8'i çok hafif derecede, 7'si hafif derecede, 4'ünde ise orta derecede iletim tipi işitme kaybı saptanmıştır. İletim tipi işitme kayıpları sensörinöral işitme kayıpları kadar olmasa da çocukların dil gelişimi yanında, sosyal ve psikolojik gelişimlerini de etkileyebilen bir problemdir ve tedavi edilmelidir. İletim tipi işitme kayıplarının tedavisinde tüm dünyada en sık kullanılan yöntem VT tatbikidir. Yarık damaklı çocuklarda da VT tatbiki işitme üzerine olumlu etkiler sağlamaktadır (1). Efüzyonlu otitis media tedavisinde uygulanan VT tatbiki işitme eşiklerini 20-30 dBnHL düzeltmektedir (10). Hem EOM'nın uzun dönem komplikasyonlarını azaltmak, hem de işitme kaybının konuşma ve dil gelişimi üzerindeki olumsuz sonuçlarını önlemek için VT tatbikinin yarık damaklı hasta grubunda erken dönemde, hatta proflaktik olarak yapılması önerilmiştir (10). Goudy ve ark. (1) ortalama yaşın 19 yıl olduğu opere yarık damaklı 101 vakalık çalışmalarında olgulara ortalama 3.1 kez VT tatbiki uygulanmıştır. Dört ve üzerinde VT uygulanan uygulanan olguların iletim tipi işitme kaybı açısından daha yüksek risk altında olduğunu belirtmişlerdir (1). Szabo ve ark. (4) doğumdan 5 yaşına kadar takip ettikleri 86 olguluk çalışmalarında yarık damaklı olgulara ortalama 1.7 kez (0-6) bilateral VT tatbiki uygulamışlardır. Sadece iki olguya VT tatbiki uygulamamışlardır. Imbery ve ark. (18) ortalama takip süresinin 50.3 ay olduğu 352 olguluk çalışmalarında yarık damaklı olgulara ortalama 2.93 kez VT tatbiki uygulamışlardır. Çalışmamızda hasta grubundaki olgulara her iki kulağa VT tatbiki ortalamamız 1.2 (1-3) olarak hesaplanmıştır. Çalışmamızda VT uygulama ortalamasının literatüre göre düşük

olmasının nedeni hasta grubundaki olgularımızın ortalama yaşının daha düşük olması olabilir. Yukarıda da belirtildiği gibi yarık damak/yarık dudaklı çocukların uzun dönem takibi şarttır, ancak ülkemizdeki sağlık uygulamasına göre, asıl problem olan yarık damak/yarık dudak tedavi edildikten sonra hastalar sıklıkla aile hekimine başvurmakta ve kulak patolojileri atlanabilmektedir. Buna göre uzun dönem takiplerinin gerekliliği konusunda aileler yanında birinci basamak hekimleri ve yarık damak yarık dudak operasyonlarının gerçekleştiren Plastik ve Rekonstrüktif Cerrahi uzmanlarının bilgilendirilmesi çocukların sosyal ve psikolojik gelişiminin normal seyri açısından çok önemlidir.

Çalışmamızda yarık damak yarık dudak rekonstrüksiyonu öncesi tüm bebeklere YDİT yapılmasına rağmen detaylı işitme değerlendirilmesi mevcut değildir. Bunun en büyük nedeni yarık damak/yarık dudak ve buna bağlı emme, beslenme ya da eşlik eden problemlerin işitme problemlerine göre daha görünür bir problem olması nedeniyle ailelerin ve sağlık profesyonellerinin bu konulara odaklanması ve tarama sonrası işitme değerlendirilmesinin ileri tarihlere ertelenebilmesidir. Çeşitli sistemlerin etkilenebildiği bir hastalık olan yarık damak/yarık dudak patolojisinde multidisipliner yaklaşım şarttır.

Sonuç olarak yarık damak onarım operasyonu sonrasında bile %41 gibi yüksek oranlarda efüzyonlu otitis media sıklığı olması, bu olguların uzun dönem kulak burun boğaz hekimince takibinin gerekliliğini ortaya koymaktadır. Yarık damakla doğan yenidoğanlara özellikle ek problemleri varsa erken dönemde işitme kaybı tanısı veya ekartasyonu için miringotomi ve/veya VT tatbiki yapılarak tanısal ABR testi yapılmalıdır. Bu olgularda orta kulak değerlerini GBT ile yapmak pek çok bulgunun açığa çıkmasına yardımcı olacaktır.
Ayrıca çeşitli sistemlerin etkilenebildiği bir hastalık olması sebebiyle yarık damaklı olgularda multidisipliner yaklaşım çok önemlidir ve bu açıdan ilgili branşlarla iş birliği halinde olunması gerekmektedir.

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Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.

Hakem Değerlendirmesi: Hakem değerlendirmesinden geçmiştir.

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Sistemik Lupus Eritematozuslu Hastalarda Hiperkalemi Nedenlerinin Değerlendirilmesi: Retrospektif, Tek Merkez Deneyimi

Evaluation of Causes of Hyperkalemia in Systemic Lupus Erythematosus Patients: Retrospective Single-Center Experience

[1]Afida Mammadova, [2]Döndü Üsküdar Cansu, [2]Cengiz Korkmaz

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Eskişehir, Türkiye

[2]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Romatoloji Bilim Dalı, Eskişehir, Türkiye

Özet

Hiperkalemi, yaşamı tehdit edici sonuçlara yol açabilen önemli bir elektrolit bozukluğudur. Hiperkalemi sıklığı ve nedenleri çalışılan popülasyona göre değişmektedir. Başlıca risk faktörleri renal yetmezlik, diyabetes mellitus (DM) ve anjiyotensin dönüştürücü enzim (ACE) inhibitörü gibi ilaçların kullanımıdır. Sistemik lupus eritematozus (SLE) seyrinde hiperkalemi nedenleri şimdiye kadar araştırılmamıştır. Amacımız, SLE'li hastalarda hiperkalemi nedenlerini ayrıntılı olarak ortaya koymak ve hiperkalemik renal tubuler asidoz (RTA) tip 4 sıklığını belirlemekti. Ocak 2010-Şubat 2020 yılları arasında Romatoloji bölümünde SLE tanısı ile takip edilen ve potasyum düzeyi ≥5.5 mEq/L (hiperkalemi) olan hastalar belirlendi. Hiperkalemi saptanan hastaların klinik ve laboratuvar bulguları dosyalarından ve dijital kayıt sisteminden retrospektif olarak tarandı. SLE dışı tanısı olanlar, hiperkalemisi olmayan hastalar çalışma dışı bırakıldı. Hiperkalemi nedenleri renal hasar/yetmezlik [akut böbrek hasarı, kronik böbrek hastalığı (KBH)], ilaçlar, hormonal nedenler (Addison hastalığı, tip 4 RTA), psödohemoliz ve diğer olarak sınıflandırıldı. Hiperkalemi saptanan 35 SLE'li hastanın yaş ortalaması 40.1±16.9 yıl iken hastaların %85.7'si kadındı. Hastaların %57.1'inde (n=20) lupus nefriti vardı. En sık görülen renal tutulum tipi %68.7 (11/16) ile sınıf 4 lupus nefriti idi. Hiperkalemi saptandığı sıradaki SLE hastalık süresi ortalaması 5.2±5.52 yıl, hastalık aktivasyon indeksi-SLEDAI ortalama 19.8±13.4 idi. Potasyum ortalaması 6.6 ±1.08 mEq/L idi. En sık hiperkalemi nedeni %45.7 (n=16) ile renal hasar/hastalık iken bunu %25.7 ile ilaç kullanımı izlemişti. 2 (%5) hastada hiperkalemi RTA tip 4'e bağlanmıştı. Gruplar hiperkalemi nedenlerine göre klinik ve laboratuvar parametreleri açısından karşılaştırıldığında renal hasar/hastalığı grubunda kreatin yüksekliği daha fazla idi (p≤0.001). SLE seyrinde hiperkalemi, genel toplumda görüldüğü gibi en çok renal hasara/hastalığa bağlı olarak ortaya çıkmaktadır. Bunun yanında RTA tip 4 de hiperkaleminin önemli bir nedenidir. Hiperkalemisi olan SLE'li hastalar sık görülen hiperkalemi nedenleri dışlandıktan sonra veya dirençli hiperkalemi varlığında hiperkalemik RTA tip 4 açısından da araştırılmalıdır.
Anahtar Kelimeler: Sistemik Lupus Eritematozus; Hiperkalemi; Hiperpotasemi; Renal Tubuler Asidoz

Abstract

Hyperkalemia is a major electrolyte disturbance with potentially life-threatening consequences. Varying prevalence and causes of hyperkalemia have been reported for study populations. Primary risk factors include renal insufficiency, diabetes mellitus (DM) and use of certain medication such as angiotensin converting enzyme (ACE) inhibitors. So far, causes of hyperkalemia in systemic lupus erythematosus (SLE) have not been investigated. Our aim here is to elaborate the causes underlying hyperkalemia and to determine the prevalence of hyperkalemic Type 4 renal tubular acidosis (RTA) in SLE patients. Among the patients followed up at the Department of Rheumatology due to SLE between January 2010 and February 2020, those with a potassium level of ≥5.5 mEq/L (hyperkalemia) were identified. For hyperkalemia patients, patient charts and digital record system were retrospectively searched for clinical and laboratory findings. Those with a non-SLE diagnosis and without hyperkalemia were excluded. Causes of hyperkalemia were classified as renal failure/insufficiency [acute kidney injury, chronic kidney disease (CKD)], medication, hormonal reasons (Addison's disease, Type 4 RTA), pseudo-hemolysis, and others. Hyperkalemia was identified in 35 SLE patients, who were 40.1±16.9 years old, on average, and 85.7% of them were female. In 57.1% of the patients (n=20) lupus nephritis was identified. The most common type of renal involvement was Class IV lupus nephritis, at a rate of 68.7% (11/16). At the time of hyperkalemia diagnosis, mean duration of SLE disease was 5.2±5.52 years and mean SLE disease activation index (SLEDAI) was 19.8±13.4. Mean potassium level was 6.6 ±1.08 mEq/L. Metabolic acidosis was detected in 40% of the patients. The most common cause of hyperkalemia was renal failure/disease in 45.7% (n=16), followed by use of medication in 25.7%. In two (5%) patients hyperkalemia was attributed to Type 4 RTA. When patient subsets were compared by their causes of hyperkalemia for clinical and laboratory parameters, subset of renal failure/disease has a higher level of creatinine (p≤0.001), but there was no difference in other parameters. In line with its occurrence in general population, hyperkalemia in SLE most often occurs due to renal failure/disease. In addition, Type 4 RTA is an important reason for hyperkalemia. SLE patients presenting with hyperkalemia should also be queried for hyperkalemic Type 4 RTA, once the common causes for hyperkalemia are ruled out or in the event of persistent hyperkalemia.
Keywords: Systemic Lupus Erythematosus; Hyperkalemia; Hyperpotassemia; Renal Tubular Acidosis

Correspondence:
Döndü ÜSKÜDAR CANSU
Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Romatoloji Bilim Dalı, Eskişehir, Türkiye
e-mail: ducansu@hotmail.com

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1. Giriş

Sistemik lupus eritematozus (SLE), cilt, eklemler, merkezi sinir sistemi ve böbrekler dahil olmak üzere birçok organı etkileyebilen sistemik otoimmün bir hastalıktır. Kadınlarda erkeklere göre daha sık görülür ve kadın/erkek oranı, ergenlik ile menopoz arasında yaklaşık 9/1'dir (1). Lupus nefriti (LN), SLE'nin en şiddetli organ tutulumlarından biridir. Hastalık patogenezi hakkında artan bilgiye ve iyileştirilmiş tedavi seçeneklerine rağmen LN, SLE'li hastalarda önemli bir morbidite ve ölüm nedeni olmaya devam etmektedir. SLE tanısından sonraki 10 yıl içinde, LN'li hastaların %5-20'sinde son dönem böbrek hastalığı gelişir. LN'li hastalarda antiproteinürik etkisi nedeniyle ve kan basıncını kontrol etmek amacıyla renin anjiotensin aldosteron sistemi (RAAS) blokajı önerilmektedir (2). Hiperkalemi, RAAS blokerlerinin önemli yan etkilerinden biridir (3). Hastanede yatan hastaların yaklaşık %1-10'unda hiperkalemi saptandığı bildirilmiştir (4.). Hiperkalemi artmış ölüm riski ile ilişkilidir ve bu durum hiperkalemiye bağlı kardiyak aritmi ile açıklanabilir. Hiperkaleminin başlıca risk faktörlerini böbrek yetmezliği ve distal nefronda potasyum atılımında edinilmiş veya kalıtsal kusurlar oluşturur. Hiperkalemi için diğer risk faktörleri arasında diyabetes mellitus (DM), anjiyotensin dönüştürücü enzim (ACE) inhibitörü, anjiyotensin reseptör blokerleri (ARB) veya potasyum tutucu diüretiklerin kullanımı yer alır (5).

SLE'de hiperkalemi özellikle renal yetmezlik seyrinde beklense de nadiren SLE ilişkili hiperkalemik renal tubuler asidoz (RTA) tanımlanmıştır (6). Bildiğimiz kadarıyla SLE'de hiperkaleminin ayrıntılı nedenleri şimdiye kadar irdelenmemiştir. Sadece bir çalışmada dirençli hiperkalemisi olan 5 hastada hiporeninemik hipoaldosteronizm araştırılmıştır. Diğer nedenler ile ilgili bilgi verilmemiştir (7).

Amacımız, SLE'li hastalarda hiperkalemi nedenlerini ayrıntılı olarak ortaya koymak ve hiperkalemik RTA tip 4 sıklığını belirlemekti.

2. Gereç ve Yöntem

Hasta seçimi

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi İç Hastalıkları, Romatoloji Bilim Dalı'nda Ocak 2010-Şubat 2020 yılları arasında SLE tanısı ile takip edilen hastalar SLE ICD kodu kullanılarak belirlendi. Hiperkalemi, potasyum düzeyi ≥5.5 mEq/L olarak kabul edildi (8). SLE için 1997 Amerikan Romatoloji Derneği (ACR) sınıflandırma kriterlerini (9) karşılayan ve en az bir ölçümde hiperkalemi saptanan hastaların klinik ve laboratuvar verileri dosyalarından ve dijital kayıt sisteminden retrospektif olarak tarandı. SLE dışı tanısı olanlar ve hiperkalemisi olmayan hastalar çalışma dışı bırakıldı.

Çalışma için Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulundan 03.11.2020 tarih ve 21 sayılı kararı ile etik onayı alınmıştır.

Klinik ve Laboratuvar Değerlendirmeler

Hastaların takip dosyalarından ve dijital kayıtlarından klinik bulguları, laboratuvar sonuçları ve renal biyopsiye ait histopatolojik sonuçları tarandı. SLE'li hastaların kümülatif organ tutulumları ve klinik bulguları, aldıkları tedaviler, laboratuvar parametrelerinden C-reaktif protein (CRP), eritrosit sedimentasyon hızı (ESH), antinükleer antikor (ANA), anti-dsDNA, anti-Sm, kompleman (C)3 ve C4 sonuçları kaydedildi.

Hastaların hiperkalemi sırasındaki demografik bilgileri (yaş, SLE hastalık süresi, SLE'ye ait organ tutulumları), kullandıkları ilaçlar, ayrıntılı tam kan sayımı (CBC), ESH, CRP, anti-dsDNA, C3 ve C4 sonuçları, sodyum, potasyum, glukoz, klor, kan üre azotu, kreatinin, serum pH, bikarbonat (HCO3) düzeyleri, proteinüri düzeyi, idrar pH, idrar potasyum, idrar sodyum düzeyleri kaydedildi. Serum ve idrar anyon açıkları ve hiperkalemi sırasında SLE hastalık aktivasyonu için SLEDAI'leri de hesaplandı. Dirençli hiperkalemisi olan hastalarda bakılan hormon düzeyleri kaydedildi.

Hiperkalemi nedenleri renal hasar/yetmezlik [akut böbrek hasarı, kronik böbrek hastalığı (KBH)], ilaçlar, hormonal nedenler (Addison hastalığı, tip 4 RTA), psödohemoliz ve diğer olarak sınıflandırıldı.

İstatistiksel analiz

Sürekli veriler Ortalama ± Standart Sapma (SS) olarak verilmiştir. Kategorik veriler ise yüzde (%) olarak verilmiştir. Verilerin normal dağılıma uygunluğunun araştırılmasında Shapiro Wilk's testinden yararlanılmıştır. Normal dağılım gösteren grupların karşılaştırılmasında grup sayısı üç ve üzerinde olan durumlar için Tek yönlü varyans analizi (One-Way ANOVA) kullanılmıştır. Normal dağılıma uygunluk göstermeyen grupların karşılaştırılmasında grup sayısı üç ve üzerinde olan durumlar için Kruskal-Wallis H testi kullanılmıştır. Oluşturulan çapraz tabloların analizinde Pearson Ki-Kare ve Pearson Kesin (Exact) Ki-Kare analizleri kullanılmıştır. Analizlerin uygulanmasında IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.), MecCalc 13.3 ve Sigma Stat 3.5 programlarından yararlanılmıştır. İstatistiksel önemlilik için $p<0.05$ değeri kriter kabul edilmiştir.

3. Sonuçlar

Hiperkalemi saptanan 35 SLE'li hastanın yaş ortalaması 40.1±16.9 yıl, SLE tanı yaşı ortalaması 35.1±18 yıl idi. Hastaların %85.7'si kadındı.

Hiperkalemi hastaların %28.6'sında (n=10) hafif (potasyum ≥5.5 mEq/L), %25.7'sinde (n=9) orta (potasyum ≥6 mEq/L) ve %45.7'sinde (n=16) ise şiddetli (potasyum ≥6.5 mEq/L) düzeyde idi.

Renal tutulum sıklığı %57.1 (n=20), otoimmun hemolitik anemi sıklığı %61 (n=21), lökopeni %54.3 (n=19) ve trombositopeni sıklığı ise %20 (n=7) olarak saptandı. Renal tutulumu olan 20 hastanın 16'sına renal biyopsi yapılmıştı. En sık görülen renal tutulum tipi %68.7 (11/16) ile sınıf 4 lupus nefriti idi. Renal biyopsi yapılmış hastaların 6'sında (%37.5) tübülointertisyel nefrit vardı. Hiperkalemik 35 SLE hastasının kümülatif klinik bulguları, laboratuvar sonuçları ve tedavileri Tablo 1'de verilmiştir.

Tablo 1. Hiperkalemisi olan SLE'li hastaların demografik özellikleri (kümülatif klinik ve laboratuvar bulguları)

	n	**%**
n	35	-
Yaş, ortalama±SS, yıl	40.1±16.9 (17-73)	-
Cinsiyet, K/E, n, %	30/5	%85.7/%14.3
SLE tanı yaşı, ortalama±SS, yıl	35.1±18 (13-82)	
SLE hastalık süresi, ortalama±SS, yıl	8.5±6.5 (0.5-22)	
Kümülatif klinik bulgular		
Cilt tutulumu, n, %	29	%82.9
Eklem tutulumu, n, %	30	%85.7
Serozit		
Perikardit, n, %	12	%34.3
Plevrit, n, %	11	%31.4
Nörolojik tutulum, n, %	5	%14.3
Renal tutulum, n, %	20	%57.1
Böbrek biyopsi sonuçlarına göre lupus nefriti evreleri (n=16)		
Sınıf 3, n, %	3	%18.7
Sınıf 4, n, %	11	%68.7
Sınıf 5, n, %	1	%6.3
Sınıf 6, n, %	1	%6.3
Lupus nefriti süresi, ortalama±SS, yıl	7.1±5.24 (1-19)	
Tubulointertisyel tutulum, n, %	6	%40
Hematolojik tutulum		
Otoimmun hemolitik anemi, n, %	21	%61
Lökopeni, n, %	19	%54.3
Lenfopeni, n, %	31	%88.6
Trombositopeni, n, %	19	%54.3
AFS sıklığı, n, %	7	%20
Laboratuvar		

ANA pozitifliği, n, %	35	%100
AntidsDNA pozitifliği, n, %	28	%80
antiSm pozitifliği, n, %	7	%26.9
Hipokomplementemi sıklığı, n, %	27	%77.1
Kümülatif ilaç kullanımı		
Siklofosfamid, n, %	17	%48.6
Mikofenolat mofeitl, n, %	22	%62.9
Azatioprin, n, %	19	%54.3
Metotreksat, n, %	3	%8.6
Steroid, n, %	31	%88.6
Hidroksiklorokin, n, %	34	%97.1

ANA; Anti nükleer antikor, AFS; Antifosfolipid sendromu, E; Erkek, ; K;Kadın, SLE; Sistemik lupus eritematozus, SS; Standart sapma

Hiperkalemi sırasındaki laboratuvar bulguları ve SLE hastalık aktivasyon indeksi

Hastaların hiperkalemi saptandığı sıradaki SLE hastalık süresi ortalama 5.2±5.52 yıl idi. Anti dsDNA pozitifliği %62.9 (n=22), hipokomplementemi sıklığı ise %62.9 (n=22) idi. Hiperkalemi sırasında hastalık aktivasyonu SLEDAI ile ölçülmüştü ve ortalama 19.8±13.4 saptandı. Bu hastaların SLE tanısı sırasındaki ortalama potasyum değerleri 4.43 ±0.4 mEq/L iken hiperkalemik dönemde saptanan potasyum ortalaması ise 6.6±1.08 mEq/L idi. Hastaların hiperkalemik dönemdeki hemogram, akut faz, elektrolit, kan gazı, idrar sonuçlarını içeren biyokimyasal testler ve diğer laboratuvar sonuçları Tablo 2'de verilmiştir.

Tablo 2. SLE'li hastaların hiperkalemi sırasındaki laboratuvar ve klinik bulguları

Hiperkalemi sırasında saptanan hasta yaşı, ortalama±SS, yıl	40.1±16.9 (17-73)	
Hiperkalemi sırasında SLE hastalık süresi, ortalama±SS, yıl	5.2±5.52 (0.5-20)	
Hiperkalemi sırasında SLEDAI, ortalama±SS	19.8±13.4 (2-56)	
Anti-dsDNA pozitifliği, n, %	22	%62.9
Hipokomplementemi sıklığı, n, %	22	%62.9
Hiperkalemi sırasında almakta oldukları ilaçlar		
Steroid, n, %	25	%71.4
Hidroksiklorokin, n, %	24	%68.6
ACE inhibitörü, n, %	4	%11.4
ARB, n, %	3	%8.6
Spironolakton, n, %	4	%11.4
NSAİİ, n, %	2	%5.7
Takrolimus, n, %	2	%5.7
Beta bloker, n, %	6	%17.1
Laboratuvar		
SLE tanısında K değeri, ortalama±SS, mEq/L	4.43±0.4 (3.7-5.51)	
Hiperkalemik dönemde		
K, ortalama±SS, mEq/L	6.6±1.08 (5.5-8.64)	
Na, ortalama±SS, mEq/L	135±6 (111-148)	
Cl, ortalama±SS, mEq/L	100±8 (71-117)	
Glukoz, ortalama±SS, mg/dL	118±85 (80-372)	
Cr, ortalama±SS, mg/dL	2.20±2.8 (0.54-16.8)	
BUN, ortalama±SS, mg/dL	36±27 (9-98)	
Hemoglobin, ortalama±SS, gr/dL	12±6.6 (7.7-14)	
Lökosit, ortalama±SS, /µL	7361±4611 (300-20690)	
Trombosit sayısı, ortalama±SS, /µL	212000±106211 (16000-588000)	
ESH, ortalama±SS, mm/h	49±33 (7-120)	
CRP, ortalama±SS, mg/dL	0.32±66 (0.32-291)	
Serum pH, ortalama±SS	7.31±0.1 (6.92-7.48)	
Serum HCO3, ortalama±SS, mEq/L	17.8±5.5 (2.8-25)	
Serum anyon gap, ortalama±SS	16.1±10 (-0.9-39)	
İdrar tetkikleri		
Proteinüri, ortalama±SS, mg/gün	1940±2960 (73-13700)	
İdrar pH, ortalama±SS	6±0.7 (5-8)	
İdrar K, ortalama±SS, mEq/L	22.7±12 (11-36)	
İdrar Na, ortalama±SS, mEq/L	53±30 (9-90)	
İdrar anyon gap, ortalama±SS	6.8±26 (-11.8-25.4)	

ACE;Anjiotensin dönüştürücü enzim inhibitörü, ANA; Anti nükleer antikor, ARB;Anjiotensin reseptör blokeri, BUN;Kan üre azotu, Cl;Klor, Cr; Kreatinin, CRP; C reaktif protein, ESH;Eritrosit sedimentasyon hızı, K; Potasyum, Na; Sodyum, NSAİİ;Non steroid antiinflamatuvar ilaçlar, SLE; Sistemik lupus eritematozus; SS; Standart sapma

SLE hastalarında hiperkalemi nedenleri

Hiperkalemik 35 SLE hastasında en sık hiperkalemi nedeni %45.7 (n=16) ile renal hasar/hastalık idi. Hastaların 9'unda akut böbrek hasarı, 7'sinde ise KBH nedenli hiperkalemi mevuttu. İkinci en sık neden ise ilaç kullanımı idi. ACE inhibitörü ve ARB kullanımı ilaca bağlı hiperkaleminin en sık nedenleri idi. Bunları hormonal nedenler (%8.6) ve psödohemoliz (%8.6) izlemişti. 2 (%5) hastada hiperkalemi RTA tip 4'e bağlanmıştı (SLE hastalarındaki hiperkalemi nedenleri Tablo 3'de verilmiştir).

Tablo 3. SLE'li hastalarda hiperkalemi nedenleri

	n	%
Renal hasar/hastalık	**16**	**45.7**
Akut renal hasar	9	56.2
KBH	7	43.8
İlaçlar	**9**	**25.7**
ACE inhibitörü	4	44.1
ARB	1	11.1
Beta bloker	1	11.1
Spironolakton	2	22.2
NSAİİ	1	11.1
Hormonal nedenler	**3**	**8.6**
Addison hastalığı	1	33.7
RTA tip 4	2	66.7
Pseudohemoliz	**3**	**8.6**
Diğer	**4**	**11.4**

ACE;Anjiotensin dönüştürücü enzim inhibitörü, ARB;Anjiotensin reseptör blokeri, KBH; Kronik böbrek hastalığı, NSAİİ;Non steroid antiinflamatuvar ilaçlar, RTA; Renal tubuler asidoz, SLE; Sistemik lupus eritematozus

Hiperkalemiye yönelik verilen tedaviler ve sonlanım

8 hastada hiperkalemiye neden olan ilaçlar kesildi, 17 hastaya tamponize mayi verildi, 8 hasta hemodiyalize alındı ve 6 hastaya antipotasyum tedavi verildi. 30 hastanın potasyum değerleri düzelirken 5 (%14.3) hastada hiperkalemi dirençli seyretti. Bu hastalarda yapılan ileri incelemeler sonrası 3 hastada hormonal nedenler saptandı. Bir hastada Addison hastalığı ve 2 hastada da RTA tip 4 tanısı konuldu.

Hiperkalemi etyolojisine göre gruplar arası karşılaştırma

Hiperkalemi nedenlerine göre gruplar klinik ve laboratuvar parametreleri açısından karşılaştırıldığında renal hasar/hastalık grubunda kreatinin yüksekliği daha fazla idi ($p \geq 0.001$). Biyokimyasal parametreler ve SLEDAI ortalamaları gruplar arasında istatistiksel olarak farklılık göstermemişti. Hiperkalemi etyolojisine göre gruplar arası klinik ve laboratuvar verilerinin karşılaştırılması Tablo 4'de verilmiştir.

Tablo 4. SLE'li hastalarda hiperkalemi etyolojisine göre gruplar arası klinik ve laboratuvar bulguların karşılaştırılması

	Renal hasar/ hastalık	İlaçlar	Hormonal nedenler	Psödo-hemoliz	Diğer	P değeri
N	**16**	**9**	**3**	**3**	**4**	**-**
Yaş, ortalama±SS, yıl	43.8±20.1	39.7±16.6	42±9.5	30±10	32.5±9.8	0.639
SLE tanı yaşı, ortalama±SS, yıl	40±23	32±12	38±11	23.3±5	29±13	0.552
SLE hastalık süresi, ortalama±SS, yıl	6.8±7	11.8±6.5	11±5.2	8.3±5.5	6±5.6	0.364
Cinsiyet, K/E	13/3	9/0	2/1	3/0	3/1	0.474
Hiperkalemi sırasında SLEDAI, ortalama±SS	25.3±15.2	13±8.9	24.6±16.1	12±7.2	15.2±8	0.140
Hiperkalemi sırasında antidsDNA pozitifliği, var/yok	13/3	7/1	2/1	2/1	3/0	0.730

Hiperkalemi sırasında hipokomplementemi, var/yok	13/3	8/0	2/1	1/0	2/1	0.105
Lupus nefriti varlığı var/yok	8/8	7/2	2/1	0/3	2/2	0.163
Tübülointertisyel tutulum, var/yok	3/3	1/3	1/1	-/-	1/2	0.858
Hiperkalemi sırasında K değeri, ortalama±SS, mEq/L	6.7±0.9	6.4±0.6	6.8±0.7	5.8±0.18	6.9±1.4	0.501
Hiperkalemi sırasında Cr değeri, ortalama±SS, mEq/L	3.5±3.7	1.04±0.31	1.7±0.7	0.6±0.07	0.95±0.14	≥0.001
Hiperkalemi sırasında idrar pH, ortalama±SS	6.1±0.8	5.9±0.5	5.5	6.3±0.7	6.5±0.5	0.289
Hiperkalemi sırasında serum pH, ortalama±SS	7.28±0.17	7.32±0.5	7.24±0.04	-	7.45	0.352

Cr; Kreatinin, E; Erkek, K; Potasyum, K; Kadın, Na; Sodyum, NSAİİ;Non steroid antiinflamatuvar ilaçlar, SLE; Sistemik lupus eritematozus; SS; Standart sapma

4. Tartışma

Hiperkalemi potasyum değerinin ≥5.5 mmol/L olarak tanımlanır. Hafif (≥5.5 mmol/L), orta (≥6.0 mmol/L) ve şiddetli (≥6.5 mmol/L) olarak ayrılmıştır. Potansiyel olarak yaşamı tehdit edici sonuçlara yol açabilen hiperkaleminin prevalansı ve insidansı belirsizdir. Çalışma populasyonu, alınan merkezler, hiperkalemi tanımı için alınan eşik değer, yaş ve cinsiyet gibi bir çok faktör prevalansı etkilemektedir. Yeni yayınlanan bir metaanalizde tüm yetişkin populasyonunda hiperkalemi prevalansının (herhangi bir tanım/eşik ile) %6.3 ve insidansının ise 100 hasta yılı başına 2.8 (2,3- 3.3) olduğu saptanmıştır (8). Acil servise başvuran ve başlangıç serum veya kan gazı potasyumu ≥6.0 mmol/L olan hastaların değerlendirildiği başka bir çalışmada ise tüm başvurular dahil edildiğinde hiperkalemi prevalansı %0.4 saptanmıştır (10). Hiperkalemi için serum potasyum düzeyini ≥ 5.5 mmol/L olarak alan 468.594 yetişkin arasında (2012-2014 yılları) en az bir kez potasyum bakılmış olan hastaların takip edildiği bir çalışmada ise hiperkalemi yıllık insidansı 100 kişide 1 olarak saptanmıştır. Bu da 2012, 2013 ve 2014 yıllarında en az bir kan testi yaptıran kişilerin sırasıyla %2,3, %2,1 ve %1,9'unu temsil etmiştir (11). Çalışmamızda tüm SLE hastalarına potasyum bakılmamış olması nedeniyle bir prevalans veremedik.

Hiperkalemi için ana risk faktörlerini böbrek yetmezliği (akut böbrek hasarı veya ileri KBH) ve distal nefronda potasyum atılımındaki kazanılmış veya kalıtsal kusurlar oluşturur. KBH'de hiperkalemi tipik olarak tahmini glomerüler filtrasyon hızının (eGFR) 15 mL/dk'nın altına düşmesinden sonra ortaya çıkar eGFR'de 15 mL/dk'lık bir azalma, hiperkalemi olasılığını yaklaşık olarak iki katına çıkarmaktadır. Hiperkalemi için diğer risk faktörleri arasında erkek cinsiyet, düşük vücut kitle indeksi, sigara, DM, adrenal hastalıklar, koroner kalp hastalığı veya inme öyküsü ve ACE inhibitörü, ARB veya potasyum tutucu diüretik kullanımı yer almaktadır (5). Bir derlemede son dönem böbrek yetmezliğinin %33.3, diyaliz bağımlı olmayan KBH'nın %14.6, DM'nin %8.4, kalp yetmezliğinin %8.6 ve akut böbrek hasarının ise %25.7 oranında hiperkalemi nedeni olduğu belirtilmiştir (8).

Hiperkalemiyi serum potasyum düzeyini ≥ 5.5 mmol/L olarak alan ve hastaların yaş ortalamasının 67.9±17 yıl, %46.1'ini kadınların oluşturduğu bir çalışmada komorbiditeler, akut ve kronik böbrek fonksiyonu ölçümleri ve serum potasyum ölçümünden önce reçete edilen ilaçlar kaydedilmiştir. Bu grupta hastaların %12.2'sinde akut böbrek hasarı olduğu görülmüştür. Komorbidite açısından bakıldığında ise DM %25.2, hipertansiyon %39.5, kalp yetmezliği %12.4, koroner arter hastalığı ise %16.4 olarak saptanmştır. Hiperkalemi saptanmadan son 90 gün içinde hastaların aldıkları ilaçların oranı ise: RAAS blokeri %43.1, aldosteron antagonisti %0.6, non steroid antiinflamatuvar ilaçlar (NSAİİ) %10.5, loop diüretik %18.4, tiazid diüretik %7.5 olarak bulunmuştur. Hiperkalemi, ileri KBH veya akut böbrek hasarı olanlarda olduğu kadar yaşlılarda da çok yaygın olarak saptanmıştır. Bu çalışmada hiperkalemi oranı,

her 10 yıllık daha büyük yaş için 2 kat daha yüksek saptanmıştır (11).

Acil servise başvuran hiperkalemik hastaların değerlendirildiği, 392 hastanın analiz edildiği çalışmada ortalama yaş 73.7 yıl olarak bulunmuştur. Bu hastaların %81.9'unun (n=321) hiperkalemiye yatkınlık oluşturan bir veya daha fazla ilaç kullandığı saptanmıştır. Bunun dışında hastaların %85.5'inde (n=335) bir veya daha fazla predispozan komorbidite bulunmuştur. Buna göre hastaların %91.3'ünde GFR ≤ 60 ml/dk, %62.8'inde non-diyaliz KBH, %50'sinde DM ve %1.8'inde ise hipoaldosteronizm saptanmıştır. %44.4 beta bloker, %25.5 ACE inhibitörü, %24 ARB, %22.4 spironolakton, %6.4 NSAİİ, %2.6 takrolimus kullanımı saptanmıştır (10).

SLE'de hiperkalemi nedenleri ile ilgili bilgiyi araştıran sadece bir yayın mevcuttur. 142 SLE hastasını içeren bu çalışmada hiperkalemi için sınır değer olarak serum potasyumu ≥ 5.5 mmol/L olacak şekilde belirlenmiştir. Bu hastaların sadece 13'ünde (%10) hiperkalemi saptanmıştır. Bu çalışmada amaç dirençli hiperkalemisi olan hastalarda RAAS'nin açıklanması idi. 13 hastanın 6'sı çalışmaya katılmayı kabul etmemiş, 2 hasta aktif lupus nefriti nedeniyle çalışma dışı tutulmuş geri kalan 5 hasta değerlendirilmiştir. Çalışılan hastaların hiçbirinde aşağıda belirtilen durumlar yokmuş: 1.şiddetli böbrek yetmezliği 2.yükselmiş serum laktat dehidrogenaz, idrar hemosiderin ve serum bilirubin seviyeleri ile hemoliz 3.lökositoz veya trombositozun neden olduğu psödohiperkalemi 4.Addison hastalığı ve 5.pH < 7.35. Bu 5 hiperkalemik SLE hastasında renin-aldosteron yanıtı araştırılmıştır. Buna göre araştırıcılar, SLE'li hiperkalemik hastaların çoğunda stimülasyona bozulmuş renin ve aldosteron yanıtı saptamışlardır. Yazarlar, SLE'deki hiperkaleminin patogenezinde hiporeninemik hipoaldosteronizmin anahtar rol oynadığını ileri sürmüşlerdir (7). SLE'de hiperkalemi ile ilgili bu tek çalışmada hiperkaleminin ayrıntılı nedenleri verilmemiştir. Çalışmamız bu açıdan bakıldığında, SLE seyrinde ortaya çıkan hiperkalemi nedenlerini ayrıntılı bir şekilde araştıran literatürdeki ilk çalışmadır. Hiperkalemi saptanan 35 hastamızda en sık hiperkalemi nedeni %45.7 ile renal hasar/yetmezlik (akut böbrek hasarı ve/veya KBH) idi. Bu sonuç literatürle uyumlu idi. Hastalarımızın 9'unda akut böbrek hasarı, 7'sinde ise KBH nedenli hiperkalemi mevuttu. 35 hastanın yarısında lupus nefriti vardı. Bu nedenle en sık neden renal hasar/yetmezlik olmuş olabilir. Hiperkaleminin en sık ikinci nedeni ise ilaç kullanımı idi. Buna göre en sık nedenler sırasıyla ACE inhibitörü, ARB, beta boker ve spironolakton idi. Literatürdeki genel verilere benzer şekilde SLE'li hastalarımızda da hiperkaleminin en sık nedenleri renal hasar ve ilaçlar iken bir hastada Addison hastalığı ve 2 (%5) hastada ise RTA tip 4 saptadık. Hiperkaleminin nadir nedenleri arasında metabolik asidoz ile seyreden RTA'lar vardır. RTA, glomerüler filtrasyon hızına bağlı olmaksızın, renal tubul işlevlerindeki bozukluk sonucu bikarbonat geri alınmasında ya da hidrojen iyonu atılmasında yetersizlikle ortaya çıkan normal anyon gapli metabolik asidoz tablosudur. RTA alt tiplerinden hipkokalemi ile seyreden formlar özellikle otoimmun hastalıklardan Sjögren sendromunda ortaya çıkarken daha nadir olarak SLE seyrinde de ortaya çıkabilir. Hiperkalemi ile seyreden tip 4 RTA SLE seyrinde çok nadir görülür ve literatürde çok az raporlanmıştır (6,12). Genel populasyonda RTA sıklığı bilinmese de 50 distal RTA hastasının değerlendirildiği bir çalışmada en sık nedenler olarak posttransplantasyon (28%) ve DM (22%) saptanırken bunu hipertansiyon (12%), SLE (12%) ve kronik renal yetmezlik (12%) izlemiştir (13). RTA SLE seyrinde görülebilirse de sıklığı ile ilgili bir çalışma yoktur (12). Çalışmamızda 35 hiperkalemik hasta içinde RTA tip 4 sıklığı %5 idi. SLE'de RTA tip 4 hastalarını derleyen bir çalışmada 7 hasta değerlendirilmiştir. Yedi hastada da renal tutulum varken, 3 hastada biyopsi kanıtlı sınıf 4 lupus nefriti saptanmıştır. Hastaların hepsi SLE açısından aktif [SLEDAI skoru ortalama 26.2±4 (23-32)] olarak bulunmuştur (6). Çalışmamızda ise hiperkalemi saptanan 35 hastanın hiperkalemi sırasındaki hastalık aktivasyonu SLEDAI ile ölçülmüştü ve ortalama 19.8±13.4 idi. SLEDAI skoru 11–19 iken yüksek aktivite ve ≥20 iken çok yüksek aktiviteyi gösterir. Hiperkalemik SLE

hastalarımızın hastalık aktivitesi ortalaması yüksek idi. Hastalık aktivasyonunun hiperkalemiye katkısı olup olmadığını söylemek için gelecekte yapılacak çalışmalara gereksinim vardır.

Hiperkalemi tedavisinde potasyum düzeyi ve EKG değişiklikleri de gözönüne alınarak intravenöz kalsiyum, glukozlu insülin, nebulize salbutamol, sodyum bikarbonat, diüretikler veya diyaliz önerilmektedir (3). Acil serviste değerlendirilen 392 hiperkalemik hastanın %47.1'ine intravenöz glukoz ve insülin, %13'üne hemodiyaliz ve %4.3'üne intravenöz sodyum bikarbonat uygulanmıştır (10). En sık hiperkalemi nedenlerini renal hasar ve ilaç kullanımı oluşturan hastalarımızın ise 8'inde hiperkalemiye neden olan ilaçlar kesilirken, 17 hastaya intravenöz glukoz-insülin verildi, 8 hasta hemodiyalize alındı ve 6 hastaya antipotasyum tedavi verildi. 30 hastanın potasyum değerleri düzelirken, 5 (%14.3) hastada hiperkalemi dirençli seyretti.

Çalışmamızın en önemli kısıtlılığı retrospektif dizaynı idi. İkincisi ise tüm SLE hastalarında potasyum düzeyi bakılmamış olmasıydı. Ayrıca hiperkalemi bazı hastalarda multifaktöriyel olmuş olabilir. Son olarak ise tüm hastalara hormon düzeylerinin bakılmamış olması hiporeninemik hipoaldosteronizmin gerçek sıklığının ortaya konulmasına engel olmuş olabilir.

Sonuç olarak hiperkalemi SLE seyrinde de ortaya çıkabilir. SLE seyrinde görülen hiperkalemi nedenleri de genel toplumda beklendiği üzere en çok renal hasar/kronik böbrek hastalığına ve ilaçlara bağlıdır. Ayrıca RTA tip 4 de SLE seyrinde hiperkaleminin önemli bir nedenidir. SLE ile izlenen hastalarda hiperkalemi saptandığında öncelikle renal nedenler açısından hasta değerlendirilmeli ve hastalar ilaç yan etkileri açısından sorgulanmalıdır. Hiperkalmik SLE'li bir hasta sık görülen hiperkalemi nedenleri dışlandıktan sonra veya dirençli hiperkalemi varlığında hiperkalemik RTA tip 4 açısından da araştırılmalıdır.

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Etik Bilgiler

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Genetic Variants in Rare Diseases Identified by WES Analysis

Nadir Hastalıklarda Tüm Ekzom Dizileme Analizi ile Saptanan Genetik Varyantlar

Özlem Görükmez

Department of Medical Genetics, Bursa Yüksek Ihtisas Training and Research Hospital, Yıldırım, Bursa

Abstract

Next-generation sequencing tests have become a part of the diagnostic process in most fields of medicine. Especially with whole-exome sequencing (WES) studies, the rate of diagnosis has increased in rare hereditary diseases. In this study, we aimed to present the results together with the clinical findings of 65 cases whose diseases are suspected to be of genetic origin. Between 2016 and 2019, patients who underwent WES testing in Bursa Yüksek İhtisas Training and Research Hospital Medical Genetics Unit were retrospectively screened and included in the study with their analysis results and clinical findings. In 27 of the 65 cases (41.5 %) included in the study, 30 significant variants were found in relation to their clinical findings. Twenty of these variants (66.7 %) have not been previously reported in literature. Rare diseases encountered in patients within a wide age range, from the fetus to 66 years of age, are presented along with their clinical findings and WES results. Thus, this study contributes to the mutation spectrum of hereditary diseases.
Keywords: Next generation sequencing, Novel, rare disease, Whole-exome sequencing

Özet

Yeni nesil dizileme testleri, tıbbın çoğu alanında tanı sürecinin bir parçası haline gelmiştir. Özellikle tüm ekzom dizileme (WES) çalışmaları ile nadir kalıtsal hastalıklarda tanı oranı artmıştır. Bu çalışmada, hastalıklarının genetik kökenli olduğundan şüphelenilen 65 olgunun sonuçlarını klinik bulguları ile birlikte sunmayı amaçladık. Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi Tıbbi Genetik Birimi'nde, 2016-2019 yılları arasında WES testi ile değerlendirilen hastalar retrospektif olarak taranarak analiz sonuçları ve klinik bulguları ile birlikte çalışmaya dahil edildi. Çalışmaya dahil edilen 65 olgunun 27'sinde (% 41.5) klinik bulgularıyla ilişkili 30 anlamlı varyant bulundu. Bu varyantların 20'si (% 66.7) daha önce literatürde bildirilmemişti. Fetustan 66 yaşına kadar geniş bir yaş aralığındaki hastalarda görülen nadir hastalıklar klinik bulguları ve WES sonuçları ile birlikte sunulmuştur. Sonuç olarak bu çalışma ile kalıtsal hastalıkların mutasyon spektrumuna katkıda bulunulmuştur.
Anahtar Kelimeler: Yeni nesil dizileme, Yeni varyant, Nadir hastalık, Tüm ekzom dizileme

Correspondence:
Özlem GÖRÜKMEZ
Department of Medical Genetics, Bursa Yüksek Ihtisas Training and Research Hospital, Yıldırım, Bursa
e-mail: ozlemgorukmez@gmail.com

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1. Introduction

Over the past few decades, with the advent of next-generation sequencing (NGS) technologies, we have witnessed significant advances in molecular biology and genetics. With access to extensive genetic information, there have been important advances in diagnosis and treatment in many fields related to medicine. However, linking rare variations to a complex phenotype continues to be difficult (Jalkh et al., 2019). Indeed, determining the cause of a disease that is presumed to be of genetic origin requires a multidisciplinary approach that begins with the identification of phenotypic findings with a detailed family history. In some cases, functional studies are needed to establish a genotype-phenotype relationship (Soden et al., 2014). Approximately 80–85 % of the mutations known to cause Mendelian diseases are located in the coding and splicing regions of a gene. The whole-exome sequencing (WES) method, which scans the coding sequence including the splicing sites representing 1–1.5 % of the human genome, is a practical and cost-effective method (Dixon-Salazar et al., 2012). For this purpose, we aimed to retrospectively evaluate the results of WES analysis in 65 patients who were followed up for a long time and/or could not be diagnosed by routine methods (Karyotype, clinical microarray, capillary electrophoresis).

2. Materials and Methods

This study was approved by the local ethics committee (Bursa Yüksek İhtisas Training and Research Hospital) and complied with the principles of the Declaration of Helsinki. Patients who were evaluated at our medical genetics unit and underwent WES study from January 2016 to January 2019 were included in this study. WES applications were performed using the SureSelect XT Library Prep Kit (Agilent, Santa Clara, CA, USA) on the Novaseq platform (Illumina, San Diego, CA, USA). All bioinformatics analyses, variant filtering, and interpretation were performed on the Sophia DDM™ platform (Sophia Genetics, Saint Sulpice, Switzerland). All variants (Single nucleotide variants and small InDels) significant in terms of genotype-phenotype compatibility were confirmed by sequencing on a capillary electrophoresis device (Applied Biosystems™ 3500, Thermofisher, USA), and segregation analyses were performed (Supplementary material). Whether the variants were reported in the literature was checked with the Human Gene Mutation Database (HGMD; https://www.hgmd.cf.ac.uk). Classification of changes not reported in the literature was made according to American College of Medical Genetics and Genomics (ACMG) criteria (Richards et al, 2015).

3. Results

Patients who were evaluated at the Medical Genetics Unit of Bursa Yüksek İhtisas Training and Research Hospital and were suspected to have a genetic origin were assessed retrospectively. As the last step, the results of the patients who underwent diagnostic WES test (no pathology detected in routine cytogenetic, molecular cytogenetic, and molecular tests according to their preliminary diagnosis) were evaluated in the light of clinical findings, and significant changes were listed (Table 1). No study was conducted to research candidate genes in undiagnosed patients, and all detected variants were on previously identified genes. The ages of the 65 patients included in the study varied widely, and most of them were in the pediatric group. A total of 57 patients (one fetus and five newborns) were under 18 years of age. Sex distributions were close to each other (female: 33, male: 32). In terms of clinical features, most of the probands (29/65) were analyzed for neurological symptoms. Others applied to our unit for different complaints related to gastrointestinal (8), multiple (6), metabolic (4), skeleton (4), muscular (3), mitochondrial (3), immune (3), endocrine (2), cardiovascular (1), respiratory (1), and genitourinary (1) systems. There was consanguinity between the parents of 38 individuals, and 16 of them had a positive family history. Three of the remaining 27 individuals had a positive family history. Thirty different variants, mostly homozygous, explaining the clinical features, were detected in 27 patients.

Table 1. Demographic/clinical characteristics and identified variants in the study patients.

ID	Sex	Age[10,11]	Clinical Findings (Pre-diagnosis)	Gene (Transcript)	cDNA (Protein)	Type	Zygosity	R/N[1]	ACMG[2]	gnomAD[3]	Inherited from	OMIM[4]	C[5]	Family History	IP[6]
3	F[7]	8m	Cholestasis	*ABCB11* (NM_003742)	c.2448+1G>A	Splicing	Homozygous	N	P[12]	0	parents	Cholestasis, progressive familial intrahepatic 2 (MIM: 601847)	Yes	No	AR[16]
4	F	28y	Spastic gait, urinary incontinence, keratoconus	*SPG11* NM_001160227	c.200_203delCTTT (p.Ser67Ter)	Nonsense	Homozygous	N	P	2:216.866	parents	Spastic paraplegia 11, autosomal recessive (MIM: 604360)	Yes	Yes	AR
5	M[8]	15y 7m	Mental retardation, seizures, ataxia	*GAMT* NM_138924	c.327G>A (p.Lys109=)	Synonymous	Homozygous	Stöckler S, et al. (1996) Am J Hum Genet, volume:58, issue:5			parents	Cerebral creatine deficiency syndrome 2 (MIM: 612736)	Yes	Yes	AR
7	M	7y 5m	Progressive liver failure	*HSD3B7* (NM_025193)	c.45_46delAG (p.Gly17LeufsTer26)	Frameshift	Homozygous	Molho-Pessach V, et al. (2012) Hepatology, volume:55, issue:4			parents	Bile acid synthesis defect, congenital, 1 (MIM: 607765)	Yes	Yes	AR
11	F	12y 10m	Progressive encephalopathy, sensorineural hearing loss	*SUCLA2* (NM_003850)	c.751G>A (p.Asp251Asn)	Missense	Homozygous	Jaberi E, et al. (2013) J Hum Genet, volume:58, issue:8			parents	Mitochondrial DNA depletion syndrome 5 (MIM: 612073)	Yes	No	AR
12	F	5y	Microcephaly, progressive vision loss, hypotonia, irritability, cerebral atrophy	*PPT1* (NM_000310)	c.538dupC (p.Leu180ProfsTer9)	Frameshift	Homozygous	Kousi M, et al. (2012) Hum Mutat, volume:33, issue:1			parents	Ceroid lipofuscinosis, neuronal, 1 (MIM: 256730)	Yes	No	AR
16	M	6y 9m	Intellectual disability	*SHROOM4* (NM_020717)	c.3012C>A (p.Cys1004Ter)	Nonsense	Hemizygous	N	P	0	mother	Stocco dos Santos X-linked mental retardation syndrome (MIM: 300434)	No	No	XL[17]
17	F	11m	Hypotonia, hydrocephalus, lack of psychomotor development, corneal opacity, febrile convulsion, increased serum creatine kinase	*POMGNT2* (NM_032806)	c.791T>G (p.Ile264Ser)	Missense	Homozygous	N	UCS[14]	0	parents	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies, type A, 8) (MIM: 614830)	Yes	No	AR
19	M	3y 1m	Severe delayed psychomotor development, dysmorphism, operated for cleft palate	*PGAP3* (NM_033419)	c.496-39_498del (?)	Splice junction loss	Homozygous	N	P	0	parents	Hyperphosphatasia with mental retardation syndrome 4 (MIM: 615716)	Yes	No	AR
20	M	11y 7m	Feeding difficulties, rigidity, hypertonicity	*SLC6A3* (NM_001044)	c.1234T>G (p.Phe412Val)	Missense	Homozygous	N	UCS	0	parents	Parkinsonism-dystonia, infantile, 1 (MIM: 613135)	Yes	No	AR
22	F	11y 5m	Generalized hypotonia, muscle weakness, ptosis	*CHAT* (NM_001142934)	c.761T>C (p.Ile254Thr)	Missense	Homozygous	Kraner S, et al. (2003) Arc Neurol, volume:60, issue:5			parents	Myasthenic syndrome, congenital, 6, presynaptic (MIM: 254210)	Yes	Yes	AR
23	M	NB[9]	Hyperammonemia	*PCCA* (NM_000282)	c.1746+4A>G (?)	Splicing	Homozygous	N	UCS	0	parents	Propionic acidemia (MIM: 606054)	Yes	No	AR
25	M	9m	Cholestasis	*SCYL1* (NM_001048218)	c.460G>T (p.Glu154Ter)	Nonsense	Heterozygous	N	P	0	mother	Spinocerebellar ataxia, autosomal recessive 21 (MIM: 616719)	No	No	AR
					c.1577C>A (p.Ala526Asp)	Missense	Heterozygous	N	UCS	0	father				

28	F	1y 9m	Developmental and psychomotor delay	*GPR56* (NM_001145770)	c.898C>T (p.Gln300Ter)	Nonsense	Homozygous	N	P	0	parents	Polymicrogyria, bilateral frontoparietal (MIM: 606854)	Yes	No	AR
29	M	1y 5m	Febrile convulsion, oculomotor apraxia, polydactyly, syndactyly, global developmental delay, molar tooth sign (Joubert Syndrome)	*CPLANE1* (NM_023073)	c.3821G>T (p.Arg1274Ile)	Missense	Homozygous	N	UCS	0	parents	Joubert syndrome 17 (MIM: 614615)	Yes	No	AR
30	F	9y	Intellectual disability	*SON* (NM_001291411)	c.4895_4898delTAAC (p.Thr1633LeufsTer9)	Frameshift	Heterozygous	N	P	0	de novo	ZTTK[19] syndrome (MIM: 617140)	No	No	AD[15]
32	F	6m	Neonatal hypotonia	*AP4M1* (NM_004722)	c.1012C>T (p.Arg338Ter)	Nonsense	Homozygous	Tuysuz B, et al. (2014) Am J Med Genet A, volume:164A, issue:7			parents	Spastic paraplegia 50, autosomal recessive (MIM: 612950)	Yes	No	AR
34	M	39y	Paraparesis, ataxia	*GJB1* (NM_001097642)	c.271G>A (p.Val91Met)	Missense	Hemizygous	Bone LJ, et al. (1995) Neurology, volume:45, issue:10			mother	Charcot-Marie-Tooth neuropathy, X-linked dominant, 1 (MIM: 302800)	No	Yes	XLD[18]
35	F	4y 5m	Dystonia, loss of ambulation, basal ganglia abnormalities	*MECR* (NM_001024732)	c.772C>T (p.Arg258Trp)	Missense	Heterozygous	Heimer G, et al. (2016) Am J Hum Genet, volume:99, issue:6			father	Dystonia, childhood-onset, with optic atrophy and basal ganglia abnormalities (MIM: 617282)	No	No	AR
					c.1009C>T (p.Arg337Ter)	Nonsense	Heterozygous	N	P	3:250.898	mother				
39	M	39y	Proximal muscle weakness, difficulty walking, wheelchair dependent	*DYSF* (NM_001130976)	c.1622G>C (p.Arg541Pro)	Missense	Homozygous	N	LP[13]	0	parents	Muscular dystrophy, limb-girdle, autosomal recessive 2 (MIM: 253601)	Yes	Yes	AR
40	F	39y	Muscle weakness, wheelchair dependent	*TCAP* (NM_003673)	c.75G>A (p.Trp25Ter)	Nonsense	Homozygous	Chamova T, et al. (2018) Neuromuscul Disord, volume:28, issue:8			parents	Muscular dystrophy, limb-girdle, autosomal recessive 7 (MIM: 601954)	Yes	Yes	AR
42	F	26y	Growth retardation, Alopecia, Gonadal dysfunction,	*ANTXR1* (NM_018153)	c.152+1G>T (?)	Splicing	Homozygous	N	P	0	parents	GAPO syndrome (MIM: 230740)	Yes	No	AR
43	M	6y	Dextrocardia, situs inversus, recurrent respiratory infections	*CCDC151* (NM_145045)	c.703_704insACCTA (p.Ala235AspfsTer5)	Frameshift	Homozygous	N	P	0	parents	Ciliary dyskinesia, primary, 30 (MIM: 616037)	Yes	No	AR
44	F	3m	Protein losing enteropathy	*PLVAP* (NM_031310)	c.339dupT (p.Ala114CysfsTer9)	Frameshift	Homozygous	N	P	0	parents	Diarrhea 10, protein-losing enteropathy type (MIM: 618183)	Yes	No	AR
46	F	NB	Short stature, midface hypoplasia, anal atresia	*HSPA9* (NM_004434)	c.376C>T (p.Arg126Trp)	Missense	Homozygous	Royer-Bertrand B, et al. (2015) Sci Rep, volume:5 article:17154			parents	Even Plus Syndrome (MIM: 616854)	Yes	Yes	AR
55	M	1m	Hypotonia, increased serum creatine kinase, cerebellar atrophy, patent foramen ovale, epilepsy, feeding difficulties	*GMPPB* (NM_013334)	c.316G>C (p.Val106Leu)	Missense	Heterozygous	N	UCS	0	father	Muscular dystrophy-dystroglycanopathy, type A, 14 (MIM: 615350)	No	Yes	AR
					c.1162T>G (p.Ter388Gly)	Stop loss	Heterozygous	N	UCS	0	mother				
56	F	14y 6m	Aplasia cutis congenita of the scalp, dysmorphism, psychomotor retardation (Adams Oliver Syndrome)	*DOCK6* (NM_020812)	c.1963G>A (p.Gly655Ser)	Missense	Homozygous	N	UCS	0	parents	Adams-Oliver syndrome 2 (MIM: 614219)	Yes	Yes	AR

1R/N: reported/novel; 2ACMG: American College of Medical Genetics and Genomics; 3gnomAD, Genome Aggregation Database; 4OMIM, Online Mendelian Inheritance in Man; 5C, consanguinity; 6IP, inheritance pattern; 7F, female; 8M, male; 9NB, newborn; 10y, year; 11m, month; 12P, pathogenic; 13LP, likely pathogenic; 14UCS, uncertain significance; 15AD, autosomal dominant; 16AR, autosomal recessive; 17XL, X-linked; 18XLD, X-linked dominant; 19ZTTK, Zhu-Tokita-Takenouchi-Kim.
Note: The classification of novel variants according to the ACMG and their frequencies in gnomAD are given. Reference publications have been listed for the reported variants.

4. Discussion

In the current study, WES results of patients who were consulted at our center from different units are presented. In 27 of 65 probands, we identified 30 different variations in known disease genes in the Online Mendelian Inheritance in Man (OMIM; https://www.omim.org/) database. Although it varies between studies, the diagnostic rate of WES is approximately 25–30 % (Bhatia et al., 2021). In our study group, the diagnostic rate was 41.5 %. Although we predicted their diagnosis, some patients were tested with WES since their genetic etiologies are quite heterogeneous. Because for these patients, the study of candidate genes sequentially or as a panel would increase the cost and cause a waste of time. Therefore, we think that our diagnosis rate is higher than reported in other studies.

In a study of 213 cases, the rate of novel variants was reported to be 69.5 % (Nair et al., 2018). In another study including 200 patients, this rate was found to be 66.9 % (Jalkh et al., 2019). Twenty of the detected variants have not previously been reported in the literature. Our rate of novel variants was 66.7 % and compatible with the literature. This study has shown us that the variants detected at the time of diagnosis in NGS-based applications such as WES which gives us a broad perspective compared to other techniques are likely to be novel.

Most of our cases showed a recessive inheritance pattern. In societies where consanguineous marriages are common, it is known that the frequency of homozygosity is high (Monies et al., 2017). In the light of this information, 24 of the diseases detected in our 27 probands were autosomal recessive, and 21 of them were homozygous for the variants identified in associated recessive disease genes.

WES is an appropriate NGS test for individuals or families whose etiology is thought to have a possible monogenic disorder (Ormondroyd et al., 2017). In our study, carried out in parallel with this aim, very rare diseases were diagnosed. In fact, the syndromes associated with genetic disorders detected in cases 44 and 35 have only been reported as case studies in the literature. Therefore, these cases have been previously contributed to the literature (Gorukmez et al., 2019; Gorukmez et al., 2019). In addition to these patients, we found pathogenic variants in the *SHROOM4* and *SON* genes, which are associated with Stocco dos Santos X-linked mental retardation syndrome and Zhu-Tokita-Takenouchi-Kim syndrome, respectively, which are extremely rare in the literature. Although the diseases observed in 26 individuals evaluated in our study were induced by Mendelian inheritance, a 9-year-old female patient carrying a pathogenic variant of the *SON* gene was sporadic, and this was the only case of a *de novo* pathogenic variant. Another rare occurrence that causes symptoms in independent systems is *SCYL1* gene mutation. Biallelic mutations in the *SCYL1* gene, under the title of spinocerebellar ataxia in OMIM, also cause hepatic problems and skeletal anomalies. This gene is also listed among the familial causes of intrahepatic cholestasis in current publications (Li et al., 2021). Compound heterozygous changes in the *SCYL1* gene were found in a 9-month-old male patient with cholestatic liver disease findings. It should be noted that in defects of this gene whose molecular pathogenesis is unclear, extrahepatic findings will emerge at a later period; therefore, our patient will need to be followed up for a long time (McNiven et al., 2021).

An interesting situation was that individuals 39 and 40 were married. Despite their kinship, both were wheelchair-dependent because of pathologies in different genes. Their situation became clear through WES analysis and family studies.

In this study, based on the variants detected in patients, we had the opportunity to diagnose other family members who were not evaluated earlier and showed similar characteristics to their

probands. This shows the importance of family screening, along with segregation analysis. Thus, while clarifying our definition, we simultaneously identified other sick individuals. This was also an important element in detailed genetic counseling.

5. Conclusion

Finding the cause of the disease using tests that provide high-level data on the human genome, such as WES, can be expressed as "looking for a needle in a haystack" which is frequently used worldwide. Clinical and laboratory findings, segregation and family studies, multidisciplinary approaches, and functional studies are the most important approaches to facilitate this process (Manolio et al., 2013; Bowdin et al., 2015). In particular, rare syndromes and the presentation of data related to them will shed light on future studies. Hence, in this study, we presented variants of 27 different genes that cause rare diseases.

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Ethics

Ethics Committee Approval: The study was approved by Bursa Yüksek İhtisas Training and Research Hospital Ethical Committee (Number: 2011-KAEK-25 2019/08-01, Date: 07.08.2019).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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Research Article / Araştırma Makalesi

Antioxidative Effects of Silymarin in A Neonatal Rat Model of Necrotizing Enterocolitis

Nekrotizan Enterokolitli Yenidoğan Rat Modelinde Silimarinin Antioksidan Etkileri

[1]Emine Esin Yalınbaş, [2]Raziye Akçılar, [3]Havva Koçak, [4]Murat Soner Çirkinoğlu, [5]Mehmet Hüseyin Metineren, [6]Harun Kaçar

[1]Department of Neonatology, Eskisehir City Hospital, Eskisehir, Turkiye

[2]Department of Physiology, Faculty of Medicine, Kutahya University of Health Sciences, Kutahya, Turkiye

[3]Department of Biochemistry, Faculty of Medicine, Kutahya University of Health Sciences, Kutahya, Turkiye

[4]Department of Child Health and Diseases, Ataturk City Hospital, Balikesir, Turkiye

[5]Department of Pathology, Faculty of Medicine, Kutahya University of Health Sciences, Kutahya, Turkiye

[6]Department of Child Health and Diseases, Darica Farabi Training and Research Hospital, Kocaeli, Turkiye

Abstract

Necrotizing enterocolitis (NEC) is the most common gastrointestinal problem in premature infants. The aim of this study is to evaluate the protective and antioxidant effects of silymarin (SLY) in newborn rats with NEC model. Twenty-eight Sprague-Dawley rats were included in the study. The rats were randomized into four groups: control (C), C+SLY, NEC and NEC+SLY. NEC was induced by hyperosmolar enteral formula feeding, and the pups were exposed to hypoxia and cold stress. Macroscopic scoring of the intestinal tissue was evaluated and tissue samples were obtained for biochemical, histopathological examination. Superoxide dismutase (SOD), glutathione peroxidase (GPx), nitric oxide (NO), malondialdehyde (MDA), total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) levels were biochemically evaluated. Results: In the NEC + SLY group, there was a considerable rise in tissue TAS ($p = 0.007$), SOD ($p = 0.004$) and GPx levels, as well as a decrease in NO levels. Significantly higher tissue MDA, TOS ($p = 0.001$) and OSI ($p = 0.001$) values were detected in the NEC group. The intestinal tissue of rats in the NEC + SLY group had better histopathology than rats in the NEC group when evaluated. Silymarin has beneficial effects against NEC in neonatal rat. It appears that SLY reduces free radical levels and oxidative stress, increases antioxidant capacity, and ameliorates the severity of intestinal damage due to NEC

Keywords: Necrotizing enterocolitis; Silymarin; Neonatal rats; Oxidative stress

Özet

Nekrotizan enterokolit (NEK), prematüre bebeklerde en sık görülen gastrointestinal problemdir. Bu çalışmanın amacı, NEK modeli oluşturulan yenidoğan sıçanlarda silimarin (SLY)'nin koruyucu ve antioksidan etkilerini değerlendirmektir. Yirmi sekiz Sprague-Dawley sıçanı çalışmaya dahil edildi. Sıçanlar rastgele dört gruba ayrıldı: kontrol (C), C+SLY, NEK ve NEK+SLY. NEK, hiperosmolar enteral formül beslenmesi ile indüklendi, yavru sıçanlar hipoksi ve soğuk stresine maruz bırakıldı. Bağırsak dokusunun makroskopik skorlaması değerlendirildi ve biyokimyasal, histopatolojik inceleme için doku örnekleri alındı. Süperoksit dismutaz (SOD), glutatyon peroksidaz (GPx), nitrik oksit (NO), malondialdehit (MDA), total antioksidan status (TAS), total oksidan status (TOS) ve oksidatif stres indeksi (OSI) düzeyleri biyokimyasal olarak değerlendirildi. NEK+SLY grubunda doku TAS ($p = 0,007$), SOD ($p = 0,004$) ve GPx düzeylerinde önemli artış ve NO düzeylerinde azalma vardı. NEK grubunda doku MDA, TOS ($p = 0,001$) ve OSI ($p = 0,001$) değerleri anlamlı derecede yüksek saptandı. NEK + SLY grubundaki sıçanların bağırsak dokusu, değerlendirildiğinde NEC grubundaki sıçanlardan daha iyi histopatolojiye sahipti. Silimarin, neonatal sıçanlarda NEK'e karşı faydalı etkilere sahiptir. SLY'nin serbest radikal düzeylerini ve oksidatif stresi azalttığı, antioksidan kapasiteyi arttırdığı ve NEK'e bağlı bağırsak hasarının şiddetini iyileştirdiği görülmektedir.

Anahtar Kelimeler: Nekrotizan enterokolit; Silimarin; Neonatal rat; Oksidatif stres

Correspondence:
Emine Esin YALINBAŞ
Department of Neonatology, Eskisehir City Hospital, Eskisehir, Turkey
e-mail: esinylnbs@gmail.com

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1. Introduction

Necrotizing enterocolitis (NEC) is a potentially fatal gastrointestinal disease that often affects premature newborns or extremely low birth weight infants (1). Malnutrition, bloating, reduced activity, blood in the stool, bile vomiting, multiple organ failure, and even death are all possible symptoms (2). Prematurity, immature intestinal barrier function, formula feeding, pathological bacterial colonization, intestinal ischemia-reperfusion injury due to hypoxia, free oxygen radicals formed in the environment as a result of infection and inflammation play an important role in the development of NEC (3,4). Silymarin (SLY) is derived from the milk thistle, silybum marianum, and has been used to treat liver illness for centuries, while it has also been researched for its therapeutic effects on cardioprotection, neuroprotection, metabolic disease progression, and cancer (5-9). Silymarin is reported to have potent antioxidant, anti-inflammatory, antiapoptotic, immunomodulatory, antifibrotic, anticancer, and antiviral effects (10,11). The effects and roles of SLY on NEC are unknown, although it is an established modality in the treatment of a variety of illnesses. As a result, the goal of our research was to see how SLY affected intestinal damage in a rat model of NEC.

2. Materials and Methods

Animals and Experimental Conditions The study was confirmed by the Ethics Committee for Animal Care and Usage at Dumlupınar University, Kütahya, Turkey. A total of 28 newborn Sprague-Dawley (SD) rats (5–6 g; ages 1–8 hours) were obtained from pregnant SD rats on day 21 of gestation. Rats were kept in a 12-hour light-dark cycle at 30°C and 60% humidity. Experimental Design; twenty eight SD neonatal rats were randomly divided into control (C), C+SLY, NEC, and NEC+SLY groups (n = 7). Three times a day, newborn rats were given 0.2 mL of a customized rodent formula (15g Similac60/40; Ross Pediatrics, Columbus, OH) mixed with 75 mL of puppy-canine milk replacement (Beaphar-Bogena, BV, Sedel, Netherlands). Experimental NEC was induced by hypoxia in an airtight chamber perfused with 100% CO_2 for 5 min. By the end of this period, the puppies were cyanotic and gasping. The rat pups were reoxygenated for 10 minutes with 100 percent O_2 and exposed to +4 C cold for 5 minutes twice daily for 4 days after hypoxia (12). The control rats were fed breast milk on a regular basis with no stimulation or intervention. SLY was given to the rats in the C+SLY and NEC+SLY groups at a dose of 100 mg/kg intraperitoneally once a day for four days. Tissue Preparation, on the fourth day of the experiment, all of the rats were sacrificed. Each rats abdomen was opened and the gastrointestinal tissues (3 cm intestinal resection, including the terminal ileum and cecum) were removed. After that, the samples were frozen in liquid nitrogen for biochemical examination and stored at -80°C until the results were available. A histopathological examination was also performed. The intestines were inspected for findings of consistency, color and dilatation related to NEC. Biochemical Analysis 0.1 g of intestinal tissue samples were weighed and 1 ml of 0.1 M pH: 7.4 phosphate buffer was added and homogenized using the Next Advance Bullet Blender Storm BBY24MCE (Next Advance, Inc., Averill Park, NY, USA) brand homogenizer and Next Advance brand zirconium oxide beads. Then the supernatant was separated by centrifuging the homogenates at 10,000 g for 15 min. and it was stored at -80°C until evaluation. Tissue protein was measured using a Protein Quantification Kit-Rapid (Sigma-Aldrich Chemie, Buchs/Switzerland). The results were given in µg/ml. Determination of SOD, MDA, NO and GPx activity. Tissue SOD, MDA and NO levels were measured using a superoxide dismutase, TBARS Assay Kit and Nitrate/Nitrite Colorimetric Measurement Kit (Cayman Chemical, Ann Arbor, Michigan, USA). The SOD, MDA and NO activity were calculated as U/mg protein, µmol/g protein and µmol/g protein, respectively. GPx measurement was performed with a glutathione peroxidase measurement kit (Sunred Biological Technology Co. Ltd., Shanghai, China). GPx activity were given in ng/mg protein. Absorbance levels were measured with a ChemWell® 2910 ELISA reader (AwarenessTechnology Inc. Martin Hwy. Palm City, USA). Determination of TAS, TOS and OSI Tissue TAS level was

measured using Rel Assay Diagnostics Total Antioxidant Status Assay Kit and tissue TOS level was measured using a Total Oxidant Status Assay Kit (Rel Assay Diagnostics, Mega Tıp San. ve Tic. Ltd. Sti., Sahinbey/Gaziantep/Turkey). TAS levels were calculated as mmol Trolox Equiv./g protein, and TOS levels as µmol H_2O_2 Equiv./g protein (13,14). Using the TAS and TOS data, the oxidative stress index (OSI=[(TOS/TAS)100]) was calculated. Histopathological Evaluation; For the macroscopic diagnosis of NEC, all tissues were examined for signs of discoloration, edema, deterioration of tissue integrity, ileal distension, bleeding, perforation and necrosis. 3 cm long ileum segment was taken from the ileocecal valve at a distance of 1 cm. It was washed with cold saline solution and fixed in a 10% formaldehyde solution at room temperature in a paraffin block. The 5 µm sections were stained with hematoxylin and eosin (H&E) and examined with a light microscope (Olympus BX51, Tokyo, Japan, 2000). The evaluation was carried out by a pathologist who did not know the characteristics of the groups to be objective. Changes in the intestines were graded on a scale of 0 to 4 in the histological evaluation: Grade 0 (normal): normal tissue structure, intact intestinal mucosa, Grade 1 (mild): little submucosa and lamina propria separation, Grade 2 (moderate): increased submucosa and lamina propria, submucosa and lamina propria separation, edema in the submucosa and muscle layers, Grade 3 (severe): severe submucosa and lamina propria separation, severe muscle and submucosa edema, local villi detachment, and Grade 4 (necrosis): villi structural loss and necrosis. A histological score of 2 or more was considered to be NEC.

Statistical Analysis

The SPSS® Statistics 16 pocket application was used for statistical analysis (Chicago, IL, USA). All of the results were presented as mean ± standard error. Multiple groups were compared using the Kruskal-Wallis test. To compare two groups, the Mann-Whitney U test was utilized. $p \leq 0.05$ were accepted as statistically significant.

3. Results

Silymarin increases SOD and GPx activity levels in the intestinal tissues Tissue SOD levels were found to be statistically significantly different among C (3.46 ± 0.32 U/mg protein), C+SLY (3.71 ± 0.48 U/mg protein), NEC (2.49 ± 0.17 U/mg protein) and NEC+SLY (3.49 ± 0.22 U/mg protein) ($p = 0.011$). The NEC group had a significantly lower tissue SOD levels than the C, C+SLY, and NEC+SLY groups ($p = 0.009$, $p = 0.013$, and $p = 0.004$, respectively) (Figure 1). The differences in the GPx levels in the intestinal tissue among the C (34.0 ± 2.68 ng/mg protein), C+SLY (37.0 ± 6.26 ng/mg protein), NEC (22.7 ± 4.31 ng/mg protein) and NEC+SLY (45.3 ± 4.01 ng/mg protein) groups were significant ($p = 0.016$). The NEC+SLY group had significantly greater GPx levels than the C and NEC groups, which were $p = 0.025$ and $p = 0.004$, respectively (Figure 1). Silymarin arranges NO levels in the intestinal tissues Tissue NO levels differed considerably among the groups of C (1.81 ± 0.68 µmol/g protein), C+SLY (0.72 ± 0.27 µmol/g protein), NEC (2.55 ± 0.96 µmol/g protein) and NEC+SLY (0.70 ± 0.26 µmol/g protein), ($p = 0.05$). The NEC group had considerably greater tissue NO levels than the C + SLY and NEC+SLY groups ($p = 0.025$, and $p = 0.003$ respectively) (Figure 1). Silymarin decreases MDA activity levels in the intestinal tissues There were notable differences in the intestinal tissue MDA levels among C (3.08 ± 0.21 µmol/g protein), C+SLY (2.21 ± 0.22 µmol/g protein), NEC (4.45 ± 1.64 µmol/g protein) and NEC+SLY (2.09 ± 0.16 µmol/g protein), ($p = 0.023$). MDA levels were substantially lower in the C + SLY group than in the C group, which was $p = 0.025$. In addition, when compared to the C and NEC groups, MDA levels in the NEC+SLY group were dramatically reduced, $p = 0.013$ and $p = 0.035$ (Figure 1). Silymarin increases TAS level and decreases TOS and OSI in the intestinal tissues Tissue TAS levels showed statistically significant variations among the groups of C, C+SLY, NEC, and NEC+SLY ($p = 0.007$). Tissue TAS levels in the NEC group were found to be considerably lower than in the C and C+SLY groups (p =

0.025 and p = 0.002). Furthermore, when comparing the NEC+SLY group to the NEC group, the TAS levels were found to be significantly higher in the NEC + SLY group, p = 0.030 (Table 1). The levels of tissue TOS and OSI showed significant disparities among the groups of C, C+SLY, NEC, and NEC+SLY (p = 0.001 and p = 0.001). The NEC group showed a considerable increase in tissue TOS and OSI levels as compared to the C, C+SLY, and NEC+SLY groups (p = 0.002, respectively) (Table 1). Silymarin improves inflammatory conditions of intestinal tissues H&E staining was used to grade the inflammatory states of each group's intestinal tissues. The NEC group had epithelial cell swelling, fragility intestinal edema, discolouration, and weakness of tissue integrity, loss of villi, and a decrease in goblet cells, according to histological evaluation. Figure 2 shows the damage scores and comparisons between the groups. When comparing the NEC+SLY group to the NEC group, the results showed that the NEC+SLY group had less intestinal inflammation.

Table 1. The total antioxidant-oxidant status and oxidative stress index values of the tissues

Groups	C (n=7)	C + SLY (n=7)	NEC (n=7)	NEC + SLY (n=7)	p
TAS	0.94 ±0.17[a]	1.07 ± 0.16[b]	0.44 ±0.03[abc]	0.72 ± 0.03[c]	0.007
TOS	1.67 ± 0.07[a]	1.64 ±0.10[b]	3.04 ±0.37[abc]	1.48 ± 0.07[c]	0.001
OSI	0.22 ± 0.04[a]	0.17 ± 0.03[b]	0.69 ± 0.06[abc]	0.25 ± 0.03[c]	0.001

p: Shows the differences between all groups (Kruskal Wallis test).
a,b,c; In each line, the difference between the means with same letters are significant, p≤0.05 (Mann-Whitney U test).
C – control; C - SLY – control -silymarin; NEC – necrotizing enterocolitis; NEC - SLY – necrotizing enterocolitis -silymarin; TAS – total antioxidant status; TOS – total oxidant status; OSI – oxidative stress index

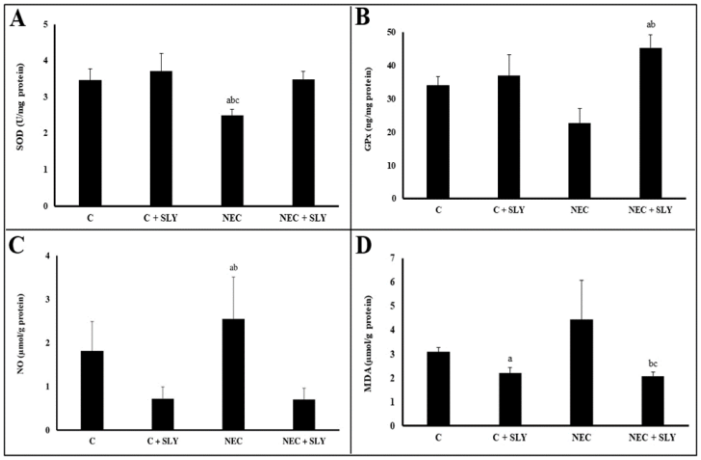
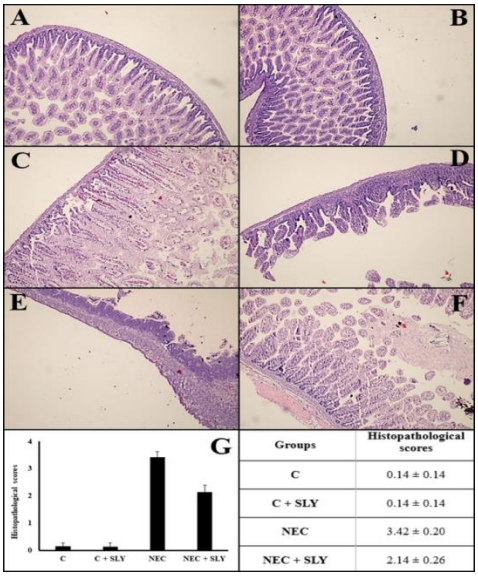


Figure 1. SOD, GPx, NO, MDA activity levels in the intestinal tissue of rats in Control (C), control + silymarin (C + SLY), necrotizing enterocolitis (NEC), necrotizing enterocolitis + silymarin (NEC + SLY) groups.

(A): [a]; Shows significance between C and NEC groups, [b]; Shows significance between C + SLY and NEC groups,
[c]; Shows significance between NEC and NEC + SLY groups (p≤0.05) (Mann Whitney U test).
(B): [a]; Shows significance between C and NEC + SLY groups, [b]; Shows significance between NEC and NEC + SLY groups (p≤0.05) (Mann Whitney U test).
(C): [a;] Shows significance between C + SLY and NEC groups (p≤0.05) (Mann Whitney U test), [b;] Shows significance between NEC and NEC + SLY groups (p≤0.05) (Mann Whitney U test).
(D): [a]; Shows significance between C and C + SLY groups, [b]; Shows significance between C and NEC + SLY groups, [c]; Shows significance between NEC and NEC + SLY groups (p≤0.05) (Mann Whitney U test).
Superoxide dismutase (SOD), Glutathion Peroxidase (GPx), Nitric Oxide (NO), Malondialdehyde (MDA)



Groups	Histopathological scores
C	0.14 ± 0.14
C + SLY	0.14 ± 0.14
NEC	3.42 ± 0.20
NEC + SLY	2.14 ± 0.26

Figure 2. Hematoxylin and eosin stained sections of intestinal tissue harvested from in Control (C), control + silymarin (C + SLY), necrotizing enterocolitis (NEC), necrotizing enterocolitis + silymarin (NEC + SLY) groups.
(A): C group, and (B): C + SLY group; Normal tissue morphology, intact intestinal mucosa and no muscular edema detected (H&E x 100). (C) (D) (E): NEC group; epithelial cell swelling, intestinal edema, discoloration, fragility and weakness of tissue integrity, loss of villi and decrease in goblet cells were detected (H&E x 100).
(F): NEC + SLY group; cell epithelium villus loss, cellular swelling, goblet cell loss were not detected (H&E x 100). (G): The histological scores of groups was statistically analyzed.

3. Discussion

NEC is particularly prevalent in premature infants. In NEC, apoptosis and necrosis form in the tissue mainly due to intestinal motility loss, mucosal integrity impairment and inflammation (15). Many agents used to treat NEC have unproven efficiency and their use is controversial. Thus, research is still required to find safe and efficient NEC-preventive treatment methods (16, 17). The goal of this study was to see if SLY has an influence on the symptoms of necrotizing enterocolitis rats. The effects of SLY in a rat model of NEC are being investigated for the first time, according to our findings. It's probable that oxidative stress contributes to the onset of NEC. The antioxidant enzyme activity of tissue SOD, GPx, and TAS was greatly reduced, whereas tissue MDA, NO, TOS and OSI concentrations with oxidative effect were significantly raised in the NEC. According to Guven et al. MDA and NO levels in the intestinal tissue of rats with NEC were higher, although SOD and GPx levels were lower (12). NO metabolism is increased in some animal models of NEC (18, 19). Enterocyte apoptosis is caused by nitric oxide, which is created by inducible NO synthase (iNOS) and reactive NO oxidation, and inhibits enterocyte proliferation and migration resulting in the intestinal barrier being ruptured (20, 21). Aydemir et al. reported that TOS levels increased, but TAS levels did not change (22). In another study, Yazıcı et al. they found no difference in TAS levels between NEC and control groups (23). In another study by Tayman et al. shown that, the TAS has been reported as decreased (24). The TOS and OSI levels were significantly higher in the NEC group, whereas the TAS level was significantly lower, according to Akduman et al. these findings were in line with prior studies had shown that the development and etiology of NEC are linked to oxidative stress (25). Silymarin has shown anti-inflammatory, antioxidative and immunomodulatory effects against diseases in various animal models (26, 27). The antioxidant effect of silymarin is thought to be due to directly removing the formed free radicals from the environment and inhibiting

specific enzymes responsible for free radical production. SLY has been tested in several experimental models and found to protect cells from reactive oxygen radical damage and strengthen cellular antioxidant systems (28, 29). Some studies have shown the antioxidant characteristic of SLY to be responsible for its protective effects on tissue (30, 31). We discovered that SLY reduced oxidative stress in NEC pups intestines by raising TAS, SOD and Gpx levels while decreasing TOS, OSI, MDA and NO levels. Although the effects of silymarin on different diseases have been shown in various studies, its effect on NEC is unknown. Therefore, we are not able to compare our results. In an animal study, Jouhari et al. reported that silymarin as an antioxidant agent, significantly reduced the size and histopathological scores of endometriotic lesions and increased serum TAS levels (32). Ghaznavi et al. demonstrated that SLY and melatonin significantly lowered the elevated renal reactive oxygen species and MDA levels, and enhanced renal glutathione level and SOD activity in rats with gentamicin-induced nephrotoxicity (33). Mazhari et al. found that SLY increased in testicular TAS, SOD and GPx levels and decreased in cyclo-oxygenase-2 (COX2) expression NO and MDA contents in experimental varicocele induced pathogenesis (34). We concluded that the antioxidant effect of SLY in newborn rats who developed NEC due to hypoxia and hypothermia may be effective in decreasing TOS, OSI, MDA, NO levels and increasing TAS, SOD, GPx levels in the intestinal tissue.

4. Conclusion

In conclusion it was determined that SLY could be beneficial in the treatment of NEC. This effect was thought to be associated with reduced intestinal tissue damage in rats with NEC, as demonstrated in both histopathological and biochemical parameters. SLY could be considered a new candidate for treatment of intestinal injury due to including increased antioxidant enzyme activities, decreased oxidative stress. SLY should clearly be considered as an alternative option for NEC treatment. However, more studies are needed to evaluate its positively affect

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Ethics

Ethics Committee Approval: The study was approved by Animal Care and Usage at Dumlupınar University Kutahya Ethical Committee (Number: 2020.11.03, Date: 26.11.2020).

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Research Article / Araştırma Makalesi

Incest Cases Evaluated at Eskisehir Osmangazi University Medical Faculty, Department of Forensic Medicine Between 2015-2019

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Ana Bilim Dalına 2015 İle 2019 Yılları Arasında Başvuran Ensest Vakalarının Adli Tıbbi Değerlendirilmesi

Yesim Yetiş, Tuğrul Kılıboz, Ayhan Güneş, Beycan Doğan, Ali Deniz Erbil, Kenan Karbeyaz

Department of Forensic Medicine, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkiye

Abstract

Incest is traditionally defined as the relationship between family members who are related . In this study, incest cases for which a forensic report was requested from Eskişehir Osmangazi University Faculty of Medicine, Department of Forensic Medicine by the judicial authorities in the 5-year period between 2015-2019 were included in the study. The cases were evaluated in terms of age, gender, education and employment status of the victim-defendant, place of residence, relationship between the victim and the accused, the place where the act took place, pregnancy status, the first application period, and the stage of the act. It was determined that 64 of 661 sexual assault cases reported by Eskişehir Osmangazi University Forensic Department between 2015-2019 were incest. It was determined that 9 (14.1%) of the cases were male and 55 (85.9%) were female. It was determined that 17 victims (26.6%) were under the age of 12. Discussion; In the presented study, the characteristics of incest cases reflected in our Forensic Medicine Department were found to be compatible with the literature. It was thought that more articles on incest should be submitted.
Keywords: Incest, Domestıc sexual abuse, Child abuse

Özet

Ensest, geleneksel olarak akrabalığı olan aile bireyleri arasındaki ilişki olarak tanımlanmaktadır. Bu çalışmada, 2015-2019 yılları arasındaki 5 yıllık dönemde adli makamlar tarafından Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Ana Bilim Dalı'ndan adli rapor istenilen ensest olgular çalışma kapsamına alınmıştır. Olgular yaş, cinsiyet, mağdur-sanığın eğitim ve iş durumu, ikamet edilen yer, mağdur sanık arasındaki ilişki, eylemin gerçekleştiği yer, hamilelik durumu, ilk başvuru süresi, eylemin aşaması açısından değerlendirilmiştir. 2015-2019 yılları arasında Eskişehir Osmangazi Üniversitesi Adli Ana Bilim Dalı'nca rapor düzenlenen 661 cinsel saldırı olgusunun 64'ünün ensest olduğu belirlenmiştir. Olguların 9'unun (% 14,1) erkek, 55'inin (% 85,9) kadın olduğu saptanmış olup mağdurların en küçüğünün 8, en büyüğünün 32 yaşında olduğu ve yaş ortalamalarının 15.4±5.1 olduğu belirlenmiştir. 17 mağdurun (% 26,6) ise 12 yaşını doldurmadığı belirlenmiştir. Sunulan çalışmada Adli Tıp Ana Bilim Dalımıza yansıyan ensest olgularının özelliklerinin literatürle uyumlu bulunmuştur. Ensest ile ilgili daha fazla makale sunulması gerektiği düşünülmüştür.
Anahtar Kelimeler: Ensest, Adli tıp, Çocuk cinsel istismar

Correspondence:
Tuğrul KILIBOZ
Department of Forensic Medicine, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkiye
e-mail: tugrulkiliboz@gmail.com

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1. Introduction

Incest is defined by law as sexual activity between family members and people with close blood relation, who are prohibited from marrying (1). Incest covers the actions of the perpetrator, who has a strong emotional connection to the victim or has an authority over the victim, towards sexual urge (2). In paragraph 3 of Article 102 of the Turkish Penal Code, the crime of sexual assault is defined as a qualified form of the crime *"against a person who has a blood or in-law's relationship, including the third degree, or by a stepfather, stepmother, stepbrother, adopter or adoptee."*; therefore, in incest cases, aggressor may be a sibling, father, grandfather, stepfather or grandfather, uncle, uncle (mother side), brother-in-law, cousins etc.

In the literature, incest has often been evaluated within the context of child abuse issues. Incest relationships should be seen as a social problem. It can lead to biological, psychological and social ill-effects on the victim, as well as damage to the family structure, which is the smallest unit of society. Although it is a socially important issue but often overlooked, the World Health Organization (WHO) regards this issue as a silently ongoing health emergency (3).

In 2014, the Ministry of Family, Labor and Social Services' Domestic Violence Against Women Survey reported that 8.9% of women in Turkey had been sexually abused before the age of 15. 15% of these women were sexually abused by family members during their childhood (4).

Incest cases are thought to be higher than reported numbers (5,6). The true prevalence of incest cases is quite difficult to determine. Family members may not cooperate in unfolding incest, which causes the incest-related data to be limited.

Children who are victims of incest experience many physical and mental disorders in both short and long term. These include indifference or over-sensitivity to sexual issues, a decline in school achievement, losing interest in education, feeling of insecurity, sleep problems, communication disorders, suicidal tendencies and dissociative disorders (7-10).

In this study, incest cases reflected in the Department of Forensic Medicine of Eskisehir Osmangazi University Faculty of Medicine were evaluated. It is aimed to share and discuss the forensic medical characteristics of the cases with the literature.

2. Materials and Methods

Incest cases out of sexual assault cases evaluated between 2015 and 2019 in the Department of Forensic Medicine at Eskisehir Osmangazi University Faculty of Medicine were included in the study. The cases in which the defendants were father, stepfather, brother, grandfather, uncle, brother-in-law were evaluated as part of incest. Sexual assault is considered all sexually explicit behaviors in which the body immunity of the victims is sexually violated, as defined in the applicable law.

The study was carried out by retrospective examination of the files in the Department of Forensic Medicine at Eskisehir Osmangazi University Faculty of Medicine. The cases were evaluated in terms of age, gender, stage of incident, victim-defendant's education and work status, place of residence, relationship between the victim and defendant, where the incident took place, pregnancy status, initial application period.

The data were analyzed through the SPSS Package statistics program. $P<0.05$ is considered statistically significant.

The study was carried out with the approval of Eskisehir Osmangazi University Non-Interventional Clinical Research Ethics Committee decision dated 17.12.2019 and numbered 25.

3. Findings

Between 2015 and 2019, 64 (9.7%) of the 661 cases of sexual assault evaluated by Eskisehir Osmangazi University Department of Forensic Science were found to be incest cases. It was determined that 9 (14.1%) of

the cases were male and 55 (85.9%) were female. The youngest of the victims was found to be 8 years old meanwhile the oldest was 32 years old, and their average age was 15.4±5.1. It was determined that 17 victims (26.6%) did not reach the age of 12 at the time of incident. The average age of female victims was 15.9±4.8 and the average age of male victims was 9.2±3.1. It was determined that 44 (68.8%) of the victims were not over the age of 15. It was determined that 8 (88.9%) of the male victims and 9 (16.4%) of the female victims were under the age of 12 (Table 1). There was a significant difference between the age group and the gender. It was determined that 88.9% of male victims were younger than 12 years old. Same rate was determined as 16.4% in female cases (P<0.0001).

Table 1. Distribution of victims' ages by their gender

Gender	Below 12 years old		Over 12 years old		Total	
	n	%	n	%	n	%
Male	8	88,9	1	11,1	9	**100,0**
Female	9	16,4	46	83,6	55	**100,0**
Total	**17**	**26,6**	**47**	**73,4**	**64**	**100,0**

Fisher's Exact Test P< 0,0001

It was determined that 25 (39.1%) of the cases lived in the village or town, while 39 (60.9%) lived in the urban area.

In 44 (68.8%) of cases, it was understood that the action took in the form of penetration. It was determined that 20 cases (31.2%) contained physical contact without penetration. Penetration findings were detected in 38 (69.1%) of the female cases. Isolated vaginal penetration was detected in 32 of the female cases, isolated anal penetration in 2 and vaginal and anal penetration findings were detected in 4. Anal penetration findings were detected in 6 of the male cases. There was no significant difference between penetration status and gender and place of life (Table 2). Physical violence was found in 3 cases (4.7%).

A significant relationship was found between penetration status and age group. While the penetration presence was 17.6% (n=3) in victims under the age of 12, penetration was determined in 87.2% (n=41) of victims over 12 years of age (Table 2, P<0.0001).

Table 2. Distribution of penetration status by gender, age group, place of residence and application period

		Penetration		No Penetration		Total	
		n	%	n	%	n	%
Gender							
Male		6	66,7	3	33,3	9	**100,0**
Female		38	69,1	17	30,9	55	**100,0**
χ 2=0,021	P>0,05						
Age Group							
Below 12 years old		3	17,6	14	82,4	17	**100,0**
Above 12 years old		41	87,2	6	12,8	47	**100,0**
χ^2=28,138	P<0,0001						
Place of Residence							
Rural		19	76,0	6	24,0	25	**100,0**

Urban		25	64,1	14	35,9	39	**100,0**
χ 2=1,004	P>0,05						
Initial application period							
0-10 days		6	26,1	17	73,9	23	**100,0**
After 10 days		38	92,7	3	7,3	41	**100,0**
χ 2=30,416	P<0,0001						

It was determined that 4 (6.3%) of the victims were in their preschool childhood, 40 were students (62.5%), 38 were primary and 2 were high school students (62.5%), and 2 female cases (3.1%) were employed. Two of the female victims were married, and in other cases the victims were found to be single.

None of the cases were reported on the same day. It was determined that 6 cases (9.4%) were reported to the judicial authorities (prosecutor's office, police, gendarmerie) within the first 3 days, 17 cases (26.6%) were reported within 4 to 10 days, 10 cases (15.6%) were reported between 10th and 30th days, 27 cases (42.2%) were reported between 1-12 months and 4 cases (6.3%) were reported 1 year after the incident. In 27 (42.2%) of the cases, it was determined that the incident occurred more than once. It was determined that there were signs of penetration in all of these 27 cases. Of the 27 cases with repeated attacks in their history, it was determined that from the first attack, 3 (11.1%) reported between 10-30 days, 20 (74.1%) between 1-12 months, and 4 (14.8%) more than a year after the incident.

It was determined that 17 of the 23 patients who reported within the first 10 days did not have penetration findings. It was determined that most of the cases (85%, n=17/20) without penetration reported earlier (10 days or earlier). However, it was determined that 86.4% (n=38/44) of the patients with penetration evidences reported later (10 days and later) (Table 2, P<0.0001).

When the proximity between the victim and the accused is evaluated, in 16 (25%) of cases, the defendant was a father, stepfather in 14 cases (21.9%), grandfather in 10 cases (15.6%), brother in 9 cases (14.1%), uncle in 8 cases (12.5%) and uncle (mother side) in 7 cases (10.9%) (Chart 1).

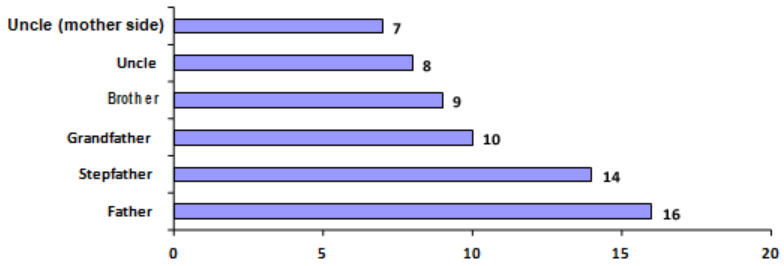

Chart 1. Distribution according to the proximity between victim and defendant

It is understood that 7 women became pregnant as a result of incest. In all 7 cases, it is determined that incest was revealed due to pregnancy. It has been observed that they did not make any official complaints until they became pregnant. In the cases in which victims became pregnant, it was determined that the fathers were defendant in 3 cases, brothers in 2 cases, uncle in 1 case and uncle (mother side) in 1 case were the defendants. In all cases where pregnancy was detected, it was determined that the defendant was revealed by DNA analysis.

All of the defendants were found to be male, the youngest was 17 years old, the oldest was 67 years old and their average age was 32.6±13.5), 33 (51.6%) were single, 21 (32.8%) were married and 10 (15.6%) were found to be widows.

When the educational status of the defendants is examined; It was determined that 50 (78.1%) were primary and 14 (21.9%) were high school graduates. There was no illiterate, college-educated defendants. 11 (17.2%) were unemployed, 6 were retired (9.4%), the remaining 47 (73.4%) all had occupations as farmers (n=19), civil servants (n=13), workers (n=8) and self-employed (n=7).

A total of 23 cases (35.9%) were found to be incapable of defending themselves in terms of physically and mentally, including 17 cases due to being underage and due to mental retardation in 4 cases.

4. Discussion

The actual frequency of incest is very difficult to determine. In this literature, incest cases, which were reflected to the unit where the study was conducted, were presented rather than the frequency of occurrence in the society (5,6). Zonguldak Bulent Ecevit University Faculty of Medicine, Department of Forensic Medicine reported that 39 incest cases were evaluated between 2010 and 2014 (11).

In a study conducted in Hatay, it was reported that 737 cases of sexual assault were evaluated in the Department of Forensic Medicine at Mustafa Kemal University Faculty of Medicine between 2013 and 2016, and 57 (7.7%) of these cases were found out to be incest cases (6). Our study found that 64 (9.7%) of the 661 cases of sexual assault were incest.

In the study presented, it was determined that 73.8% of the defendants were primary school graduates, none of them were college educated, 18.5% (n=12) of the defendants were unemployed, 36.9% (n=24) were farmers and 7.7% (n=5) were self-employed. Similar to our study, although incest cases are seen in families from all socio-economic levels; It has been reported that it is more common in families from low socio-economic backgrounds in the reports made to child protection services.

In this study, the average age of male victims was 8.5±2.7, while those of female victims were 15.3±4.2 and all cases were 14.1±4.7. Similarly, in a study evaluating victims of sexual assault in our country, 51.7% of the cases were between the ages of 11 and 15 (14). Again, a study of 418 cases by Grossin and his colleagues found that the average age of victims of sexual crime was 15.9 years (15). Studies of sexual offences reported that men were mostly subjected to sexual acts at an early age (15,16,17).

Only 3 (4.7%) of the cases in our study had physical findings in general physical examination. Since physical examination findings, which are important in the discovery of sexual abuse, are often undetectable, their diagnostic value is limited. Events can be carried out with different types of sexual behaviors and these actions may not cause a traumatic finding (18,19). Physical findings are more infrequent, especially in incest cases (20).

If the time between the incident and the initial examination is prolonged, it becomes difficult to obtain medical evidence to help clarify the incident. In a study of 275 cases, it was reported that only 1.8% of victims of sexual crime were examined on the same day (20). In another study that evaluated 418 cases of sexual assault, it was reported that 39% of the cases were reported to have been investigated within the first 3 days. In the same study, it was determined that 51% of the cases who reported in the first 3 days and 8% of the victims who reported later were attacked by people they did not know at all (15). In the study presented, it was determined that none of the cases were reported on the same day. It was determined that 6 cases (9.4%) were reported to the judicial authorities (prosecutor's office, police, gendarmerie) within the first 3 days, 17 cases (26.6%) were reported within 4 to

10 days, 10 cases (15.6%) were reported between 10th and 30th days, 27 cases (42.2%) were reported between 1-12 months and 4 cases (6.3%) were reported 1 year after the incident.

In the literature on sexual assault, it has been reported that victims who are generally attacked by people they know have reported to the judiciary later (21,22). It was determined that especially in cases with penetration, the report was made later (23). This situation is attributed to the fact that the concept of virginity is still very important in our country and therefore the victims are afraid after the incident and have difficulty in telling about the incident. In the present study, in accordance with the literature, it was determined that there were no signs of penetration in 17 of 23 cases reported within the first 10 days. It was determined that most of the cases without penetration (85%, n=17/20) reported earlier (10 days and earlier). However, it was determined that 86.4% (n=38/44) of the cases with signs of penetration reported later (10 days and later).

The detection of incest is often coincidental. It may occur as a result of noticing abnormal behaviors in the child, taking the child to the doctor due to a physical injury or genital infection, and unexpected pregnancy (24,25).

In the study, it was understood that 7 women became pregnant as a result of incest. In all 7 cases, it was determined that incest was revealed due to pregnancy. It has been observed that they did not make any complaints until they became pregnant. In the cases in which victims became pregnant, it was determined that the fathers were defendant in 3 cases, brothers in 2 cases, uncle in 1 case and uncle (mother side) in 1 case were the defendants. In all cases where pregnancy was detected, it was determined that the defendant was revealed by DNA analysis.

The findings of our study were found to be consistent with the incest-related literature. The investigation process, which includes the detection of incest and the forensic medical evaluation, is quite challenging. Cross-sectional studies and case reports related to incest will contribute to the understanding of the subject and raise awareness. However, it is thought that multicenter and different disciplines should work together in order to fully understand incest and develop solutions. As with all cases of sexual crime reflected in the forensic units, it is important to provide a multidisciplinary working environment with the relevant branches in the forensic reporting process.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Number: 25, Date: 17.12.2019).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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Research Article / Araştırma Makalesi

Change in the Frequency of Autoimmune Diseases in Children During the COVID-19 Pandemic and Lock-Down Period Compared to the Pre-Pandemic Period

COVID-19 Pandemisi ve Karantina Döneminde Çocuklarda Otoimmün Hastalıkların Sıklığının Pandemi Öncesi Döneme Göre Değişimi

[1]Birgul Kırel, [2]Aslı Kavaz Tufan, [3]Ayse Sulu, [4]Gonca Kılıc Yıldırım, [2]Nuran Çetin, [5]Koray Harmancı, [3]Birsen Uçar, [6]Sabiha Şahin, [1]Enver Şimsek, [7]Kürşat Bora Çarman, [8]Ömer Kılıç, [9]Eren Göçhasanoğlu, [9]Sümeyye Emel Yel, [10]Hülya Ozen, [7]Ersin Yüksel, [1]Can Aydın, [7]Coşkun Yarar

[1]Department of Pediatric Endocrinology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[2]Department of Pediatric Nephrology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[3]Department of Pediatric Cardiology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[4]Department of Pediatric Metabolism and Nutrition, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[5]Department of Pediatric Allergy and Immunology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[6]Department of Pediatric Emergency, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[7]Department of Pediatric Neurology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[8]Department of Pediatric Infection, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[9]Department of Pediatrics, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[10]Department of Medical Informatics, Gulhane Faculty of Medicine, University of Health Sciences, 06018 Ankara, Turkey

Correspondence:
Nuran ÇETİN
Eskisehir Osmangazi University, Faculty of Medicine, Department of Pediatric Nephrology, Eskisehir, Turkiye
e-mail: nurancetin17@hotmail.com

Abstract

We aimed to determine the frequencies of new-onset disease/attacks of autoimmune diseases (AD) during the COVID-19 pandemic and lock-down period compared to the pre-pandemic period. The patients (n=171) (aged between 0-18 yrs.) who were applied with AD to our hospital during the one year period before and first year of the COVID-19 pandemic and lock-down were included in this study. The frequencies of hospital applications with new-onset disease/attacks of AD were investigated retrospectively and compared between the two periods. The number of new-onset disease/attacks in the pre-pandemic and pandemic periods were determined as follows, 111 and 65 respectively (p<0.001). The proportions of applications to hospital in patients with post-streptococal disease and Henoch-Schönlein purpura have decreased during the pandemic, while a significant increase in frequency of new-onset type 1 diabetes mellitus has been observed. The frequency of applications for minimal change disease, systemic lupus erythematosus and Guillain Barre syndrome and multiple sclerosis did not alter substantially between the two periods. None of the patients were diagnosed with COVID-19. During the COVID-19 pandemic and lockdown period, the frequencies of AD diseases such as Henoch-Schönlein purpura and post-streptococal disease have decreased considerably indicating indirectly that infectious agents related with the etiology/course of AD and thus highlights the importance of isolation and hygiene measures. Increased frequency of type diabetes mellitus during this period suggests that factors other than infections may be effective in the etiopathogenesis of disease, or that protective agents or their effects might have decreased or changed.
Keywords: COVID-19 pandemic and lock-down, Autoimmune diseases, Children.

Özet

COVID-19 pandemi ve kapanma döneminde pandemik öncesi döneme kıyasla yeni başlangıçlı hastalık/otoimmün hastalıkların ataklarının sıklığını belirlemeyi amaçladık. Bu çalışmaya COVID-19 pandemisi ve kapanma döneminin bir yıl öncesi ve ilk yılı boyunca hastanemizde otoimmun hastalık tanısı ile izlenen hastalar (n = 171) (0-18 yaş arası) dahil edildi. Yeni tanı alan hasta sayısı ve otoimmun hastalığın atak sayılarının sıklıkları geriye dönük olarak araştırıldı ve iki dönem arasında sıklıklar karşılaştırıldı. Pandemi öncesi ve pandemik dönemde yeni başlangıçlı hastalık/atakların sayısı sırasıyla 111 ve 65 olarak belirlendi (p <0.001). Post-streptokal hastalık ve Henoch-Schönlein purpurası hastalarında hastaneye başvuru oranları pandemi sırasında azalırken, yeni tanı tip 1 diyabetes mellitus sıklığında önemli bir artış gözlendi. Minimal lezyon hastalığı, sistemik lupus eritematozus, Guillain Barre sendromu (GBS) ve multipl skleroz için başvuru sıklığı iki dönem arasında anlamlı bir farklılık göstermedi. Hastaların hiçbirine COVID-19 teşhisi konmadı. COVID-19 pandemisi ve kapanma dönemi boyunca, Henoch-Schönlein purpurası ve post-streptokal hastalık gibi otoimmun hastalıkların sıklıkları, otoimmun hastalık etiyolojisi ve seyrinde infeksiyöz ajanların rol oynadığını destekleyecek şekilde önemli ölçüde azalmıştır. Bu durum izolasyon ve hijyen ölçümlerinin önemini vurgulamaktadır. Bu dönemde tip 1 diyabet mellitus sıklığının artmış sıklığı, enfeksiyonlar dışındaki faktörlerin hastalığın etiopatogenezinde etkili olabileceğini veya koruyucu ajanların veya etkilerinin azalmış olabileceğini veya değişebileceğini düşündürmektedir.
Anahtar Kelimeler: COVİD-19 pandemi ve kapanma dönemi, Otoimmün hastalıklar, Çocukluk çağı

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1. Introduction

On February 11, 2020 by World Health Organization (WHO); the disease by this infection was defined as COVID-19 and as a pandemic on March 11, 2020. The first case of COVID-19 in Turkey was officially announced on March 11, 2020. It continues to spread rapidly all over the world and cause a large number of deaths.

From the beginning of the pandemic, in order to prevent the spread and transmission of the infection, isolation measures have been taken by both individuals and governments all around the world as in our country, which also lead to severe socio-economic bad consequences. Measures and interventions to prevent the transmission and spread of this virus have been a part of our lives and our lifestyle has changed and people's mobility and contact decreased. Although intermittently, a nationwide curfew was imposed, which still continue on weekends and for children and people over the age of 65 until March 2021. Schools were closed and online education started(1). There have been limitations in workplaces and flexible working order has been introduced. All social activities, religious activities, all kinds of sports and travel activities were stopped. Eating and drinking outside the home were restricted. Many individuals provide for their needs through online shopping. Restrictions for the shopping and public transport capacity, obligation to wear a mask, social isolation and the obligation to leave physical distance, personal and social hygiene measures and many other obligatory interventions for prevention of spread of the virus has been applied. Thus, the contact of people with each other has been minimized. Due to all these isolation and hygiene measures, it is thought that other infections via airborne and faecal-oral transmission have been decreased and therefore the frequency of morbidity associated with infections has also decreased as well as COVID-19. It has been observed that admissions/visits to hospitals have decreased due to the fear of contamination of the virüs(2-6).

Autoimmune diseases are characterized by persistent inflammatory reactions and the presence of autoantibodies due to loss of immune tolerance leading to various organ damage and dysfunction(7). Viral and bacterial infections are one of the environmental factors that trigger autoimmunity(8). During infections caused by these microorganisms, autoimmune reaction starts with mechanisms such as molecular mimicry, bystander activation, epitope spreading and presentation cryptic antigens(9). Virus-induced AD can be counted as systemic lupus erythematosus (SLE), type-1 diabetes mellitus (DM), multiple sclerosis (MS), Gullian Barre syndrome (GBS), encephalitis and autoimmune myocarditis(10).

SLE, which is the prototype of autoimmune disorders, begins with periods of exacerbation and remission in childhood in about 20% of cases, causing irreversible tissue damage and even premature death(11). The exact etiology of SLE is still unknown. However, infections play a role as an environmental factor inducing or promoting the onset and exacerbations of SLE in genetically susceptible individuals(12). MS is a chronic, immune-mediated, neurodegenerative disorder of the central nervous system. At about 3 to 10% of all MS patients initiates first clinical symptoms in childhood or adolescence(13, 14). Viral pathogens may play a role in MS pathogenesis and relapses(15). GBS is a typical post-infectious disease which progresses rapidly shortly after an infection caused by viruses and bacteria, usually without recurrence(16). It has been reported that viral infections have both a triggering and protective role in the development of type-1 DM(17).

Idiopathic nephrotic syndrome (INS), is the most frequent glomerular disease in childhood In children >1 year of age, minimal change disease (MCD) is the most common cause of nephrotic syndrome, accounting for 70%–90% of patients(18). In some cases with INS, an upper respiratory tract infection, an allergic reaction, vaccines, malignancies or another factor may precede the development or relapses of the disease(19).

The etiology of HSP is not well known. Approximately one and a half of the cases of

HSP are preceded by an upper respiratory tract infection(20). It can also be triggered by viral infections, vaccinations, and insect bites. Another AD in which bacterial infections play a role in its etiology is post-streptococcal disorder (PSD). PSD occurs within 3-4 weeks after group A beta-hemolytic streptococcal tonsillopharyngitis. The poor treatment of this infection is the main cause of PSD(21).

In this study, we aimed to determine that if there was a change in the frequencies of AD in the one year period before COVID-19 pandemic and in the first one-year period of the COVID-19 pandemic, where strict hygiene and isolation measures were applied on a personal and social basis.

2. Materials and Methods

Study population

The patients aged between 0 and 18 years applied to the pediatric departments of our hospital in the one-year periods before the COVID-19 pandemic (from March 11, 2019 to March 11, 2020) and during the first year period of the pandemic and strict lock-down (from March 11, 2020 to March 11, 2021). The frequency of applications with a new-onset disease or attacks/relapses of AD and the clinical characteristics of the patients were retrospectively obtained from the hospital records. COVID-19 PCR test was negative in all patients whose data were included in the study during the pandemic period. Data of patients with positive COVID-19 PCR test were not included in the study. In order to exclude AD due to COVID 19, the data of patients with a history of contact or known to have had COVID 19 before were excluded from the study.

The diagnosis and management of MCD was done according to KDIGO guideline(22). EULAR/PRINTO/PRES criteria were used in the diagnosis of HSP(23). The Systemic Lupus International Collaborating Clinics (SLICC) criteria were used in the diagnosis of SLE(24). Multiple sclerosis was diagnosed according to McDonald criteria(25). Global International Diabetes Federation (IDF) / International Society for Pediatric and Adolescent Diabetes (ISPAD) 2011 Guideline was used for type 1 DM diagnosis(26).

Ethical Approval

This study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki (Number: 8, Date: 26.01.2021).

Statistical Analysis

Data analysis was performed with IBM SPSS v21. Qualitative variables were given as count and percentages in the tables. Normality of quantitative variables were evaluated with Shapiro Wilk test. For the normally distributed groups, comparisons were performed with independent samples t test, while Mann-Whitney U test was used for non-normal distributed group comparisons. The relationship between the types of diseases and the time of the patient admission to hospital was evaluated with Pearson Chi-square analysis. For significant Chi-square test results, in each row column proportions were compared using z test with a Bonferroni correction. Significant differences between the column proportions denoted with different letters in each row. P values less than 0.05 were considered significant.

3. Results

The data of 171 patients were included in the study. The total number of patients admitted during the pre-pandemic and pandemic periods were 108 and 63, respectively ($p<0.001$). The number of applications of the patients in the pre-pandemic and pandemic period was 111 and 65, respectively. The distribution of the number of the patients and applications according to AD is shown in Table 1.

Table 1. The number of applications and patients according to the autoimmun diseaes

Disease	Pre-pandemic Period					Pandemic Period				
	Previously diagnosed									
	Total Admission n (%)	*Sex (F/M)*	*Total Patient (n)*	*Attack /Relapse (n)*	*New Onset Disease (n)*	*Total Admission* n (%)*	*Sex (F/M)*	*Total Patient (n)*	*Attack /Relapse (n)*	*New Onset Disease (n)*
Type 1 diabetes mellitus	25 (22.5)[a]	11/14	25		25	34 (52.3)[b]	20/14	34		34
Post Streptococal Disorders	20 (18)[a]	12/8	20		20	1 (1.5)[b]	1/0	1		1
Minimal change disease	15 (13.5)a	13/2	15	7	8	10 (15.4)[a]	7/3	10	6	4
Henoch Sheinlein purpura	29 (26.1)[a]	15/14	29		29	6 (9.2)[b]	4/2	6		6
Systemic lupus erythromatosus	7 (6.3)[a]	6/1	7		7	5 (7.7)[a]	5/0	5		5
Multiple sclerosis	13 (11.7)[a]	19/1	8	11	2	8 (12.3)[a]	6/0	6	8	
Guillain Barre syndrome	2 (1.8)[a]	0/2	2		2	1 (1.5)[a]	0/1	1		1
Total	111	108				65		63		

**Having same letter in a row denotes that column proportions of application time period categories do not differ significantly at the 0.05 level.*

While the number of patients and applications for other AD decreased during the pandemic period, it was observed that the number of patients with newly diagnosed DM increased by 36%. The total number of patients and applications who applied with other AD other than DM were 83/29 and 86/31 during the prepandemic and pandemic periods, respectively, and the number of patients and the number of hospital visits decreased by 65% and 64%, respectively, during the pandemic period.

A 93 of these patients who applied during the pre-pandemic period and 51 of the patients who applied during the pandemic period were diagnosed with a new-onset disease. During the pandemic period, the number of patients diagnosed with a new-onset disease decreased by 18%. While the number of patients applied with attack/relapse in the pre-pandemic period was 15 and the total number of attacks was 18. In pandemic period, the number of patients and the total number of attacks were 12 and 14, respectively.

The number of patients with DM were 25 (aged 4-17.5 years) and 34 (2-18 years) during the pre-pandemic and pandemic periods, respectively. All diabetic patients were hospitalized, and PCR tests were negative for COVID-19 in all. There was 36% increase in the frequency of new-onset diabetes during the pandemic period. The number of admissions with ketoacidosis of these patients were 12 and 18, respectively in the two periods. Difference in terms of age, HbA1c levels (12,2% and 11,95% in the pre-pandemic and pandemic periods, respectively) and the frequency of ketoacidosis was not found between the two periods ($p>0.05$).

During the pandemic period, the applications with PSD were decreased significantly compared to the prepandemic period (Table 1). In the pre-pandemic period, 20 new applications of PSD were observed (15 with new-onset acute rheumatic fever, 4 with rheumatic heart disease, 1 with poststreptococcal reactive arthritis). The patients'ages ranged from 5 to 18 years. The major criterias were carditis in 8 patients, carditis with polyarthralgia in 4 patients, carditis with chorea in 5 patients, polyarthritis in 2 patients and monoarthritis in 1 patient. During the pandemic period, there was no admission with the reactivation and only one new patient (13-years-old boy) was applied

with polyarthritis with elevated acute phase reactants and diagnosed with acute rheumatic fever. The PCR test for COVID-19 of him was negative.

The number of patients followed-up with a diagnosis of new-onset HSP were 29 (aged 2.8-15.9 years) and 6 (aged 3.5-16.1 years) respectively in the pre-pandemic and pandemic periods. All of these patients were newly diagnosed HSP cases. Compared to the pre-pandemic period, the number of patients presenting with newly diagnosed HSP was 80% less during the pandemic period (Table 2). 12 patients in the pre-pandemic period and 2 patients in the post-pandemic period were hospitalized and treated.

In the pre-pandemic period, 15 patients (aged 2.3-15.3 years) were followed-up with MCD (8 new-onset MCD, 7 relapsed). Nine patients were treated by hospitalization. Ten patients (aged 4.5-16.5 years) were admitted with MCD syndrome (4 new-onset, 6 relapsed) during the pandemic period.

In these both periods, 7 (aged 10.2-15.8 years) and 5 patients (aged 12.5-19 years), respectively were diagnosed with new-onset SLE. There was no patient presenting with SLE attack in both periods.

During the pre-pandemic period, a total of 10 patients were followed-up with MS. Two patients (aged 6.3-17 years) diagnosed with new-onset disease of MS. Eight patients (aged 14.1-17 years) which were previously being followed-up with MS presented with a total of 11 attacks in the pre pandemic period. One patient also had Sjögren's syndrome and another patient had type 1 DM. All these patients were treated by hospitalization. During the pandemic period, a total of 6 MS cases (aged 16-17.5 years) which were previously diagnosed with MS, were admitted with total of 8 attacks. One patient also had type-1 DM.

The number of patients diagnosed with GBS were 2 (9.4- and 10.8-years old) and 1 (3.3-year old) respectively in the pre-pandemic and pandemic periods. There was not statistically significant difference in the frequencies of SLE, MCD, MS and GBS between the two periods (Table 1).

4. Discussion and Conclusion

We investigated the changes in the frequencies of AD diseases in which infections play a role in the etiology and/or clinical course in one-year periods before and during the COVID-19 pandemic and lock-down. Our results showed that there was significant decreases in the frequencies of the PSD, HSP and an increase in the frequency of new-onset diabetes during the pandemic.

It has been reported that the number of applications to the emergency services and/or hospital visits related to all kinds of health problems from all over the world has decreased considerably. In the early stages of the pandemic, some people even postponed their visits to the hospital for serious problems due to the fear of transmission of SARS-CoV-2 (2-6). We also experience this situation in our routine practice in our hospital.

It is obvious that the transmission and frequency of other infectious diseases beside COVID-19 infection decrease during the lock-down period when strict hygene and isolation measures were taken on a personal and social basis. In a study conducted in France, COVID-19 lock-down were associated with a significant reduction in pediatric infectious disease spread by airborne transmission[6]. Therefore, we investigated whether there was a change in some AD in which an infection played a role in the etiopathogenesis and clinical course during the pandemic and lock-down period compared to pre-pandemic period. The symptoms/diseases investigated in this study such as diabetes, ketoacidosis, convulsion, respiratory distress, fever, rash, arthrtis and eudema etc. require urgent treatment and can't be handled at home. So, in the presence of these symptoms or conditions, it is not possible to postpone hospital admissions due to the risk/fear of transmission of COVID-19.

In our study, during the pandemic period, the frequencies of applications for infection related morbidities/diseases except new-onset

DM have decreased by 65%. This result indirectly demonstrates the relation of infections with the etiology/clinical course of the AD.

In our study, it has been determined that the frequencies of some AD such as PSD and HSP, have decreased significantly during the pandemic period. It is known that group A Streptococcus infections play a crucial role in the disease's pathogenesis of HSP as well as viral infections and other factors(27). Although its role in HSP development is not as direct as PSD development, our finding indicates that hygiene measures and isolation during the pandemic is highly effective in preventing the transmission of group A beta-hemolytic streptococcus infection as well as development of PSD and HSP.

It was determined that the frequencies of these AD diseases such as MS and SLE, MCD, MS and GBS in both pre-pandemic and pandemic periods were quite low and there was no statistical difference between these two periods. On the other hand, from France, Harambat et al. reported that the relapse rate of nephrotic syndrome during the pandemic period was not different than the period before the pandemic as in our study(28).

Viruses are suggested to be one of the environmental agents that play a role in the emergence and progression of autoimmunity that plays a role in the ethiopathogenesis of DM. However, it has been reported that viral infections have a protective role for DM(17). The hygiene hypothesis suggests that increased hygiene habits in early childhood and western hygiene lifstyle, leads to less frequent microbial infections that play a role in the emergence of allergic and AD diseases in advanced ages. According to this hypothesis, DM and other AD occur more frequently in the countries where the industry is developed and fewer infectious diseases were observed(29). We found that the frequency of new-onset diabetes in the pandemic period has increased considerably when the severe and widespread isolation and hygiene measures are taken. This result indicates that other factors may be more effective than infectious factors in the etiopathogenesis of diabetes or that protective agents may have decreased or changed during this period. It comes to mind that one of these factors may be increased level of psychological stress. In addition, this finding may be explained by the hygiene hypothesis. However, it can be said that duration of the current pandemic period is too short for a comment to be made related with the hygiene hypothesis in the pathogenesis of DM.

Our hospital is a regional reference hospital and there has been no change in the diabetic patient referral conditions to our hospital in terms of change in socio-demographic status and presence of pediatric endocrinologists in our region during the time of this study. Therefore, it cannot be said that diabetic patient referrals to our hospital have decreased or increased with that reason.

In addition, could the increase in diabetes frequency that we detected during the pandemic period be related to SARS-CoV-2 infection question comes to mind. In a multicenter study conducted in United Kingdom, it was reported that the prevalence of new onset type-1 diabetes increased by 80% between March and June 2020 in two centers compared to previous years. SARS-CoV-2 PCR positivity was found in five of these patients. They suggested that the increased frequency of this disease may be related to the exposure to SARS-CoV-2(30). We think that the increase in DM prevalence is related to the change in environmental factors. SARS-CoV-2 PCR test in our patients with DM were negative and none of patients with DM in our study study had a history and symptoms of SARS-CoV-2 infection. On the other hand, in a study conducted in Germany, the frequency of type-1 DM in children during the pandemic and lock-down period covering 13 March to13 May 2020 was not different from the frequency observed during the same periods of the previous years(31). In our study, the frequency of admissions with ketoacidosis of new-onset DM were not different between the pre-pandemic and pandemic periods. Kamrath et al. reported that the frequency of ketoacidosis especially severe ketoacidosis in type-1 diabetic children increased in Germany during the pandemic period(32).

There are several limitations in our study. Firstly, this study is retrospective study.

Secondly, this study have small patient number. Thirdly, not all children were tested for the SARS-CoV-2 antibody.

In conclusion, the frequency of applications of morbidities/diseases associated with infections have decreased considerably with the isolation and hygiene measures applied during the period of COVID-19 pandemic and lock-down compared to pre-pandemic period. This decrease was observed to be more pronounced in the diseases in which bacterial infections as well as viral infections play a directly or indirect role in the ethiopathogenesis or attacks/relapses such as PSD, HSP. No difference was observed in the frequency of diseases associated with mainly with viral infections such as INS, SLE, MS have been found. Our results indirectly indicate that infections may have a role in the emergence of AD diseases and prevention of infections is important. On the other hand, increase in the frequency of DM during this period suggests that factors other than infections are also effective in the etiopathogenesis of this disease, or that protective agents or its effects may have decreased or changed during this period.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Number: 8, Date: 26.01.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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Research Article / Araştırma Makalesi

Severe Measles Cases Requiring Pediatric Intensive Care Unit Admission

Çocuk Yoğun Bakım Ünitesine Yatış Gerektiren Ağır Kızamık Vakaları

[1]Eylem Kıral, [2]Ayşe Filiz Yetimakman

[1]Eskisehir Osmangazi University Faculty of Medicine, Pediatric Intensive Care Unit, Eskisehir, Turkiye

[2]Kocaeli University Faculty of Medicine, Pediatric Intensive Care Unit, Izmit, Turkiye

Abstract

Measles is a vaccine-preventable disease, and the disease burden is reduced with widespread pediatric measles immunization. Sporadic and severe cases might be observed during local outbreak situations, especially among unvaccinated people or vaccine non-eligible age groups, including infancy. In this study, we retrospectively evaluated the clinical and laboratory findings, and outcomes of children with measles requiring pediatric intensive care unit admission. We retrospectively evaluated medical records of 14 children with measles, who were followed up in the pediatric intensive care unit of Sanliurfa Training and Research Hospital between January 1st and June 30th, 2019. The median age was 9.5 months (range between one and 120 months). The most common reasons for admission to the pediatric intensive care unit were bronchopneumonia (n: 10) and/or sepsis. Two were diagnosed with pediatric acute respiratory distress syndrome, four patients had sepsis, and one patient had meningoencephalitis. The mortality rate was 14.2%. Risk factors associated with intensive care unit admission included being unvaccinated, being malnourished, having an underlying condition, and the development of bronchopneumonia as a complication. The mortality rate of measles, which is a preventable disease despite early treatments in the pediatric intensive care unit, is high, especially in unvaccinated children and those who have underlying conditions.

Keywords: Children; outbreaks; Measles; Mortality; Bronchopneumonia; Pediatric intensive care unit.

Özet

Kızamık aşı ile önlenebilir bir hastalıktır. Yerel salgın durumlarında, özellikle aşılanmamış kişilerde sporadik ve ciddi vakalar gözlenebilir. Bu çalışmada, çocuk yoğun bakım ünitesinde yatış gerektiren kızamık tanısı kesin olan çocukların klinik ve laboratuvar bulgularını ve sonuçlarını geriye dönük olarak değerlendirdik. 1 Ocak-30 Haziran 2019 tarihleri arasında Şanlıurfa Eğitim ve Araştırma Hastanesi çocuk yoğun bakım ünitesinde izlenen 14 kızamık tanılı çocuğun tıbbi kayıtları geriye dönük olarak değerlendirildi. hastaların median yaşı 9,5 aydı (1 ile 120 ay arasında değişiyordu). Pediatrik yoğun bakım ünitesine en sık yatış nedenleri bronkopnömoni (n: 10) ve/veya sepsis idi. İki hastada pediatrik akut solunum sıkıntısı sendromu, dört hastada sepsis ve bir hastada meningoensefalit tanısı konuldu. Mortalite oranı %14,2 idi. Yoğun bakım ünitesine kabul ile ilişkili risk faktörleri arasında aşılanmamış olma, yetersiz beslenme, altta yatan bir durumun olması ve komplikasyon olarak bronkopnömoni gelişimi yer almaktadır. Önlenebilir bir hastalık olan kızamık nedeniyle yoğun bakım yatışı gereksinimi olan çocuklarda ölüm oranı erken müdahalelere rağmen yüksektir.

Anahtar Kelimeler: Çocuk, salgınlar, Kızamık, Ölüm, Bronkopnömoni, Çocuk yoğun bakım ünitesi

Correspondence:
Eylem KIRAL
Eskisehir Osmangazi University Faculty of Medicine, Pediatric Intensive Care Unit, Eskisehir, Turkiye
e-mail: dr_eylem@hotmail.com

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1. Introduction

Measles is an acute highly transmissible viral infection associated with morbidity and mortality among unvaccinated or vaccine-ineligible populations. The most common complication of measles is otitis media, while other severe complications, such as pneumonia or neurological conditions, can cause severe clinical conditions that result in admission to the pediatric intensive care unit (PICU) (1).

According to WHO, the measles vaccine has saved the lives of nearly 31.7 million people around the World since 2000 (2). There are also local outbreaks of measles. The annual recorded incidence of measles decreased by 88% between 2000 and 2016, from 145 to 18 cases per million people, but increased to 120 in 2019 before decreasing to 22 in 2020. In 2020, 26 major and disruptive outbreaks (more than 20 cases per million) were recorded throughout five WHO regions; 17 (65%) of these outbreaks occurred in African nations (3). Between 2000 and 2010 reported measles-containing vaccine first dose (MCV1) coverage improved globally from 72 percent to 84 percent between 2000 and 2010, peaked at 86 percent in 2019, and then decreased to 84 percent in 2020 during the COVID-19 pandemic (3). Measles deaths have been reduced by 94 percent since 2000. However, measles remains an important public health problem.

This study aims to assess the clinical and laboratory data of patients with measles requiring pediatric intensive care unit admission in 2019 in Sanliurfa, Turkey.

2. Materials and Methods

In this study, medical records of patients with measles requiring PICU admission, have been retrospectively evaluated in the Ministry of Health Sanliurfa Training and Research Hospital between January 1st and June 30th, 2019. The diagnosis of measles has been confirmed with laboratory tests (ELISA tests, specific IgM, and IgG antibodies) in cases that fulfill the criteria for definitive diagnosis, in addition to clinical findings (fever, malaise, cough, coryza, and conjunctivitis, Koplik spots, a maculopapular rash). Ethics approval was obtained from the Harran University Local Ethical Committee. Age, gender, anthropometric measurements, vaccination status, socioeconomic status, history of contact with a measles case, diagnosis upon admission to the intensive care unit, receipt of treatment (vitamin A, antibiotics), and complications were evaluated. From medical records, complete blood counts, peripheral blood smears, serum C-reactive protein (CRP) and procalcitonin levels, arterial blood gas analysis, and blood culture results were noted. Pediatric risk of mortality (PRISM) scores were recorded for all patients with the worst clinical and laboratory data within the first 24 hours (4). Supportive extracorporeal therapies such as renal replacement therapy and plasma exchange therapy were recorded. The outcomes of the patients have been classified as ”died” or “discharged”.

3. Results

Clinical and laboratory parameters of 14 children (8 boys and 6 girls) requiring PICU admission have been evaluated (Table 1-3). The median age of the patients was 9.5 months (range between one and 120 months). Three children (21.4%) were aged between 0-3 months, eight children (57.1%) were aged between 3-12 months, and three children were above 12 months (15 months, 69 months, and 120 months, respectively).

Four children (28.5%) have had contact with a patient who had a measles-like rash, while one patient had contact with a patient who had been diagnosed with measles in another city. All of the patients were positive for measles IgM. One patient had a serological test three weeks after being admitted because of technical difficulties; the results showed that this patient had measles IgG. All of our patients received vitamin A supplements (age-appropriate doses) after the diagnosis of measles.

Eleven children with measles were younger than the age for the measles-containing vaccine in the National Immunization Program of the Ministry of Health Turkey, and two children (> 1 year) had missed their MMR vaccine Schedule (unvaccinated refugees). In three cases, siblings of the patients had a history of measles. Five patients (35.7%) were immigrants with Syrian backgrounds, and one of these was a resident of an immigrant camp. One patient had albinism, three patients had neuromotor retardation and epilepsy, and one of them had a ventricular septal defect and aortic coarctation. Anthropometric measurements (weight-for-age) of five patients (35.7%) were lower than the 3rd percentile for age, and two patients were between the 3-10th percentile for (14.2%).

Table 1. Demographical findings, clinical findings of 14 children with measles

Case Number	Age (Months)	Gender	*Vaccine status*	Underlying disease	GCS	*Complications*
1	1	M	unvaccinated	-	10	Septic shock, PARDS, acute renal injury
2	3	F	unvaccinated	-	15	Bronchopneumonia
3	8	F	unvaccinated	-	15	Bronchopneumonia
4	12	M	unvaccinated	NMR, epilepsy	13	Bronchopneumonia
5	6	F	unvaccinated	-	15	Bronchopneumonia
6	5	M	unvaccinated	-	15	Bronchopneumonia
7	10	F	unvaccinated	NMR, epilepsy	13	Sepsis
8	12	M	unvaccinated	-	15	Bronchopneumonia
9	120	F	unknown	NMR, epilepsy, severe malnutrition	9	Bronchopneumonia, Empyema, Sepsis
10	2	F	unvaccinated	-	13	Sepsis
11	15	M	unvaccinated	Albinism	8	Bronchopneumonia, TAMOF
12	10	M	unvaccinated	VSD, AoC	13	Bronchopneumonia, PARDS
13	9	M	unvaccinated	-	15	Bronchopneumonia
14	69	M	unvaccinated	-	9	Status epilepticus, Suspected Meningitis

CRP: C- reactive protein; GCS: Glasgow coma score; Gender F: Female, M: Male; AoC: Aortic Coarctation; NMR: Neuromotor retardation; PARDS: Pediatric Acute Respiratory Distress Syndrome; PCT: Procalcitonin; TAMOF: Thrombocytopenia-associated multiple-organ failure; WBC: White blood cell; VSD: Ventricular septal defect

Table 2. Laboratory findings of 14 children with measles

Case Number	WBC (mm^3)	Platelet (mm^3)	Lactate (mmol/L)	CRP (mg/dL)	PCT (ng/mL)
1	32,290	20,000	12.1	283	100
2	27,000	429,000	0.7	69	2
3	30,000	380,000	1	39	0.5
4	25,000	221,000	0,6	32	0.6
5	10,300	473,800	0.8	61	0.5
6	18,000	547,000	1.6	86	1.5
7	33,000	230,000	3.8	157	30
8	21,500	365,000	2	76	0.5
9	19,690	325,000	3.9	180	100
10	19,100	266,700	3.5	82	55
11	23,000	44,000	6	53	85
12	17,500	274,000	2.0	70	0,6
13	24,000	690,000	0.8	16	0.7
14	28,120	234,000	1.8	277	1

CRP: C- reactive protein, PCT: Procalcitonin; WBC: White blood cell

Table 3. Clinical interventions in PICU, PRISM score, predicted mortality and outcome of 14 children with measles

Case Number	Antibiotic	ECT	Mechanical Ventilation	PRISM score	Predicted Mortality	Length of PICU stay (days)	Outcome
1	Cefotaxime Linezolid	Peritoneal dialysis	IMV	19	30%	14	Discharged
2	none	-	-	13	11%	7	Discharged
3	none	-		10	6.2%	3	Discharged
4	none	-	-	13	11%	5	Discharged
5	none	-	-	15	11.7%	4	Discharged
6	none	-	-	9	5.1%	3	Discharged
7	Cefotaxime Vancomycin	CVHDF	-	18	25.8%	5	Discharged
8	none	-	-	5	1.7%	3	Discharged
9	Meropenem Vancomycin	-	IMV	23	49.5%	21	Died
10	Cefotaxime	-	-	18	25.8%	4	Discharged
11	Cefotaxime Vancomycin	PLEX, CVVHDF	IMV	36	93.5%	12	Died
12	Cefotaxime Vancomycin	-	IMV	21	39.3%	10	Discharged
13	none	-		13	11%	3	Discharged
14	Cefotaxime Vancomycin	-		16	18.7%	6	Discharged

CVVHDF: Continuous veno-venous hemodiafiltration; ECT: Extracorporeal Treatment; IMV: Invasive mechanical ventilation; PICU: Pediatric intensive care unit; PLEX: Therapeutic plasma exchange; PRISM: Pediatric risk of mortality

All patients were admitted to isolated rooms in the PICU. Fever and a maculopapular rash were the most common presenting symptoms for all the patients. The period between the onset of symptoms and presentation varied between 12 and 72 hours. Ten children were admitted from the Pediatric Emergency Unit and four patients were admitted from the inpatient wards. PRISM scores vary between 5 and 36, and predicted mortality according to PRISM scores was between 1.7 and 93.5%. Ten patients were admitted with respiratory distress due to bronchopneumonia, requiring oxygen supplementation. Two children were diagnosed with pediatric acute respiratory distress syndrome (pARDS). A 69-months-old boy presented with a seizure, a lumbar puncture was performed for suspected meningoencephalitis; the cerebrospinal fluid (CSF) protein level was 60 mg/dL and the glucose level was 50 mg/dL. CSF gram staining was negative, but measles serology could not be confirmed in the CSF sample. Two patients had culture-negative sepsis. During the intensive care unit stay, one patient had pancytopenia and two patients had ARDS secondary to bronchopneumonia and sepsis (Figure 1). Two patients required chest tube drainage due to pneumothorax and empyema.

The length of PICU admission varied from 3–21 days, and hospital admission were 5–41 days. One patient who had albinism and presented with atypical symptoms of measles was treated in the PICU unit for 12 days and needed continuous venovenous hemodiafiltration (CVVHDF) and plasma exchange therapy because of multiorgan failure caused by pARDS and septic shock. Despite all supportive therapies, the patient died. One patient, who needed to be admitted to the intensive care unit twice during the clinical course, died three weeks after acute presentation with empyema and sepsis.

In this study, we present 14 cases of measles who needed to be admitted to an intensive care unit, two of whom died because of complications from measles.

In our study, 11 patients were under the age of vaccination for measles-containing vaccines according to the National Immunization Program. Metin et al. evaluated 44 pediatric measles cases in Ankara, Turkey, between 2012 and 2013, and they showed that all of these patients either missed scheduled vaccinations or were smaller than the age of vaccination as in our study (9). In 2014, in a study carried out in the USA, Gastanaduy et al. showed that among 178 cases of measles, only 10% had received the measle vaccine (10).

The primary method of protecting children under the age of vaccination is through high immunization rates in the population (11). Yörük et al. showed that the region with the highest vaccination rejection rate is Southeastern Anatolia Region where Sanlıurfa is located. The biggest reason for vaccine rejection is the fear that the ingredients in the vaccine may cause undesirable effects (12). Reduced vaccination rates make neonates and infants high-risk groups for measles, which can cause problems that necessitate hospitalization to an intensive care unit and, in some cases, death. In our case series, two children missed their measles-containing vaccine schedule. Missing the vaccine shot for a disease in which vaccination is the principal method for prevention, is the underlying etiology of the infection in these patients.

Complications have been reported in 30% of measles cases. It is known that the risk of severe complications is higher in infants younger than one year of age and adults. One to six percent of the patients who have measles have pneumonia, 6% have gastroenteritis, 7–9% have severe otitis media, and loss of sight and encephalitis are each encountered in one in 1000 cases (13). In our study, ten of the patients in the PICU had bronchopneumonia, three had sepsis, and one had meningoencephalitis. One patient had pancytopenia, two patients had pARDS secondary to bronchopneumonia and sepsis. Two of our patients needed CVVHDF and plasma exchange therapy because of sepsis-associated organ dysfunction with thrombocytopenia-associated multiple organ failure. In our study, although they were in contact with the measles case, none of the patients were vaccinated or received intravenous immunoglobulin (IVIG) treatment (14).

One of every 20 measles cases results in mortality in developing countries (15). Donadel

et al. tried to determine the mortality risk factors of measles cases in infants and children under the age of 59 months. They found that 93% of the patients who died, were not vaccinated with an age-appropriate dose of measles-containing vaccine. The presence of malnutrition and children with bronchopneumonia have an increased risk for mortality (16). In our study, none of our patients were vaccinated, 50% had malnutrition (underweight/ low weight-for-age), 35.7% had an underlying disease, and 71.4% of patients developed bronchopneumonia. Despite all treatment modalities, the mortality rate was 14.2 % in the PICU. In our study, one patient died during a measles infection and another died when s/he was admitted to the PICU two weeks after the acute infection. We enrolled only children with severe conditions requiring PICU, and the predicted mortality regarding pediatric risk of mortality at admission was higher than 20% in six out of 14 cases.

Our study has some limitations. This is a retrospective, short-term interval, single-center experience and includes only children requiring PICU.

4. Conclusion

Respiratory tract infections, ARDS, and sepsis are among the important clinical states that cause mortality and morbidity in measles patients admitted to the intensive care unit. Despite early treatment, the mortality rate of measles is high, particularly in unvaccinated children and those with underlying conditions. Complications and high mortality observed in intensive care patients highlight the importance of maintaining a high measles vaccine coverage, with enhanced targeting of the unvaccinated population.

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Ethics

Ethics Committee Approval: The study was approved by Harran University Local Ethical Committee (Number: 20, Date: 23.11.2020).

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Research Article / Araştırma Makalesi

Hippoterapinin Serebral Palsili Çocuklarda Denge ve Motor Fonksiyona Etkisinin Değerlendirilmesi

Evaluation of the Effect of Hippotherapy on Balance and Motor Function in Children with Cerebral Palsy

[1]Arife Derda Yücel Şen, [1]Kürşat Bora Çarman, [1]Coşkun Yarar, [2]Cafer Yıldırım, [3]Uğur Bilge

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Çocuk Nöroloji Bilim Dalı, Eskişehir, Türkiye

[2]Eskişehir Osmangazi Üniversitesi, Hippoterapi Uygulama ve Araştırma Merkezi, Eskişehir, Türkiye

[3]Eskişehir İl Sağlık Müdürlüğü, Eskişehir, Türkiye

Özet

Serebral palsi kronik nörolojik bir hastalık olup tedavinin temelini fizik tedavi oluşturmaktadır. Hippoterapi bu klasik tedavi yöntemine ek olarak uygulanabilmektedir. Çalışmamızda hippoterapinin serebral palsi hastalarına olan etkisi araştırıldı. Çocuklara tedavi öncesi ve sonrasında Kaba Motor Fonksiyon Ölçeği-88 (KMFÖ-88) ve Berg Denge Ölçeği uygulandı. On iki haftalık terapi sonrasında KMFÖ-88 ve Berg Denge ölçeği puanlarında istatiksel olarak anlamlı artış belirlendi. Bu ön çalışmamız hippoterapi uygulamasının pediatrik serebral palsi hastalarının tedavisinde kullanılabileceğini göstermektedir.
Anahtar Kelimeler: Serebral palsi, Hippoterapi, Denge, Çocuk

Abstract

Cerebral palsy is a chronic neurological disease and the mainstay of treatment is physical therapy. Hippotherapy can be applied in addition to this classical treatment. Our study investigated the effect of hippotherapy on patients with cerebral palsy. Gross Motor Function Scale-88 (GMFS-88) and Berg Balance Scale were administered to the children before and after the treatment. After 12 weeks of therapy, a statistically significant increase was determined in the GMFS-88 and Berg Balance scale scores. This preliminary study shows that hippotherapy can be used in the treatment of pediatric cerebral palsy patients.
Keywords: Cerebral palsy, Hippotherapy, Balance, Children

Correspondence:
Arife Derda YÜCEL ŞEN
Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Çocuk Nöroloji Bilim Dalı, Eskişehir, Türkiye
e-mail: derdayucel@hotmail.com

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1. Giriş

Serebral palsi (SP) "gelişmekte olan beyinde oluşan lezyon ya da zedelenme sonucu ortaya çıkan, ilerleyici olmayan ancak yaşla birlikte değişebilen, kalıcı hareket, duruş ve motor fonksiyon bozukluğu" şeklinde tanımlanmaktadır (1). SP etiyolojisi multifaktöriyel ve çeşitlidir. Motor yetersizliğe sıklıkla görme, işitme sorunları, mental retardasyon, dil gelişiminde gerilik, epilepsi ve ikincil olarak gelişen kas-iskelet sorunları eşlik edebilir. Dünyada SP sıklığı 1000 canlı doğumda 2-3 arasında değişen oranlarda bildirilmektedir (2). Ülkemizde yapılan bir araştırmada ise SP sıklığı 1000 canlı doğumda 4.4 olarak saptanmıştır (3). SP tedavisinin temelini fizik tedavi uygulamaları oluşturmaktadır. Son zamanlarda hippoterapinin SP'de motor kazanımlar sağlayabilen klasik rehabilitasyon programına yardımcı bir yöntem olarak tedavide fayda sağlayabileceğini gösteren çalışmalar mevcuttur (4-6).

Hippoterapi, motor ve duyusal girdi sağlamak için atların çok boyutlu sırt hareketlerinin kullanıldığı bir terapi stratejisidir. Nörolojik fonksiyonların ve duyusal süreçlerin iyileştirilmesine dayanır ve özellikle fiziksel yetersizlikleri olan bireylerin rehabilitasyon programlarına katkı sağlamaktadır. Hippoterapi, atın hareket biyomekaniği sonucunda oluşan çok boyutlu sırt hareketinin, biniciye insan yürüyüşünün mekaniğine benzer şekilde ritmik ve tekrarlayan bir hareket modeli sağlaması esasına dayanır. Hipoterapinin birincil amacı, bireyin dengesini, postürünü, motor becerilerini ve hareketliliğini iyileştirmektir. Hippoterapi, disiplinler arası bir ekip yaklaşımı kullanan bireyselleştirilmiş bir terapi modelidir (7-9).

Eun Sook Park (10) ve arkadaşları elli beş SP'li çocuğu dahil ettikleri çalışmalarında çocuklarda hipoterapinin kaba motor fonksiyon ve fonksiyonel performans üzerinde yararlı etkileri olduğunu bildirmişlerdir. Alemdaroğlu E ve ark dokuz çocukla yürüttükleri çalışmada hippoterapi uygulanan SP hastalarında kas spastisitesini azaldığını tespit etmişlerdir (11).

Ülkemizde hippoterapinin terapötik etkilerini araştırmayı amaçlayan bilimsel çalışmaların sayısı maalesef sınırlıdır (12).

Bu çalışmada standart fizyoterapi uygulamalarına ek olarak bireyselleştirilmiş hippoterapi programı uygulamaları alan SP'li çocukların denge ve motor fonksiyonlarındaki gelişimleri ile karşılaştırılması amaçlandı.

2. Gereç ve yöntem

Araştırma Ekim 2021- Mart 2022 tarihileri arasında Eskişehir Osmangazi Üniversitesi, Hippoterapi Uygulama ve Araştırma Merkezi' nde gerçekleştirildi. Çalışmaya Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Çocuk Nöroloji Bilim Dalı' nda takip ve tedavisi devam eden 20 SP hastası davet edildi.

Daha önce hippoterapi programına alınmış, son 6 ay içinde botulinum toksini A uygulaması yapılmış, dorsal rizotomi veya son 18 ay içinde ortopedik cerrahi girişim uygulanmış olan hastalar araştırmaya dâhil edilmedi.

Araştırma protokolü Eskişehir Osmangazi Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından onaylandı (karar no:2021/42) ve tedavi programı başlamadan önce tüm hastaların ebeveynleri tarafından bilgilendirilmiş gönüllü olur formu imzalandı ve tüm hastalara terapi sırasında yaşanabilecek kazalara karşı sigortası yapıldı. Bu çalışma, Avrupa Birliği Komisyonu tarafından "Support to Civil Society Networks and Platforms" çağrısı "Sağlığa Erişim" başlığı altında IPA/2019/413-002 referans kodlu "Hippoterapi Türkiye" projesi tarafından desteklenmektedir.

Hippoterapi hastalara haftada iki gün 1'er saat olmak üzere toplam 12 hafta boyunca uygulandı.

Çalışma döneminde tüm dünyada ülkemizde yaşanan COVID-19 pandemisi sebebiyle 6 ve terapiye uyum sağlayamama nedeniyle 4 olmak üzere toplam 10 hasta 12 haftalık araştırma süresini tamamlayamadan ayrıldılar. Araştırma toplam 10 hasta ile tamamlandı. Çalışma öncesinde ve sonunda SP hastalarına kaba motor fonksiyonlar, Kaba Motor

Fonksiyon Ölçeği-88 (KMFÖ-88) ve Berg Denge Ölçeği uygulandı. Her iki ölçeğin Türkçe geçerlilik ve güvenirlik çalışmaları tamamlanmıştır.

Kaba Motor Fonksiyon Ölçeği-88 (KMFÖ-88) ile (A) yatma-yuvarlanma, (B) oturma, (C) emekleme-diz üstü durma, (D) ayakta durma ve (E) yürüme-koşma-zıplama alt başlıklarında 0 ile 3 puan arasında puanlama yapılarak değerlendirildi ve tedavi öncesi ve sonrası bulgular belirlendi.

3. Bulgular

Çalışmaya katılan SP hastası çocukların altısı kız dördü erkekti. Katılımcıların ortalama yaşı 76.70 ± 30.75 (33-139) ay olarak hesaplandı. Hastaların ortalama gestasyon yaşı 33.3 (28-40) hafta olarak belirlendi. Çalışma grubun sosyodemografik özellikleri tablo 1' de yer almaktadır. Çalışma grubunun on iki haftalık Hippoterapi öncesi ve sonrası Berg Denge Skalası ve KMFÖ-88 sonuçları arasında istatistiksel olarak anlamlı artış saptandı. Kaba Motor Fonksiyon Ölçeği-88 (KMFÖ-88) alt puanlama parametreleri incelendiğinde üç alt parametresinde artış gözlendi ancak diğer iki parametrede ise değişiklik belirlenmedi (Tablo2).

Tablo 1. Çalışma grubunun sosyodemografik özellikleri

Özellik	**n (%)**
Cinsiyet	
Kız	6 (60)
Erkek	4 (40)
Ortalama gestasyon haftası	33.3 ± 4.44 hafta (min 28- maks 40)
Ortalama doğum ağırlığı	1987.00 ± 895.16 gram (min 1080-mak 3800)
Antropometrik ölçümler	
Ortalama vücut ağırlığı	23.14 ± 9.68 kg (min 12.00-maks 45.60)
Ortalama boy	112.70 ± 14.26 cm (min 88-maks 134)
SP tipi	
Kuadriplejik SP	4 (40)
Diplejik SP	3 (30)
Hemiplejik SP	3 (30)
Kaba motor işlev ölçeği	
Seviye I	1
Seviye II	4
Seviye III	3
Seviye IV	1
Seviye V	0

Tablo 2. Hastaların KMFÖ-88 ve Berg Denge Skalası sonuçları

	Terapi öncesi		**Terapi sonrası**		
	Ortalama (SD)	**Ortanca (min-maks)**	**Ortalama (SD)**	**Ortanca (min-maks)**	**P değeri***
KMFÖ toplam puan	66.24 ± 21.30	70.34 (23.92-88.14)	73.32 ± 22.67	78.46 (26.60-95.64)	< 0.05
Uzanma-yuvarlanma	97.02 ± 8.11	100(74.20-100)	99.60 ± 1.26	100 (96-100	> 0.05
Oturma	87.82 ± 27.10	100 (16.60-100)	90.33 ±23.16	100 (28.30-100)	>0.05
Sürünme-dizüstü durma	60.71 ± 34.70	67.85 (0-100)	69.51 ± 34.68	84.52(0-100)	<0.05

Ayakta durma	44.29 ± 32.44	53.84(0-79.48)	57.62 ± 34.58	69.22 (2-92.30)	<0.05
Yürüme, koşma, zıplama	38.81 ± 28.56	27.77 (5-84.72)	49.37 ± 33.77	40.96 (5-9583)	<0.05
Berg Denge Skalası	23.90 ± 16.25	23 (1.00-51.00)	31.00± 18.39	31 (3.00-55.00)	< 0.05

SD: standart sapma
** non parametrik wilcoxon analizi olasılık değeridir*

4. Tartışma

Atların sağlığa olan faydalarına ilişkin belgeler, savaşta yaralanan Yunan ve Romalı askerlerin iyileşmeyi kolaylaştırmak için bineklerine geri yerleştirildiği milattan önce beşinci yüzyıldan beri var olmuştur. Atlar, Almanya' da 1600' lü yıllara kadar özel olarak terapötik fayda için kullanılmıştır ve hippoterapi şu anda dünya çapında 30' dan fazla ülkede uygulanmaktadır (13,14). Hippoterapinin birincil amacı, bireyin dengesini, duruşunu, işlevini ve hareketliliğini iyileştirmektir. Hippoterapi, disiplinler arası bir ekip yaklaşımına sahip bireyselleştirilmiş bir tedavi yöntemidir. SP tedavisinin temelini klasik fizik tedavi ve rehabilitasyon uygulamaları oluşturmakla birlikte son zamanlarda bu tedavilere ek olarak hippoterapinin SP hastalarının tedavilerinde de yeri olabileceği belirtilmektedir (6). Atın ritmik, sağ-sol simetrik yürüyüş hareketi, çocuğu orta hat boyunca tekrar tekrar ileri geri hareket ettiren kritik faktör olabilirken, atın çevresi spastik addüktör kaslara yumuşak, sürekli bir esneme hareketi sağlar. Atın bacaklarının güçlü itişleri, güçlü vestibüler ve proprioseptif uyarım sağlar ve vücut farkındalığını artırırken, tekrarlanan küçük postüral denge ayarlamaları, çocuğun daha normatif bir orta hat ve simetrik ağırlık taşıma duygusu kazanmasına yardımcı olur.

Ülkemizde toplam 10 SP hastası ve 10 sağlıklı çocuğun katıldığı bir araştırmada 10 haftalık hippoterapi sonrasında çalışma grubunda KMFÖ-88 puanlarında anlamlı artış saptanmıştır. Özellikle yatma-yuvarlanma, oturma, emekleme-diz üstü durma, ayakta durma ve yürüme- koşma-zıplama alt parametrelerinde artış belirlenmiştir. Cherng ve ark (15) 14 SP'li hastanın bulunduğu 16 haftalık hippoterapi uygulaması sonrası, hastaların KMFÖ parametrelerindeki iyileşme anlamlı bulunmuştur. Ayrıca, etkinin en az 16 hafta sürdüğü görülmüştür. McGibbon ve ark (16) yaptığı çalışmada da benzer şekilde hippoterapi sonrası motor fonksiyonlarda iyileşme gözlenmiştir. Casady ve ark (17) on haftalık hippoterapi uygulaması ile 7 SP'li hastanın dâhil edildiği toplam 10 çocukta, yatma-yuvarlanma parametresi hariç tüm KMFÖ-88 parametrelerinde önemli gelişmeler saptamışlardır. Deutz ve ark (18) 73 SP'li hastada yaptığı çalışmada da hippoterapinin SP'li çocuklarda dik durmayı ve yürümeyi teşvik etme konusunda belirgin terapötik etkisinin olduğunu ileri sürmektedir. Bizim çalışmamızda ise uzanma-yuvarlanma ve oturma alt parametrelerinde fark gözlenmedi. Sürünme-dizüstü durma, ayakta durma, yürüme, koşma, zıplama alt parametrelerinde ise anlamlı fark saptandı.

Araştırmamızda kaba motor fonksiyonları değerlendirmede kullanılan KMFÖ-88, SP'li çocukların takibinde ve uygulanan tedavinin etkinliğini göstermede yararlı bir yöntemdir. Testin yardımcı cihaz ve donanım gerektirmemesi, ucuz olması, video-teyp kaydı ile aynı duyarlılıkta olması, test içi ve testler arası güvenilirliğinin yüksek olması bu yöntemin olumlu yönleridir. Ancak motor gelişimdeki niteliksel değişiklikleri göstermedeki yetersizliği ve uygulamanın zaman alması, pratik kullanımda zorluklara neden olabilmektedir.

SP'li çocuklarda, postüral kontrol ve denge ayrılmaz şekilde ilişkili olduğu için çalışmamızda ayrıca hippoterapinin denge üzerine olan etkisi de değerlendirildi. Hippoterapinin denge üzerine olumlu etkisi belirlendi. Araştırmamız literatürle benzer sonuçlara ulaşmıştır (6). Kang ve ark (19) hippoterapinin SP'li çocukların dengesi üzerindeki etkisini araştırdığı çalışmasında; geleneksel fizik tedavi ile hippoterapinin, SP'li çocukların dengesini tek başına geleneksel

fizik tedavi yöntemlerinden daha iyi geliştirdiği sonucuna ulaşmıştır.

Hippoterapi atların kullanıldığı bir yöntemdir. Canlı hayvanlarla terapi uygulaması bazen hayvan kaynaklı nedenlerden dolayı aksayabilmektedir. Bu sorunların önüne geçmek amacıyla son zamanlarda at binme simülasyon cihazları kullanılmaktadır. Chinniah ve ark at binme simülasyon cihazı kullanarak yaptıkları çalışmada 12 haftalık terapi sonrasında KMFÖ-88 skorlarında yalnızca konvansiyonel fizik tedavi uygulanan çocuklara oranla daha fazla artış saptamışlardır (20).

Sonuç olarak bu araştırma, hippoterapinin SP'de motor kazanımlar sağlayabilen klasik rehabilitasyon programına yardımcı bir yöntem olduğunu gösteren klinik bir ön çalışmadır. Bu araştırmanın en önemli sınırlılıkları; olgu sayısının yetersizliği, motor fonksiyonlar açısından grup içi homojenitenin olmaması ve COVID-19 pandemisi döneminde gerçekleştirilmesidir.

Bu 12 haftalık klinik ön çalışmanın sonucunda elde edilen pozitif gelişmelerin hippoterapi konusunda yapılacak araştırmalara ışık tutacağı düşünülmektedir.

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Research Article / Araştırma Makalesi

Evaluation of Self-Care Levels and Affecting Factors in Diabetes Patients

Diyabet Hastalarında Öz Bakım Düzeyi ve Etkileyen Faktörlerin Değerlendirilmesi

[1]Büşra Yumuşak, [2]Önder Sezer, [2]Hamdi Nezih Dağdeviren

[1]Erzurum Şenkaya İlçe Devlet Hastanesi, Erzurum, Turkiye

[2]Trakya University Faculty of Medicine Department of Family Medicine, Edirne, Turkiye

Abstract

One of the most important factors in the management of diabetes is the level of self-care of patients. It reduces mortality and morbidity and is an important marker in the course of the disease. In our study, we aimed to evaluate the self-care level of diabetic patients admitted to our hospital and the factors that may affect self-care. Diabetes patients admitted to the Diabetes and Obesity Outpatient Clinic of our hospital were examined in a 4-month period between May 15, 2021 and September 15, 2021. After verbal information, a 71-question questionnaire including sociodemographic characteristics, lifestyle, education and treatments, body mass index, waist circumference and Diabetes Self-Care Scale was applied face-to-face to patients who agreed to participate in our study. Measurements were made by the researchers. $p<0.05$ was accepted as statistical significance. The study included 132 diabetic patients, 83 women and 49 men. The mean score obtained from the Diabetes Self-Care Scale was 96.25±19.61. Factors that interacted with self-care were educational status ($p<0.001$), income level ($p<0.001$), receiving education about the disease from the doctor ($p=0.007$), diet ($p=0.003$) and exercise ($p=0.005$) in the treatment, frequency of control ($p<0.001$), waist circumference ($p<0.001$) and body mass index ($p<0.001$). Management of existing patients is as important as prevention of diabetes. Self-care is an important factor in the management of the disease. Every intervention to increase self-care leads to positive results in the management of the disease.

Keywords: Self-care; Diabetes mellitus; Body mass index; Diet; Exercise

Özet

Diyabet hastalığının idamesinde en önemli faktörlerden bir tanesi hastaların öz bakım düzeyidir. Mortalite ve morbiditeyi azalttığı gibi, hastalığın seyrinde önemli bir belirteçtir. Çalışmamızda hastanemize başvuran diyabet hastalarının öz bakım düzeyi ile birlikte, öz bakıma etki edebilecek faktörlerin değerlendirilmesi amaçlanmıştır. Hastanemiz Diyabet ve Obezite Polikliniği'ne başvuran diyabet hastaları, 15 Mayıs 2021 – 15 Eylül 2021 tarihleri arasında 4 aylık süreçte incelenmiştir. Sözel olarak yapılan bilgilendirme sonrasında çalışmamıza katılmayı kabul eden hastalara sosyodemografik özellikler, yaşam şekilleri, aldıkları eğitim ve tedaviler, beden kitle indeksi, bel çevresi ve Diyabet Öz Bakım Ölçeği'ni içeren 71 soruluk anket yüz yüze uygulanmıştır. Ölçümler araştırmacılar tarafından yapılmıştır. $p<0,05$ istatistiksel anlamlılık olarak kabul edilmiştir. Çalışmaya 83'ü kadın, 49'u erkek, 132 diyabet hastası dahil edilmiştir. Diyabet Öz Bakım Ölçeği'nden alınan puan ortalaması 96,25±19,61 olarak saptanmıştır. Öz bakım ile etkileşen faktörler olarak eğitim durumu ($p<0,001$), gelir seviyesi ($p<0,001$), hastalık ile ilgili eğitimi doktordan almak ($p=0,007$), tedavide diyet ($p=0,003$) ve egzersizin ($p=0,005$) yer alması, kontrol sıklığı ($p<0,001$), bel çevresi ($p<0,001$) ve beden kitle indeksi ($p<0,001$) tespit edilmiştir. Diyabetin önlenmesi kadar önem verilmesi gereken bir konu da, mevcut hastaların yönetimidir. Öz bakım, hastalığın yönetiminde önemli bir etkendir. Öz bakımın arttırılması için yapılan her müdahale, hastalığın yönetiminde olumlu sonuçlara neden olmaktadır.

Anahtar Kelimeler: Özbakım; Diabetes mellitus; Beden kitle indeksi; Diyet; Egzersiz

Correspondence:
Önder SEZER
Trakya University Faculty of Medicine Department of Family Medicine, Edirne, Turkiye
e-mail: ondersezerdr@gmail.com

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1. Introduction

Diabetes is a chronic metabolic disorder caused by defects in insulin deficiency or action, requiring continuous medical care and dedication. The main aim of treatment is to ensure glycemic control during the day, to prevent acute and chronic complications, to solve the accompanying problems, and thus to improve the expected survival and quality of life in patients with diabetes (1).

Today, chronic diseases that share similar risk factors with diabetes constitute an important health problem. With the rapid change in lifestyle, the prevalence of type 2 diabetes is rapidly increasing in developed and developing societies (2).

In its 10th Diabetes Atlas published in 2021, the International Diabetes Federation reported that 537 million adults worldwide have diabetes. This number, which means that approximately 1 in every 10 people has diabetes, is thought to be 783 million in 2045 (3).

According to the 2010 Turkiye Diabetes, Hypertension, Obesity and Endocrinologic Diseases Prevalence Study (TURDEP-2) conducted in Turkiye, the prevalence of diabetes increased from 7.2% to 13.7% between 1998 and 2010 and the level of awareness about diabetes was reported as 45% (4).

The American Diabetes Association predicted that the financial burden of diabetes in the United States was 132 billion US dollars in 2002 and would increase to 192 billion US dollars by 2020 (5). In a study conducted in Turkiye in 2009, in which the cost of complications of type 2 diabetes was investigated, the financial burden of cardiovascular, renal, ophthalmologic and neurologic complications in individuals with diabetes was examined, and it was estimated that the cost to the Social Security Institution would be 13 billion TL (6).

In order to reduce this burden, it is important that patients are aware and have strong self-care. Patients who can self-monitor their blood glucose levels, pay attention to their diet and lifestyle and follow the recommendations of the physician can both maintain their diabetes with less cost and keep their quality of life high by protecting them from complications (7). In diabetes, which is a chronic disease, adherence to appropriate self-care behaviors increases glycemic control (8).

In our study, we aimed to evaluate the level of diabetes-related self-care and factors that may interact with self-care in adult patients who applied to the diabetes outpatient clinic of our hospital.

2. Materials and Methods

Our study is a cross-sectional study and was conducted between May 15, 2021 and September 15, 2021 in patients with diabetes mellitus diagnosed for at least 1 year who applied to Trakya University Health Center for Medical Research and Practice Obesity and Diabetes Outpatient Clinic. Ethics committee approval was obtained with the decision of Trakya University Faculty of Medicine Scientific Research Ethics Committee on 26 April 2021 (No:2021/197). After obtaining verbal consent from the patients, a total of 71-question questionnaire consisting of sociodemographic data, education and treatments received, lifestyle, height-weight, waist circumference and body mass index (BMI), and Diabetes Self-Care Scale (DSCS) was applied by face-to-face interview method. Height, weight and waist circumference measurements were made by the researchers.

Diabetes Self-Care Scale

The Diabetes Self-Care Scale was developed in the USA in 2005 under the leadership of Lee and Fisher to determine the self-care levels of individuals diagnosed with diabetes mellitus (9). The Cronbach alpha level of the original scale was 0.80. The Turkish validity and reliability study of the scale was conducted by Karakurt in 2008. The results of the analysis showed that the Turkish version of the scale had a 0.81 Cronbach alpha level, had high validity and reliability, and was suitable for application to the Turkish population (10). The scale is a 4-option Likert-type scale and contains 35 items. The

minimum score is 35 and the maximum score is 140; the higher the score, the better the self-care level in patients with diabetes. A score of 92 and above is considered acceptable. The items in the scale include feeding time and status, doing regular physical activity, using treatment as recommended, measuring and recording blood glucose, going to doctor follow-ups for blood glucose control, foot care and understanding its importance, personal hygiene methods, and having knowledge about diabetes and the complications it may cause.

Statistical analysis

Considering the number of patients in Trakya University Health Center for Medical Research and Practice Obesity and Diabetes Outpatient Clinic for the previous months, it is expected that approximately 300 diabetes patients will apply during the study period. When the sample size was calculated with 5% type-1 error and 80% power, at least 114 individuals were planned to be included in the study. A total of 132 patients who agreed to participate within the specified period were included in the study.

Statistical analysis of the data was performed with SPSS 19 package program. Numerical data are given as mean, standard deviation, minimum and maximum values; distribution data are given as n (number) and % (percentage). In the analysis of our data, descriptive statistics and nonparametric tests Mann Whitney-U, Kruskal-Wallis were conducted. Spearman analysis were used for correlation analysis. Statistical significance level was considered significant when $p<0.05$.

3. Results

A total of 132 participants, 83 (62.9%) female and 49 (37.1%) male, were included in the study.

The mean score of the diabetic patients who participated in our study was 96.25±19.61 (minimum 50, maximum 125).

The mean DSCS scores of the participants according to the sociodemographic attributes were given in the table (Table 1).

Table 1. The mean scores of the participants according to the sociodemographic attributes

		n (%)	Mean of DSCS	p
Gender	Female	83 (62.9)	97.48±19.60	0.305*
	Male	49 (37.1)	94.18±19.66	
Educational status	Illiterate	7 (5.3)	64.85±7.86	<0.001**
	Primary school	62 (46.9)	92.77±19.68	
	Secondary school	14 (10.7)	102.50±15.50	
	High school	28 (21.2)	99.60±18.87	
	University or higher	21 (15.9)	108.38±10.14	
Marital status	Single	35 (26.5)	99.37±19.71	0.223*
	Married	97 (73.5)	95.13±19.56	
Income and expenditure status	Income less than expenditure	41 (31.1)	85.60±20.94	<0.001**
	Income equal to expenditure	62 (47.0)	98.79±17.33	
	Income more than expenditure	29 (21.9)	105.89±15.57	
Duariton of diabetes	< 5 years	39 (29.5)	93.00±21.19	0.181**
	5-10 years	29 (21.9)	92.06±22.07	
	> 10 years	64 (48.5)	100.14±16.80	
Presence of diabetes in the family	Yes	80 (60.6)	97.71±18.54	0.505*
	No	52 (39.4)	94.01±21.14	

*n=number, DSCS: Diabetes Self Care Scale, *Mann-Whitney U, **Kruskal-Wallis H*

Of the participants who received diabetes-related education, 96 (72.7%) stated that they received education on foot care, 103 (78.1%) on nutrition plan, 100 (75.8%) on exercise, 103 (78.1%) on hyperglycemia, 105 (79.6%) on drug use, and 99 (75.0%) on hypoglycemia. The number of participants who stated their doctor as the source of information was 84 (63.6%), 80 (60.6%) said a nurse, 20 (15.2%) said family and friends, 41 (31.1%) said written or visual media (TV, books, magazines, newspapers, etc.), and 14 (10.6%) said social media (Twitter, Facebook, Instagram, etc.). Patients who received information from the doctor had statistically significantly higher scores on the DSCS (p=0.007).

The mean DSCS scores of the participants according to the treatment they used were given in the table (Table 2).

Table 2. The mean DSCS scores of the participants according to the treatment they used

		n (%)	Mean of DSCS	Median	P*
Diet	Yes	106 (80.30)	98.96±18.71	102	**0.003**
	No	26 (19.70)	85.23±19.66	81	
Exercise	Yes	4 (3.03)	98.98±19.05	102	**0.005**
	No	128 (96.97)	87.75±19.16	84.5	
Oral Antidiabetics	Yes	90 (68.18)	95.50±20.50	99.50	0,698
	No	42 (31.82)	97.88±17.68	102	
Insulin	Yes	70 (53.03)	99.65±17.61	102	0,068
	No	62 (46.97)	92.41±21.14	97	
Herbal products	Yes	4 (3.03)	85.75±27.42	85.5	0,469
	No	128 (96.97)	96,58±19.37	100.5	

*n=number, DSCS: Diabetes Self Care Scale, *Mann-Whitney U*

While 20 (15.2%) of the participants visited the doctor once a month, 19 (14.4%) visited the doctor once in every 2 months, 41 (31.0%) once in every 3 months, 20 (15.2%) once in every 6 months, and 32 (24.2%) once a year. A statistically significant correlation was found between the frequency of diabetes control and the score on the DSCS (p<0.001). It was determined that the self-care level increased as the frequency of control increased.The distribution of diabetes-related complications and the mean scores of the DSCS were given in the table (Table 3)

Table 3. Complications due to diabetes and mean scores of DSCS

		n (%)	Mean of DSCS	Median	p*
Eye disease	Yes	18 (13.6)	98.83±21.9	103	0.229
	No	114 (86.4)	94.44±19.4	98	
Kidney disease	Yes	28 (21.2)	90.50±21.3	97	0.181
	No	104 (78.8)	96.26±19.2	100	
Nerve damage	Yes	31 (23.5)	89.23±21.8	98	0.107
	No	101 (76.5)	96.82±18.9	101	
Cardiovascular disease	Yes	21 (15.9)	86.33±19.6	95	**0.019**
	No	111 (84.1)	96.68±19.4	101	
Foot wound	Yes	15 (11.4)	91.67±21.6	99	0.544
	No	117 (88.6)	95.47±19.6	99	
Cerebrovascular disease	Yes	7 (5.3)	77.57±20.4	72	**0.036**
	No	125 (94.7)	96.02±19.3	99	

*n=number, DSCS: Diabetes Self Care Scale, *Mann-Whitney U*

It was found that as the educational status and income level increased, the participants' DSCS scores increased (p<0.001 for both). Among the participants, 2 (1.5%) were underweight, 20 (15.1%) were normal, 42 (31.9%) were overweight, 39 (29.5%) were mildly obese, 22 (16.7%) were moderately obese, and 7 (5.3%) were morbidly obese. A statistically significant and inverse correlation was found between self-care level and body weight, waist circumference and body mass index (BMI) (Table 4).

Table 4. Relationship between the DSCS score and body weight, height, waist circumference and BMI

	Mean of DSCS	Median	r	p
Body weight (kg)	83.54±17.57	80.5	-0.393	**<0.001**
Height (cm)	164.81±8.36	164	-0.011	0.897
Waist circumference (cm)	105.13±16.73	105	-0.410	**<0.001**
BMI	30.76±6.12	30.17	-0.412	**<0.001**

BMI: Body mass index, DSCS: Diabetes Self Care Scale, r: Spearman rho

No statistical significance was found between the participants' DSCS scores and gender (p=0.305), marital status (p=0.223), duration

of diabetes (p=0.181), hospitalization due to diabetes (p=0.341), and presence of diabetes in the family (p=0.505).

4. Discussion

Diabetes is a chronic health problem whose importance is increasing day by day in the world due to its frequency and the problems it causes in the patient's life. With the rapid change in lifestyle, the prevalence of type 2 diabetes is increasing rapidly in all societies. Diabetes negatively affects individuals of all ages.

The key point in healthy aging of patients with diabetes mellitus is self-care. Patients should take over the management of their disease by gaining knowledge and skills and improving the methods and techniques they apply in the self-care process (11,12). People who can take care of themselves and change their lifestyle can be effectively protected from complications.

The mean score of the diabetic patients who participated in our study was found to be 96.25±19.61 (minimum 50, maximum 125). Since the minimum acceptable score level of the scale is 92, the mean self-care score in our study can be considered as acceptable. In the study of Karakurt (10) conducted in Turkiye, the mean score of the DSCS was found to be 82.84, and 81.6 in the study of Karasoy (13). The reason for these differences may be the sociocultural differences in the regions where the studies were conducted.

In our study, no statistically significant difference was found in terms of the score of the DSCS according to gender. However, unlike our study, there are studies in the literature in which self-care in female diabetic patients was found to be higher than male patients (10,14,15). It can be said that social differences between men and women in Edirne are less than in other studies and therefore self-care levels are similar.

It has been found in many studies that education level and diabetes are related, and diabetes is seen more frequently as the education level decreases (16,17). According to the results of our study, it was observed that the lower the level of education, the lower the score on the DSCS. Our results are similar to the literature in this respect. Dehghani-Tafti et al. reported that diabetics who graduated from primary school had lower self-care behavior scores than university graduates (18). Based on this, they argued that self-care behaviors would increase with increasing education levels. In the self-care study conducted by Kassahun et al. in 2016, it was determined that the education level of diabetes patients was low and the mean score of the DSCS decreased as patient education decreased (19). Similar to our study, Alheik et al. reported in

their self-care study conducted in 2019 that self-care management was increasing in diabetes patients with university and higher education (20). Based on all research findings, we can think that individuals with diabetes who have a higher level of education value self-care more and understand its importance better. This shows that individuals with low education level are at higher risk and that education of these individuals should be emphasized.

In our study, it was found that the patients' score on the DSCS and the regular application of physical exercise and dietary treatment had a statistically significant effect on each other. These results of our study are similar to the literature (15,21-23). The high self-care levels of patients who perform regular physical activity and follow dietary recommendations may be the most important step taken by individuals to manage their diseases.

A statistical significance was found between the patients' diabetes-related education status and the DSCS score. Accordingly, the self-care levels of patients who received education and information were found to be higher than those who did not. In a 2017 study evaluating the factors affecting self-care, it was stated that one of the most important reasons affecting the low self-care level of patients was that patients did not have sufficient information about diabetes and its regulation. A decrease was observed in the diabetes self-care level of patients who were not informed (24). In a similar study on diabetes self-care conducted by Ishak et al., it was determined that patients with a higher level of knowledge in line with the education they received about diabetes had a higher level of self-care (25). Orem stated that there is a parallel interaction between the self-care power of the person and the level of knowledge in the self-care theory and that a sufficient level of knowledge further improves the self-care power (26). In their 2019 study, Alhaik et al. stated that educational programs to be organized for diabetes will contribute positively by increasing the level of knowledge about self-care (20). Education is a factor that makes a difference not only in diabetes but in every aspect of life. The high and significant average supports this idea. At the same time, it shows that the education given to the patients has achieved its purpose. The patient who requests information about how to do self-care from the health counselor is open to putting what they have learned into practice and getting better. In our study, the mean score of the DSCS was found to be significantly higher in patients whose source of information was a doctor. The reason for this is that the patient who receives information from a scientifically trained person is better at self-care.

In our study, a statistically significant relationship was found between the frequency of diabetes control and self-care. Those with 6-month and less frequent check-ups had lower self-care levels than those with more frequent check-ups. Similar to our study, in the studies of Kalaycı, and Usluoğlu, the mean scores of those who had frequent check-ups were higher (27,28). Frequent visits to controls show that patients care about treatment and controls. The patient who comes to health visits frequently will notice the slightest change in the course of his/her disease; then will request the appropriate treatment from the health counselor as soon as possible. Possible complications will be recognized and intervened early in the patient who will be in constant communication with health professionals. Patients with poor self-care can be invited to visits more frequently, leading to an improvement in self-care and complication rates.

Self-care levels were found to be lower in patients with cardiovascular and cerebrovascular complications in our study. The reason for this may be that patients who develop inadequacy in organ functions after vascular complications have difficulty in self-care. Ishak et al. also found that self-care levels were significantly lower in patients with microvascular complications, which is consistent with our study (25).

A statistically significant and inverse correlation was found between the self-care level of the participants and BMI. Obese individuals are also expected to have worse self-care. Exercise and diet are part of self-

care. The high level of self-care in participants who exercised regularly in our study supports this idea. Our study shows that all patients with diabetes should be followed up in terms of obesity, and risk management should be performed.

Waist circumference is considered to be 88 cm for women and 102 cm for men. In the study of Karakurt, waist circumference was 104.84 cm before self-care training and 103.87 cm after training (10). In the study by Wolf et al. in which type 2 diabetes patients were trained for 12 months and the results were evaluated, 118.1 cm. was found and a decrease in waist circumference was observed after training (29). Education not only raised the awareness of the patients but also helped them to avoid obesity with their diet. In our study, the mean waist circumference of the patients was found to be 105.13±16.73 cm. Positive effects on self-care and obesity with education will improve the course of the disease.

Our study showed that high self-care in diabetic patients is important in disease maintenance. Self-care is also influenced by many factors, many of which can be changed at any stage of the health system. Our study has shown that focusing on modifiable factors, rather than focusing on drug therapies, can lead to much more favorable outcomes in the course of the disease. At the same time, education provided by competent people makes a significant positive difference in the self-care of people with diabetes.

Limitations

Our study was conducted at Trakya University Health Center for Medical Research and Practice Obesity and Diabetes Outpatient Clinic. Differences in the other centers where the patients were followed up and the health services they received may change the self-care outcomes. Due to sociocultural differences, multicenter and larger studies are needed to reflect Turkiye in general.

5. Conclusion

The prevalence of diabetes is increasing with the change in lifestyle all over the world and it is predicted to be an even more serious problem in the coming years. Improving the course of the disease and reducing mortality and morbidity are as important as interventions to prevent the disease. Improvement interventions related to self-care constitute the basis of success in the fight against the disease in individuals with diabetes. Increasing income, increasing the frequency of check-ups, giving nutrition and exercise the importance they deserve, decreasing waist circumference and BMI, along with education provided by competent people are factors that should be given importance in increasing self-care and managing the disease.

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Ethics

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Research Article / Araştırma Makalesi

Laparoscopic Adrenalectomy: A Single-Center's Experience

Laparoskopik Adrenalektomi: Tek Merkez Deneyim

Murat Güner, Cengiz Aydın

Sağlık Bilimleri Üniversitesi Izmir Tepecik Egitim ve Araştırma Hastanesi Genel Cerrahi Kliniği, Izmir, Turkey

Abstract

Laparoscopic adrenalectomy (LA) has become the "gold standard" for treating most adrenal lesions. The purpose of this study was to evaluate the results of 98 consecutive laparoscopic adrenalectomies performed over 15 years at a single center. Ninety-eight patients who underwent laparoscopic adrenalectomy between 2006 and 2021 at the Izmir Tepecik Training and Research Hospital were included in this retrospective study. Previous abdominal surgery, American Society of Anesthesiologists (ASA) score, tumor size and location, surgical procedures, and postoperative results with histologic diagnosis and complications were analyzed from patient archives. The mean age of the patients was 53.38 ±13.55 years. The mean size of the adrenal lesions was 59.1 (range, 23 to 130) mm. Nineteen (19.4%) patients required conversion to open adrenalectomy. The rate of conversion was found to be significantly higher in patients with intraoperative complications (p<0.001) and lesions larger than 8 cm (p=0.032). The mean length of hospital stay was 6.3 (range, 2-32) days. Laparoscopic adrenalectomy is the standard treatment for adrenal lesions. Tumor location, histopathologic type, and the age of the patients should not be considered a contraindication for laparoscopic adrenalectomy. Intraoperative complications and lesions larger than 8 cm are seen as the most important reason for conversion to open adrenalectomy.

Keywords: Laparoscopic adrenalectomy; Laparoscopic surgery; Adrenalectomy; Endocrine surgery

Özet

Laparoskopik adrenalektomi (LA) adrenal lezyonunların tedavisinde "altın standart" tedavi yöntemi haline gelmiştir. Bu çalışmanın amacı tek merkezde 15 yıllık sürede uygulanan 98 laparoskopik adrenalektomi sonuçlarını değerlendirmektir. Bu retrospektif çalışmaya 2006-2021 yılları arasında İzmir Tepecik Eğitim ve Araştırma Hastanesi'nde laparoskopik adrenalektomi uygulanan doksan sekiz hasta dahil edildi. Hastaların tümör boyutu ve lokalizasyonu, ASA skoru, daha önce geçirilmiş abdominal cerrahi varlığı, uygulanan cerrahi işlem, histopatolojik tanı ve intraoperatif komplikasyon sonuçları hasta arşivlerinden analiz edildi. Hastaların yaş ortalaması 53.38 ±13.55 idi. Adrenal lezyonların ortalama boyutu 59.1mm (23-130 mm) idi. On dokuz (% 19.4) hastada açık adrenalektomiye dönüldü. İntraoperatif komplikasyon gerçekleşen (p<0.001) ve 8 cm'den büyük lezyonu (p=0.032) olan hastalarda açık cerrahiye dönüş oranı anlamlı olarak yüksek bulundu. Ortalama hastanede kalış süresi 6.3 gün (2-32 gün) olarak bulundu. Laparoskopik adrenalektomi adrenal lezyonlar için altın standart tedavi yöntemidir. Tümör lokasyonu, yaş veya histopatolojik tip laparoskopik adrenalektomi için kontrendikasyon değildir. İntraoperatif komplikasyon ve 8 cmden büyük lezyonlar açık adrenalektomiye dönüşün en önemli nedenleridir.

Anahtar Kelimeler: Laparoskopik adrenalektomi; Laparoskopik cerrahi; Adrenalektomi; Endokrin cerrahi

Correspondence:
Murat GÜNER
Sağlık Bilimleri Üniversitesi Izmir Tepecik Egitim ve Araştırma Hastanesi Genel Cerrahi Kliniği, Izmir, Turkey
e-mail: mgunerus@yahoo.com

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1. Introduction

Laparoscopic adrenalectomy was first described by Gagner et al. in 1992. Since then, it has become the gold standard treatment method for adrenal lesions (1). Two techniques have been described for laparoscopic adrenalectomy, transperitoneal adrenalectomy, and retroperitoneal adrenalectomy. Also, some studies are indicating that robotic technologies can be used safely in addition to these surgical procedures (2). Laparoscopic adrenalectomy (LA) is preferred to open adrenalectomy (OA) surgery because of less blood loss, lower complication rates, less postoperative pain, shorter hospital stay, and better cosmetic results (3). Open surgery is indicated in the case of radiologic evidence of tumor invasion into the periadrenal tissue, local recurrent tumor of a previously resected adrenal mass, and patients with severe cardiopulmonary disease (4). Although there is no definite contraindication, studies are recommending open adrenalectomy in malignant lesions because of the potential of incomplete resection, tumor spillage, and capsular disruption that can cause local tumor recurrence and metastasis (5). Size is an important variable in predicting malignancy. Although it is reported in the literature that lesions larger than 6 cm are suitable for open surgery due to their malignant potential, studies are reporting that giant lesions can be successfully resected with laparoscopic adrenalectomy (6-7).

2. Materials and Methods

A total of 98 laparoscopic adrenalectomies performed between 2006 and 2021 were evaluated retrospectively.

Preoperative

All patients, tumor size and location, previous abdominal surgery, American Society of Anesthesiologists (ASA) score, surgical procedures, and postoperative results with histologic diagnosis, length of hospital stay, and complications were evaluated retrospectively. All patients underwent preoperative imaging studies [computed tomography (CT) or magnetic resonance imaging (MRI)] to study the morphologic characteristics and size of the lesions. Before surgery, all patients underwent a complete preoperative endocrine evaluation to determine the hormonal activity of the adrenal tumor. In patients with suspected pheochromocytoma, patients were preoperatively treated with alpha-blockers (doxazosin 20 mg/day) (additional beta-blockers in case of co-existing tachycardia) and intravenous volume expansion with colloids and crystalloids. Preoperative steroid treatment was administered to patients with Cushing's disease and serum potassium levels were checked and corrected in patients with Conn's syndrome, preoperatively.

Patients selection

ASA score ≤ III, age less than 82 years, and functioning benign adrenal tumors were the main surgical inclusion criteria. Patients with suspected local invasive malignant adrenal neoplasm were recommended open surgery and excluded from the study.

Surgery

For all patients, the lateral transabdominal approach was used with the patient in the lateral decubitus position. We used a Veress needle to induce pneumoperitoneum. We used four trocars for both right and left-side adrenalectomies. In all patients, the lesion was excised through en bloc resection, and there was no capsular disruption during dissection. At the end of the procedure, surgical specimens were positioned in an endo-bag and removed through the operative trocar.

Postoperative management

In all patients, normal diet and mobilization started on the first postoperative day. Abdominal drainage was performed on all patients and drainage was removed on the first or second postoperative day. Postoperative complications were recorded.

Statistical analysis

Statistical analyses were performed using the SPSS software ver. 22.0 (IBM, Armonk, NY, USA). According to the distribution of variables, a Chi-square (χ^2) or Fisher exact

test was used to compare differences in discrete or categorical variables, respectively). Continuous variables were compared using the Student's t-test because of a lack of normal data distribution, continuous variables were assessed using the Mann–Whitney U test, and the significance of the difference in terms of median levels was investigated using the Kruskal–Wallis test. A p-value < 0.05 was considered statistically significant.

3. Results

After obtaining approval from the local ethics committee, the study was conducted at Izmir University of Health Sciences Tepecik Training and Research Hospital General Surgery Clinic between January 2006 and December 2021. A total of 98 patients who underwent laparoscopic adrenalectomy were included in the study. The patients' age, sex, previous abdominal surgery, ASA score, lesion size and location, lesion histopathologic type, surgical procedures, morbidity, and mortality were evaluated. There were 65 women (66.3%) and 33 men (33.7%). The mean age was [mean+standard deviation (SD)] 53.38±13.55 years. The mean lesion size was 59.1 ± 16.71 mm. The mean surgical time was 141.04±24.78 min. The mean length of hospital stay was 6.4 (range, 2-32) days. There were 19 (19.4%) cases of conversion to open surgery. Three patients died during the 30-day perioperative period. The demographic characteristics of patients who were recruited in the study are summarized in Table 1.

Table 1. The demographic characteristics of the patients

Age (Mean+SD) years	53.38 ±13.55
Sex (M/F)	33/65
Operation site*	
Right n (%)	39 (39.8%)
Left n (%)	59 (60.2%)
Operation time (min)	144.85±24.78 min
Tumor size (Mean+SD) mm	59.1 ± 16.71
Tumor diameter >8 cm n (%)	19 (19.4%)
ASA Score	
ASA1 n (%)	57 (58.2%)
ASA2 n (%)	24 (24.5%)
ASA3 n (%)	11 (11.3%)
First Radiologic imaging	
CT n (%)	68 (69.3%)
MRI n (%)	30 (30.6%)
Previous abdominal surgery n (%)	9 (9.2%)
Conversion to open surgery n (%)	19 (19.4%)
Complications n (%)	11 (11.3%)
Hospital stay (day) (Min-Max)	6.36 (2-32)
Mortality n (%)	3 (3.1%)

Pathologic reports are reviewed and shown in Table 2. Forty-two (42.9%) patients had cortical adenoma, 20 (20.4%) had pheochromocytoma, and nine (9.2%) patients had metastasis. The most common primary tumor causing metastasis was lung cancer in six patients, renal cell cancer in two, and colon cancer in one patient, respectively.

Table 2. Histologic type of adrenal lesions

Histological type	Patients (%)
Adenoma	42 (42.9)
Hyperplasia	5 (5.1)
Pheochromocytoma	20 (20.4)
Myelolipoma	8 (8.2)
Hamartoma	1 (1.0)
Cyst	9 (9.2)
Carcinoma	3 (3.1)
Hemangioma	1 (1.0)
Metastasis	9 (9.2)

Nineteen of 98 patients' surgery bean as LA and was converted to OA, nine due to bleeding, five for tenacious adhesions, and five for insufficient exposure. Bleeding was the most common cause of converting to OA. There was no statistical difference between the sexes regarding the rate of conversion from LA to OA (p=0.449). No statistical difference was found between right and left-sided masses in terms of the rate of conversion from LA to OA (p=0.311). There was no statistical difference between the histopathologic subtypes and the rate of conversion to OA (p=0.210), but conversion to OA was reversed in one patient with carcinoma.

When the rates of conversion to OA with previous abdominal surgery were evaluated, no statistical difference was found (p=0.821). There was no statistical difference between the ASA score and the rate of conversion to OA (p=0.178). Intraoperative complications were found to be an important factor in conversion to OA (p<0.001). There was no statistical difference in the rate of conversion to OA between patients diagnosed using preoperative CT or MRI (p=0.651).

Patients converted to OA and patients who completed LA were aged a mean of 60.26±13.80 years and 51.72±13.04 years, respectively. The mean age was found to be significantly higher in the patients who were converted to OA (p=0.013).

The median tumor size was found as 50 (min: 23, max: 130) mm in the LA group and 70 (min: 32, max: 125) mm in the converted OA group. There was no statistical difference between the two groups according to tumor size (p=0.317). Conversion to OA was needed in seven of 19 patients with adrenal lesions larger than 8 cm. When the lesions larger than 8 cm and lesions smaller than 8 cm were compared according to conversion rates, a significant difference was found (p=0.032).

The mean length of hospital stay was 5 (min: 2, max: 32) days in patients whose surgeries were completed laparoscopically and 7 (min: 4, max: 28) days in patients who were converted to open surgery. The length of hospital stay was found to be significantly longer in patients who were converted to OA (p<0.001).

Five of the patients with intraoperative complications were male and six were female. There was no statistical difference between the intraoperative complication and sex (p=0.350). No statistical difference was found between intraoperative complication and localization or histopathologic subtype (p=0.353 and p=0.90, respectively).

When previous abdominal surgery and intraoperative complications were evaluated, no significant difference was found (p=0.260). When intraoperative complications were evaluated according to the ASA score, ASA1 (n=0), ASA2 (n=10), ASA3 (n=1) were found, respectively (p=0.056). Although no statistically significant difference was found, the rate of patients with complications in the ASA2 risk group was found as 17.8%. The median tumor size of the patients with intraoperative complications was found as 55 (min: 39, max: 120) mm (p=0.411).

There was no significant difference between tumor size and histopathologic findings (p=0.139). Due to bleeding, splenectomy was required in three patients and nephrectomy in three patients. Serious vena cava injuries occurred in two patients, which were repaired intraoperatively. However, postoperative bleeding recurred in these patients and they were reoperated; both patients died during the follow-up period. One patient who needed a nephrectomy because of bleeding died of pulmonary thromboembolism. Six patients had postoperative complications. The 30-day morbidity rate was 6.1%; pulmonary infection in two patients, wound infection in two patients, and bleeding in two patients

4. Discussion

The adrenal glands are in a hard-to-reach area due to their location, thus large incisions are needed in open surgical procedures, but we can reach this area more easily with laparoscopic surgery. There are studies indicating that adrenal lesions larger than 8 cm are not suitable for laparoscopic surgery (8-9). However, it has been reported in the literature that adrenal lesions with a size of 18 cm can also be removed laparoscopically (10).

In our study, the median tumor size was found as 50 (min: 23, max: 130) mm in the LA group and 70 (min: 32, max: 125) mm in the converted OA group. However, conversion to OA was needed in seven of 19 patients with adrenal lesions larger than 8 cm. When the lesions larger than 8 cm and lesions smaller than 8 cm were compared according to the conversion rate, a significant difference was found (p=0.032).

Size is not a contraindication for laparoscopic adrenalectomy, but there are studies in the literature that accept 6 cm or 8 cm as the limit (11,12). LA in large lesions is more difficult than in smaller lesions and it is associated with significantly longer surgical time, increased intraoperative blood loss, and higher conversions rates. Patients with lesions larger than 8 cm should be evaluated more carefully and the possibility of conversion to open surgery should be kept in mind.

LA is currently the gold standard for the treatment of adrenal tumors (4,5). Conversion from LA to OA during surgery may be necessary to prevent complications. In a study, BMI ≥30 kg/m^2, tumors of >5 cm in diameter, and histologic type were significantly associated with conversion to open surgery (13). In our study, 19 of 98 (19.4%) patients whose surgery began as LA was converted to OA: nine for bleeding, five for tenacious adhesions, and five for insufficient exposure. Intraoperative complications were found an important factor in conversion to OA (p<0.001). Bleeding was the most common cause of converting to OA. No statistically significant results were found between conversion rates and sex, lesion side, or histopathologic type of lesion. In our hospital, resident training is given and laparoscopic adrenalectomy is performed by different surgical teams, and these surgeons are not of equal surgical experience. Bleeding is seen as the most important cause of conversion to open surgery, and in our opinion, surgical experience is one of the most important reasons for conversion to OA.

In our study, when the histopathologic types were examined, the most common lesion was adenoma 42.9%, followed by pheochromocytoma 20.4%, and metastasis 9.2% (Table 2). The most common cause of adrenal metastases is the lung, followed by renal malignancies and others (14). In our study, the most common primary tumor causing metastasis was lung cancer (n=6, renal cell cancer (n=2), and colon cancer (n=1), respectively. There are studies reporting that adrenalectomy improves outcomes in selected patients with metastatic disease (15,16). Open surgery is recommended in the presence of metastases in many studies (17,18). In our study, nine patients with metastases underwent laparoscopic adrenalectomy, and conversion to OA was needed in four of nine patients.

Age is an independent risk factor for postoperative complications or mortality, but in selected patients, major surgical procedures can be performed safely and comparable results can be achieved in the young population (19,20). According to age, patients who were converted to OA and patients who completed LA were found to be aged 60.26±13.80 years and 51.72±13.04 years, respectively. The mean age was found to be significantly higher in the patients who were converted to OA (p=0.013). Weinandt et al. stated that laparoscopic adrenalectomy could be safely performed in patients aged over 75 years of age without a significant increase in postoperative morbidity (21). Minimally invasive surgery for all age groups seems to be the best option; although the mean age of the patients who were converted to open surgery was found to be higher in our study, we do not think that age alone is a contraindication for laparoscopic surgery.

Adrenal lesions are found in approximately 4-6% of routine abdominal imaging examinations for other indications, often as incidental asymptomatic adrenal lesions (22). CT is the most commonly used technique for adrenal lesions and MRI is the second-line modality for the investigation of adrenal lesions (23). In our study, CT was used as first-line imaging in 68 (69.3%) patients and MRI was used as first-line imaging in 30 (30.6%) patients. There was no statistical difference in the rate of conversion to OA or intraoperative complications between patients

whose disease was diagnosed preoperatively using CT or MRI (p=0.651).

Although studies are reporting the length of hospital stay as 2-4 days (24,25), some authors have reported a longer length of hospital stay (4-7 days) (26,27). Hermosa et al. found a significant difference between a prolonged hospital stay and tumor size larger than 9 cm, day of operation, estimated blood loss ≥60 mL, and drainage (28). In our study, the mean length of hospital stay was 5 (min: 2, max: 32) days in patients whose surgery was completed laparoscopically and 7 (min: 4, max: 28) days in patients who were converted to open surgery. The length of hospital stay was found to be significantly longer in the patients who were converted to OA (p<0.001).

There is a risk of complications in every patient who undergoes surgery. Although complication rates decrease with surgical experience, complications can be seen due to reasons such as malignancy, anatomic variations, adhesions, and insufficient exposure. The most common complications during laparoscopic adrenalectomy are vascular injuries, intestinal injuries, liver and spleen injuries, pleural injuries, and pancreas injuries (29). In our study five of the patients with intraoperative complications were male and six were female. There was no statistical difference between the intraoperative complications and sex, localization, histopathologic subtype, or previous abdominal surgery (p=0.350, p=0.353, p=0.90, and p=0.260, respectively). Due to bleeding, splenectomy was required in three patients and nephrectomy in three patients. Serious vena cava injury occurred in two patients and the vena cava was repaired intraoperatively. However, postoperative bleeding recurred in both patients and they were reoperated but died in the follow-up period. One patient who needed a nephrectomy because of bleeding died of massive pulmonary thromboembolism.

This study is a retrospective study and has some limitations. The surgical procedures were performed by different surgeons, and each surgeon's experience with laparoscopic adrenalectomy is not equal. Therefore, we cannot evaluate the number of cases required for the learning curve. Postoperative initiation of oral feeding, use of drains, and time to discharge differ between surgeons and affect the length of stay in the hospital.

5. Conclusion

Minimally invasive surgery is increasingly used in all surgical procedures. LA is a safe procedure for suitable patients with acceptable complications and low conversion rates. Intraoperative complications and lesions larger than 8 cm are seen as the most important reasons for conversion to open surgery.

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Ethics

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Factors Affecting Tolerance Development in Children with Food Allergies

Besin Alerjisi Tanılı Hastalarda Tolerans Gelişimi ve Toleransa Etki Eden Faktörler

Yasemin Ersözlü, Hülya Anıl, Koray Harmancı

[1]Department of Pediatric Infection Diseases Scholl of Medicine Acibadem University, Istanbul, Turkiye

[2]University of Eskişehir Osmangazi, Department of Pediatric Allergy and Immunology, Eskisehir, Turkiye

Abstract

Although the prevalence of food allergy (FA) is unknown, it is estimated to have increased in recent years. In general, food allergies are more common in the pediatric age group than in adults. In our study, we aimed to determine the development of tolerance and the factors affecting it in children with food allergies. Medical records of cases followed up for FA were retrospectively reviewed between 2013 and 2016. Gender, age of first symptom, duration of breastfeeding, family history of atopy, multiple food allergies, concomitant allergic diseases and clinical evidence of the cases were evaluated. In addition, prick test results, total IgE and specific IgE levels, food challenge test results and tolerance development were evaluated. Of 319 patients 57.7% (184) were male. The average age of onset of symptoms was 3 months. The most common symptoms were related to the gastrointestinal system (69.9%), the skin (22.3%) and the respiratory system (6.3%). When the tolerance development rates were investigated by years, it was found that the tolerance developed 87.1% in the first year, 5.9 % in the second and 2.8% in the third year. The most common allergens are cow's milk (71.3%), eggs (17.6%), peanuts (2.8%), nuts (2.04%) and other foods such as strawberries, cocoa, peaches. The mother's smoking status was significantly associated with the development of tolerance. The rate of development of tolerance in the first year was significantly higher in non-Ig E-mediated allergies and single food allergies.
Keywords: Food allergy, Prognosis, Tolerance

Özet

Besin alerjisinin prevelansı bilinmemekle birlikte son yıllarda giderek arttığı tahmin edilmektedir. Genel olarak besin alerjileri pediatrik yaş grubunda erişkine oranla daha sık görülür. Çalışmamızda; polikliniğimizde gıda alerjisi tanısı olan hastalarımızın, doğal seyri, tolerans gelişimi ve toleransa etki eden faktörleri belirlemeyi hedefledik. Ocak 2013-Ocak 2016 yılı arasında polikliniğimizde Besin Alerjisi tanısı alan hastaların dosyaları retrospektif olarak incelendi. Hastaların cinsiyetleri, ilk semptom yaşı, anne sütü alma süresi, ailede atopi öyküsü, çoklu besin alerjisi, ek alerjik hastalık varlığı ve klinik bulguları değerlendirildi. Hastaların prik test sonuçları, total IgE, spesifik IgE, düzeyleri ve tolerans geliştirme durumları değerlendirildi. 319 hastanın 184'ü erkek (%57.7) idi. Hastaların 127'sinde (%39.8) ailede atopi öyküsü ve 71'inde (%22.3) çoklu besin alerjisi mevcuttu. Hastalarda görülen en sık semptom, %65.8 gastrointestinal sistem, %21 cilt bulguları, %6.3 solunum bulgularıydı. Hastaların semptom yaşı 5.8 ± 9,7 ay; tanı yaşı 6.6 ± 9.08 aydı. Hastaların yıllara göre tolerans geliştirme oranları; Birinci yıl 287 (%87,1) ikinci yıl 19'unda (%5,9) üçüncü yıl 9'unda (% 2,8) olarak saptandı. En sık alerjen gıda inek sütü (%71,3), yumurta (%17,6), fıstık (2,8), fındık (%2,04) olmakla beraber diğer gıdalar çilek, kakao, şeftali, buğday, soya, balık olarak saptandı. Çalışmamızda ilk yılda annenin sigara kullanımı ile besin alerjilerinde tolerans gelişimi arasında anlamlı fark saptanmıştır. Non Ig E aracılı besin alerjisi olanlar ve tek besine karşı alerjen olan hastalarda ilk yılda tolerans gelişimi anlamlı oranda faza saptanmıştır.
Anahtar Kelimeler: Besin alerjisi, Prognoz, Tolerans

Correspondence:
Yasemin ERSÖZLÜ
Department of Pediatric Infection Diseases Scholl ofMedicinei Acibadem Universit, Istanbul, Turkiye
e-mail: yaseminersozlu@gmail.com

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1. Introduction

There is a significant increase in childhood allergic diseases worldwide. The prevalence of these diseases varies from country to country and even in different regions of the same country (1). Since these changes cannot be explained by genetic factors alone, environmental factors are also blamed.

The main allergenic foods are cow's milk, chicken eggs, soybeans, wheat in childhood, peanuts, shellfish, fish and nuts in adults. Other allergenic foods include legumes, vegetables, fruits, beef, lamb, pork, chicken, and turkey meat (2-7). Sensitization with food antigen can occur not only by ingestion of food but also after inhalation and skin contact. In addition, cross-reactions can occur with allergens such as birch pollen, profilins, latex, and lipid transfer protein (8,9).

The healthy immune system maintains unresponsiveness towards to potential food allergens. Various hypotheses such as integration of vitamin D deficiency, hygiene and dual allergen exposure hypothesis have been proposed to explain the increase in FA. Morst recently investigated hypothesis is dual allergen hypothesis. Randomise controlled trials recommend including possible common food allergies such as peanuts and eggs in complementary foods nutritional regimens starting at approximately 6 months but not before 4 months. National Institutes of Health recommendations promotes the early introduction of peanut for the prevention of peanut allergy(46). Oppositevly the study Enquiring about tolerane (EAT) suggest that early introduction of allergenic food in sufficient quantity from 3 months of age may be able to help prevent food allergies developing in children(47). Future advances understanding oral tolerance in human subjects will largely determine treatment.

In our study; we aimed to determine the factors that affect the natural course, development of tolerance and tolerance of our patients diagnosed with food allergy.

2. Materıals and Methods

Between January 2013 and January 2016, the files of the patients diagnosed with Food Allergy in the outpatient clinic of Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Allergy-Immunology Department were retrospectively analyzed according to the questionnaire form prepared. Local ethical committees approved all studies.

Food allergy was diagnosed by clinical history, allergy tests, elimination of cow's milk from the diet and food challenge test. The diagnosis of non-IgE mediated food allergy was made in the presence of clinical symptoms, the disappearance of symptoms with elimination diet and the occurrence of symptoms when suspected food was given again. From the polyclinic files of the children who were followed up with a diagnosis of food allergy, gender, first symptom age, breastfeeding time, age at starting additional foods, family history of atopy, multiple food allergy, presence of additional allergic disease, inhaled allergen sensitivity, and clinical findings were obtained. The time interval between milk protein intake and reaction formation and the pattern of milk protein intake were evaluated. Prick test, prick to prick test results with pasteurized milk, total IgE, milk and casein specific IgE levels and reactions food challenge test were evaluated. Tolerance development status of the patients was evaluated according to the results of the loading test performed both at home or in clinic and information received from the families.

In statistical analysis, chi-square test was used in comparison of categorical data, T test (Student's T test) in independent groups in case of assumptions in comparison of numerical measurements, and MannWhitney U test if assumptions were not provided. Mann Whitney U test was used for comparing two independent groups, while Pearson chi-square and Fisher's chi-square tests were used for comparison of categorical variables. Two ratio tests were used in the frequency distribution test (f) and chi-square analysis was used in the test of cross tables. A value of $p < 0.05$ was considered statistically significant in all tests.

3. Results

Between January 2013 and December 2016, 416 children who were followed up with a diagnosis of food allergy were found. Forty-three children with a diagnosis of food allergy

excluded during their follow-up and 16 patients with a diagnosis of inflammatory bowel disease were excluded from the study. 17 patients whose ICD codes were entered incorrectly and 21 patients whose follow-up data could not be accessed were excluded from the study. A total of 319 patients were included in the study. The characteristics of the patients included in the study are shown in Table 1.

According to immunological mechanisms, 220 of the patients (69.9%) had non-IgE-mediated, 48 (15%) had Ig E-mediated, and 51 (16%) had mixed disease. The clinical findings of the patients are summarized in Table 2.

Table 1. Characteristics of patients with food allergies

Gender	**n**
Male	184 (57,7%)
Female	135 (42,3%)
Age of first symptom (months)	**3 (2-6)**
Breastfeeding time (months)	**12 (9-17,25)**
Additional food starting age (months)	**6 (5-6)**
Family history of atopy	**127 (39,8%)**
Presence of multiple food allergies	**72 (22,6%)**
Prematurity	**24 (7,5%)**
Presence of additional allergic diseases	**101 (31,3%)**
Asthma	9/101
Rhinitis	18/101
Atopic dermatitis	74/101

Table 2. Clinical findings of patients with food allergies

Clinical finding	**n (%)**
Skin manifestations	71 (22,3)
Urticaria	7 (9,9)
Atopic dermatitis	60 (84,5)
Angioedema	4 (5,6)
GIS findings	223 (69,9)
Bloody stool	61 (27,35)
Mucus stool	72(32,28)
Bloody mucus stool	41(18,3)
Vomiting	12 (5,38)
Abdominal pain	10 (4,48)
Diarrhea	11 (4,93)
Constipation	14 (6,27)
Bloody vomiting	2 (0,9)
Respiratory symptoms	20 (6,3)
Rhinitis	3 (15)
Wheezing	9 (45)
Cough	8 (40)
Anaphylaxis	5 (1,6)

The most common symptoms in children with food allergy were GIS findings in 223 (69,9%) patients, skin findings in 71 (22,3%) patients, and respiratory system findings in 20 (6,3%) patients. It was determined that five (1,6%) of the patients developed anaphylaxis after consuming food which is an allergen.

When the patients were separated according to food allergens, the most common allergen was cow's milk (71,3%). Other common allergens were eggs (17,6%), peanuts (2,8%), and hazelnuts (2,04%).

In the first year controls while tolerance development was observed in 278 (87,1%) of patients, it did not develop in 40 (12,5%) of patients (Table 3). Tolerance did not develop in 22 patients at the second year and in 13 patients at the third year follow-up.

Table 3. Distribution of tolerance development by years

Tolerance development	First year	Second year	Third year
No	41 (12,8%)	22 (6,8%)	13 (4%)
Yes	278 (87,1%)	19 (5,9%)	9 (2,8%)
Total	319	41 (12,8%)	22 (6,9%)

In tolerance development; gender, family history of atopy, social environment, prematurity, breastfeeding time, starting month of supplementary food, eosinophilia, total and specific IgEs, food prick test were not significant. The mothers of 267 (96%) of 278 (87,1%) patients with tolerance development in the first year were non-smokers (p <0.01). In patients who developed tolerance in the second year and in the third year, the history of smoking in the mother was lower than those who did not develop tolerance, but the difference was not statistically significant.

While 225 (91,1%) of 278 (87,1%) children with tolerance development at the end of the first year showed an allergic reaction to a single food; 53 (19,1%) of them are allergic to multiple foods. Those who are allergic to a single food develop more tolerance than patients with multiple food allergies, which is statistically significant (p <0.01). All children with tolerance development in the second year had a single food allergy. Tolerance did not develop in those with multiple food allergies (p <0.001).

When allergen types are classified as cow's milk, egg and other; 209 (75,2%) of the children with tolerance development in the first year were allergic to cow milk, 15 (5,4%) to eggs, 54 (19,4%) to other foods (p <0.01). Only 1 (5,3%) of 19 children who developed tolerance in the second year were allergic to eggs (p <0.01). 2 (22,2%) of 9 children with tolerance development in the third year were allergic to eggs (p = 0.544). The development of tolerance in cow's milk allergy was found to be significantly higher than other allergens.

When the characteristics of 13 patients without tolerance development in the third year were examined, 7 (53,8%) were male and 6 (46,2%) were female. 12 (92,3%) were living in the urban area. The mothers of 10 (76,9%) were not smoking. 6 (46,1%) of them had non Ig E mediated disease. Twelve (92,3%) of them had multiple food allergies. Variablers affecting tolarence development are summarized in Table 4.

Table 4: Variables affecting tolerance development

		First year tolerance development			Second year tolerance development			Tertian year tolerance development		
		No	**Yes**	***p* value**	**No**	**Yes**	***p* value**	**No**	**Yes**	***p* value**
Smoking	No	28 %68,3	267 %96	**<0,01**	17 %77,3	11 %57,9	>0,05	10 %76,9	7 %77,8	>0,05
	Yes	13 %31,7	11 %4		5 %22,7	8 %42,1		3 %23,1	2 %22,2	
İmmune mechanism	Ig E	14 %34,1	34 %12,5	**<0,01**	9 %40,9	5 %26,3	>0,05	4 %30,8	5 %55,6	>0,05
	NonIgE	21 %51,2	199 %71,6		9 %40,9	12 %63,2		6 %46,2	3 %33,3	
	Mixed	6 %14,6	45 %16,2		4 %18,2	2 %10,5		3 %23,2	1 %11,1	
Number	Multiple food	19	53	**<0,01**	19	0	**<0,01**	12	7	>0,05

		%46,3	%19,1		%86,4			%92,3	%77,8	
Allergen type	Single food	22 %53,7	225 %80,9		3 %13,6	19 %100		1 %7,7	2 %22,2	
	Cow milk	16 %39	209 %75,2	**<0,01**	0	16 %64,2	**<0,01**	0	0	>0,05
	Egg	2 %4,9	15 %5,4		2 %9,1	1 %5,3		0	2 %22,7	
	Other	23 %56,1	54 %19,4		20 %90,9	2 %10,5		13 %100	7 %77,8	

Bold entries are statistically significant p values

4. Discussion

In many Western countries, diseases such as asthma and atopic dermatitis and allergic rhinitis have been increasing in the last 50-60 years and constitute a significant burden on the society and health systems (11-15). It is thought that the frequency of food allergy has increased in the past 10-20 years with atopic diseases and this situation is due to many different risk factors (16-20).

When studies on food allergies in the literature are examined, the most common finding is skin reactions, followed by gastrointestinal findings (14-18). GIS symptoms have been reported as 30.3% (22) in France, 49.3% (23) in the UK, 20.9% (24) in Lithuania, and 27.6% (21) in the European country. Skin reactions were followed by gastrointestinal system finding(23). In our study, the most common symptoms in children with food allergy were related to the gastrointestinal system (GIS) (69.9%). This was followed by skin findings in 22.3% of patients and respiratory system symptoms in 6.3% of patients. The reason for our different findings can be attributed to the difference in the patient population referred to as our hospital, a top-level healthcare institution.

When the children were categorized according to food allergens, the most common allergen was cow's milk (71.3%). This was followed by egg (17.6%), peanut (2.8%), and hazelnut (2.04%). Strawberry, cocoa, peach, wheat, soy and fish were other responsble food allergens. In the study conducted by Orhan et al. (20) in children aged 6-9 years, the most common allergenic foods were red meat (31,8%), cow's milk (18,1%), cocoa (18,1%), chicken egg (13,1%) and kiwi (13,6%) respectively has been reported. However, foods that cause allergies change with age. In our study, we attribute the difference of the foods most frequently responsible to food allergies from other studies conducted in our country to the age group evaluated. Egg and milk are the most common causes of food allergy in all countries (1,21,23,24).

Most of the patients develop tolerance to foods in advanced ages (28,29). In our study, tolerance developed in 87.5% of the children in the first year, 6.8% in the second year, and 2.8% in the third year. Shek (28) showed that 28 of 66 children with egg allergy and 16 of 33 children with cow's milk allergy developed tolerance over time. Similarly, Dannaeus et al. (30) found that 4 out of 12 children with cow's milk allergy, 20 out of 55 children with egg allergy, 5 out of 32 children with fish allergy developed tolerance, but none of the cases with peanut and tree nut allergy developed tolerance. Dias (19) reported in a retrospective study that 44% of 79 children with cow's milk allergy were still allergic by the time they reached the age of 10. In a study conducted in Sweden, it was found that 50% of children with egg allergy passed their allergies by the age of 3 (32). In another study, 52% of children with egg allergy developed tolerance at the age of 3 and 66% at the age of 5 (33). Savage (34) found that the development of tolerance to egg allergy was slower than predicted. The results of this study suggest that, contrary to what was previously known, egg allergy is not a food allergy that usually occurs at school age, but a food allergy that is

likely to persist in later life. Sicherer (35) showed in his multicenter observational study that age of tolerance is not as high as suggested by Savage. The different results of these studies on tolerance developmental ages seem to be influenced by many different factors such as genetic and phenotypic characteristics of the studied population and inclusion criteria.

Although passive smoking is known to be a risk factor for asthma, there is no information about whether it increases the risk of food allergy (25,36,37). There are publications indicating that smoking during pregnancy increases the prevalence of allergic diseases (38,39). Avoiding smoking during pregnancy is recommended for primary prevention from allergic diseases (40). In our study, the mothers of 96% of the patients with tolerance development in the first year were not smoking. Only 4% of their mothers were smoking. A significant relationship was found between the mother's smoking and the development of tolerance in the first year. The mothers of the children with tolerance development in the second and third years smoked at a higher rate than the mothers of the children who developed tolerance in the first year. The smoking rates of the mothers of the children with and without tolerance in the second and third years were not statistically different.

The majority of patients (80.9%) who developed tolerance at the end of the first year had allergies to a single food. These patients develop a higher rate of tolerance than those who are allergic to more than one food. In a study, it was reported that 18% of patients who developed tolerance until the age of 4 were also allergic to other foods and that multiple food allergy had no effect on the development of tolerance (41). Multiple food allergies have been reported in 3.5% of children under 2 years of age and 30.5% of children over 2 years of age with persistent cow's milk allergy (42). In the same study, the presence of allergies to other foods was reported as a risk factor for persistent cow's milk allergy. In a study investigating the differences between single food allergy and multiple food allergy, although not statistically significant, food allergy remission at 2 years of age was found to be less in those with multiple food allergies. In accordance to our study another multicenter study revealed multipl food allergy is a risk factor for late tolerance. Although different results were reported in the literature, it was observed in our study that multiple food allergies had no effect on the development of tolerance. In our study, we think that the effect of multiple food allergies on the development of tolerance may change after the patients are exposed to other food allergens in the next follow-up period.

191 (68.7%) of 278 children who had tolerance development in the first year started to consume complementary feeding after the 4th month. 87 of them (31.3%) switched to additional food before 4 months. All 19 children with tolerance development in the second year and all 9 children with tolerance development in the third year switched to additional foods after the 4th month. A statistically significant relationship was not found between the age of starting the supplementary food and the development of tolerance. It was suggested that families with a high risk of allergic diseases should not give additional food to their atopic children in the first six months. It was recommended to postpone dairy products until the 12th month, eggs until the 24th month, peanuts, hazelnuts, fish and seafood until the 36th month. However, after 2008, European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (APA) are recommended to start supplementary foods in the first 4-6 months (29,34).

When the allergen types are classified in 3 groups as cow's milk, egg and others; Of the 278 patients with tolerance development in the first year, 209 were allergic to cow's milk, 15 to eggs, and 54 to other foods. Tolerance development was higher in those with cow's milk allergy than those allergic to eggs and other foods. There have been several studies of natural hiatory of cow's milk allergy and predictors of remission. The largest multicentre European case series in food allergy, EuroPrevall study, in which standardized evaluation including DBPCFC, population with DBPCFC, %57 comfirmed cow's milk allergy developed tolerance within 1 year(48).

199 (71.6%) of 278 (87.1%) allergy diagnosed patients who developed tolerance in the first year is non Ig E, 45 (16.2%) of the sample is

mixed. 34 (12.2%) of them are food by Ig E-mediated mechanisms. Likely others we found Ig E mediated aleergies are more resistant to tolerance. Of %21 Children aged 16 in which had increased cow's milk spesific IgE were notified non- tolerated (49). The strict elimination diet resulted in improvement of symptoms and tolerance to allergic food usually with in 1 year (43).

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Number: 24, Date: 14.11.2016).

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Research Article / Araştırma Makalesi

Review of Factors Contributing to the Imaging of the Coronary Arteries in Coronary Computed Tomography Angiography and Implications for Imaging Practice

Koroner Bilgisayarlı Tomografik Anjiografide Koroner Damarların Görüntülenmesine Katkı Sağlayan Faktörlerin Gözden Geçirilmesi ve Bunların Çekim Pratiğine Yansıması

Nevin Aydın

Eskişehir Osmangazi University Faculty of Medicine, Department of Radiology, Eskisehir, Turkiye

Abstract

We aimed to review factors affecting the opacification of the coronary arteries in coronary computed tomography angiography (CTA) and evaluate their reflections on imaging practices. Coronary CTA images were retrospectively evaluated. The measurements performed from the central part of the left main coronary artery (LMCA) were divided into two groups optimal CTA (in the range of 300-400 Hounsfield units) and non-optimal CTA. Weight, heart rate, tube current, amount of contrast agent, region of interest (ROI), the short axis diameter of the left ventricle at the midventricular line in the end-diastolic phase, the field of view (FOV), and contrast + saline injection time were compared between the two groups. P<0.05 was accepted as the statistical significance limit. Eighty-three patients were included in the study, and their mean age and standard deviation were 58±18.56 years. In the study, 35 patients (42.3%) had non-optimal CTA and 48 (57.8%) had optimal CTA according to LMCA density. Patient weight (p<0.05), amount of contrast (p<0.01), FOV (p<0.05), and contrast + saline injection time (p<0.01) were significantly higher and tube current was significantly lower (p < 0.05) in the optimal CTA group compared to the non-optimal CTA group. As a result of the logistic model established with independent variables that affected the non-optimal CTA scan, tube current and amount of contrast agent were found to be significant. To bring coronary CTA to a more optimal level, radiologists should work on a patient basis, revising contrast agent protocols and adapting them to each patient.

Keywords: Coronary Computed Tomography Angiography, Computed Tomography, Coronary Arteries, Imaging of Coronary Arteries, Coronary Artery Contrast Enhancement

Özet

Koroner bilgisayarlı tomografik anjiografide (BTA) koroner damarların opasifikasyonuna etki eden faktörlerin gözden geçirilmesi ve bunların çekim pratiğine yansımalarını değerlendirmeyi amaçladık. Retrospektif olarak koroner BTA çekimleri değerlendirilmiş olup sol ana koroner arter (LMCA) santral kesiminden yapılan ölçümlere göre 300-400 Hounsfield Unit aralığında yapılan ölçümler optimum kabul edilip, bunun dışındakiler optimum olmayan grup olarak kabul edildi. İki grup kilo, kalp atımı, tüp akımı, kontrast miktarı, region of interest (ROI), end diastolik fazda midventriküler hatta sol ventrikül kısa aks çapı, Field of View (FOV), kontrast+ serum fizyolojik (SF) verilme süresi kıyaslandı. İstatistiksel anlamlılık sınırı olarak p<0,05 kabul edildi. Çalışmaya 83 hasta dahil edilmiş olup hastaların yaş ortalamaları ve standart sapması 58 ± 18.56 yıl olarak saptandı. Çalışmada LMCA dansitesine göre 35 hasta (42.3%) optimum olmayan grupta olup, 48 hasta (57.8%) optimum olan gruptaydı. Çalışmada LMCA dansitesine göre 48 hasta (57.8%) optimum olan grupta olup, 35 hasta (42.3%) optimum olmayan gruptaydı. Koroner BTA çekimi optimum olan hastalarda optimum olmayan hastalara göre kilo değerleri (p<0.05), kontrast madde miktarı (p<0.01), FOV değerleri (p<0.05), kontrast+SF verilme süresi değerleri (p<0.01) anlamlı düzeyde yüksek, tüp akımı (p<0.05) anlamlı düzeyde düşük olarak saptandı. Optimum olmayan BTA tetkikine etkili bağımsız değişkenlerle oluşturulan logistik regresyon modeli sonucunda; tüp akımı ve kontrast madde miktarı anlamlı bulunmuştur. Koroner BTA çekimlerini daha optimal düzeye taşıyabilmek için hasta bazlı çalışılmalı, kontrast protokollerini değiştirerek hastaya uyarlamalıyız.

Anahtar Kelimeler: Koroner Bilgisayarlı Tomografi Anjiyografi, Bilgisayarlı Tomografi, Koroner Arterler, Koroner Arter Görüntüleme, Koroner Arter Kontrastlanması

Correspondence:
Nevin AYDIN
Eskişehir Osmangazi University Faculty of Medicine, Department of Radiology, Eskisehir, Turkiye
e-mail: drnevinaydin@gmail.com

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1. Introduction

Coronary computed tomography angiography (CTA) is a leading non-invasive test for imaging the coronary arteries, diagnosing stenosis, and planning the treatment of patients (1). Coronary CTA is performed with different protocols, including retrospective and prospective electrocardiogram (ECG) triggering, depending on the suitability of the patient and the availability of equipment (2-4). The adequate contrast enhancement of the coronary arteries during coronary CTA is important since it affects the diagnostic performance in the evaluation of coronary plaques and stenosis caused by these plaques (5). Plaque stenosis cannot be optimally visualized in imaging performed below <300 or above >500 HU in the coronary arteries (5-7). Variables such as contrast volume, injection time, flow rate, saline infusion, and tube kilovoltage affect contrast enhancement (8-12).

In this study, we aimed to provide solutions that can be integrated into imaging practices by comparing the coronary CTA images with and without optimal contrast enhancement according to the measurements performed from the central part of the left main coronary artery (LMCA).

2. Materials and Methods

Patient Population

Ethics committee approval was obtained prior to the study (approval number: E-25403353-050.99-192715, decision number: 15, decision date: 01.06.2021), and patients were retrospectively screened. Eighty-three coronary CTA examinations undertaken in our hospital between 2019 and 2021 were included in the study. The amount of contrast agent given to the patients was determined retrospectively. Manual measurements were performed from the proximal central part of LMCA, as much central as possible, by placing regions of interest (ROI) and excluding the arterial wall. In the measurements, the scans obtained in the range of 300-400 HU were considered optimal while those outside this range were considered non-optimal. The two groups were compared in terms of weight, heart rate, tube current (milliampere(mA)), amount of contrast, ROI, the short axis diameter of the left ventricle at midventricular line in the end-diastolic phase, the field of view (FOV), and contrast + saline injection time. Before the procedure, 50 mg beta-blocker (Metoprolol, AstraZeneca) was orally given to the patients with a heart rate of >75 beats/minute. Patients whose heart rate did not decrease after medication and/or those with a heart rate of >90 beats/minute were excluded from the study.

Imaging and Contrast Protocol, and CTA Imaging Analysis

Coronary CTA examinations were retrospectively performed with a 128-slice device (GE, Revolution EVO, USA) triggered by ECG, and the images of the patients were evaluated by a radiologist (N.A. with 10 years' experience). The radiologist evaluated the contrast protocol blindly. Coronary CTA parameters were as follows: slice thickness: 0.625 mm, window level/window width: 100/800, phase: 75%, and matrix size: 458x458. The coronary arteries were assessed on AW Server version 3.2 Ext. 1.2 and software (CardIQ Xpress). Contrast agents were given to the patients at the same standards (Opaxol 350 mg/ml; Iohexol). We use biphasic injection protocol with volume ranging from 65 to 110 mL followed by a 20-30 mL saline (13). The amount of contrast agent was increased in overweight patients. Real-time monitoring was undertaken with SmartPrep during the CTA scan. The bolus tracking method was used. ROI was placed in the descending aorta, and a 200 HU value was used as the cut-off (Figure 1). In drug injection, the flow rate was applied as 5 mL/s. CTA was performed at 120 kilovolt (kV) in overweight patients and in patients with a normal weight.

Statistical Analysis

Mean, standard deviation, median, minimum, and maximum values were obtained as descriptive statistics for continuous data, and percentages for discrete data. The Shapiro-Wilk test was used to examine the conformity of continuous data to a normal distribution. In the comparison of continuous data between

two groups, the t-test was used for normally distributed data, and the Mann-Whitney U test for data without a normal distribution. Risk factors for non-optimal coronary CTA were analyzed with the multivariate logistic regression analysis. IBM SPSS Statistics v. 20 was used in the statistical analyses, and $p < 0.05$ was accepted as the statistical significance limit.

3. Results

Eighty-three patients were included in the study, and their mean age and standard deviation were 58 ± 18.56 years. According to LMCA density, 48 (57.8%) were in the optimal CTA group and 35 patients (42.3%) were in the non-optimal CTA group. The descriptive statistics of the patients are given in Table 1.

Table 1. Descriptive statistics of the study data

	Mean ± SD	Median (Min-Max)
Age (year)	58 ± 18.56	61 (34-82)
Weight (kilogram)	79.73 ± 12.93	80 (53-124)
Heart rate (beats/minute)	64.35 ± 7.47	64 (50-87)
Tube current (milliAmpere)	503.23 ± 51.87	504 (249-559)
Amount of contrast agent (milliliter)	89.58 ± 12.52	90 (65-110)
ROI*(square millimeter)	0.61 ± 0.14	0.6 (0.4-0.9)
Left ventricular short axis diameter (millimeter)	45.78 ± 6.67	46 (31-66)
FOV* (centimeter)	24.71 ± 8.64	19 (17-42)
LMCA* density (Hounsfield Unit)	371.59 ± 67.40	363 (224-540)
Contrast + saline injection time (second)	39.92 ± 2.50	40 (35-44)

ROI, region of interest; FOV, field of view; LMCA, left main coronary artery

When the two groups were compared in terms of the investigated parameters, patient weight ($p < 0.05$), amount of contrast agent ($p < 0.01$), FOV ($p < 0.05$), and contrast + saline injection time ($p < 0.01$) were significantly higher and tube current was significantly lower ($p < 0.05$) in the optimal CTA group compared to the non-optimal CTA group. There was no significant difference between the two groups in relation to the heart rate, ROI, and left ventricular short axis diameter values ($p > 0.05$ for all). The detailed data are presented in Table 2.

Table 2. Comparison of the Optimal CTA and Non-optimal CTA groups

	Optimal CTA Group (n = 48)	**Non- optimal CTA Group** (n = 35)		
	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)		***P*-value**
Weight (kilogram)	82.13 ± 12.55 80.5 (58-124)	76.46 ± 12.91 78 (53-105)	t = -2.007	0.048
Heart rate (beats/minute)	65.31 ± 7.18 64 (53-87)	63.03 ± 7.78 63 (50-83)	t = -1.382	0.171
Tube current (milliAmpere)	493.08 ± 60.10 504 (249-559)	517.14 ± 33.93 524 (400-559)	U = 620.0	0.042
Amount of contrast agent (milliliter)	92.71 ± 11.94 90 (70-110)	85.29 ± 12.18 85 (65-110)	t = 2-.773	0.007
ROI* (square millimeter)	0.61 ± 0.14 0.60 (0.40-0.90)	0.62 ± 0.15 0.60 (0.40-0.90)	U = 799.5	0.704
Left ventricular short axis diameter (millimeter)	46.29 ± 4.89 46 (36-59)	45.09 ± 8.56 45 (31-66)	t = -0.749	0.457
FOV* (centimeter)	26.19 ± 9.33 19 (17-42)	22.69 ± 7.23 19 (17-39)	U = 628.0	0.046
Contrast + saline injection time (second)	40.54 ± 2.39 40 (36-44)	39.06 ± 2.44 39 (35-44)	U = 559.0	0.008

ROI, region of interest; FOV, field of view

In the examination of the risk factors for the non-optimal measurement of LMCA density on CTA, the independent variables that were found to be significant in the univariate analysis (weight, heart rate, tube current, amount of contrast agent, FOV, and contrast + saline injection time) were included in the multivariate logistic regression analysis. The multivariate logistic regression model was obtained using the backward stepwise method. The results showed that tube current and amount of contrast agent were significant parameters affecting LMCA measurements. An increase in the mA values of the patients by 1 unit increased non-optimal LMCA measurements by 1.018 times, while an increase of 1 unit in the amount of contrast agent reduced it by 1.063 times (Table 3).

Table 3. Logistic regression model for factors affecting a Non-optimal CTA scan

	Regression coefficient (SE)	OR	95% CI		*P*-value
Tube current (milliAmpere)	0.018 (0.008)	1.018	1.002	1.034	0.025
Amount of contrast agent (milliliter)	-0.061 (0.021)	1.063	1.020	1.109	0.004

CTA, computed tomography angiography; CI, confidence interval; SE, standard error

4. Discussion

Coronary CTA is one of the important tests used for the imaging of the coronary arteries, and the quality of imaging directly affects the evaluation of these structures. In our study, the imaging parameters of optimal and non-optimal CTA scans were compared according to the measurements performed from LMCA. The mean weight of the patients, amount of contrast agent, FOV, and contrast + saline injection time were determined to be significantly higher, and tube current was found to be significantly lower in the optimal CTA group compared to the non-optimal CTA group. The logistic regression model created with independent factors that affected LMCA density values not being measured optimally revealed tube current and amount of contrast agent to be significant variables.

In the literature, it has been stated that insufficient contrast enhancement is obtained at injection times below 10 seconds, while there are streak artifacts in the right atrium at injection times above 20 seconds. Therefore, it is recommended to keep the injection time in the range of 10-20 seconds (14). Since the automatic injection in our hospital has a single outlet, we created a biphasic protocol for the injection of contrast and saline There is also triphasic injection protocol in the literature that contains an undiluted contrast, followed by a diluted contrast media and finally salin chaser. The diluted of contrast media can be varied. The triphasic injection protocol provides a better evaluation of the right heart compared to the biphasic protocol (15). In our study, as the amount of contrast agent increases, the contrast injection time will also increase, which may explain the differences between the optimal and non-optimal CTA groups.

Applying a single standard protocol in CTA scans by disregarding the characteristics of each patient, such as height and weight can cause serious problems in imaging practices. In the literature, systems with dedicated contrast protocol software have been used, and patient-related parameters used in our study were mostly determined with manual adjustments (16).

In our study, optimal images being obtained in overweight patients can be attributed to increased contrast volume applied in these patients. In a study by Mihl et al., adequate contrast enhancement was obtained in all patient groups in which contrast protocol software was used, while no contrast enhancement was detected in coronary CTA in overweight patients in the control group in which this software was not utilized (16). In our study, we increased the contrast agent volume in overweight patients to a certain extent and obtained optimal images in these patients without using the software. Thus, it

can be concluded that it is important to apply a contrast protocol to each patient considering their characteristics. Coronary CTA is a dynamic test rather than a standard scan. Therefore, patient characteristics should be taken into account in imaging practices. However, while increasing the contrast volume in patients, the risk of contrast-induced nephropathy (CIN) should not be overlooked. While evaluating the patient in terms of CIN, attention should be paid to the glomerular filtration rate, presence of severe heart disease, presence of dehydration, diabetes mellitus, and multiple contrast uptake in less than 24 hours (17).

As the FOV value increases, the dose taken by the patient also increases. The imaging area is a parameter that can vary from patient to patient. In a study by Muenzel et al., the use of small and large FOV values were compared in 256-slice multidetector computed tomography, and the authors reported that the diagnostic image quality did not change according to FOV (18). A small FOV can naturally be selected in patients with a body-mass index of <30 kg/m^2 (19). In the current study, the FOV value was significantly higher in patients with optimal CTA compared to the non-optimal group. This may be related to the higher rate of overweight patients in the optimal CTA group. In routine practice, radiologists should use the minimum FOV value to include all the coronary arteries in the image. And also radiologists should adjust this parameter according to the patient's body mass index.

According to the logistic regression model obtained from our study, a 1-unit increase in the mA values of the patients increased the non-optimal LMCA measurements on CTA by 1.018 times. When the literature is examined, it is observed that the use of low kV, close to a K-edge value of 33 keV, can both reduce the contrast dose and help obtain images with better quality (20). This result can be attributed to the 33 keV K-edge value as the mA will decrease as the dose value decreases. So better image quality can be achieved.

In a study by Wang et al. 80 kV was used for coronary CTA for non-obese patients, and Wang et al. reduced the radiation and iodine dose without compromising image quality (21). In our study, we evaluated tube current values for optimization in coronary cta.

In a previous study, there was no significant difference in contrast enhancement between the weight-adjusted (1.0 mL/kg) and fixed (80 mL) contrast dose protocol groups in measurements performed with a 64-slice multidetector computed tomography device, but the mean visual score for beam-hardening artifacts were significantly lower in the weight-adjusted- than the fixed-iodine-dose protocol (22).

In our study, an increase of 1 unit in the contrast agent volume reduces non-optimal LMCA measurements by 1.063 times. This suggests that increased contrast dose can result in better images in certain patient populations.

There are several limitations to this study. First, the body mass index values of the patients were not evaluated because the height values of the patients could not be reached due to the retrospective design of the study. Second, measurements from the proximal were considered sufficient, and those from the distal coronary segments were not included in the evaluation. Lastly, kV values not being evaluated can be considered a limitation.

5. Conclusion

To bring coronary CTA scans to a more optimal level, we should work on a patient basis, revising and adapting contrast protocols according to each patient. The logistic regression model obtained from the current study showed that decreased mA value and increased amount of contrast agent resulted in more optimal CTA scans.

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Ethics

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Research Article / Araştırma Makalesi

Papain HepG2 Hücrelerinde Kaspaz-3 ve Kaspaz-9 Genlerini Düzenleyerek Apoptozu İndükler

Papain Induces Apoptosis by Regulating Caspase-3 and Caspase-9 Genes in HepG2 Cells

[1]Meliha Koldemir Gündüz, [1]Fatih Kar, [2]Güllü Kaymak

[1]Kütahya Sağlık Bilimleri Üniversitesi, Mühendislik ve Doğa Bilimleri Fakültesi, Mühendislik Temel Bilimleri Bölümü, Kütahya, Türkiye

[2]Kütahya Sağlık Bilimleri Üniversitesi, Simav Sağlık Hizmetleri Meslek Yüksekokulu, Tıbbi Hizmetler ve Teknikler Bölümü, Kütahya, Türkiye

Özet

Hepatosellüler karsinom (HCC), kansere bağlı ölüm sıralamasında ikinci sırada yer alır ve dünya genelinde sıklığı artmaktadır. Papain proteolitik bir enzimdir ve potansiyel antikanser ajanıdır. Çalışmanın amacı, papainin insan hepatom HepG2 hücre hattındaki sitotoksik etkisinin apoptoz üzerinden değerlendirilmesidir. Papainin sitotoksisitesi MTT yöntemi ile belirlendi. Papain uygulanan HepG2 hücrelerinin morfolojik değişiklikleri, akridin portakalı ve etidyum bromür (AO/EB) ikili boyaması ile değerlendirildi. Apoptotik aktivite qPCR yöntemi ile apoptoz düzenleyici kaspaz-3 ve kaspaz-9 genlerinin anlatımları ile tespit edildi. HepG2 hücrelerine 48 saat boyunca 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml papain uygulaması sonucunda IC50 değeri 53 µg/ml bulundu. Apoptotik belirteçler olan kaspaz 3 ve 9 gen ifadeleri, HepG2 hücrelerinde papain uygulaması sonucunda önemli ölçüde arttı. Sonuç olarak, papain HCC tedavisi için, apoptoz düzenleyici genlerin anlatımını indükleyerek antikanser etkiye sahip olabilir.
Anahtar Kelimeler: Papain; HepG2; Hepatosellüler karsinom; Sitotoksisite; Apoptoz.

Abstract

Hepatocellular carcinoma (HCC) ranks second in cancer-related death and its incidence is increasing worldwide. Papain is a proteolytic enzyme and a potential anticancer agent. The aim of the study is to evaluate the cytotoxic effect of papain in human hepatoma HepG2 cell line through apoptosis. The cytotoxicity of papain was determined by the MTT method. Morphological changes of Papain-treated HepG2 cells were evaluated by acridine orange and ethidium bromide (AO/EB) dual staining. Apoptotic activity was determined by the expression of apoptosis regulator caspase-3 and caspase-9 genes by qPCR method. As a result of the administration of 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml and 10 µg/ml papain to HepG2 cells for 48 hours, the IC50 value was found to be 53 µg/ml. Caspase 3 and 9 gene expressions, which are apoptotic markers, were significantly increased as a result of papain administration in HepG2 cells. In conclusion, papain may have anticancer effect for HCC treatment by inducing expression of apoptosis regulatory genes.
Keywords: Papain; HepG2; Hepatocellular carcinoma; Cytotoxicity; Apoptosis.

Correspondence:
Meliha KOLDEMİR GÜNDÜZ-
Kütahya Sağlık Bilimleri Üniversitesi, Mühendislik ve Doğa Bilimleri Fakültesi, Mühendislik
Temel Bilimleri Bölümü, Kütahya, Türkiye
e-mail:
meliha.koldemirgunduz@ksbu.edu.tr

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1. Giriş

Kanser, halk sağlığı ve ekonomide ciddi etkisi olan küresel bir sorundur. Hepatoselüler karsinom (HCC), karaciğerin ana hücre tipi olan hepatositlerden kaynaklanan malign bir tümördür. Dünyada en sık görülen primer karaciğer tümörü ve beşinci en yaygın tümördür (1). Moleküler düzeyde, HCC heterojen bir hastalıktır. Karaciğer karsinogenezi, sonunda malign transformasyona yol açan farklı genetik değişikliklerin ilerleyici birikimi yoluyla onlarca yıl sürebilir (1). Diğer kanser türlerinde olduğu gibi karaciğer kanserinin tedavisinde yan etkileri nedeniyle toksik olmayan, çok hedefli ve ilaç direnci olmayan tedavilere ihtiyaç vardır. Bu nedenle sınırlı toksik etkiye sahip doğal etken madde kullanımı önemlidir. Beslenme veya diyet faktörleri, oldukça etkili kemopreventif ajanlar olarak hareket etme yetenekleri nedeniyle büyük ilgi görmektedir (2). Kanser tedavisinde doğal etken maddelerin diyetle olası kullanımları, tedavide yeni çözümlerin geliştirilmesine katkı sağlayabilir. HCC' nin çeşitli etkenlerini hedef alan birçok bitkisel bileşiğin HCC' ye karşı etkili olduğu kanıtlanmıştır (3, 4). Bitkisel ilaçların antikanser etkisi temel olarak immünomodulasyon, hücre döngüsünü durdurma ve kanser hücrelerinde apoptozu indükleme ile gerçekleşir (5).

Papain (EC 3.4.22.2), papaya (Carica papaya L.) lateksinden izole edilen bir endolitik bitki sistein proteaz enzimidir. Papain enzimi papain süper ailesine ait proteolitik bir enzimdir. Canlılarda birçok biyolojik süreçte önemli göreve sahiptir (6). Papain, tıpta yaygın kullanılan bir enzimdir ve proteinlere, kısa zincirli peptitlere, amino asit esterlerine ve amid bağlantılarına karşı kapsamlı proteolitik aktivite gösterir (7). Papain, sağlıklı dokularda proteolizi engeller ve sağlam dokular üzerinde zararlı etkisi olmayan kalıntı giderici ajan olarak görev yapar (8). Papain enzimi uzun zamandır yaralanma, travma ve alerjileri tedavi etmek için kullanılmaktadır (7). Kanser hücrelerinin çoğunda, onları koruyan ve uzun süre fark edilmeden çoğalmalarını sağlayan fibrin kaplamalar bulunur. Papain kanser hücrelerindeki bu fibrin yapıyı kırma yeteneğine sahiptir. Papainin bu özelliği potansiyel bir kanser önleyici madde olduğunu gösterebilir (9). Papainin sitokinler ile iletişim kurduğu düşünülmektedir. Papain α-2-makroglobulinlere kolayca bağlanabilir ve sitokinlere karşı daha yüksek afiniteye sahip α-2-makroglobulin-proteinaz kompleksleri oluşturabilir. Papain ayrıca tümör gelişimi ve metastazında anahtar rol olan CD-44, CD-49, CD-54 ve CD-58 gibi adezyon molekülleri ile etkileşime girerek aktivitelerini azaltır ve tümör metastazını önleyebilir (10).

Apoptoz mekanizması üzerinde kaspaz-3 ve kaspaz-9 proteinleri önemli rol oynar. Kaspazlar, sistein proteazlar olarak da adlandırılırlar ve hücre sitoplazmasında lokalize olurlar. Kaspazların temel görevi DNA polimeraz enzim aktivitesini önleyerek hücrenin apoptoza gitmesini sağlamaktır (11). Hücrede meydana gelen patolojik durumlardaki sinyaller kaspazları aktif hale getirir (kaspaz-8, kaspaz-9). Aktif kaspazlar, apoptoz aktive edici faktör-1 (apaf-1) aktifleştirerek sitokrom c'nin serbest hale gelmesini sağlar. Daha sonra apaf-1, sitokrom c ve kaspaz-9 apoptozomu oluşturur. Apoptozom böylece kaspaz-3 aktifleştirir ve hücrenin apoptoza uğramasına neden olur (12). Bu çalışmada HepG2 hücrelerinde papainin olası sitotoksik ve apoptozu indükleme potansiyeli kaspaz-3 ve kaspaz-9 üzerinden araştırıldı.

2. Gereç ve Yöntemler

Hücre Kültürü

İnsan hepatoselüler karaciğer kanseri (HepG2, ATCC® HB-8065 ™) hücre soyu, *American Type Culture Collection* (ATCC) (Manassas, USA) temin edildi. HepG2 hücreleri EMEM (*Eagle's Minimum Essential Medium*; ATCC, USA) + %10 Fetal Bovin Serum (FBS; ATCC, USA) ve penisilin / streptomisin (100 µg/ml; Gibco, US) içeren besi yerinde tutuldu. Hücreler, 37 ° C'de % 5'lik $C0_2$ etüvde kültürlendi.

Hücrelere Papain Uygulanması

Ticari olarak temin edilen papain (Sigma) besi yeri içinde çözündürülerek mekanik olarak

hazırlandı. HepG2 kanser hücrelerine 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml papain ilave edildi ve hücreler 48 saat inkübe edildi. Kontrol hücrelerine sadece kültür ortamı eklendi.

Sitotoksisite Analizi

MTT [3-(4,5-dimethyldiazol-2-yl)-2,5 diphenyl Tetrazolium Bromid] yöntemi ile hücre topluluğundaki canlı hücrelerin oranı kolorimetrik olarak tespit edildi. Flasklarda çoğaltılan hücreler uygulama yapılmadan 24 saat önce 96 kuyucuklu mikroplakalara 5000 hücre /200µl besi yeri olacak şekilde ekilerek inkübasyona bırakıldı. Hücrelere farklı dozlarda papain özütleri uygulandı. HCl/izopropanol yöntemi kullanılarak elde edilen boya yoğunluğu spektrofotometre ile 570 nm dalga boyundaki absorbansta ölçüldü ve canlı hücre oranı tespit edildi (13). Veriler, GraphPad Prism 7.0 programı (GraphPad Software, Inc., La Jolla, CA, ABD) ile analiz edildi. IC_{50} değerinin hesaplanması için, GraphPad Prism 7.0 programı kullanılarak doğrusal olmayan regresyon analizi ile veriler normalize edildi.

Hücre Canlılık Analizi

Papain uygulaması sonucunda hücrelerin canlılık oranları, tedavi edilmemiş kontrol hücrelere kıyasla hesaplandı. Tedavi edilmemiş hücrelerin yaşamsallığı %100 kabul edilerek ve hücrelerin canlılık yüzdeleri aşağıdaki şekilde hesaplandı.

% canlılık oranı: (Tedavi edilen hücre/ tedavi edilmemiş hücre)X100

Akridin Oranj/ Etidyum Bromid Boyama

Hepatosit hücrelerindeki apoptozun belirlenmesi için floresan mikroskopta görüntüleme sağlayan Akridin Oranj - Etidyum Bromid boyama tekniği kullanıldı. Akridin Oranj (AO) 100 µg/ml ve Etidyum Bromid (EB) 100 µg/ml fosfat tamponunda (PBS) hazırlandı. 6 kuyucuklu mikroplakalara 50000 hücre ekildi ve 24 saat inkübasyon yapıldı. 48 saat papain uygulanmasının ardından besi yeri uzaklaştırıldı ve HepG2 hücreleri üzerine 200 µl EB/AO ilave edildi. Floresan mikroskop (Zeiss Axio Vert A.1) kullanılarak 480-505-535 nm'de analiz edildi.

RNA İzolasyonu ve Real-Time PCR Analizi

HepG2 hücrelerinden total RNA, *RNeasy Protect Mini Kit* (Qiagen, Germany) kiti kullanılarak üretici firmanın yöntemine göre elde edildi. Total RNA örnekleri analiz yapılana kadar −80°C saklandı. cDNA sentezi, *transcriptor HiFi cDNA synthesis* kit kullanılarak yapıldı (Roche). RT-qPCR reaksiyon karışımı (BlasTaq 2X qPCR MasterMix (G890, Applied Biological Materials Inc) RT-qPCR çalışması için hazırlandı. Kaspaz-3 ve kaspaz-9 gen anlatımları qPCR kullanılarak ABI StepOnePlus (Applied Biosystems, Germany) cihazı ile analiz edildi. Analiz edilen her numune için en az üç kez ölçüm yapıldı. 40 ve üzerindeki Ct değerleri matematiksel hesaplamalara dahil edilmedi. Gen anlatım oranları, referans gen (β-aktin) ifadesi kullanılarak hesaplandı. Spesifik gen ürünlerinin varlığı, $2^{-\Delta\Delta Ct}$ yöntem analizi ile doğrulandı. Primer dizileri: Kaspaz-3 (F) 5′-GCTCCTAGCGGATGGGTGCTA-3′ ve (R) 5′- GATTTCAAGGCGACGCCAACCA-3′; Kaspaz-9 (F) 5′-AGCCACCTGAGTAGCTTGGA-3′ ve (R) 5′-CTGCACTTTGGGAGGCTAAG-3′; β-Aktin (F) 5′-AGCAAGAGAGGCATCCTCACC-3′ ve (R) 5′-ACAGGGATAGCACAGCCTGGA-3′.

İstatistiksel Analizler

Tüm deneysel veriler, ortalama ± SD olarak sunuldu. İlk olarak, sonuçlar Shapiro-Wilk normallik testi yardımıyla normalize edildi. Normal olarak dağıtılan veriler, tek yönlü varyans analizi (ANOVA) kullanılarak değerlendirildi ve çoklu karşılaştırmalarda Tukey post-hoc testi ile analiz edildi. İstatistiksel analizlerde SPSS 21 ve GraphPad Prism 7 programları kullanıldı. p değerleri <0.05 istatistiksel olarak anlamlı kabul edildi.

3. Bulgular

Papainin HepG2 hücreleri üzerindeki sitotoksik etkisi

HepG2 hücrelerine papain uygulamadan önce hücreler 24 saat standart besi yeri içerisinde kültüre edildi. Hücre kültürü ortamına 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml papain eklendi ve 48 saat boyunca inkübe edildi. Kontrol hücrelerine sadece kültür medyumu eklendi. Papain uygulaması sonucunda hücrelere MTT testi yapıldı. MTT testi ile elde edilen sonuçların GraphPad Prism 7.0 programı ile istatistiki analizi yapıldı. HepG2 hücrelerine 48 saat 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml papain uygulaması sonrasındaki istatistiksel analize göre papainin 48. saatteki IC_{50} değeri 53 µg/ml olarak hesaplandı. Elde ettiğimiz bu sonuçlar, papainin hepatoselüler karsinom hücreleri üzerinde sitotoksik etkiye sahip olduğunu göstermektedir.

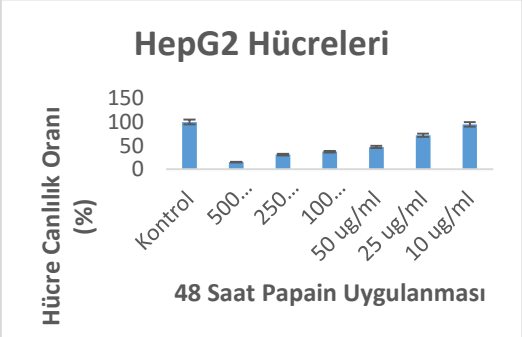
Hepatoselüler karsinoma hücrelerine 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml papain uygulanması sonucu kontrol ile kıyaslandığında hücre canlılığı sırasıyla %15, %31, %37, %47, %72 ve %95 olarak tespit edildi. 500 µg/ml, 250 µg/ml ve 100 µg/ml papainin HepG2 hücreleri için öldürücü etkiye sahip olduğu tespit edildi. 50 µg/ml, 25 µg/ml ve 10 µg/ml papain uygulamasının HepG2 hücrelerinde çoğalmayı engelleyici etkiye sahip olduğu tespit edildi **(Şekil 1).**

MTT sonuçlarına göre üç farklı papain konsantrasyonu (26.5 µg/ml, 53 µg/ml, 267 µg/ml) belirlendi ve diğer deneysel prosedürlerde kullanıldı.

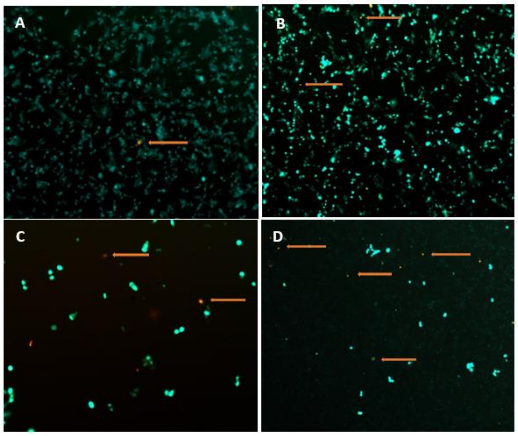
Apoptotik Etkinin Değerlendirilmesi

Papainin hepatoselüler karsinoma hücre hattında apoptoz üzerindeki etkilerini belirlemek için etidyum bromür/akridin portakal boyaması yapıldı. Kaspaz 3 ve Kaspaz 9 gen ekspresyon seviyeleri qPCR analizi ile belirlendi. HepG2 hücrelerine 26.5 µg/ml, 53 µg/ml, 267 µg/ml papain uygulaması sonucunda apoptotik boyanmış hücrelerin miktarı, floresan mikroskop analizine göre doza bağlı olarak kontrol hücrelerine kıyasla arttığı tespit edilmiştir **(Şekil 2).**

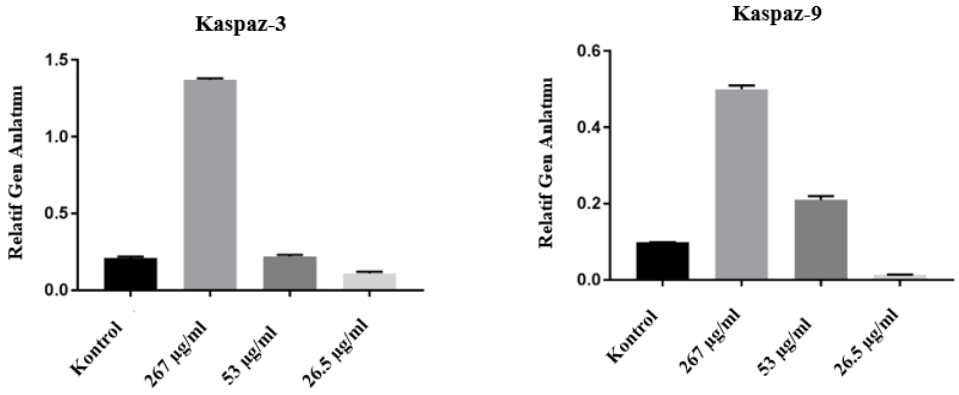
HepG2 hücrelerine hepatoselüler 26.5 µg/ml, 53 µg/ml, 267 µg/ml papain uygulaması sonrasında kaspaz-3 ve kaspaz-9 gen anlatım seviyeleri analiz edildi. 48 saat 26.5 µg/ml papain uygulanan HepG2 hücreleri ile kontrol HepG2 hücreleri karşılaştırıldığında kaspaz-3 ve kaspaz-9 gen anlatım seviyeleri sırasıyla 0.50 ve 0.14 kat azaldığı tespit edildi ($p<0.05$) (Şekil 3). 48 saat 53 µg/ml papain uygulanan hücreler ile kontrol hücreler karşılaştırıldığında kaspaz-3 ve kaspaz-9 gen anlatım seviyeleri sırasıyla 1.03 ve 2.30 kat arttığı tespit edildi ($p<0.05$) (Şekil 3). 48 saat 267 µg/ml papain uygulanan HepG2 hücreleri ile kontrol HepG2 hücreleri karşılaştırıldığında kaspaz-3 ve kaspaz-9 gen anlatım seviyeleri sırasıyla 6.59 ve 5.06 kat arttığı tespit edildi ($p<0.05$) **(Şekil 3).**



Şekil 1. *Farklı konsantrasyonlardaki papainin HepG2 hücrelerindeki sitotoksik etkisi. Hücreler, 48 saat süreyle 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml papain ile muamele edildikten sonra MTT testi* yapıldı.



***Şekil 2**. Papainin apoptotik etkileri. Apoptotik hücre sayılarını belirlemek için HepG2 hücreleri üzerinde EB/AO boyaması yapıldı. Apoptotik hücreler (turuncu) sayıldı ve apoptotik hücrelerin yüzdesi hesaplandı (A. Kontrol hücreler, B. 26.5 µg/ml 48 saat papain uygulanan hücreler, C.53 µg/ml 48 saat papain uygulanan hücreler, D. 267 µg/ml 48 saat papain uygulanan hücreler).*



***Şekil 3.** Papain ile tedavi edilen gruplar ve kontrol hücreleri üzerinde kaspaz-3 ve kaspaz-9 genlerinin mRNA ekspresyon seviyeleri. Gen ekspresyon seviyeleri, gerçek zamanlı PCR ile belirlendi ve β-aktin mRNA seviyelerine göre normalleştirildi. $p < 0.05$*

4. Tartışma ve Sonuç

Kanser dünya genelinde en ölümcül hastalıklardan biridir. Radyoterapi, cerrahi ve kemoterapi kanserle mücadelede büyük katkı sağlasa da dünyanın bu en yıkıcı hastalığını durdurmak için yeterli değildir (14). Konvansiyonel kemoterapi, normal hücreler üzerinde seçici olmayan etkisi nedeniyle hasta için gönüllü işkence haline gelmiştir (9). Cerrahi müdahaleler günümüzde, HCC' li bireyin hayatta kalması için en etkili tedavi yöntemidir. Ancak cerrahi müdahale oldukça azdır ve HCC sonrası metastaz oranının çok yüksek olması tedaviyi etkilemektedir (15). HCC' si olan bireylerde antikanser ilaçlarına karşı bir direnç geliştiği gözlemlenmektedir (16). Bu nedenle yan etkileri minimum ve etkili tedavisi maksimum olan yeni ajanlara ihtiyaç bulunmaktadır.

Xu ve ark., papain hidrolize sorgum kafirin hidrolizatlarının, HepG2 hücrelerindeki antioksidan ve antikanser etkilerini araştırdıkları çalışmalarında, 50 ve 200 µg/mL papain hidrolize sorgum kafirin uygulamasının HepG2 hücre büyümesini etkili bir şekilde azaltarak antikanser potansiyeli olduğunu göstermişlerdir (17). Akila ve ark. HepG2 hücreleri üzerinde

papainin sitotoksisitesini araştırdıkları çalışmada, 125 µg/ml papain uygulamasının hücre canlılığı üzerine etkisini %49.20, 1000 µg/ml papain uygulamasında inhibisyon konsantrasyonun %85 olduğunu bu dozun HepG2'ye karşı maksimum (%85) sitotoksisite etkisine sahip olduğunu rapor etmişlerdir (18). Bu çalışmadai HepG2 hücrelerine farklı dozlarda papain (500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml ve 10 µg/ml) uygulanması sonucunda yapılan istatistiksel analize göre 48. saatteki IC_{50} değeri 53 µg/ml hesaplandı.

Papainin HepG2 hücrelerindeki tedavi edici etkisini apoptoz üzerinden değerlendirmek için apoptozu regüle eden kaspaz-3 ve kaspaz-9 genlerinin anlatımına bakıldı. Ayrıca apoptotik değerlendirme için EB/AO boyama yapıldı. Li ve ark. papain altın nanopartikül kaplı 5-FU'nun akciğer kanserine karşı etkilerini araştırdığı çalışmada, 5-FU'nun antikanser etkisini arttırdığı tespit edilmiştir (9). Al-Fatlawi ve ark. HCC'yi tedavi etmek amacıyla bitkisel ekstraktların HepG2 hücreleri üzerindeki apoptotik etkiyi araştırdıkları çalışmada bitkisel madde uygulaması sonucunda kaspaz-3 ve kaspaz-9 genlerinin anlatımlarının arttığını tespit etmişlerdir (2). Mansour ve ark. HepG2 hücrelerine verdikleri bitkisel ilaçlar ile standart tedavide kullanılan ilaçların sinerjik etkisini araştırdıkları çalışmalarında kaspaz aktivitesinin arttığını ve kanser tedavisinde etkili olduğunu göstermişlerdir (19). Bu çalışmada HepG2 hücrelerin uygulanan papainin IC_{50} dozunun kaspaz 3 ve 9 genlerinin anlatımını arttırdığını rapor ettik. Bu sonuçlar papainin hepatoselüler karsinoma için tedavi edici olduğunu gösterebilir.

Bu çalışma, papainin HepG2 hücrelerine karşı antikanser aktiviteye sahip olduğunu göstermektedir. Papain hepatoselüler karsinoma tedavisinde terapötik potansiyel oluşturabilir. Bu gözlem, kanser tedavisinde bitkisel ilaç kullanımında yeni bir boyut kazandırabilir. Bununla birlikte, papainin metabolizma üzerindeki etkilerini belirlemek için daha ileri çalışmaların yapılması gerekmektedir.

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Onam: Yazarlar hücre kültürü çalışması olduğu için olgulardan imzalı onam almadıklarını beyan etmişlerdir..

Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.

Hakem Değerlendirmesi: Hakem değerlendirmesinden geçmiştir.

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Relationship Among Peer Relations, Parental Attachment Styles, and Level of Tendency to Violence in Adolescents Diagnosed with Attention Deficit and Hyperactivity Disorder

Dikkat Eksikliği ve Hiperaktivite Bozukluğu Tanısı olan Ergenlerde Akran İlişkileri, Ebeveyne Bağlanma Stilleri ve Şiddet Eğilimi Düzeyleri Arasındaki İlişki

Barış Güller, Didem Ayyıldız, Ferhat Yaylacı

Dortcelik Children's Hospital, Child and Adolescent Psychiatry, Bursa, Turkiye

Abstract

In recent years, parental factors have been emphasized among the factors that predict violent behavior, which is observed more frequently in adolescents with Attention Deficit and Hyperactivity Disorder (ADHD) compared to healthy controls. However, the relationship between parental attachment styles and violent behaviors of ADHD patients remains unclear. In the present study, it was aimed to investigate the effects of parental attachment styles and other related factors such as peer relations or psychosocial factors on the tendency to violence in adolescents followed up with the diagnosis of ADHD. Adolescents aged 12-18 years (n=115) who were newly diagnosed or being followed up with the diagnosis of attention deficit hyperactivity disorder (ADHD) between August 2021 and April 2022 in a Child and Adolescent Psychiatry Outpatient Clinic were included in the study. The parents of the participants were asked to fill out a detailed researcher form and the "Strengths and Difficulties Questionnaire-parent form" (SDQ). "Peer Relationship Scale", the "Violence Tendency Scale" and the Parent and Peer Attachment Inventory- brief form (IPPA-R) were given to the adolescents to fill out. Hierarchical linear regression analyses indicated that peer relationship problems (PRS-loyalty subscale) (B= .926, p= .001), psychiatric difficulties (the SDQ-total) (B= .547, p=.001) and the parental alienation (mother) (B=.430, p=.015) variables were statistically significantly associated with violence tendency. Identifying environmental factors that predict violence in youth with ADHD without co-morbid conduct disorder is crucial for the development of preventive interventions.

Keywords: ADHD, Violence, Attachment, Peer groups, Alienation, Adolescent psychiatry.

Özet

Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB) olan ergenlerde sağlıklı kontrollere göre daha sık görülen şiddet davranışını yordayan faktörler arasında son yıllarda ebeveyn faktörlerinin üzerinde durulmaktadır. Ancak DEHB hastalarının ebeveyn bağlanma stilleri ile şiddet davranışları arasındaki ilişki belirsizliğini korumaktadır. Bu çalışmada, DEHB tanısı ile izlenen ergenlerde, ebeveyn bağlanma biçimleri ile akran ilişkileri ya da psikososyal faktörler gibi ilişkili diğer faktörlerin şiddet eğilimine etkisinin araştırılması amaçlanmıştır. Bir Çocuk ve ergen psikiyatrisi polikliniğinde Ağustos 2021-Nisan 2022 tarihleri arasında Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB) tanısı ile takip edilmekte olan veya yeni tanı alan 12-18 yaş arası ergenler (n=115) çalışmaya alınmıştır. Katılımcıların ailelerinden detaylı bir araştırmacı formu ve "Güçler ve Güçlükler Anketi-ebeveyn formu" (SDQ) doldurmaları istenmiştir. Ergenlere doldurmaları üzere "Akran İlişkileri Ölçeği", "Şiddete Eğilim Ölçeği" ve Ebeveyn ve Akrana Bağlanma Envanteri kısa formu verilmiştir. Hiyerarşik doğrusal regresyon analizleri, akran ilişkileri sorunları (PRS-sadakat alt ölçeği) (B= .926, p= .001), psikiyatrik güçlük düzeyleri (SDQ-toplam) (B= .547, p=.001) ve ebeveyne yabancılaşmanın (B=.430, p=.015) şiddet eğilimi ile istatistiksel olarak anlamlı düzeyde ilişkili değişkenler olduğunu göstermektedir. Davranım bozukluğu eş tanısı olmayan DEHB'li gençlerde şiddeti ön gördüren çevresel etmenlerin belirlenmesi önleyici müdahalelerin geliştirilmesi açısından önem arz etmektedir.

Anahtar Kelimeler: DEHB, Şiddet eğilimi, Bağlanma, Akran grupları, Ebeveyne yabancılaşma, Ergen, Psikiyatri.

Correspondence:
Barış GÜLLER
Dortcelik Children's Hospital, Child and Adolescent Psychiatry, Bursa,-Turkiye
e-mail: drbarisguller@gmail.com

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1. Introduction

Attention Deficit and Hyperactivity Disorder (ADHD) is a chronic, neurodevelopmental disorder with hyperactivity/impulsivity and/or attention deficit symptoms that onset in early childhood and persist in most individuals at varied degrees throughout the life. Its worldwide prevalence has been reported as 5.29% and girl/boy rate as 1:4 (1). Although, genetic factors play an important role in the emergence of ADHD, parental environmental factors (such as mother's smoke or emotional stress during pregnancy, presence of ADHD in parents) are also held responsible (2).

Violence is defined as the use of physical force or threats against oneself, another person, a particular community or group, which may result in injury, death, physical harm, certain developmental disorders or deprivation by World Health Organization (2002). The association between ADHD and aggressive behaviors has well been established. Regardless of the presence of Oppositional Defiant Disorder (ODD) and Conduct disorder (CD) diagnoses that frequently co-morbid with ADHD, aggressive behaviors are more common in patients with ADHD. In longitudinal studies, a significant increase was found in children diagnosed with ADHD compared to healthy controls in terms of the presence of aggressive behaviors, committing crimes and other antisocial behaviors (3,4). Individual and environmental factors contribute to the onset and maintenance of aggressive behaviors in children and youths with ADHD. Behavioral such as hyperactivity/impulsivity, or neurocognitive (low IQ/EQ) features are among the individual factors associated with violence (5-7). It has previously been suggested that low ADHD symptom and emotional stress levels were protective factors for violent behaviors (8). It has also been known that children and adolescents with ADHD experience problems with peers (9,10) and their difficulties in social area have been pointed out as one of the factors predicting aggressive behaviors in children and adolescents with ADHD (11).

Environmental factors that have an important role on aggressive behaviors includes strict child rearing techniques, impaired family functions, lack of social support or low socio-economic status (12-17). In previous studies, it has been suggested that ADHD symptoms (18,19) and aggressive behaviors (12) observed in children with ADHD were closely related to parental attitudes. It has been found that social deficits associated with violent behavior in children with ADHD can also be reduced with positive parenting skills (20).

In recent years, the relationship between insecure attachment styles and coping behaviors (21) and ADHD symptoms (22) has increasingly been investigated. Although it is not yet clear whether attachment problems in early childhood cause ADHD symptoms or whether ADHD symptoms negatively affect parent-child attachment (23); Previous research has found that children with ADHD have less secure (24), more unstable (25) and disorganized attachment representations than controls (26).

The aim of this study was to investigate the relationships among peer relations, adolescent's perceived attachment styles, disease-related factors (ADHD subtype, disease duration) and violence tendency in cases followed up with ADHD diagnosis in a Child and Adolescent Psychiatry outpatient clinic.

2. Material and Methods

Participants and procedure

Adolescents aged 12 to18 years who were newly diagnosed or followed up with ADHD diagnosis in the Child and adolescent psychiatry outpatient clinic in August 2021-April 2022 were recruited to the study (115). Adolescents who have chronic medical illnesses or the impression of mental retardation in the mental examination were excluded. In addition, patients who have received or are currently receiving individualized education program were not included to our study sample. Since ODD and CD are disorders frequently associated with ADHD, patients who were diagnosed by clinical interview based on DSM-5 and with the neurodevelopmental co-morbidities such as ODD, CD, Specific Learning Disorder (SLD) were included in the study. The

diagnostic interviews of the patients were performed by a specialist child and adolescent psychiatrist. The parents were asked to fill out a detailed form prepared by the researcher, which includes parent's age, educational level, occupation, average monthly income of the family, and psychiatric and medical history of first- and second-degree relatives as well as child's age, gender, academic success, and medical history. Only parents of ADHD patients receiving treatment were asked to answer questions about how long their children had been treated. "Strengths, and Difficulties Questionnaire-parent form" (SDQ) were filled by one of the parents, while adolescents were asked to fill out "Peer Relation Scale (PRS)", "The Scale of Tendency to Violence" and Inventory of Parent and Peer Attachment-revised (IPPA-R). Permissions for the study was obtained from …… University, Faculty of Medicine Clinical Research Ethics Committee (date 26.05.2021 and number 2021-6/63).

Measures

The Scale of Tendency to Violence has been developed by Gökay et al. in 1995 to determine the violence tendency of the secondary school students. The 4-point likert-type scale is made up of 20 items and none of them reverse. High scores from the scale indicate a high tendency to violence. Cronbach alpha value (0.76) calculated for the scale shows that the scale has internal consistency (a>0.60).

Peer Relationship Scale (PRS) is a measurement tool that was developed by Kaner (27) to assess peer relations. PRS is a 5-point Likert-type questionnaire including 18 questions consists of four sub-dimensions: Commitment, Trust and Identification, Self-Disclosure and Loyalty. The total score can also be obtained. Higher score indicates positive relationships with friends. I's been suggested that the psychometric properties of the scale were sufficient.

Inventory of Parent and Peer Attachment (IPPA)-brief form adopted from the scale IPPA originally consisted of 28 items is used to evaluate attachment of children, adolescents, and young adults. In our study, the 12-item brief form of the scale was filled by the adolescent separately for each parent. It is rated as 1 to 7 (1-never, 7-always) and consists of 3 sub-scales: "Trust", "Communication" and "Alienation". The Turkish validity and reliability study of the brief form of the scale was carried out by Günaydın et al. (2005) and it was stated that the scale had high internal consistency and test-retest reliability (28).

Strengths and Difficulties Questionnaire (SDQ)-parent form

The questionnaire, which is completed by parents for ages 4-16 and by adolescents for ages 11-16, is used to determine emotional and behavioral difficulties. The scale is composed of 5 subscales: Conduct Problems, Emotional Problems, Attention Deficit and Hyperactivity, Peer Relationships and Pro-social Behaviors. A mean score can be obtained for each subscale, as well as the "Total Difficulty Score" can be calculated with the sum of the first four. "Pro-social behavior" subscale scores indicate positive functionality. Turkish validity and reliability study of the scale was carried out by Güvenir et al. (2008) and it was found to be consistent and reliable in the Turkish sample (29).

Statistical Analysis

The data were evaluated by using the Statistical Package for the Social Sciences (version 20) program. Descriptive statistics were shown as mean–standard deviation or percentages (%). A 95% confidence interval was used to assess the data. Independent samples t-test was used for comparisons between groups formed based on violence tendency scores. Although the educational level and working status of the parents were ordinal variables, they were accepted as dummy variables and calculated as continuous variables in our study. The sum of the scores was expressed as socio economic status (SES). The correlations were tested by Spearman correlation analysis. Finally, the variables that could affect the violence tendency scores were evaluated using hierarchical linear regression analysis in the

group formed by excluding cases with co-morbid conduct disorder. The independent variables were gender and SES in the first step; SDQ-total variable in the second step; PRS-loyalty in the third step and IPPA-alienation (mother) in the final step. For all analyses statistical significance was set at $P < .05$.

3. Results

The sample was composed of 115 adolescents with a mean age of (M=14.02, SD=1.97). Thirty-four of 115 participants (29.6%) were girls; 81 (70.4%) were boys. 46.5% (47 of 101) were ADHD-combined, 44.6% (45 of 101) were ADHD-attention deficit, 8.9% (9 of 101) were ADHD-hyperactivity sub-groups. 10.4% (12) of all participants (115) had a diagnosis of conduct disorder in addition to ADHD. Cases with a diagnosis of SLD (15) accounted for 13% of all participants while cases with ODD (8) 7% of them. According to the information received from the parents, it was learned that about a quarter of the participants (29) (25.2%) received disciplinary punishment or suspension from school, and only 3 of them (%2.6) were in court for any crime.

The average score from the Scale of Tendency to Violence was (M=42.17, SD=10.37). When the tendency to violence scores of the participants (115) were evaluated according to varied ranges; the rates were as follows: 21-40 (55, 47.8%), 41-60 (53, 46.1%), 61-80 (7, 6.1%). ADHD-combined subtype (47) and ADHD-attention deficit subtype (45) groups were similar in terms of violence tendency score (p=.235)

Statistical analyses were made by dividing all subjects into 2 groups as those who scored below 40 points (50) and those who scored 40 points or more (64) from the scale of tendency to violence. The high-scored violence tendency group was significantly differed from low-scored group with regard to PRS-loyalty subscale score (t= 2.667, p=.009, 95% Confidence Interval (CI): .40-2.73). The mean values of IPPA-alienation subscale scores for both mothers (t= 2.782, p=.006, 95 % Confidence Interval (CI): .80-4.80) and fathers (t= 3.101, p= .002, 95 % Confidence Interval (CI): 1.21-5.52) were also found to be significantly higher in the high-scored group. SDQ subscale scores were also compared between the groups assigned based on the violence tendency scores. SDQ-conduct (t= 3.569, p= .001, 95 % Confidence Interval (CI): 0.66-2.31), SDQ-emotional (t= 2.181, p=.031, 95 % Confidence Interval (CI): .08-1.71), SDQ-hyperactivity (t= 2.528, p= .013, 95 % Confidence Interval (CI): 0.21-1.76), SDQ-pro-social (t= -2.081, p= .040, 95 % Confidence Interval (CI): -1.74--.04) subscale values were significantly differed in the high-scored violence tendency group. (Comparisons regarding sub-scale scores were given in the table 1).

Table 1. Comparison of the Peer Relationship Scale, Inventory of Parent and Peer Attachment-brief form, and Strengths and Difficulties Questionnaire-parent form sub-scale scores between high-scored and low-scored groups based on the Tendency to Violence Scale

		Tendency to violence (≥40) (n=65)	Tendency to violence (<40) (n=50)	t	p
Strengths and Difficulties Questionnaire-parent form (SDQ)	**SDQ-conduct**	4.18±2.4	2.70±1.7	3.569	**.001**
	SDQ-emotional	4.43±2.1	3.54±2.2	2.181	**.031**
	SDQ-hyperactivity	7.18±2.0	6.20±2.1	2.528	**.013**
	SDQ-peer relations	4.00±1.9	3.92±1.6	.230	.819
	SDQ-prosocial	6.82±2.4	7.72±2.0	-2.081	**.040**
	SDQ-total	19.81±5.6	16.36±4.9	3.436	**.001**
Peer Relationship Scale (PRS)	**PRS-commitment**	28.10±8.5	30.34±8.2	-1.414	.160
	PRS-trust and identification	12.78±3.6	13.94±3.7	-1.644	.103
	PRS-self-disclosure	8.29±3.5	7.42±3.5	1.297	.197
	PRS-loyalty	7.43±3.2	5.86±2.9	2.667	**.009**
Inventory of Parent and Peer Attachment-brief form for mothers(IPPA)	**IPPA-trust**	15.95±5.3	17.76±4.5	-1.905	.059
	IPPA-communication	19.36±6.0	19.90±6.2	-.459	.647
	IPPA-alienation	12.18±6.1	9.38±4.1	2.782	**.006**
Inventory of Parent and Peer Attachment-brief form for fathers(IPPA)	**IPPA-trust**	16.29±5.0	16.96±4.8	-.712	.478
	IPPA-communication	16.79±6.5	18.82±6.7	-1.607	.111
	IPPA-alienation	12.46±6.3	9.10±4.8	3.101	**.002**

The correlation analyses indicated that both the SDQ- total score r (114) = .389, p<.001) and PRS- loyalty subscale score r (114) = .418, p<.001) were positively correlated with the Scale of Tendency to Violence. There was no correlation between age and violence tendency (r (115) = .043, p=.651). Age was also not correlated with PRS sub-scores, except self-disclosure (r (115) = .268, p=.004). No significant correlation was found between disease duration and violence tendency score (r (107) = -.061, p=.533). And no correlation was found between the level of academic achievement and the tendency to violence. However, negative correlations were found between SDQ-conduct (r (113) = -.201, p=.033) and SDQ-hyperactivity (r (113) = -.196, p=.038) subscales and academic achievement level.

The variables that could affect the violence tendency scores were evaluated using hierarchical linear regression analysis in the group formed by excluding cases with co-morbid conduct disorder (n=103). Gender and SES variables were entered as the first block and the results indicated that the model wasn't significant. After entry of the SDQ-total variable at the second block, the model was significant (F = 6.693, p < .001, 17.8 %, R squared change = .154). When the PRS-loyalty variable was entered in the third block, the model was still statistically significant (F= 8.986, p< .001) (28.1 %, R squared change = .103). In the final model, IPPA- alienation (mother) variable was entered, and total variance explained by the model as a whole was 32.6% (R squared change= .045) (F= 8.814, p<.001). The PRS-loyalty (B= .926, p= .001), the SDQ-total (B= .547, p=.001) and the IPPA- alienation (mother) (B=.430, p=.015) variables were the factors significantly influence violence tendency scores according to the final model (table 2).

Table 2. Hierarchical linear regression analysis findings for variables predicting Tendency to Violence Scale Score

	Unstandardized Coefficients		Standardized Coefficients	Sig.
	B	Std. Error	Beta	
Model 1				
SES	.536	.377	.145	.159
gender	1.402	2.230	.064	.531
Model 2				
SES	.692	.350	.187	.051
gender	.381	2.073	.017	.855
SDQ-total	.719	.172	.398	**<.001**
Model 3				
SES	.629	.330	.170	.060
gender	.757	1.951	.035	.699
SDQ-total	.639	.164	.353	**<.001**
PRS-loyalty	1.032	.284	.325	**<.001**
Model 4				
SES	.548	.323	.148	.093
gender	.631	1.900	.029	.740
SDQ-total	.547	.163	.303	**.001**
PRS-loyalty	.926	.279	.292	**.001**
IPPA-alienation (mother)	.430	.174	.223	.015

Note: SES: Socio-economic statue, SDQ: Strengths and Difficulties Questionnaire, PRS: Peer Relationship Scale, IPPA: Inventory of Parent and Peer Attachment

4. Discussion and Conclusion

Our findings demonstrated that almost half of the participants scored above average on the violence tendency scale and when the factors affecting the violence tendency score were evaluated with hierarchical regression analysis; In the last step, total psychiatric difficulty (SDQ-total), peer relations (PRS-loyalty) and IPPA-alienation (for mothers) sub-scale scores were found to be statistically significant variables associated with violence tendency in adolescents with ADHD.

Previous adult studies showed that childhood ADHD was a very important predictor (even above substance use) of violent offence, especially impulse control problems and emotional instability symptoms increased the risk of incidents in the institutional settings (30). Violent behavior and ADHD are similarly multi-factorial conditions in which genetic and environmental factors play a role (31,32). Factors that predict violent behavior accompanying ADHD have been extensively researched. Low connectedness to school, poor academic achievement, high peer delinquency have been suggested among individual factors, while negative parenting attitudes, impaired parental mental health and parent's high emotional expression as familial factors (17). In a 10-year follow-up study has found a linkage between domestic violence (as witness, perpetrator, or victim) and more severe offending behavior (33). In another longitudinal study, protective factors were investigated as well as risk factors that predicted violent behavior in youths, and it has been found that lower ADHD symptom severity, lower emotional distress and less peer delinquency were protective factors (8). In our study, the group formed by excluding cases with co-morbid conduct disorder was subjected to analysis, and the total psychiatric difficulty score variable was adjusted by hierarchical regression analysis. According to our results, the peer relations-loyalty continued to be significant even after the psychiatric difficulty score variable was controlled. It has been suggested that impairments in social area in children with ADHD persists in adolescence, these children are more rejected by their peers, and the risk of being bullied is heightened (34). In a study conducted in the USA by following up 622 African-American youth between the ages of 12 and 22, factors such as male gender, more rejection by peers, and more ADHD symptom severity in late adolescence were increased in the group in which aggressive -offense persisted from adolescence into adulthood (35). In addition to being ostracized by friends, it has been seen as making delinquent friends increases the risk of violence behavior. According to the results of an epidemiological study in Iceland with a large sample (age of 16-24), it was determined that ADHD symptoms explained 8.2%-8.8% of the variance in nonviolent and violent delinquency, respectively, but these effects were largely mediated by co-morbid conditions such as substance use, conduct disorder and delinquent peers (36). Children and adolescents, excluded by their friends, can form groups with peers who exhibit similar characteristics at school or in the neighborhood. It should be considered that these groupings may play a role in joining criminal gangs in the future (37). It was a significant finding in this respect that only the loyalty subscale of the peer relations scale (PRS) was revealed as predictor of violence tendency in the present study.

Another variable that remained significant at the last step in the hierarchical regression analysis was the IPPA-alienation subscale. Higher rate of parental alienation has been shown in previous studies in children and adolescents with psychiatric disorders such as eating disorders (38), depression (39) or psychological conditions such as low self-esteem (40), anxiety sensitivity (41) or pathological internet use (42). In a recent study from Poland, attachment styles of 13–16-year-old adolescents with ADHD were evaluated with a scale similar to our study. Insecure styles were found in both groups, ADHD+ODD and ADHD only, compared to healthy controls, and those with co-morbid ODD differed significantly from those with only ADHD (43). Considering the relationship between attachment and violent behavior; there has been a study conducted in

community sample showed that youths who involved in bullying experiences (either bully or victim) have worse communication and trust with their parents and are more alienated by parents (44). There has been also a clinical study in 2006 with 91 boys (8-12-year-old) with disruptive behavior disorder and various antisocial behaviors. Higher quality of parent-child attachment was associated with lower parent-rated aggression, lower social stress, and higher levels of self-esteem, according to the results of this study (45). In that study, a subscale in which parents evaluated their own attachment levels was used. In the current study, IPPA was a good tool in terms of allowing the assessment of adolescents' self-perceived attachment levels. We believe that our research will serve as a base for future studies on this subject. Our research revealed that 81.7% of adolescents, which constituted the sample of our study, attended school regularly, and none of them stated that they used substances. The rate of participants who committed crimes and went to court was also very low. However, it was observed that more than half of the cases scored moderate-severe on the violence tendency scale. Taken together, our findings would seem to suggest that the sub-dimensions of peer relations-loyalty and IPPA-alienation remained significant as determining factors in the tendency to violence even after controlling for the psychiatric difficulty total score variable. It is plausible that a number of limitations could have influenced the results obtained. To begin with, sample size was small and psychiatric co-morbidities were not determined by structured interviews. In addition, the fact that ADHD symptom severity was not evaluated with standardized scales in our study was a limitation. It is known that there is a positive relationship between the severity of ADHD symptoms and the violent behaviors in patients with ADHD. In our study, the psychiatric difficulties of the youths were evaluated with the SDQ scale, and total score from this scale was controlled in the hierarchical regression analysis. Evaluation of newly diagnosed and follow-up patients together was another limitation. Finally, the mental health of the parents could also have been examined by structured interviews and statistically controlled. Increasing knowledge about environmental factors that may contribute to the violence tendency may enable the development of preventive interventions in youths with ADHD who do not have co-morbid conduct disorder. Further work needs to be performed to enlighten the relationship between parental attachment and violence tendency in youths with ADHD.

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Ethics

Ethics Committee Approval: The study was approved by Uludag University Clinical Research Ethical Committee (Number: 2021-13/9, Date: 22.09.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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Research Article / Araştırma Makalesi

Göz Hastalıkları Açısından Kör Noktada Bulunan 65 Yaş Üzeri Evde Bakım Hastalarında Oküler Özellikler

Ocular Characteristics of Home Care Patients Over the Age of 65 Who Are on the Verge of Developing Ocular Diseases

[1]İbrahim Ethem Ay, [2]Ayşen Til

[1]Afyonkarahisar Sağlık Bilimleri Üniversitesi Göz Hastalıkları Anabilim Dalı, Afyonkarahisar, Türkiye

[2]Burdur Sağlık Müdürlüğü Halk Sağlığı Daire Başkanlığı, Burdur, Türkiye

Özet

Bu çalışmanın amacı, evde bakım hizmeti alan 65 yaş üzeri yaşlılarda ne sıklıkta yasal körlük, katarakt, glokom, senil maküla dejenerasyonu ve kuru göz hastalığı görüldüğünü tespit etmek ve göz patolojilerinin olguların kırılganlık düzeyiyle ilişkisini incelemektir. 1 Nisan 2021-31 Mayıs 2021 tarihleri arasında 74 olguya bir ilçede evde bakım hizmeti alan 65 yaş üzeri yaşlıların göz bulguları değerlendirilmiş ve her olguya Edmonton Kırılganlık Anketi uygulanmıştır. Çalışma kesitsel özellikte bir saha araştırması olarak planlanmış ve bir göz hastalıkları uzmanı tarafından olgular taşınabilir oftalmik muayene cihazlarıyla evlerinde değerlendirilmiştir. 18 (%24.3) olguda hafif düzey, 36 (%48.6) olguda ileri düzeyde görme kaybı ve 8(%10.8) olguda yasal körlük tespit edilmiştir. 4 (%5.4) olguda oküler hipertansiyon ve glokom, 15(%20.3) olguda kuru göz ve 40 (%54.1) senil maküla dejenerasyonu izlenmiştir. 46 (%62.2) olgunun kataraktı olduğu, 26'sının (%35.1) daha önceden katarakt cerrahisi geçirdiği görülmüştür. Senil maküla dejenerasyonuna (p=0.004) ve görme keskinliğine (p=0.003) göre kırılganlık düzeyleri arasında istatistiksel olarak anlamlı farklılık tespit edilmiştir. Glokoma (p=0.169), katarakta (p=0.152) ve kuru göze (p=0.918) göre kırılganlık düzeylerinde istatistiksel olarak anlamlı bir farklılık bulunmamıştır. Katarakt, glokom, kuru göz, senil maküla dejenerasyonu ve şiddetli görme kaybı 65 yaş üzeri evde bakım hastalarında yüksek oranda görülmektedir. 65 yaş üzeri evde bakım hastalarının görme kaybı ile kırılganlık düzeyleri arasında anlamlı korelasyon saptanmış olup, evde bakım hastalarının göz muayeneleri aksatılmamalıdır.
Anahtar Kelimeler: Yaşa bağlı maküla dejenerasyonu, Katarakt, kuru göz, Yasal körlük, Evde bakım hizmetleri

Abstract

The purpose of this study is to determine how frequently legal blindness, cataract, glaucoma, senile macular degeneration, and dry eye disease are seen in the elderly over the age of 65 receiving home care services, as well as to investigate the relationship between ocular pathologies and frailty levels. The eye findings of 74 elderly over the age of 65 who received home care services in a district were evaluated between April 1 and May 31, 2021, and the Edmonton Frailty Questionnaire was used in each case. The study was designed as a cross-sectional field study, with cases evaluated at home by an ophthalmologist using portable ophthalmic examination devices. Mild visual impairment was found in 18 (24.3%) of the cases, severe visual impairment in 36 (48.6%), and legal blindness in 8 (10.8%). 4 (5.4%) cases had ocular hypertension and glaucoma, 15 (20.3%) had dry eye, and 40 (54.1%) had senile macular degeneration. There were 46 (62.2%) cases with cataracts and 26 (35.1%) with previous cataract surgery. Frailty levels were found to differ statistically by senile macular degeneration (p=0.004) and visual acuity (p=0.003). Frailty levels did not differ statistically by glaucoma (p=0.169), cataract (p=0.152), or dry eye (p=0.918). Cataract, glaucoma, dry eye, senile macular degeneration, and severe vision loss are common among home care patients over 65. Vision loss and frailty levels were found to have a significant correlation in home care patients over the age of 65, indicating the importance of home care patients having regular ocular examinations.
Keywords: Age-related macular degeneration, Cataract, Dry eye, Home care services, Legal blindness

Correspondence:
İbrahim Ethem AY
Afyonkarahisar Sağlık Bilimleri Üniversitesi Göz Hastalıkları Anabilim Dalı, Afyonkarahisar, Türkiye
e-mail:
ibrahimethemay@windowslive.com

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1. Giriş

Yaşlanma ile birlikte bireylerin günlük yaşam aktivitelerinde kısıtlılıklar meydana gelmesi ve demografik dönüşüme bağlı olarak sağlık hizmet sunumlarında değişiklik yapılmasına ihtiyaç duyulması beklenen bir durumdur ve nüfus yaşlanmasına bağlı olarak evde sağlık hizmeti ihtiyacının giderek artış göstereceği düşünülmektedir. Amerika'da 2030 yılında 65 yaş üzeri popülasyonun 72 milyonu aşacağı, Dünya'da ise yaşlı popülasyonun 2050 yılında 1,6 milyara ulaşacağı öngörülmektedir ve yaşlanan nüfusla birlikte sağlık sorunlarında artış görüleceği oldukça açıktır1-3. Kuşkusuz ki, yaşlanan nüfusun artan sağlık problemleri göz hastalıkları alanında da artış gösterecektir ve örneğin 2013 yılında tüm dünyada 64,3 milyon olarak rapor edilen glokom hastası sayısının, nüfus yaşlanmasının etkisiyle 2040 yılında yaklaşık 112 milyona çıkması beklenmektedir4. Çünkü ilerleyen yaşla birlikte retinal ganglion hücrelerinde yaşlanmaya bağlı apoptoziste artış gözlenebilir ve buna bağlı olarak glokom sıklığında artış bildirilmiştir5. Ayrıca ilerleyen yaşla birlikte retinada da bir takım patolojik değişiklikler meydana gelebilir ve yaşa bağlı maküla dejenerasyonu gibi, ileri yaşla birlikte görme keskinliğini önemli ölçüde düşüren hastalıkların sıklığının artması beklenir6. Nitekim yaşa bağlı maküla dejenerasyonu 2015 yılında 26,6 milyon kişiyi etkilemiştir. Nüfus yaşlanma hızı da göz önüne alındığında 2050 yılında 55,1 milyon kişinin yaşa bağlı maküla dejenerasyonu nedeniyle yaşam kalitesinin düşmesi beklenmektedir7.

Ayrıca yaşa bağlı sıklığında artış görülmesi beklenen göz patolojilerinden birisi de kuru gözdür ve hem gözyaşı bezlerinde yaşa bağlı gelişen atrofi gelişmesi, hem de meibomian bezlerindeki yıpranma nedeniyle, yaşla birlikte göz kuruluğunda artış gözlenebilir8,9. Yaşla birlikte sıklığı artan oküler patolojilerden birisi de katarakttır. Örneğin; katarakt prevelansı 45-49 yaş grubunda %6 iken 85-89 yaş grubunda %77'ye kadar yükselmektedir ve 2015 yılında 111,7 milyon hasta tespit edilmiştir. 2050 yılında ise katarakt hasta sayısının 240,8 milyona yükselmesi beklenmektedir10.

Neden ne olursa olsun küresel olarak, yaklaşık 1 milyar insanın tedavi edilebilir ancak henüz tedavi edilmemiş bir görme bozukluğuna sahip olması dikkat çekicidir. Çünkü bu insanların 65,2 milyonu katarakt ve 6,9 milyonu glokom nedeniyle gelişen orta / şiddetli görme kusuru nedeniyle yeti yetimine uğramıştır11.

Dünya'da yaşlanmaya bağlı demografik dönüşümün sonucu olarak göz hastalıkları görülme sıklığının zamanla artması beklenmektedir. Ancak glokom, katarakt ve yaşa bağlı maküla dejenerasyonu gibi hastalıkların ulusal düzeyde prevelansının tespit edildiği bir çalışma bulunmamaktadır. Hastalıkların görülme sıklıklarında yaşanan artışın bireysel ve toplumsal sonuçlarına da dikkat çekmek gerekmektedir. Geriatrik popülasyonun yaşam kalitesinin artırılması, tedavi edilebilir körlüklerin önlenmesi, tedavi ve rehabilitasyon hizmetlerinin erken planlanması için dezavantajlı bireylerin, sağlık hizmetine erişimi kolaylaştırılmalıdır. Bu çalışmanın amacı; güvenli sağlık hizmeti erişiminde zorluk yaşayabileceği düşünülen ve evde sağlık hizmeti alan 65 yaş ve üzeri kişilerin görme keskinliği düzeylerinin tespit edilmesi ve kuru göz, glokom ve oküler hipertansiyon, katarakt ve senil maküla dejenerasyonu gibi önlenebilir körlük nedenleri olan hastalıklarının saptanarak, söz konusu göz hastalıkları ile yaşlıların kırılganlık düzeyi arasındaki ilişkinin belirlenmesidir.

2. Gereç ve Yöntem

Çalışmamız kesitsel tipte bir araştırmadır. Çalışmanın evrenini 1 Nisan 2021 ile 31 Mayıs 2021 arasında bir ilçede evde bakım hizmeti alan 65 yaş ve üzeri 98 kişi oluşturmaktadır. Örneklem hesabına gidilmeden tüm hastalar çalışmaya dahil edilmiştir. Demansı olan on dört kişi, araştırmanın yapıldığı tarihler arasında başka bir yerde ikamet eden beş kişi, hastanede yatarak tedavi olan üç kişi ve araştırmaya katılmayı kabul etmeyen iki kişi araştırmanın dışında bırakılmıştır. Geriye kalan 74 kişinin tamamı araştırmaya dahil edilmiştir.

Veriler, muayene öncesi yapılan anket formu ve muayene kayıtlarından oluşmaktadır. Anket formunda olguların yaşı, cinsiyeti, eğitim durumu, kronik hastalık varlığı, günlük kullandıkları ilaç sayıları ve bir göz problemi nedeniyle sağlık hizmetlerine erişimde güçlük yaşayıp yaşamadıkları sorgulanarak sosyodemografik verileri derlenmiştir. Ayrıca hastalara Türkçe için geçerlik güvenilirlik çalışmaları yapılmış olan Edmonton Kırılganlık Ölçeği soruları sorulmuştur. Ölçek, dokuz kırılganlık alanından (bilişsel durum, genel sağlık durumu, fonksiyonel bağımsızlık, sosyal destek, ilaç kullanımı, beslenme, ruh hali, kontinans ve fonksiyonel performans) oluşmaktadır. Bu kırılganlık alanlarından "genel sağlık durumu" ve "ilaç kullanımı" iki soru ile, diğer alanlar ise tek soru ile değerlendirilmektedir. Ölçekten minimum 0 puan, maksimum 17 puan alınabilmektedir. Ölçekten alınan toplam puanın artması kırılganlık şiddetinin arttığını göstermektedir. Kırılganlık düzeyi kırılgan değil (0-4 puan), savunmasız (5-6 puan), hafif kırılganlık (7-8 puan), orta derecede kırılganlık (9-10 puan) ve şiddetli kırılganlık (11-17 puan) olarak gruplandırılmıştır12,13.

Kayıtlı hastaların göz muayeneleri hastaların evinde, göz hastalıkları uzmanı olan bir hekim (İ.E.A) tarafından yapılmıştır. Hastaların her iki gözünün görme keskinliği, ayrı ayrı ve 6 metre mesafeden taşınabilir Snellen eşeliyle ve gerekli olgularda pinhole yardımıyla tespit edilmiştir. İyi gören gözü 6/12 - 6/18 arası görenler hafif görme bozukluğu, 6/18 - 3/60 arası görme keskinliği olanlar ciddi görme bozukluğu ve iyi gören gözü 3/60 ve altında görme ise yasal körlük olarak değerlendirilmiştir. Hastaların göziçi basınçları taşınabilir rebound tonometri (MSLYZ06, Guangdong, China) yardımıyla ölçülmüştür. Göziçi basıncı 21mm Hg ve altında ise normal, 21 mm Hg'nın üzerinde ise oküler hipertansiyon olarak kabul edilmiştir. Halihazırda glokom tanısı almış ve antiglokomatöz damla kullanan olgular ise göziçi basınçları normal değerde ölçülmüş olsa dahi glokom pozitif grupta değerlendirilmiştir. Ön segment muayenesi taşınabilir el biyomikroskobu (Portable Slit Lamp, Reichert Inc, NY, USA) yardımıyla yapılmıştır. Retinada olası bir patolojiden kuşkulanılan hastalara akıllı telefona adapte edilebilen VolkinView (VolkinView, OH, USA) cihazıyla fundus muayeneleri yapılmıştır (Figür 1a ve 1b).

Olgulara lokal anestezi olmaksızın alt göz kapağının dış 1/3 kısmına denk gelecek şekilde Schirmer strip (Biotech, Ahmedabad, India) koyularak beş dakika beklemek suretiyle Schirmer testi yapıldı ve sonrasında floresein strip (Biotech, Ahmedabad, India) üzerine bir damla saline damlatılmasının ardından x10 büyütmede mavi kobalt filtre altında muayenesi gerçekleştirilerek gözyaşı filmi kırılma zamanı testi (TBUT) uygulandı14,15. TBUT 5 saniyeden düşük olanlar kuru göz kabul edildi16. Lokal anestezi olmadan Schirmer testi 10mm'nin altında çıkan olgular kuru göz kabul edildi. Her iki testte de kuru göz bulgusu saptanmamış olsa dahi, kuru göz nedeniyle raporu ilaç kullanan hastalar kuru göz hastası olarak kabul edildi.

Kataraktı olan olgular ve katarakt ameliyatı olmuş psödofakik olgular aynı grup altında ve kataraktı olmayan olgular diğer bir grupta olmak üzere olgular iki ayrı grupta değerlendirilmiştir. Senil Maküla Dejenerasyonu için fundus muayenesinde 5'ten fazla drusen varlığı olan ve makülasında yaşa bağlı skatrisyel değişiklikleri olan olgular senil maküla dejenerasyonu kapsamında değerlendirilmiştir.

Etik Deklarasyon

Çalışma Helsinki Deklarasyonu'na uygun olarak yürütülmüş olup, çalışma için yerel etik komiteden onay alınmıştır (2021/229).

İstatistiksel Analiz

Çalışmada elde edilen veriler Statistical Program in Social Sciences (SPSS) 21.0 paket programı kullanılarak analiz edilmiştir. Sürekli değişkenler ortalama ± standart sapma, kategorik değişkenler ise sayı ve yüzde olarak rapor edilmiştir. Verilerin normal dağılıma uygun olup olmadığını ortaya koymak amacıyla Shapiro – Wilk normallik testi kullanılmıştır. Normal

dağılıma uymadığı tespit edildiği için sayısal değişkenlerin karşılaştırmalarında Mann whitney u testi kullanılmıştır. Kategorik değişkenler ise $\chi 2$ testi ile karşılaştırılmıştır. Gerekli durumlarda Yates düzeltmesi yada Fisher'in exact testi kullanılmıştır. P değerinin 0,05'ten küçük olması istatistiksel olarak anlamlı kabul edilmiştir.

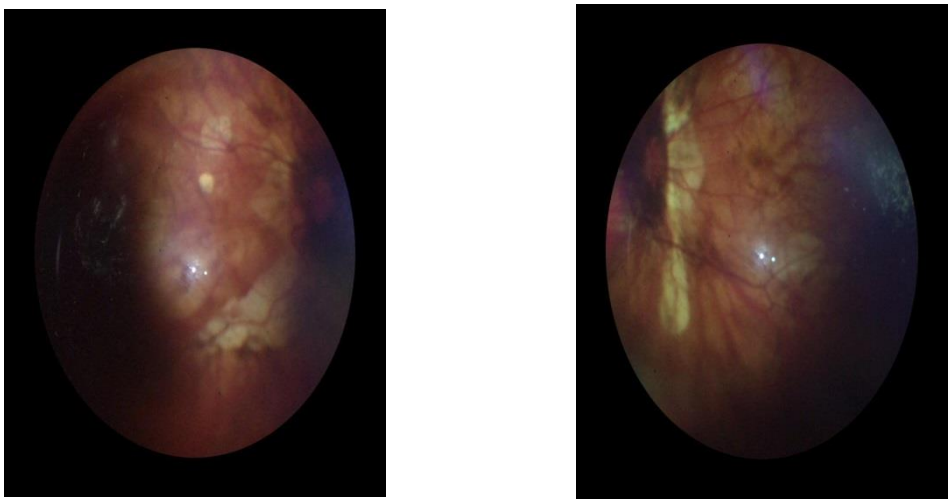
3. Bulgular

Çalışmamıza 65 yaş ve üzeri toplam 74 evde bakım hastası katılmış olup, kişilerin 53'ü (%71.6) kadındır. Olguların yaş ortalaması 84.1±8.7 (65-99) saptanmıştır. Hastaların 41'i (%55.4) okuma yazma bilmemektedir. Araştırma kapsamındaki kişilerin 52'si (%70.0) çocukları ile birlikte, 18'i (%24.3) eşi ile birlikte yaşamaktadır. Çalışmamıza katılan 48 kişi (%64.8) emekli maaşı, 12 kişi (%16.2) yaşlılık aylığı almaktadır ve 5 kişi (%6.8) yardım kuruluşlarının desteğiyle ihtiyaçlarını karşılamaktadır. 9 kişinin (%12.2) ise düzenli bir aylık geliri bulunmamaktadır.

Çalışmamıza katılan 62 kişinin (%83.8) en az bir tane kronik hastalığı vardır. 51 kişi (%68.9) hipertansiyon, 32 kişi (%43.2) diyabetes mellitus, 13 kişi (%17.6) astım, 11 kişi (%14.9) serebrovasküler hastalık, 9 kişi (%12.2) hiperlipidemi ve 5 kişi (%6.8) kanser tanısı nedeniyle tedavi almaktadır. Yaşlıların düzenli olarak kullandığı ilaçları sorgulandığında; 58 kişinin (%78.3) her gün 1-3 adet, 9 kişinin (%12.2) her gün en az 4 adet ilaç kullandığı tespit edilmiştir. 7 kişinin (%9.5) ise sürekli kullandığı bir ilacı olmadığı bilgisi kayıt altına alınmıştır.

Çalışmamıza katılan yaşlıların son bir yıl içersinde sağlık hizmetine erişimleri sorgulandığında; önerilen doktor kontrolü olmasına rağmen 17 kişinin (%23.0) kontrollerine gidemediği, 19 kişinin (%25.7) görme ile ilgili şikayetlerinin olmasına rağmen göz hastalıkları uzmanına muayene olamadığı saptanmıştır. Görme ile ilgili şikayeti olmasına rağmen göz hekimine gitmeyen 19 kişinin göz muayene sonuçları incelendiğinde altısında (%31.6) ciddi görme kaybı ve üçünde (%15.8) yasal körlük tespit edilmiştir. Bu olguların muayenesinde iki kişide (%10.5) göziçi basıncı yüksekliği, sekizinde (%42.1) katarakt saptanmıştır. Fundus muayenesinde yedisinde (%36.8) makula dejenerasyonu tespit edilmiştir ve hastalar ileri inceleme için üçüncü basamak hastaneye yönlendirilmiştir. Çalışmamıza katılan 65 yaş ve üzeri kişilerin Edmonton Kırılganlık Ölçeği puanları incelendiğinde; üç kişinin (%4.1) kırılgan olmadığı, altı kişinin (%8.1) görünürde savunmasız, 18 kişinin (%24.3) hafif kırılgan, dokuz kişinin (%12.2) orta kırılgan ve 38 kişinin (%51.4) şiddetli kırılgan olduğu bulunmuştur.

Çalışmamıza katılan 65 yaş ve üzeri kişilerin görme keskinliği muayenesi sonucunda 18 kişinin (%24.3) hafif görme bozukluğu, 36 kişinin (%48.6) ciddi görme bozukluğu yaşadığı ve sekiz kişinin (%10.8) yasal körlük sınırında görme bozukluğu olduğu bulunmuştur. Ayrıca dört kişide (%5.4) oküler hipertansiyon ve glokom, 15 kişide (%20.3) kuru göz, 19 kişide (%25.7) diyabetik retinopati ve 40 kişide (%54.1) senil maküla dejenerasyonu tespit edilmiştir. 46 kişide (%62.2) katarakt saptanmış, 26 kişinin (%35.1) önceden katarakt ameliyatı olduğu tespit edilmiştir. Oküler hipertansiyon ve glokoma ($p=0.169$), katarakta ($p=0.152$) ve kuru göze ($p=0.918$) göre kırılganlık düzeylerinde istatistiksel olarak anlamlı bir farklılık bulunmamıştır. Senil maküla dejenerasyonuna ($p=0.004$) ve görme keskinliğine ($p=0.003$) göre kırılganlık düzeyleri arasında istatistiksel olarak anlamlı farklılık tespit edilmiştir. Senil maküla dejenerasyonu olan hastaların 80'inde orta-şiddetli kırılganlık tespit edilmiş olup, senil maküla dejenerasyonu olmayan hastaların %44.1'inde orta-şiddetli kırılganlık saptanmıştır. Yasal körlük düzeyinde görme keskinliği olan hastaların %87.5'inde, ciddi görme bozukluğu olan kişilerin %77.8'inde, hafif görme bozukluğu olan hastaların %55.6'sında ve iyi gören hastaların %16.7'sinde orta-şiddetli kırılganlık tespit edilmiştir.



Resim 1a ve 1b. Akıllı telefona adapte edilebilen fundus kamera ile çekilen yüksek miyop bir olgunun retina görüntüsü.

4. Tartışma

Son yıllarda tüm dünyada yaşlı nüfus giderek artış göstermektedir. Bununla birlikte nüfus yaşlanmasının sonucu olarak kronik hastalık sıklıklarında artış yaşanmaktadır. Yeni tanı ve tedavi yöntemleri ile yaşam kaliteleri yükseltilmeye çalışılmaktadır. Ancak yaşlıların sağlık hizmetlerinden yararlanma konusunda gençler kadar şanslı olmadıkları bilinen bir gerçektir. Ne yazık ki, ileri yaş, kırsalda yaşama ve düşük gelir düzeyi gibi eşitsizlikler pek çok yaşlının düzenli göz muayenesi ve tedavisinin gecikmesine yol açmaktadır. Bu nedenle pek çok yaşlı erken tanı ve tedavi ile önlebilir nedenlerden dolayı görme kayıpları ya da körlük yaşamaktadır. Yaşlılarda göreme bozukluğu ya da körlük, yaşlıların bağımlılıklarını arttırmakta, maksimum fiziksel ve ruhsal sağlığa kavuşmalarına engel olmaktadır17. Dünya genelinde erişkin nüfus arasında yasal körlük oranı %2.4 olarak bildirilmiştir18. Çalışmamızda ise bu oran %10.8 olarak bulunmuştur. Altmış beş yaş üzeri ve evde bakım hizmetlerinden yararlanan engelli popülasyonda yasal körlüğün daha sık görülmesi öngörülebilecek bir durumdur. Bu olguların sağlık erişiminde yaşadıkları güçlükler, göz polikliniklerinde randevu olmalarındaki fiziksel engellerle birleşince, göz sağlığı muayenesi açısından adeta kör noktada bulunan bu gruptaki olgular için gelişen teknolojiyle birlikte yeni çözümler üretilmesi gerektiği açıktır.

Çalışmamızda evde sağlık hizmeti alan 65 yaş ve üzeri kişilerde katarakt, senil maküla dejenerasyonu görülme sıklığı sırasıyla %97.3 ve %54.1 olarak bulunmuştur. 65 yaş üzeri insanlarda katarakt sıklığı Avusturalya'da 56% ve İspanya'da %65-%69 olarak bulunmuştur19,20. Çalışmamızda katarakt prevelansı 65 yaş ve üzeri kişiler arasında literatürden belirgin olarak daha fazla saptanmıştır. Bunun nedeni çalışmamızın kırsalda, evde bakım alan 65 yaş ve üzeri hastalarda yapılmış olması olabilir. Ayrıca çalışmamıza katılan kişilerin yaş ortalaması 84.1±8.7 (65-99) olarak belirlenmiştir ve ileri yaşlılık diyebileceğimiz bu dönemde katarakt ve yaşa bağlı maküla dejenerasyonu gibi hastalıkların görülme sıklığının artması kaçınılmazdır. Yapılan geniş kapsamlı bir çalışmada 60 yaş ve üzeri kişilerde senil maküla dejenerasyonu sıklığı %25.3 olarak bildirilmiştir21. Çalışmamızda senil maküla dejenerasyonu sıklığının daha yüksek bulunmuş olmasının nedeni, sağlık hizmet kullanımlarında yaşanan gecikmeler ve hastaların ileri yaşlılık döneminde olması olabilir.

Yaşa bağlı maküla dejenerasyonu için 60 yaş üzeri popülasyonda prevalans %17.5 ile %25.3 arasında bildirilmiştir22,23. Bizim çalışmamızda tespit edilen oran ise daha

yüksek bulunmuştur. Bunun başlıca sebebi olarak çalışmaya dahil edilen olguların yaş ortalamasının 84.1±8.7 (65-99) tespit edilmesi ön plana çıkmaktadır ve çalışmamızın daha ileri yaştaki popülasyonda yürütüldüğü görülmektedir. Bununla birlikte engelli olarak evde bakım hizmetlerinden yararlanan kişilerin sosyodemografik düzeyinin düşük olduğu ve nispeten kötü beslenme koşullarına sahip olabilecekleri de senil maküla dejenerasyonu açısından bir risk faktörü olabilir. Ayrıca evde sağlık hizmeti alan 65 yaş ve üzeri kişilerde glokom prevelansı %5.4 olarak bulunmuştur. 2004-2018 yılları arasında Norveç'te toplumda glokom sıklığı %1.4 iken, 70 yaş ve üzeri nüfusun yaklaşık %8'inin glokom hastası olduğu tespit edilmiştir24. Nüfus yaşlanmasının etkisiyle glokom hasta sayısında beklenen artış ve yaş grupları dikkate alındığında glokom prevelensının literatürle uyumlu olduğu görülmüştür. Çalışmamızda elde edilen bulgular literatür ile glokom ve glokom şüphesi olan hastalar açısından uyumlu görünmektedir.

Yaşlılığın kuru göz için başlı başına bir risk faktörü olduğu düşünüldüğünde, araştırmaya katılan evde bakım hastalarında bu denli sık kuru göz görülmüş olması beklenen bir durumdur. Literatürde 60 yaş üzeri olgularda kuru göz prevalansı çeşitli araştırmalarda %21,6 ile %34.4 arasında bildirilmiştir ve yaşla birlikte kuru göz sıklığında artış olduğu belirlenmiştir25,26. Evde bakım hizmeti alan yaşlılarda kuru göz sıklığı ile ilgili bir çalışmaya literatürde rastlayamadık ancak engelli bireylerin ileri yaşa ek olarak sürekli kapalı ve klimalı ortamda, vakitlerini genelde tablet, telefon, televizyon gibi ekran maruziyeti ile geçirmesiyle kuru gözün sık görülmüş olması ilişkili olabilir27-29.

Çalışmamızda 65 yaş ve üzeri evde sağlık hizmeti alan kişilerin %25.7'sinin görme ile ilgili şikayetlerinin olmasına rağmen göz hekimine gidemediği bulunmuştur. Çalışmamızda evde sağlık hizmeti alan yaşlıların sağlık hizmetinden yararlanma oranının düşük olduğu görülmektedir. Görme şikayetleri olmasına rağmen göz hekimine gidemeyen hastaların bir çoğunda görme kayıpları ve görme kayıpları ile sonuçlanabilecek ciddi hastalıklar tespit edilmiştir. Bu durum dezavantajlı grupların sağlık eşitsizliklerinin ortadan kaldırılmaması sonucu ortaya çıkabilecek sorunların bir göstergesidir. Tüm bunların yanı sıra 65 yaş ve üzeri kişilerde senil maküla dejenearsyonu varlığında ve görme keskinliği düştükçe kırılganlık düzeyleri daha yüksek bulunmuştur. Çalışmamıza düşük gelir seviyesine sahip, kırsalda yaşayan ve dezavantajlı yaşlılar dahil edilmiştir. Sonuç olarak önlenebilir körlük nedenleriyle görme azlığı yaşayan ve buna bağlı daha zor koşullarda yaşamak zorunda kalan evde bakım hastalarının göz sağlığı taraması ve tedavilerinin düzenlenmesi için gelişen teknolojinin sağlık hizmetlerinde kullanımı uygun olacaktır.

Çalışmamız evde sağlık hizmeti alan 65 yaş ve üzeri kişilerde düzenli göz muayeneleri ile önlenebilir göz hastalıkları nedeniyle yaşanan görme kayıplarının ve kırılganlıklarının azaltılabileceğini göstermiştir. Ayrıca 65 yaş ve üzeri kişilerde katarakt, glokom ve oküler hipertansiyon, kuru göz, senil maküla dejenerasyonu ve ciddi görme kaybı görülme sıklığı oldukça yüksek bulunmuştur. Görme kaybı yaşayan ve senil maküla dejenarasyonu olan yaşlıların kırılganlık düzeylerinin yüksek olması göz sağlığının kırılganlık ile doğrudan ilişkili olduğunu göstermiştir. Yaşlılığın kaçınılmaz bir sonucu olarak görülen göz hastalıklarının erken tanı ve tedavisi için rutin göz taramalarının evde sağlık hizmetleri kapsamına alınması gerekmektedir.

Çalışmamızın avantajları; çalışmamız evde sağlık hizmeti alan 65 yaş ve üzeri kişiler arasında göz hastalıklarının görülme sıklıklarını ortaya koyması açısından önemlidir. Literatürde ulaşabildiğimiz çalışmalar arasında yaşlıların evinde uzman göz hekimi tarafından muayenelerinin yapıldığı ilk ve tek saha taraması olması açısından çok büyük bir öneme sahiptir. Saha taramalarının uzman göz hekimi tarafından gerçekleştirilmiş olması hastalara yerinde tanı koyulmasını sağlamıştır. Bu haliyle, Dünya literatüründe göz hastalıkları uzmanı tarafından evde bakım hastalarının doğrudan muayenesi ile yapılan bir çalışmaya rastlayamadık. Nispen V.R. ve arkadaşlarının 2019 yılında Hollanda'da yaptıkları çalışma literatürde ulaşabildiğimiz çalışmalar arasında çalışmamıza en yakın olandır30. Çalışma Hollanda'da evde sağlık hizmetlerinden

yararlanan yaşlıların göz sağlığını korumak ve geliştirmek amacıyla yapılmıştır. Hemşireler tarafından evde bakım hastalarının sadece uzak ve yakın görme keskinliği tespit edilmiş ve hastalara manuel görme alanı taraması uygulanmış ve ihtiyaç halinde göz hekimine sevki sağlanmıştır. Türkiye'de de uzman göz hekimi sayısının yetersiz olması nedeniyle, evde sağlık hizmeti kapsamına alınması önerilen rutin göz taramalarının yapılandırılmış eğitim alan hemşireler ile yapılması uygulamanın sürdürülebilirliğini sağlayabilir.

Çalışmamızın kısıtlılıkları; çalışmamız sınırlı bir bölgede ve evde sağlık hizmeti alan 65 yaş ve üzeri kişiler üzerinde gerçekleştirilmiştir ve tüm topluma genellenmesi uygun değildir. Çalışmanın bir kontrol grubu içermemesi önemli bir kısıtlılıktır. Bununla birlikte çalışmamıza katılan yaşlı sayısının az olması da Edmonton Kırılganlık Ölçeği ile göz hastalıkları arasındaki ilişkiyi tam olarak göstermekte yetersiz kalabileceği düşünülmektedir. Kuru göz için yalnızca Schirmer ve TBUT testlerinin kullanılmış olması, OSDI skoru ile anket yapılmamış olması da çalışmanın bir başka kısıtlılığıdır. Ayrıca uzman göz hekimi sayıları düşünüldüğünde çalışmanın sürdürülebilir olmadığı ve evde sağlık hizmeti kapsamına bu haliyle alınamayacağı çok açıktır. Ancak evde bakım hastalarının göz sağlığına dikkat çekmesi ve yeni ufuklar açması nedeniyle çalışmamızın anlamlı olduğunu düşünüyoruz.

5. Sonuç

Evde bakım hastalarının göz muayenelerinin aksamaması için, evlere ziyarete giden pratisyen hekim ve yardımcı sağlık personeline gerekli eğitimler verilebilir. Taşınabilir görme eşeli ile görme keskinlikleri ölçülebilir ve her vizitte görme keskinlikleri kayıt altına alınabilir. Böylece görmesinde azalma olan hastaların kısa süre içinde ileri sağlık merkezine sevki sağlanabilir. Schirmer testi ile kuru göz taraması yapılabilir. Glokomun taraması ve kontrolü için taşınabilir tonometrilerin kullanımı teşvik edilmelidir. İlerleyen teknolojiyle birlikte akıllı telefona adapte edilebilen fundus görüntüleme cihazlarının da evde bakım hastalarının göz sağlığı taramasında kullanımı söz konusu olabilir.

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Araştırma Makalesi / Research Article

Effect of Epley Maneuver on Balance Change in Benign Paroxysmal Positional Vertigo

Vertigolu Hastalarda Epley Manevrası Öncesi ve Sonrasında Denge Değişimi

[1]Nevsun Pıhtılı Taş, [2]Nihat Susaman

[1]Department of Physical Medicine and Rehabilitation, Elazig Fethi Sekin City Hospital, Elazig, Turkiye.

[2]Department of Otolaryngology, Elazig Fethi Sekin City Hospital, Elazig, Turkiye.

Abstract

Benign paroxysmal positional vertigo (BPPV) is the most common cause of peripheral vertigo. It has been supported in the literature that the patients' balance is getting better with the Epley maneuver. The aim of the study is, to evaluate the effect of the Epley maneuver on balance in patients with BPPV with a balance device. The prospective clinical study was completed with 104 patients. Before and after the Epley maneuver, static and dynamic balance changes were evaluated with a balance device with eyes open and closed. The mean age of the patients was 45.8±16.34 (range, 18-83). 75 patients (72.1%) were female and 29 patients (27.9%) were male. Stable area with eyes open (p=0.137), 'stable length with eyes open (p=0.184), 'stable angle with eyes open (p=0.155), 'stable rate with eyes open (p=0.100), 'stable area with eyes closed' (p=0.06) and 'stable angle with eyes closed' (p=0.310) values were not significantly different between pre-and post-Epley measurements. There was a significant difference between the values of "stable length with eyes closed" (p=0.00), and "stable speed with eyes closed" (p=0.007) before and after the Epley maneuver. Better static balance with the Epley maneuver showed that, body stability and postural balance could be better controlled after the Epley maneuver. There was no improvement in dynamic balance. This suggested that, patients with BPPV could not adapt to changes in proprioceptive and visual stimuli. The Epley test is an effective method for getting better balance disorder and the prevention of related complications which is an important problem in patients with vertigo.
Keywords: Vertigo, Epley, Balance, HUR Btg4 Balance System

Özet

Benign paroksismal pozisyonel vertigo (BPPV), periferik vertigonun en sık nedenidir. Epley manevrası ile hastaların dengesinin düzeldiği literatürde desteklenmiştir. Çalışmanın amacı, BPPV'li hastalarda Epley manevrasının denge üzerine etkisini denge cihazı ile değerlendirmektir. Prospektif klinik çalışma 104 hasta ile tamamlandı. Epley manevrası öncesi ve sonrasında, statik ve dinamik denge değişiklikleri gözler açık ve kapalı halde denge cihazı ile değerlendirildi. Hastaların yaş ortalaması 45,8±16,34 (dağılım, 18-83) idi. 75 hasta (%72,1) kadın ve 29 hasta (%27,9) erkek idi. Gözler açık stabil alan (p=0.137), 'gözler açık stabil uzunluk, (p=0.184), 'gözler açık stabil açı (p=0.155), 'gözler açık stabil hız (p=0.100), 'gözler kapalı stabil alan' (p=0.06) ve 'gözler kapalı stabil açı' (p=0.310) değerlerinde Epley öncesi ve sonrası ölçümler arasında anlamlı fark yoktu. Epley manevrası öncesi ve sonrası, gözler kapalı stabil uzunluk" (p=0,00) ve "gözler kapalı stabil hız" (p=0.007) değerleri arasında anlamlı fark vardı. Epley manevrası ile daha iyi statik denge, Epley manevrasından sonra vücut stabilitesinin ve postüral dengenin daha iyi kontrol edilebileceğini gösterdi. Dinamik dengede düzelme saptanmadı. Bu durum BPPV'li hastaların proprioseptif ve görsel uyaranlardaki değişikliklere uyum sağlayamadığını düşündürdü. Epley testi, vertigolu hastalarda önemli bir sorun olan denge bozukluğunu iyileştirmede ve buna bağlı komplikasyonların önlenmesinde etkili bir yöntemdir.
Anahtar Kelimeler: Vertigo, Denge, Epley, HUR Btg4 Denge Sistemi

Correspondence:
Nevsun PIHTILI TAŞ
Department of Physical Medicine and Rehabilitation, Elazig Fethi Sekin City Hospital, Elazig,Turkey
e-mail: nevsunpihtili@gmail.com

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1. Introduction

Vertigo is classified as peripheral and central vertigo depending on the location of the vestibular dysfunction. Although vertigo is seen in all age groups, its incidence increases with age. The frequency of vertigo in individuals aged 18-79 years is 7.4% 1,2. There is no underlying cause in 50-70% of the cases and this variation of vertigo is called idiopathic or primary benign paroxysmal positional vertigo (BPPV). This clinical condition, which often develops as a result of peripheral diseases, can also be seen in neurological and metabolic diseases. The symptoms are more severe in peripheral vertigo than in central vertigo. Common peripheral vestibular diseases are vestibular neuritis, Meniere's disease, otitis, trauma, BPPV, and ototoxic drug use Peripheral vestibular disorders are characterized by dizziness, which is the most common clinical form of vertigo 3. BPPV, which is a sudden-onset disease triggered by certain positions of the head and lasts for seconds, is responsible for 50% of vertigo in advanced age groups. Moreover, it is twice more common in women than in men. The diagnosis of BPPV is clinical and with a careful anamnesis, an opinion can be obtained at a rate of 70%. In patients without any pathology after Ear Nose Throat (ENT) and neurological physical examination, vestibular tests can mainly determine the channel and type of BPPV. Detection of rotatory nystagmus during the Dix-Hallpike test described in 1952 is diagnostic for BPPV. It is the gold standard diagnostic test in BPPV and has a sensitivity of approximately 80% 4-6. Dizziness in patients with BPPV usually begins while lying down and is affected by head movements 7. Another important feature of the disease is the spontaneous regression of clinical findings within weeks or months with self-limiting treatment 8. Repositioning maneuvers and vestibular rehabilitation exercises are also considered to be effective and safe 9. Described by John M. Epley in 1992, the Epley maneuver is the most commonly used test to treat BPPV 10,11.

Decreased postural control in patients with BPPV limits functionality. Disruption in balance; causes an increase in falls, fractures, and other fall-related injuries. Therefore, disturbances in balance should also be taken into account in patients with vertigo 3,4.

Balance is simply the ability to maintain the body's center of gravity on the base of support 6. Studies have shown that balance ability is impaired in BPPV patients after sudden head movement 5. Different video-based systems, accelerometer methodologies, and devices were used to test balance. Despite the large number of studies showing the effect of the Epley Maneuver on vertigo symptomatology, there is little literature in the literature that addresses the clinical aspects of vertigo symptoms and postural balance after the maneuver. To the best of our knowledge; A study evaluating the response to the Epley maneuver with the HUR Btg4 Balance Master System® has not been found in the literature. Therefore, our study, it was aimed to evaluate the change in static-dynamic balance with the balance device before and after the Epley maneuver applied in BPPV patients.

2. Material and Methods

The clinical-prospective study included 104 patients aged 18-70 years who applied to our hospital's ENT clinic between March 2020 and March 2021 with the complaint of vertigo. All patients underwent physical examination (neurological and neurotological) by an ENT specialist. Patients with a history of transient vertigo related to head position ranging from 1 day to 2 years and whose blood pressure was controlled were included in the study. Patients did not use all anti-vertigo drugs or sedatives 48 hours before the maneuver. For the differential diagnosis of peripheral and central vestibular disorders, appropriate case history, otoscopic examination, and audiological evaluation such as pure tone audiometry, impedance audiometry, and subjective vestibular evaluation were performed. Epley maneuver was applied to patients diagnosed with BPPV. Balance assessment with the device was evaluated before the Epley maneuver and in the first week after the maneuver. Patients who agreed to participate in the study were included. In accordance with the Declaration of Helsinki, an informed consent form was obtained from the patient group.

History of orthopedic disorders, neurologic disorders, psychiatric disorders, the use of anti-vertigo or psychotropic medication; who did not previously undergo vestibular rehabilitation or maneuvers cognitive impairment, alcohol consumption within 24 hours of the test, pregnancy, cerebrovascular disease, visual and auditory deficits BPPV patients with bilateral involvement were excluded from the study.

Clinical data and objective balance measures were evaluated at baseline and one week after the maneuver using the HUR Btg4 Balance Master System® (HUR International, FINLAND) balance device (Figure1). Static and dynamic balance assessments of the patients were performed.

Balance rating

1) Static evaluation: After standing on a foam-based solid surface with eyes open and closed, the area, length, speed, and angle parameters of the oscillation and the oscillation times and distances in all directions were evaluated in the oscillation test. This test was repeated three times. Visual system or proprioception impairment was evaluated with this test.

2) Dynamic evaluation: The leaning angle is based on the person's height and how far the center of pressure moved from the normal position. The person leans forward, backward, right, and left with eyes open, and the average values of swing speed (degrees per second) and distance are measured.

Our study was approved by the Local Ethics Committee. (Decision date: 02.01.2020; Decision number: 18).

3. Results

In the study in which 104 patients participated, the mean age of the patients was 45.8±16.34 years. 75 patients (74%) were female and 29 patients (26%) were male (Table 1). The mean body mass index was 25.06±3 kg/m2, migraine was present in 22 (9.2%) patients (Table 1). No significant difference was found between pre and post-Epley values for 'stable area with eyes open (p=0.137), 'stable length with eyes open (p=0.184), 'stable angle with eyes open (p=0.155), 'stable speed with eyes open (p=0.100), 'stable area with eyes closed' (p=0.06) and 'stable angle with eyes closed' (p=0.310). However, a significant difference was found between pre- and post-Epley values for 'stable length with eyes closed' (p=0.00) and 'stable speed with eyes closed' (p=0.007) (Table 2).

No significant difference was found between pre- and post-Epley values for 'tendency to deviate to right with eyes open, 'tendency to deviate to left with eyes open, 'tendency to deviate to right with eyes closed, and 'tendency to deviate to left with eyes closed' (p>0.05) (Table 3).

Table 1. Demographic and clinical characteristics

	Patients (n=104)	*P*
Age (mean ± SD)	45.64± 16.3	0.98
Gender (F/M)	75/29(9	0.72
BMI (mean ± SD)	25.06± 3.5	0.24
Ear fullness (yes / no) %	55.6/44.4	0
Headache (yes / no) %	67.7/32.3	0
Migraine (yes / no) %	22.2/77.8	0
Tinnitus (right / left) %	67/33	0
Disease onset (sudden / gradual) %	60/40	0
Course of dizziness (continuous/intermittent) %	35/65	0
Affected by head movement (yes / no) %	89/11	0

SD: Standard deviation, F: Female, M: Male

Table 2. Static balance assessment results

Parameters	Before Epley Maneuver (Mean ± SD)	After Epley Maneuver (Mean ± SD)	*p* value* (Wilcoxon's test)
Stable area with eyes open (mm^2)	271± 316.4	280.3± 433.8	0.137
Stable length with eyes open (mm)	276.4 ±158.9	267.7 ±108.8	0.184
Stable angle with eyes open (degree)	18.45± 59.9	5.6 ±61.01	0.155
Stable speed with eyes open (mm/sec)	11.07± 18.78	6.3± 3.5	0.100
Stable area with eyes closed (mm^2)	500.3±353	424 ±211	0.06
Stable length with eyes closed (mm)	116.63± 111.8	267.7 ±108.8	0.00
Stable angle with eyes closed (degree)	3.2± 65.4	14.37± 81.37	0.310
Stable speed with eyes closed (mm/sec)	12.19 ±9.57	10.7± 5.9	0.007

SD: Standard deviation

Table 3. Dynamic Balance Assessment Results

	Before Epley Maneuver (Mean ± SD)	After Epley Maneuver (Mean ± SD)	*p* value* (Wilcoxon's test)
Tendency to deviate to right with eyes open	50.2± 2.5	54.06± 38.8	0.800
Tendency to deviate to left with eyes open	49.7± 2.5	49.7 ±2.9	0.995
Tendency to deviate to right with eyes closed	50.3± 2.5	49.5± 5.4	0.441
Tendency to deviate to left with eyes closed	49.6± 2.5	52.08± 2.7	0.180

SD: Standard deviation

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Data were expressed in mean±standard deviation or median and interquartile range (25th and 75th percentiles) in parametric or non-parametric tests, respectively. The normality assumption of the related data was checked by the Shapiro-Wilk test. Independent samples t-test or Mann-Whitney U test was used to compare each variable between the groups according to the normality test result. The paired t-test or Wilcoxon signed-rank test was used in the case of within-subject comparisons. The effect size of the analyses was calculated. A p-value of <0.05 was considered statistically significant.

4. Discussion

In this study, we examined the change of balance on static and dynamic grounds by using the HUR balance device before and after the Epley maneuver in patients with BPPV. According to our results, it has been shown that the Epley maneuver provides an improvement in static balance. On the other hand, it was determined that no improvement could be achieved in the dynamic balance, which is the sudden response of people to the deterioration of balance while in motion.

BPPV is the most common and treatable vestibular cause of vertigo 3,13-15. Body balance is a complex system that is affected by visual, vestibular, and somatosensory systems, muscle harmony especially muscle tone 16. Muscles provide postural balance and are effective in standing upright against gravity. Balanced stance is coordinated in response to changes in the center of gravity 17. A balance disorder is seen in approximately 30% of people over the age of 65 and in 50% of people over the age of 80 18. Cardiovascular, metabolic, osteoarthritic diseases 19,20, and carotid vertebral artery stenosis are the factors that increase the risk with age, balance disorder, and dizziness 21. This age-related decrease in postural balance control has been interpreted as a deterioration

of sensory, motor, or cognitive systems 22. Although patients with known metabolic and cardiovascular diseases were not included in our study, the mean age of our patients was 45.8 + 16.34.

Balance is examined in two sub-sections as static and dynamic balance. Static balance is defined as the ability to control postural sway while standing still. Dynamic balance is the ability to predict postural changes that occur during movement and to give appropriate responses to balance changes. Balance devices help to evaluate different body balances and to objectively evaluate static and dynamic balance changes 23. We found improvements in measurement results, especially in static evaluations, with the Epley maneuver. BPPV patients show increased postural instability in some static and dynamic balance with altered or absent visual input for several weeks after the maneuver 24,25. A study by Horak et al., compared individuals with vestibular dysfunction and individuals with normal vestibular function and showed that vestibular and somatosensory system disorders caused balance disturbances in the patient group 26. Stambolieva and Angov compared body balance in healthy adults and in patients with BPPV using static posturography with eyes open and closed both before and after the Epley maneuver and showed that the patients' balance changed after the maneuver and that the maneuver provided a vertical standing position by affecting the visual-vestibular system 27. In another study evaluating the effectiveness of the Epley maneuver on treatment and balance using posturography, a significant improvement in stability was observed in patients after Epley, which is consistent with our study 16. Consistent with the studies in our study, we aimed to show the effect of Epley on the balance; we found significant improvement in static balance after Epley. This made us think that body stability and postural balance could be better controlled after Epley. No significant changes were observed before and after Epley in eyes-open static assessments. Our evaluation, in line with other studies, has shown that visual and/or proprioceptive senses are effective in maintaining body balance in patients with vestibular disorders. In the evaluations of the stable area with eyes closed, length and velocity, there were significant changes before and after Epley. The decrease in the swing area and speed showed the accuracy and efficiency of the maneuver, as well as suggesting that it contributed to the improvement in balance. In a study in which patients with BPPV were evaluated after the Epley maneuver, a significant improvement was found in the evaluations of the patients with eyes closed, similar to our study 28.

We did not detect any significant improvement in dynamic balance scores. This made us think about whether patients with BPPV could adapt to changing proprioceptive and visual stimuli. Normal dynamic stability may not be achieved in all patients after a successful Epley maneuver 29. Dannenbaum et al. In their study on vestibular-evoked exercise training, a significant increase in the dynamic balance score was observed in patients 30. Shumway-Cook et al. also found a significant improvement in dynamic gait index after vestibular stimulated exercise training 31. In a study of 26 patients undergoing vestibular rehabilitation, it was found that there was a significant improvement in dynamic balance and self-sufficiency compared to patients treated with the Epley maneuver alone 32. Supported by the literature; vestibular rehabilitation exercises are important for significant improvement in dynamic balance 33. This situation supports that vestibular stimulated exercise training should be added to the treatment except for the Epley maneuver in order to improve the dynamic balance. This explains the absence of change in dynamic balance in our study. In the literature, we could not find any other study in which the balance was evaluated with the HUR balance device we used in our study. There are very few studies in which the change in balance is evaluated with the device before and after Epley treatment, especially in patients with vertigo. In our study, the usability of the Epley maneuver in treatment, especially its effect on the balance parameters of the individuals, was revealed more clearly with the measurements made with the device.

The main limitations of the study; are the small sample size, we don't have a control group, cannot to apply vestibular stimulated exercise training to our patients, and cannot to follow up with our patients. Dizziness is multifactorial in its cause. It requires diagnosis and treatment in the physical, psychological and emotional areas. Comparing Epley's maneuver with other treatment methods, patients could be re-evaluated with vestibular rehabilitation for dynamic balance improvement. Further work can be done in this context.

5. Conclusion

The Epley test is an important and effective method for getting better balance disorder, which is an important problem in patients with vertigo, and the prevention of related complications. The inclusion of patients in a vestibular balance training program in addition to maneuvers will also contribute more positively to their recovery.

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Ethics

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Olgu Sunumu / Case Report

Cerebrospinal Fluid and Serum Autoantıbodıes in Drug-Resistant Temporal Lobe Epilepsıes: Case Series

Tedaviye Dirençli Temporal Lob Epilepsili Olgularda Serum ve Bos'ta Otoantikorlar: Olgu Serisi

[1]Sibel Canbaz Kabay, [2]Erdem Tuzun, [1]Gonul Akdag, [1]Mustafa Cetiner, [3]Selahattin Ayas, [4]Handan Ozisik Karaman, [5]Fatma Akkoyun Arikan

[1]Department of Neurology, Kutahya Health Sciences University Faculty of Medicine, Kutahya, Turkiye

[2]Department of Neuroscience, Istanbul University, Aziz Sancar Institute of Experimental Medical Research, Istanbul, Turkiye

[3]Department of Neurology, Eskişehir City Hospital, Eskisehir, Turkiye

[4]Department of Neurology, Canakkale 18 Mart University Faculty of Medicine, Canakkale, Turkiye

[5]Department of Neurology, Kutahya Health Sciences University Faculty of Medicine, Kutahya, Turkiye

Abstract

We aimed to investigate the presence of neuronal antibodies in serum and cerebrospinal fluid(CSF) analysis of patients with drug resistant temporal lobe epilepsy. We evaluated 8 patients who accepted lumbar puncture with a diagnosis of drug resistant temporal lobe epilepsy. Neuronal autoantibodies were found to be negative in both serum and CSF in all patients. We investigated neuronal antibodies and clinical features in cases who were followed up for drug-resistant temporal lobe epilepsy and suspected of autoimmune epilepsy. Although neuronal antibodies were not detected in CSF and serum examinations, this may be related to the early age of onset in our study group. Autoimmune epilepsy should be considered among the differantial diagnosis with a subacute clinic, unusually high seizure frequency, variety and variability of seizures, resistance to antiseizure medications(ASMs), presence of an autoimmune disease in the person or his/her family, history of cancer or viral prodroma, demonstration of CNS inflammation and detection of neural antibodies.
Keywords: Temporal lobe epilepsy; Cerebrospinal fluid neuronal antibody; Serum neuronal antibody

Özet

Nöbet önleyici ilaca(NÖİ) dirençli temporal lob epilepsili hastaların serum ve beyin omurilik sıvısı (BOS) analizinde nöronal antikor varlığını araştırmayı amaçladık. İlaca dirençli temporal lob epilepsisi tanısı ile izlenen, lomber ponksiyonu kabul eden 8 hastayı değerlendirdik. İlaca dirençli temporal lob epilepsisi nedeniyle takip ettiğimiz ve otoimmün epilepsi şüphesi duyduğumuz olgularda nöronal antikorları ve klinik özellikleri araştırdık. Tüm hastalarda hem serum hem de BOS'ta nöronal otoantikorlar negatif bulundu. BOS ve serum incelemelerinde nöronal antikorlar saptanmasa da bu durum çalışma grubumuzda epilepsi başlangıç yaşının erken olması ile ilişkili olabilir. Subakut bir klinik, nöbet sıklığının alışılmadık derecede yüksek olması, nöbetlerin çeşitliliği ve değişkenliği, NÖİ'lara direnç, kişide veya ailesinde otoimmün hastalık varlığı, kanser öyküsü veya viral prodrom varlığı, santral sinir sistemi inflamasyonun gösterilmesi, nöral antikorların varlığında Otoimmün epilepsi ayırıcı tanıda düşünülmelidir.
Anahtar Kelimeler: Temporal lob epilepsisi; Beyin omurilik sıvısı nöronal antikoru; Serum nöronal antikor

Correspondence:
Gönül AKDAĞ- Department of Neurology, Kutahya Health Sciences University Faculty of Medicine, Kutahya, Turkiye
e-mail. gonulakdag@yahoo.com.tr

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1. Introduction

Autoimmune encephalitis is characterized by a subacute onset clinically manifestated with various combinations as in epileptic seizures, neuropsychiatric disorders, autonomic dysfunctions and movement disorders. In addition, presence of multifocal and variable frequent seizures resistant to antiseizure medications (ASMs), comorbit autoimmune diseases, antibodies in serum and cerebrospinal fluid (CSF) samples which reflect an inflammation and radiological demonstration of the inflammation in the mesial temporal region also support the immune etiology(1,2).

Temporal lob epilepsies of an autoimmune origin generally develop on the basis of limbic encephalitis as mentioned before, the most frequently detected antibodies are: N-methyl-D-aspartate receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and gamma-aminobutyric acid receptor (GABAR) (A and B subtypes), voltage dependent potassium channel (VGKC) complex (leucine-rich glioma-activated protein 1 (LGI1) or contact-related protein 2 (CASPR-2)), glutamic acid decarboxylase (GAD) (5) and antibodies against the glycine receptor (GlyR) (2, 4). In epilepsy patients, the prevalence of neuronal autoantibodies ranges from 2.6 to 34% depending on the study design and patient selection. The essentiality of early diagnosis of an autoimmune etiology and immunotherapy poses significant importance by means of the improvement of symptoms(5).

Neuronal autoantibodies have also been demonstrated in patients with chronic epilepsy without a prior history of encephalitis who are resistant to ASMs (2, 3, 6-9). The number of studies investigating the presence of CSF neuronal autoantibodies are limited (3, 4, 10-13). Therefore, we investigated the presence of serum and CSF neuronal autoantibodies in this study to determine the presence and possible role of neuronal autoantibodies in patients with drug-resistant temporal lobe epilepsy.

2. Materials and Methods

240 patients over the age of 18 who were diagnosed with temporal lobe epilepsy and followed up for at least 1 year in our clinic were evaluated. Eight of 39 patients who followed drug resistant epilepsy, accepted lumbar puncture (LP). Patients with extratemporal lobe epilepsy who did not consent for LP, patients with contraindications for LP and less than 18 years of age were not included in the study. Patients' gender, age, age of epilepsy onset, duration of epilepsy, seizure frequency, seizure type, history (febrile seizures, trauma…etc.) including family history characteristics, comorbidities, brain Magnetic Resonance Imaging (MRI) images, Electroencephalography (EEG) findings and the number of ASMs were evaluated.

Serum and cerebrospinal fluid obtained from patients were frozen at -80°C. Presence of NMDAR, AMPAR, $GABA_BR$, LGI1, CASPR-2, GAD antibodies were looked for. ELISA method for GAD antibody and immunofluorescence method using plasmid transfected HEK293 cells for NMDAR, AMPAR, $GABA_BR$, LGI1 and CASPR2 antibodies (Euroimmun, Luebeck, Germany) were applied.

3. Results

Thirty-nine (16.25%) of 240 patients with temporal lobe epilepsy had drug-resistance. Eight patients (20.5% of resistant epilepsies) who accepted LP were included in the study. The mean age of the patients was 33.37 ± 9.07 years (minimum 20, maximum 50), the mean age of epilepsy onset was 9.22 ± 8.33 years (minimum: 4 months, maximum: 25 years). The demographic and clinical characteristics of patients are given in Figure 1.

NMDAR, AMPAR, $GABA_BR$, LGI1, CASPR-2 and GAD autoantibodies were negative in both serum and CSF of all patients.

Patient number	Gender	Age	Past medical history	Family history	Age at the onset of epilepsy (years)	Duration of epilepsy (years)	Seizure type	Seizure frequency (per month)	EEG	Antiseizure medications (mg)	MRI
1	Male	20	none	none	13	7	Focal to bilateral tonic-clonic seizures	3	Right>left fronto-temporal discharge	levetiracetam 3000, oxcarbazepine 1800, lacosamide 400, topiramate 200	Normal
2	Male	29	none	epilepsy	2	27	Focal to bilateral tonic-clonic seizures	20	bilateral temporo-parietal discharge	levetiracetam 3000, valproic acid 1500, lacosamide 400, clobazam 20	Normal
3	Male	38	febrile seizure	none	9	29	Focal seizures with impaired awareness	8	Right temporal discharge	levetiracetam 3000, carbamazepine 400, topiramate 200, lacosamide 300	Normal
4	Male	40	psychiatric comorbidity	none	0,5	39,5	Focal seizures with impaired awareness; focal to bilateral tonic-clonic seizures	4	Right fronto-temporal discharge	carbamazepine 1200, lamotrigine 400, lacosamide 300	Nonspecific T2 hyperintense lesion
5	Female	29	mental retardation, febrile seizure	epilepsy	0,3	29	Focal seizures with impaired awareness	1	Right temporo-parietal discharge	levetiracetam 2500, oxcarbazepine 600, valproic acid 1000, clonazepam 2	Normal
6	Female	30	perinatal hypoxia, meningitis	none	25	5	Focal to bilateral tonic-clonic seizures	1	Right fronto-temporal discharge	levetiracetam 3000	bilateral mesial temporal sclerosis
7	Female	31	Head trauma and operation	epilepsy	12	19	Focal seizures with impaired awareness	3	Right>left fronto-temporal discharge	levetiracetam 3000, carbamazepine 1000, zonisamide 300	right mesial temporal sclerosis
8	Female	50	Febril seizure, head trauma	none	12	38	Focal seizures with impaired awareness	5	Right temporo-parietal discharge	levetiracetam 3000, valproic acid 1500, carbamazepine 1200, clobazam 10	Nonspecific T2 hyperintense lesion

Figure 1. The demographic and clinical characteristics of patients

4. Discussion

Elisak et al. investigated the neuronal antibodies and clinical features in patients with chronic temporal lobe epilepsy. Neuronal antibodies (3 GAD, 2 CASPR-2) were detected in serum in 5% and in the CSF in 2.5% of 165 patients(11). The prevalence of GAD antibody positivity in serum was % 5.9 (3). CSF GAD antibody was examined in 11 of 15 patients with GAD antibody and 2 of them were positive (3). In another study by Höftberger et al., the 22 patients evaluated (CSF (5 patients), Serum (3 patients), CSF + serum (14 patients)) had AMPA receptor antibodies and 19/19 CSF positivity and 14/17 serum positivity(4). Antibodies were shown in all the patients whose CSF was examined. We did not detect any neuronal antibodies in CSF examinations of 8 patients who were under follow-up with a diagnosis of chronic epilepsy in this study. The low number of patients is considered to be the most important factor leading to this result.

More studies in which only serum samples were examined are present, too. Brenner et al. evaluated 416 patients diagnosed with chronic and acute epilepsy; 11% of them (chronic epilepsy 26/newly diagnosed epilepsy 20) had antibodies against (VGKC (8/12), voltage dependent calcium channel (VGCC) (0/0), GAD (4/3), NMDA-R (3/4), GLY-R (10/1), VGKC and GLY-R (1/0)) (6). Studies show that the selection of the patient group is one of the most important reasons affecting the prevalence of antibodies. We did not detect neuronal antibodies in serum examinations of the 8 patients we followed up with the diagnosis of chronic epilepsy. The results were valuable due to the fact that antibodies were studied in both serum and CSF together despite the small number of our patients. We think that evaluation of the patients in the chronic period, not involving the patients with encephalopathy and long epilepsy periods may lead to this result. It was observed in the literature that the initial findings excluding limbic encephalitis could be psychiatric complaints, psychosis, hyponatremia or tumors. These findings were detected in 64% of the patients: both onconeural and cell surface antibodies were detected at a rate of 32% and the presence of this antibody was influential in long-term outcomes (4). In this study, the researchers reported that they evaluated the CSF results as the NMDAR antibody could falsely be positive at 3% of healthy people (12). It has been reported that NMDAR antibody positivity in CSF is important for NMDAR encephalitis and immunotherapy response (10). It was seen that investigating the presence of antibodies in serum and CSF of the patients is important.

It has been reported that the late-onset TLE (mean age of epilepsy onset of 54 (19-64) years) is more common in seropositive patients (11). In another study evaluating autoimmune epilepsies, the age of seizure onset was 56.0 years (5-79) (1). Studies showing that there is no difference between seropositive and seronegative patients in terms of age epilepsy onset are also present in the literature (6, 8, 9, 14). The mean age of epilepsy onset in present study was 9.22 ± 8.33 years (minimum: 4 months, maximum: 25 years). This range may be due to the fact that different antibodies are more prominent at different ages. In addition, we think that the disease varied depending on whether it had an acute or chronic course.

There was no autoimmune comorbidity in patients with neuronal antibodies (GAD and CASPR-2) (11). Some studies showed no difference between seropositive and seronegative groups in terms of autoimmunity (8). In our patient group, no autoimmune comorbidity was present.

No history of trauma, perinatal complications and febrile convulsions were reported in the seropositive patient group in previous studies (11). 43% of the patients had precipitating factors (25% history of febrile convulsions, 7% a central nervous system (CNS) infection, 5% hypoxia, 4% head trauma and 2% other events) in the study investigating the presence of antibodies in patients with MTLE-HS (15). It has been reported in the literature that no difference exists between seropositive and seronegative groups in terms of febrile convulsion history and birth trauma (8). Risk factors (febrile convulsion, head trauma, family history of epilepsy, perinatal hypoxia and meningitis) were present in 75% of our patients. Studies indicate that the prevalence of psychotic attacks is high in the seropositive group (8, 14). One of our patients (12.5%) had a psychiatric comorbidity. It has been reported in the literature that physicians must suspect from autoimmune epilepsy in patients without risk factors for epilepsy and with seizure onsets at a late age (11). The absence of autoimmune etiology in our patients may be related to the lower age of epilepsy onset.

Nonspecific white matter changes (38.5%) were shown to be significantly higher in seropositive patients (14). In 31.25% of another group of patients with autoimmune epilepsy had normal MRI (1). While 50% of our cases had normal MRI, 25% had nonspecific T2 hyperintense lesions. NMDAR antibody screening is recommended for male patients with partial seizures, normal MRI and no clear etiology(12). MRI of 3 (75%) of our male patients was normal, 1 (25%) of our patients had nonspecific hyperintense changes and CSF NMDAR antibody results in 4 male patients were negative.

One of the limitations of our study is the lack of examination for Oligoclonal Band(OCB).

5. Conclusion

We investigated neuronal antibodies and clinical features in cases with drug-resistant temporal lobe epilepsy that we suspected an autoimmune etiology. Although neuronal antibodies were not detected in CSF and serum examinations, this result may be related to the early age of onset in our study group. Autoimmune epilepsy should be considered among the differantial diagnosis with a subacute clinic, unusually high seizure frequency, variety and variability of seizures, resistance to ASMs, presence of an autoimmune disease in the person or his or her family, history of cancer or viral prodroma, demonstration of CNS inflammation (by laboratory tests or MRI) and detection of neural antibodies (1). When neuronal antibodies are detected, immunotherapy to be applied together with ASM(s) and screening for malignancy according to the antibody will enable early treatment of patients.

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Ethics

Informed Consent: Consent forms were obtained from the patients and the study was approved by the Ethics Committee of Çanakkale Onsekiz Mart University (Decision No: 14-01 date: 23.07.2014).

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Olgu Sunumu / Case Report

Role of Decongestive Therapy for Lymphedema in A Patient After Liver Transplantation: A Case Report

Karaciğer Nakli Sonrası Bir Hastada Lenfödem için Dekonjestif Tedavinin Rolü: Bir Olgu Sunumu

[1]Merve Akdeniz Leblebicier, [1]Gülsüm Bakçepinar, [2]Emine Cihan

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Kutahya Health Sciences University, Kutahya, Turkey

[2] Department of Therapy and Rehbilitation, Physiotherapy Program, Vocational School of Health Sciences, Selcuk University, Konya, Turkey

Correspondence:
Emine CİHAN
Department of Therapy and Rehabilitation, Physiotherapy Program, Vocational School of Health Sciences, Selcuk University, Konya, Turkey
e-mail. pteminecihan@gmail.com

Abstract

Lymphedema is defined as the abnormal accumulation of protein-rich fluid in the interstitial space as a result of deterioration in lymphatic system functions. In our case, we describe a patient that developed lymphedema symptoms in his right upper extremity following liver transplantation. After the lymphedema diagnosis, the patient underwent complex decongestive therapy, which included 30 sessions of manual lymphatic drainage (30 minutes a day) and 30 sessions of multilayer bandaging (five days a week). There was an improvement in both the shoulder joint range of motion and circumferences measurements of the hand and arm after treatment.Based on this case, we recommend manual lymph drainage as a preventative in the early period after organ transplants affecting the lymphatic system.
Keywords: Lymphedema, Transplantation, Liver lymph, Decongestive therapy

Özet

Lenfödem, lenfatik sistem fonksiyonlarındaki bozulma sonucu interstisyel boşlukta proteinden zengin sıvının anormal birikimi olarak tanımlanır. Olgumuzda karaciğer nakli sonrası sağ üst ekstremitede lenfödem semptomları gelişen bir hastayı tanımladık. Lenfödem tanısından sonra hastaya 30 seans manuel lenfatik drenaj (günde 30 dakika) ve 30 seans çok katmanlı bandaj (haftada beş gün) içeren dekonjestif tedavi uygulandı. Tedaviden sonra hem omuz eklemi hareket açıklığı hem de el ve kol çevre ölçümlerinde iyileşme oldu. Bu olgudan hareketle lenfatik sistemi etkileyen organ nakillerinden sonra erken dönemde koruyucu olarak manuel lenf drenajını öneriyoruz.
Anahtar Kelimeler: Lenfödem, Transplantasyon, Karaciğer lenfi, Dekonjestif tedavi

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1. Introduction

Lymphedema is defined as the abnormal accumulation of protein-rich fluid in the interstitial space as a result of deterioration in lymphatic system functions for various reasons (1). Lymphedema cases are rarely observed after transplantation surgeries. The cause of lymphedema after liver transplantation can be shown as the share of the liver in the amount of lymph in the thoracic duct. The hepatic lymphatic system is a drainage system consisting of three parts: portal, sublobular and superficial (or capsular), which is claimed to produce 25-50% of the lymph in the thoracic duct. Most of the hepatic lymph drains into the portal lymphatics (2).It is known that the lymph vessels in the liver become dilated during transplantation in transplantation surgeries. The reason for this is thought to be lymphatic stasis caused by the interruption of lymph flow during surgery (3). It has been shown that in lymphedema, the lymph protein that mixes with the blood is more concentrated in the proximal part of the thoracic duct (4). In this case, our aim was to emphasize that a response to decongestive treatment can be obtained in the late period in the treatment of lymphedema and that it is important to follow-up in terms of lymphedema in post-transplant patients.

2. Material and Methods

Case-Presentation

Patient

A 67 year-old male patient with a body mass index of 25.46 visited our hospital with severe edema on his right arm and right hand. He had been diagnosed with cryptogenic cirrhosis seven years earlier and hepatocellular carcinoma three years after the cirrhosis diagnosis. Four years after the carcinoma diagnosis, the patient underwent liver transplantation. Liver transplantation was performed in 2018 and it was obtained from a brain-dead donor. Patient has been on everolimus therapy since transplantation. After this operation, swelling developed in the right arm of the patient, and his symptoms became severe in about two months. At four months after liver transplantation, lymphoscintigraphy was performed, which showed mild dermal back flow at the right forearm and decreased uptake of the right axillary lymph nodes. Based on these findings, the patient was diagnosed with lymphedema caused by lymphatic obstruction. It was determined that lymphedema developed due to trauma to the lymphatic pathways. In addition, the arterial and venous Doppler ultrasonography of the patient revealed subcutaneous edema, which was more prominent in the distal right upper extremity.

Clinical Evaluation

When the patient was first diagnosed, stage 2 lymphedema was present in the right upper extremity. The clinical stage of the patient was determined according to the 2020 diagnostic criteria in the literature (5).

In the musculoskeletal examination of the patient, there was swelling in the right arm (Figure 1a), and limited range of motion (ROM) of the right shoulder joint. Shoulder range of motion for flexion, extension, abduction, external rotation and internal rotation were measured using goniometer. Right shoulder range of motion was limited in all directions. The measurements of the right shoulder range of motion before and after the treatment are given in Table 1. The skin was hard on palpation, and non-pitting edema was present. His laboratory tests were normal. The upper extremity volumes were calculated using the truncated cone method before and after treatment. The right and left arm circumferences were measured using a inflexible plastic tape at 4-cm intervals, starting from the carpometacarpal joint, and the volume of each limb was calculated from the circumference using the frustum model (6). The patient's quality of life and upper extremity functionality were evaluated with the Lymphedema Quality of Life Questionnaire-Arm (LYMQOL-Arm)(7). LYMQOL is a scale developed to evaluate the effect of lymphedema on patients' quality of life and consists of four 28 items. Symptom, appearance, function, and mood are evaluated. Responses were evaluated on a four-point Likert scale (1= not at all, 2= a little, 3= a lot,

4= a lot). Each item received a score between 1 and 4, with higher scores indicating a worse QoL(8). The measurements were taken before and after therapy.

Treatment

The treatment was completed in a total of 6 weeks, 5 days a week. After the lymphedema diagnosis, the patient underwent Complex Decongestive Therapy (CDT), which included 30 sessions of manual lymphatic drainage (MLD)(30 minutes a day), 30 sessions of multilayer bandaging (five days a week) and exercise. CDT is acknowledged as the primary treatment of lymphedema(9). CDT is carried out in two phases (intensive and maintenance) and consists of MLD, multilayer bandaging, compression garment, exercise (with compression bandage or compression garment), and skin care. The objective of CDT include limb volume reduction with stimulating lymphatic transport and prevention of complications and recurrence (10). MLD was performed from proximal to distal lymphatic direction with light skin massage by a trained physiotherapist. Non-elastic compression bandages were applied and changed daily. The patient was also asked to follow an exercise program consisting of 30 sessions of shoulder muscle strengthening and shoulder joint range of motion exercises with theraband. Extremity elevation and skin care, such as skin hygiene were also recommended. In skin care, proper cleaning and moisturizing of the skin was ensured. The extremities were kept dry and clean, and the skin was evaluated daily in terms of scratches, infection, rash, and redness. The patient was followed up for nail care. No interventional procedure that could cause trauma to the skin was performed(11).

3. Results

After the treatment, the measurements of the shoulder joint range of motion and arm circumferences and LYMQOL- Arm were repeated. The initial LYMQOL-Arm score was7.91, which decreased to 5.98 after treatment. The initial main extremity volume of the lymphedema side was 3.190 ml. which decreased to 2.990 ml after therapy. Shoulder mobility increased in all directions (Table 1). There was also a decrease in swelling and color change in the right upper extremity after treatment (Figure 1b).

Table 1. Degree of right shoulder range of motion before and after treatment

Shoulder range of motion (°)	Before Treatment	After treatment
Flexion	120	170
Extension	45	45
Abduction	90	160
External rotation	40	65
Internal rotation	30	50

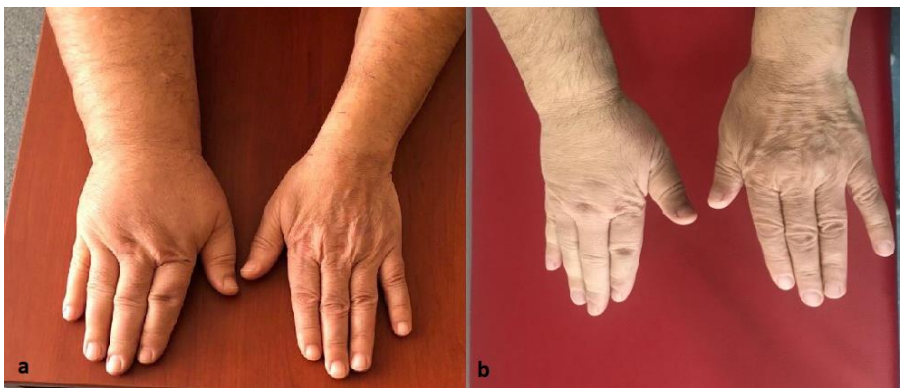

Figure 1. (a) Upper extremities before treatment (b) Upper extremities after treatment

4. Discussions

In this case report, we described the sudden onset of edema in a previously healthy arm of a liver transplant patient, who was systematically diagnosed with secondary lymphedema. After this diagnosis, the patient was successfully treated with CDT. Although the literature contains many cases of secondary lymphedema, only a few patients developed this condition after liver transplantation. The first case of lymphedema after liver transplantation was reported by Saab et al. in 2006. In this case, it was considered that the continuation of chylous as cites accumulation after liver transplantation might be a reason for the abnormalities in the lymphatic system (12). In another case report, Seong et al. described lymphedema due to lymphatic obstruction in the lower extremity after liver transplantation, similar to our case. The patient was treated with lymphaticovenular anastomosis. Lastly, Motse et al. reported a case of lymphedema associated with the use of immunosuppressant sirolimus after liver transplantation (13).

The mammalian target of rapamycin inhibitors (everolimus and sirolimus) potently inhibits vascular endothelial growth factor-C-driven proliferation and migration of lymphatic endothelial cells, which may cause damage to lymphatic vessels and ultimately lymphedema (14). In our case, lymphedema was considered to be due to trauma to the lymphatic pathways. The rapid development of lymphedema after liver transplantation may also be an indication for this. In our case, while the patient was receiving immunosuppressive therapy, everolimus was also added to his treatment, but the development of lymphedema occurred before the start of everolimus therapy. Therefore, although everolimus causes lymphedema, we were not able to establish a relationship between the treatment applied and lymphedema development. Ersoy et al. reported a patient that developed lymphedema due to everolimus after kidney transplantation and recovered when the treatment was terminated (15).

CDT is an effective and safe treatment. According to the circumferences measurements and quality of life evaluation of our patient, his treatment was effective. Although we applied CDT to the patient at two years after the development of lymphedema, there was an improvement in both the shoulder joint range of motion and circumferences measurements of the hand and arm. In the literature, several studies have revealed the positive effects of CDT on lymphedema volume and health-related quality of life in breast cancer-related lymphedema (16, 17). Kim et al. showed that after CDT, the quality of life significantly improved, and this was correlated with the reduction in the limb volume (16). In another study, Mondry et al. showed the reduction of the limb volume after a four-week CDT program (17). To our knowledge, this is the first case report to show that CDT is effective in post-transplant lymphedema. The treatment applied not only decreased the lymphedema volume but also increased the quality of life and functionality.

In this rare case, we improved the patient's quality of life with our treatment method. We observed an increase in shoulder mobility. Based on this case, we recommend manual lymph drainage as a preventative in the early period after organ transplants affecting the lymphatic system. CDT is required in cases where lymphedema develops.

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Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Medical Practices: MAL, GB Design:.MAL, EC Data Collection or Processing: GB Analysis or Interpretation: EC Literature Search: MAL, EC Writing: MAL, EC

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Olgu Sunumu / Case Report

Diagnostic Inexperience of Takayasu Arteritis in Pediatric Neurology: A Case Report and Mini-Review of the Literature

Pediatrik Nörolojide Takayasu Arteritinin Tanısal Deneyimsizliği: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

[1]Turgay Cokyaman, [2]Yücel Sınmaz, [3]Nilüfer Aylanc, [4]Ayşe Burcu Akıncı, [5]Betül Sözeri

[1]Department of Pediatrics, Division of Pediatric Neurology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey

[2]Department of Pediatrics, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey

[3]Department of Radiology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey

[4]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Acıbadem University, Faculty of Medicine, Istanbul, Turkey

[5]Department of Pediatrics, Division of Pediatric Rheumatology, University of Health Sciences Istanbul Ümraniye Training and Research Hospital, Istanbul, Turkey

Correspondence:
Turgay ÇOKYAMAN
Department of Pediatrics, Division of Pediatric Neurology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey
e-mail. drturgay@comu.edu.tr

Abstract

Takayasu arteritis (TA) is a chronic inflammatory vasculitis involving the aorta and its main branches. It usually starts with systemic inflammatory signs after ten years of age. Neurological symptoms seen depend on aneurysmatic, stenotic and thromboembolic events in the affected vessels. It is rarely seen in childhood and presentation with epileptic seizure is extremely rare in infantile age. In this case report, a 22-month-old child who was admitted with epileptic seizure and had a large infarction in the area matching the right middle cerebral artery (MCA) watershed. Symptoms and imaging findings due to infarction developed hours after epileptic seizure. First, low molecular weight heparin treatment was started. Following the development of multiple aneurysmatic-stenotic lesions in the left brachial artery and profunda branch, diagnosed as TA. It was added to oral steroid and azathioprine. Resistant seizures were controlled with levetiracetam and valproic acid in the poststroke period. Multidisciplinary follow-up is ongoing with anticoagulant, antiepileptic and immunosuppressive treatments. TA rarely occurs in the infantile period with acute neurological symptoms such as epileptic seizure and stroke. It is important to make diagnosis early in order to reduce the neurological comorbidities that may occur in the long term.
Keywords: Takayasu arteritis; Seizure; Stroke; Children

Özet

Takayasu arteriti (TA), aort ve ana dallarını tutan kronik inflamatuar bir vaskülittir. Genellikle on yaşından sonra sistemik inflamatuar bulgularla başlar. Etkilenen damarlarda görülen nörolojik semptomlar anevrizmatik, stenotik ve tromboembolik olaylara bağlıdır. Nadiren çocukluk çağında görülür ve infantil yaşta epileptik nöbet ile prezentasyon oldukça nadirdir. Bu olgu sunumunda, epileptik nöbet ile başvuran ve sağ orta serebral arterin (MCA) beslediği alanda geniş bir enfarktüs gelişen 22 aylık bir çocuk sunulmuştur. Enfarktüse bağlı semptomlar ve görüntüleme bulguları epileptik nöbetten saatler sonra gelişti. Önce düşük molekül ağırlıklı heparin tedavisi başlandı. Sol brakiyal arter ve derin dalda çok sayıda anevrizmatik-stenotik lezyon gelişmesi üzerine TA tanısı konuldu. Oral steroid ve azatioprine eklendi. İnme sonrası dönemde levetirasetam ve valproik asit ile dirençli nöbetler kontrol altına alındı. Antikoagülan, antiepileptik ve immünsüpresif tedaviler ile multidisipliner takibi devam etmektedir. TA, infantil dönemde epileptik nöbet ve inme gibi akut semptomlarla nadiren ortaya çıkar. Uzun vadede ortaya çıkabilecek komorbiditeleri azaltmak için erken tanı koymak önemlidir.
Anahtar Kelimeler: Takayasu arteritis, Seizure, Stroke, Children

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1. Introduction

Takayasu arteritis (TA) is a chronic, inflammatory and granulomatous vasculitis that may involve the aorta, aortic arc, abdominal aorta, renal and iliac arteries. Most pediatric cases are diagnosed in the adolescent period and it is more common in the female sex. It is more frequent in Asian countries, especially Japan, compared to the west [1]. In Turkey, the incidence is 12.8 per million adults; however, the incidence in children is not clearly known. The pathogenesis of the disease is not fully known, though fibrosis develops in arterial walls as a result of immune-mediated inflammatory mechanisms. As a result of this situation, there is stenosis in the large arteries and it may cause stroke in 10-20% of patients [2]. To date, presentation with epileptic seizures in early childhood is limited to a few case reports. Our report presents a case attending with focal seizure and confusion in the early childhood period who received TA diagnosis during long-term follow-up.

2. Case report

With no previous health problem, a 22-month-old male patient, born at term by elective cesarean weighing 3300 g, attended with right focal seizure and confusion developing after trivial trauma. With no feature in his history, the child's family history included controlled epilepsy in the father. With no cardiac, hematologic and rheumatologic disease history, the patient had no history of medication use. Height was 85 cm (10-25 p), body weight 10.5 kg (3-10 p), head circumference 49.5 cm (25-50 p), body temperature 36.8 ℃, and heart rate 90 beats/min (according to age 80-110 beats/min). Arterial pressure was 90/45 mmHg (75 p) and no pressure differences were identified between the four extremities. Neurological examination found confusion, right light reflex was weak compared to the left and there was central facial paralysis. Deep tendon reflexes were increased on the left, normal on the right with plantar reflex on the left extensor. Muscle power was 3/5 on the left and normal on the right, with sensory and sphincter examinations normal. Other system examinations did not any pathology. Laboratory tests reported leukocyte count 15.000 (103/uL), hemoglobin 11 g/dL, hematocrit 32%, platelet count 392.000 (x103/uL), C-reactive protein 0.32 mg/dL (0-0.8 mg/dL), erythrocyte sedimentation rate 19 mm/hr. Serum electrolytes, renal and liver function tests, coagulation tests, muscle enzymes and viral serology (Herpes simplex virus type 1-2, Ebstein-Barr virus, Cytomegalovirus, Hepatitis virus A and B) tests did not pathology. Electrocardiography had normal sinus rhythm and echocardiography did not identify pathology. On first attendance, the patient's brain computerized tomography (CT) was assessed as normal; however, magnetic resonance (MR) imaging identified broad infarctus compatible with the right middle cerebral artery (MCA) watershed. MR angiography observed very fine calibration at the right internal carotid artery (ICA) cervical level and after the petrous area, the right MCA and anterior cerebral artery (ACA) were not observed (Figure-1:a-i). Hematologic, cardiologic and infectious research were negative, and the patient had normal tandem mass spectrometry and lactate levels. During follow-up with enoxaparin prophylaxis, the patient developed multiple aneurysms in the right brachial artery and profunda branch and oral steroids and azathioprine were added to treatment on recommendation of pediatric rheumatology. Short-duration focal seizures and worsening electroencephalography (EEG) findings were controlled by oral levetiracetam and sodium valproate treatment. Follow-up continues with multidisciplinary approach by the pediatric neurology, hematology, rheumatology, and physiotherapy and rehabilitation units.

Table-1. Simple approach to pediatric stroke and Takayasu arteritis differential diagnosis.

	Hematological evaluation	Hematology consultation, complete blood count, PT-APTT, D-dimer, fibrinogen, ESR, CRP
		Protein C, S, Antithrombin deficiency
		Factor V Leiden
		Prothrombin *G20210A*
		MTHFR *C677T*
		Lipoprotein (a) elevations
		Sickle cell anemia
Initial evaluation	Cardiological evaluation	Cardiology consultation, ECG, ECHO, murmurs, four limb blood pressure measurements and blood pressure discrepancy Congenital heart disease Endocarditis Rheumatic fever Cardiomyopathy
		Arrhythmia
	Infectious causes	Specific anamnesis, characteristic examination and laboratory findings and consultation with infectious diseases specialist Tuberculosis
		Brucellosis
		Varicella
		Syphilis
Inflammatory vasculitis	Kawasaki disease, Polyarteritis nodosa	Specific anamnesis, characteristic examination and laboratory findings Mostly medium and small vessels are involved
	Giant cell arteritis	Frequent in adults, infrequent in a children
	Moyamoya disease	Characteristic brain MR sign, puff of smoke
Autoimmune diseases	Systemic lupus erythematosus, Sarcoidosis	In teenage, butterfly rash, depression, psychosis, photosensitivity, renal disorder, more nonspecific white matter lesions Lung, lymph nodes, skin and eyes involvement, uveitis and arthritis, very often small vessel vasculitis
Non-inflammatory vasculopathies	Fibromuscular dysplasia	Renovascular disease and hypertension, headache, pulsatile tinnitus, subarachnoid hemorrhage, claudication of the legs or arms, Frequent renal artery involvement, stenosis, occlusion, dissection or aneurysm
	Ehlers-Danlos type IV, Marfan syndrome	Marfanoid phenotype, joint hypermobility, ectopia lentis, stretchy and fragile skin
	Neurofibromatosis type I	Lisch nodules, skin fold freckling, cafe au lait spots, neurofibromas, narrowed or ectatic vessels, vascular stenosis, aneurysm, or moyamoya-like disease
Post-chemotherapy or radiotherapy	Malignancy and treatment history	

PT:prothrombin time, APTT:activated partial thromboplastin time, ESR:erythrocyte sedimentation rate, CRP:c-reactive protein, MTHFR:methylenetetrahydrofolate reductase, ECG:electrocardiography, ECHO:echocardiography, MR:magnetic resonance imaging. [References 3, 14, 15 and 16 were made use for Table-1.]

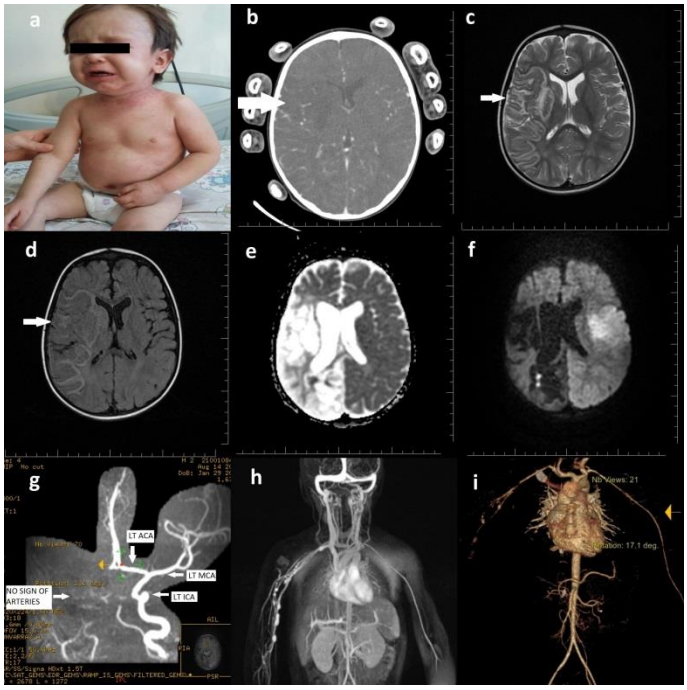

Figure-1. a) patient image (parental permission was obtained), b) initial T1 brain MR; hypointense large subacute infarct area in the right cerebral hemisphere corresponding to the watershed area of the middle cerebral artery, c) axial T2 and d) T2 flair image; subacute hyperintense appearance of the same infarct area, e) three months later, brain ADC image; hyperintense appearance including right hemisphere frontotemporoparietal and occipital lobes, lentiform and caudate nuclei in chronic stage, f) four months later, brain DWI image; large hypointense infarct area in the right hemisphere (chronic stage) but hyperintense new infarct area on the left MCA watershed area, g) brain MR angiography; right ICA and MCA could not be visualized but ACA was visualized thin calibration. Left ACA, MCA, contours and signal intensities were normal, h) one year later, right subclavian MR angiography; multiple aneurysmatic dilatations in the right brachial artery trace, i) upper extremity and abdomen 3D CT angiography; the entire aorta is in normal calibration, and the right common carotid is thinner than the left. Multiple aneurysms are observed in the right brachial artery and its profunda branch.

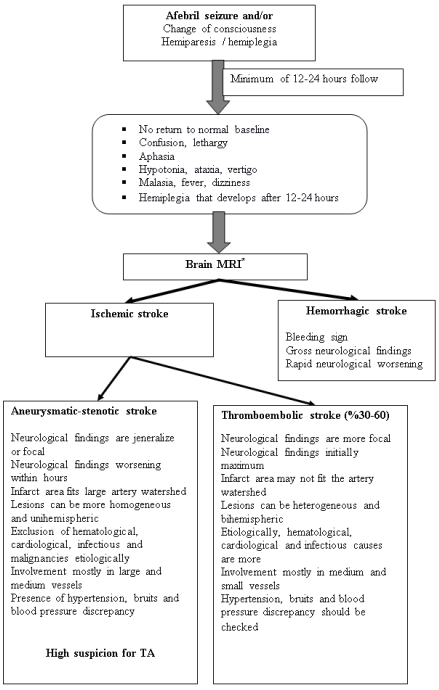

Figure-2. Brief diagnostic scheme for the Takayasu arteritis in pediatric neurology [References 13, 15, 17, 18, 19, and 20 were made use for this diagram in Figure-2.]

3. Discussion

In the pediatric period, very few cases are reported to attend with epileptic seizure in TA. In our case, the initial symptom was afebrile seizure with lengthened postictal confusion and left hemiplegia developing hours later. In the normal progression of disease in TA, attendance with systemic findings like lethargy, weight loss, fever, myalgia and arthralgia in the first phase is at the fore [3]. In the second phase (pulseless phase), arterial stenosis findings become more pronounced with findings like hypertension, claudication and neurological manifestations like headache, dizziness, visual disturbances, transient ischemic attack and stroke observed [4,5]. Our case was attended to with neurological symptoms compatible with the second phase of the disease. In this context, when we examine the literature studies by Sahin et al. (2018), Misra et al. (2015) and Aeschlimann et al. (2017) found mean age of presentation was 12.9, 14 and 12.4 years, respectively [6-8]. Again in these studies, it is notable that the female sex was dominant (nearly 75% of cases). Attendance symptoms were hypertension, bruits and blood pressure (BP) discrepancy. Sahin et al. reported 1/16 cases while Misra et al. reported 2/29 cases presented with epileptic seizure. In the literature, a case report by Weiss et al. (2008) reported that TA presented with epileptic seizure [9]. It has been reported that stenosis of the right vertebral artery and right brachiocephalic arteries was detected in MR and CT angiography in a 14-year-old Hispanic girl who presented with right-sided weakness, right facial droop and confusion. While left frontal ischemia was detected in the initial CT and MR of this case, BP discrepancy between the right and left extremities was reported in the physical examination, but not epileptic seizure [10]. In addition, it was reported that diffuse stenosis of the entire aorta and stenosis of the left subclavian artery 1/3 origin were detected in the CT aortagram of a 10-year-old girl who presented with headache, multiple recurrent seizures and altered consciousness. Interestingly, the diagnosis of PRES was made based on brain imaging findings in this case whose hypertension was detected in the right arm, but whose pulse was not palpable in the left arm [11].

As a result, the presentation of TA with epileptic seizure is a very rarely observed admission symptom and it is not included in the the European League Against Rheumatism / the Paediatric Rheumatology International Trials Organisation / the Paediatric Rheumatology European Society diagnostic criteria [12].

In arterial ischemic strokes, obstruction is generally secondary to thromboembolism and infarctus develops in accordance with by the watershed areas of the affected arteries. Infarctus in thromboembolic events are generally bihemispheric and display heterogeneous patterns, while relatively homogeneous and broad-area infarctus may indicate stenosis in large arteries. Additionally, strokes in small children may occur with findings like convulsions, lethargy, fever and headache which may be very frequently interpreted in favor of central nervous system (CNS) infection. A study by Deda and Teber (2010) revealed the etiologic risk factors for stroke cases monitored in the pediatric neurology clinic in detail [13]. In this study, the majority of stroke cases were revealed to be due to hematologic causes (Factor VIII elevation, Factor V Leiden mutation, Factor IX elevation, protein C and S deficiency, homocysteinemia and prothrombin 20210 A and MTHFR gene mutation). They reported causes of stroke with lower incidence were acquired or congenital heart diseases, CNS infections, malignancies and congenital metabolic diseases.

When we look at the pediatric neurology perspective, it is not a mistaken approach to leave vasculitis like TA toward the end of the list of differential diagnoses for an infant attending with epileptic seizure. In fact, in our case, stroke findings settled 24 hours after epileptic seizure. Considering the difficulty of sedation for brain MR or MR angiography of an infant with continuing postictal confusion or lethargy, priority for hematologic and cardiologic pathologies with identification of

infarctus and exclusion of CNS infections, it is unavoidable that a final diagnosis like TA is delayed. According to our graphical illustration prepared with a review of the literature in order to identify TA, which has severe neurologic sequelae potential, as the cause of stroke in the shortest period, TA should be suspected with identification of the lack of postictal return to normal baseline, the persistence of changes in consciousness such as lethargy-confusion, development of gross motor losses like hemiplegia, and identification of broad and unihemispheric infarctus compatible with large artery watershed area on brain imaging. If results cannot be obtained from hematologic, cardiac and infectious assessments, the diagnosis of TA can be reached from our diagnostic scheme (Figure-2). Knowing anamnesis and specific clinical and laboratory findings for inflammatory and autoimmune diseases included in differential diagnosis will shorten the time to reach the final diagnosis (Table-1).

In conclusion, clues warning of TA may include the continuation of postictal changes in consciousness for a long period after epileptic seizure, the occurrence of gross neurological findings during monitoring and identification of broad infarctus area compatible with large arteries (ICA, MCA or ACA) watershed on brain imaging.

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Derleme / Review

Obezite Tedavisinde Farmakolojik Yaklaşımlar

Pharmacological Approaches in Obesity Treatment

Elif Erdoğan Erden, Zeynep Gül Yazıcı, Cansu Kılıç Tatlıcı, Şule Aydın, Fatma Sultan Kılıç

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Tıbbi Farmakoloji Anabilim Dalı, Eskişehir, Türkiye

Özet

Obezite; dünyada ve ülkemizde giderek artış gösteren bir salgın hastalık haline gelmektedir. Tedavi edilmediği durumlarda morbidite ve mortaliteye sebep olmaktadır. Obezite gelişiminde kişisel ve çevresel faktörler rol almaktadır. Nörolojik ve metabolik yolaklarla kontrol edilen enerji homeostazındaki bozulma obezite ile sonuçlanmaktadır. Obezite gelişimi sonrası tedavi sürecinde ilk basamak hayat tarzı ve diyet değişiklikleridir. Ancak çoğu zaman ikinci basamak tedavilere ihtiyaç duyulur. Bu aşamada obezite patofizyolojisi göz önünde bulundurularak farmakoterapi seçenekleri değerlendirilir. Kişinin genetik altyapısı, enerji homeostazındaki bozulma ve çevresel etkenler obezite oluşumunda rol oynamaktadır. Bu nedenle genetik mutasyonlar sonucu oluşan eksiklikler ve enerji homeostazında etkili yolaklar hedeflenerek farmakolojik yaklaşımlar kullanılır. Bunlar arasında hali hazırda kullanılan orlistat, cetilistat, liraglutid, lorkaserin, burpropion/naltrekson kombinasyonu, fentermin/topiramat kombinasyonu, metformin gibi seçenekler mevcutken, genetik mutasyonlar sonucu oluşan obezitede etkili metreleptin ve setmelanotid gibi obezite endikasyonu için onay almış ve endikasyon dışı kullanılarak obezitede fayda sağlanmış ajanlar mevcuttur. Obezite tedavisi için farmakolojik yaklaşımlar gün geçtikçe artmaktadır. Günümüzde obezite tedavisinde umut vadeden semaglutid, oksitosin, bromokriptin, resveratrol, β3 adrenerjik reseptör agonistleri ,velneperit, davalintide (AC2307), glukoz-bağımlı insülinotropik polipeptid (GIP) analogları, beloranib, tesofensin gibi birçok seçenek de mevcuttur. Bunların yanında obezitenin önlenmesine yönelik aşı çalışmaları da sürdürülmektedir. Obezite risk faktörlerini, gelişim sürecini bütüncül olarak ele aldığımızda obezitenin önlenmesi ve tedavisi için seçenekler artmakta olup obeziteye karşı mücadelede elimizi güçlendirmektedir.
Anahtar Kelimeler: Obezite, İlaç tedavisi, Aşı, İlaç

Abstract

Obesity is becoming an increasing epidemic disease in the world and in our country. Unless it is treated it causes morbidity and mortality. Individual and environmental factors play a role in the development of obesity. The impairment in energy homeostasis, which is controlled by neurological and metabolic pathways, results in obesity. The first step in the treatment process of obesity is lifestyle and diet changes. However, second-line treatments are often needed. At this stage, pharmacotherapy could be an option considering the pathophysiology of obesity. The genetic background of the person, the impairment in energy homeostasis and environmental factors play a role in the formation of obesity. For this reason, pharmacological approaches are used by targeting deficiencies caused by genetic mutations and effective pathways in energy homeostasis. Among these, there are options such as orlistat, cetilistat, liraglutide, lorcaserin, burpropion/naltrexone combination, phentermine/topiramate combination, metformin, which are currently used, while meterleptin and cemelanotide, which are effective in obesity caused by genetic mutations, have been approved for the obesity indication and benefit in obesity by using off-label. agents are available. Pharmacological approaches for the treatment of obesity are increasing day by day. There are also many options being investigated such as semaglutide, oxytocin, bromocriptine, resveratrol, β3 adrenergic receptor agonists, velneperit, davalintide (AC2307), glucose-dependent insulinotropic polypeptide (GIP) analogues, beloranib, and tesofensin. In addition to these, there are also ongoing vaccine studies for prevention of obesity. When we consider the obesity risk factors and the development process holistically, the options for the prevention and treatment of obesity increase and strengthen our hand in the fight against obesity.
Keywords: Obesity, Pharmacotheraphy, Vaccine, Drug

Correspondence:
Elif ERDOĞAN ERDEN
Eskişehir Osmangazi Üniversitesi, Tıp Fakültesi Tıbbi Farmakoloji Anabilim Dalı , Eskişehir, Türkiye
e-mail: eliferdoganerden@gmail.com

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1. Giriş

Obez hastaların kilo verme sürecinde öncelikle yaşam tarzı ve diyet değişiklikleri yapılır, fakat bunlar çoğunlukla yeterli olmamaktadır. Bu nedenle uzun süredir obezite için medikal tedavi seçenekleri üzerine çalışılmaktadır (1). Obezite tedavisinde etkili olabilmek için enerji alımını, metabolizmasını ve tüketimini sistematik olarak değerlendirmek gerekmektedir (2). Vücut kitle indeksi (VKİ) ≥ 27 olup diyabet ve hipertansiyon gibi obezite ile ilişkili ko-morbiditesi olan, VKİ≥30 olup yaşam tarzı değişikliklerinden fayda sağlanamamış hastalara farmakoterapi önerilmektedir (3).

Obezitenin medikal tedavi sürecinde uzun yıllar boyunca Amerika Birleşik Devletleri'nde (ABD) amfetamin ve orlistat, Avrupa'da ise yalnızca orlistat kullanılmıştır (4). Ancak tedavi seçeneklerinde yıllar içinde değişiklikler olmuştur (5).

Amfetamin; 1887 yılında sentezlenmiş olup enerji sağlama ve uyanıklık arttırma, öfori gibi etkileri bulunan bir moleküldür. Depresyon ve narkolepsi tedavisi için kullanıldığı dönemde kilo verdirici etkisi gözlemlenmiştir. Amfetamin, dopaminerjik sinyalleri arttırır ve ödül sistemini etkileyerek, kötüye kullanım ve bağımlılığa sebep olur (6).

Aminoreks, fentiletilamin yapısına sahiptir. Santral sinir sisteminde (SSS) noradrenalin (NA) salınımını arttırarak iştahta azalma sağlar. 1965 senesinde Avustralya, İsviçre ve Almanya'da kullanılmaya başlanmıştır. Ancak 1968'de primer pulmoner hipertansiyon insidansında artışa neden olmasından dolayı piyasadan çekilmiştir (6).

Sibutramin ise serotonin ve NA geri-alım inhibitörüdür. Gıda alımını azaltarak etkinlik gösterir. 1997'de obezitenin uzun dönem tedavisi için kullanılmaya başlanmıştır. NA reseptör agonistlerinin tipik yan etkilerinden olan ağız kuruluğu, uykusuzluk, kabızlık, baş ağrısı gibi etkileri vardır. Kardiyovasküler güvenilirlik değerlendirmesi için yapılan SCOUT (Sibutramine Cardiovascular Outcomes) çalışması sonucu kalp krizi, inme ve ölüm oranlarında %16 artış görülmesi sonucu Avrupa'da kullanımı sonlanmıştır. 2010'da ABD'de piyasadan çekmiştir (6).

Kannabinoid reseptörü tip 1(CB1R) antagonisti olan rimonabant Avrupa İlaç Ajansı (European Medicines Agency-EMA) tarafından kullanım onayı almış ancak Amerikan İlaç ve Gıda Dairesi (U.S. Food and Drug Administration-FDA) tarafından onaylanmamıştır. İntihar düşüncesi riskini arttırması nedeniyle 2009 yılında piyasadan çekilmiştir (5).

Amfetaminin yüksek bağımlılık yapıcı etkisi, aminoreksin ve sibutraminin ciddi kardiyopulmoner yan etkisi, rimonabantın ciddi psikiyatrik yan etkisinin olması obezite tedavisini yan etki profili daha güvenilir ilaçlara yönlendirmiştir. Bu arayış sonucunda liraglutid, lorkaserin, bupropion/naltrekson kombinasyonu ve fentermin/topiramat kombinasyonu olmak üzere 4 yeni ilaçla birlikte obeziteye karşı farmakolojik tedavi yaklaşımları artmıştır. ABD'de hepsi kullanılmaktayken, Avrupa'da ise EMA tarafından onaylanmış olan liraglutid ve bupraopion/naltrekson kombinasyonu kullanılmaktadır (4).

Bu derlemenin amacı günümüzde gittikçe artarak çocukluk dönemi dahil olmak üzere tüm yaş gruplarını etkileyerek birçok hastalık ile neden-sonuç ilişkisine sahip olan obezitenin tedavi seçenekleri hakkında genel bir bilgi sağlamaktır. Bu konuyla ilgilenen kişilere çizecekleri yol haritası için yardımcı olmaktır.

A-Obezite Endikasyonu İle Kullanılan İlaçlar

1-Orlistat

Orlistat santral olarak etkili olmayan, gastrointestinal sistemde lokal olarak etki eden bir ajandır. Gastrik ve pankreatik lipaza bağlanarak inaktive eder ve intestinal mukozada trigliseritlerin hidrolizini ve uzun zincirli yağ asitlerinin emilimini azaltır. Bunun sonucunda, yiyeceklerle tüketilen yağ asidinin yaklaşık üçte birinin emilimini

engeller. Yani iştah etkilenmeden kalori alımı azalır, (1, 7, 8).

Çoğunlukla yağda çözünür vitamin (A,D,E,K vitaminleri) düzeylerinde düşüklük, yağlı dışkılama, karın ağrısı, fekal inkontinans ve gaz gibi gastrointestinal sistem yan etkileri nedeniyle kullanımı sınırlanır. Ancak bu yan etkiler lifli beslenme ile azabilir. Uzun dönemli kullanıldığında uygun vitamin takviyesi yapılması gerekebilir. Kronik malabsorbsiyon, kolestaz ve gebelikte kullanımı kontrendikedir (9).

Tedavi sürecinin 3 aylık döneminde başlangıç vücut ağırlığının %5'i, 6 aylık döneminde ise %10'unun kaybedilmesi beklenmektedir. Genellikle tedavi süreci 12 ayı aşmazken, 24 aydan daha fazla kullanılması önerilmemektedir (7).

2-Cetilistat

Orlisat gibi gastrik ve pankreatik lipazı inhibe ederek etki gösterir. Randomize, plasebo kontrollü, çift-kör klinik bir çalışmada cetilistat ile 12 hafta boyunca tedavi edilen obez hastalarda sağlanan ≥5% kilo kaybı, bel çevresinde azalma, HbA_{1C} seviyesinde azalma kontrol grubuna göre anlamlı bulunmuştur. Orlistatın diyare, gaz ve yağlı dışkılama gibi yan etkileri cetilistat ile belirgin şekilde daha az görülmektedir (10).

3-Liraglutid

Liraglutid, insanlarda endojen olarak üretilen glukagon benzeri peptid-1 (GLP-1)'den yapısal olarak farklı bir türevidir. Modifiye yapısından dolayı, liraglutid plazmadaki GLP-1'den daha kararlıdır ve plazma proteinlerine güçlü bir şekilde bağlanır. Liraglutid, G proteini ile kenetli GLP - 1 reseptörlerine (GLP-1R) bağlanarak etki gösterir. Santralde ventral tegmental bölge (VTA) ve nükleus akkumbens (NAc)-' gibi santral ödül yolağında önemli merkezlerde GLP-1R eksprese edildiği için gıda alımında etkili olur (4).

Periferde ise liraglutid, gastrik vagal afferentleri uyararak gastik boşalmayı yavaşlatır ve erken dönemde doygunluk hissi sağlayıp tokluk süresini uzatarak anoreksijenik etki gösterir (4). Liraglutid kilo kaybını enerji tüketimindeki artış ile değil, enerji alımındaki azalmayla sağlar (5). Liraglutid farklı seviyelerde glukoz homeostazını, pankreas β hücrelerinin yaşam süresini, insülin sekresyonunu ve beslenme davranışını da etkiler (4). Viseral yağ miktarını azaltır ve yağ asidi oksidasyonunu arttırır. Aynı zamanda liragutidin diyabetik sıçanların subkutan yağ dokusunda kahverengi yağ dokusu(BAT) marker genlerinin ekspresyonunu arttırarak yağ dokunun kahverengileşmesini çoğalttığı ve metabolik anormallikleri düzelttiği görülmüştür (11).

GLP-1R aganositleri ve analoglarının en sık görülen yan etkisi çoğunlukla tedavinin erken döneminde görülen bulantıdır. Bunun yanında kabızlık, diyare ve kusma gibi diğer gastrointestinal etkilere de sebep olabilirler, ancak daha nadirdir (12). Kendisinde veya ailesinde medüller tiroid kanseri veya tip 2 multipl endokrin neoplazi (MEN) hikayesi olanlarda kullanımı kontraendikedir (9).

4-Lorkaserin

Lorkaserin, selektif 5-hidroksitriptamin$_{2C}$ (5-HT_{2C}) reseptör agonistidir, serotonerjik nörotransmisyonu seçici olarak arttırır. 2012'de her 2 cinsin de dahil edildiği 3 randomize klinik çalışma sonucunda onaylanmıştır (4). 5-HT_{2C} reseptörleri serotoninin anorektik etkisinden sorumludur ve kilo vermede etkilidir (6). Bu reseptörlerin aktive edilmesiyle proopiomelanokortin (POMC) nöronlarından α-melanosit uyarıcı hormon (α-MSH) salınır. α-MSH, melanokortin 4 reseptörü (MC4R) agonizmasıyla iştahı azaltır (1).

Lorkaserin ve diyet bir arada iştah artışında önemli derecede azalma sağlar. Lorkaserinin beyinde ödül sistemi aktivitesinde azalma sağladığı fonksiyonel manyetik rezonans görüntüleme ile desteklenmiştir. Prediyabetten diyabete ilerleyişi yavaşlatırken, prediyabetten öglisemik duruma geçişi de arttırır. Bu durumda diyabete karşı koruyucu bir etki oluşturur (6). Ancak 5-HT reseptör agonistlerinin neden olduğu kapak fibrozisi ve mitral yetersizlik lorkaserin kullanımından

sonra da ortaya çıkabilir. Bu nedenle lorkaserin kullanılması planlandığında kar–zarar oranı göz önünde bulundurulmalıdır (13).

5-Bupropion/Naltrekson Kombinasyonu

Bupropion/naltrekson, iştah baskılamada ve kilo kaybındaki farmakolojik sinerjistik etkilerinden yararlanılarak kombinasyon olarak pazarlanmaktadır (4).

Bupropion indirekt sempatik agonist dietilpropion ile yapısal olarak benzeyen, dopamin (DA) ve NA için presinaptik taşıyıcıları bloke ederek etki gösteren monoamin geri-alım inhibitörü bir antidepresandır. Hipotalamusta sinaptik aralıkta bu transmitterlerin konsantrasyonlarındaki artış, bupropionun anorektik etkisinden sorumludur. Arkuat ve paraventriküler çekirdeklerde yer alan dopaminerjik ve noradrenerjik terminaller açlık ve tokluğu kontrol eder. Bupropionla, dopaminerjik nörotransmisyonun artışıyla anoreksik etki ortaya çıkabilir (4). Aynı zamanda hipotalamik POMC (Proopiyo melano kortin) nöronlarını uyararak iştahı azaltır ve enerji tüketimini arttırır (6).

Naltrekson ise opioid ve alkol bağımlılığının tedavisi için onaylanan, oral olarak kullanılan aktif bir μ-, κ- ve δ - opioid reseptör antagonistidir. Kemirgen obezite modellerinde endojen opioid sistemi beslenme davranışını kontrol ederek kilo vermede etkili olsa da insanlarda naltreksonun zayıf anorektik etkisi tek başına kilo vermede yeterli değildir. Ancak bupropion ile birlikte sinerjistik etki göstererek kilo kaybı sağlar. Naltrekson, bupropionun POMC nöronları üzerindeki etkisini arttırarak etkili olur. Aynı zamanda opioid reseptörlerinin naltrekson ile kronik olarak bloke edilmesi de hipotalamusta POMC gen ekspresyonunda artış oluşturur (4, 5). Naltrekson β-endorfinin oreksijenik etkilerini de engellemektedir (6).

Bupropion irritabilite, baş dönmesi, uykusuzluk, baş ağrısı, bulantı-kusma, iştah azalması, anksiyete, yorgunluk ve tremor gibi yan etkiler oluşturabiliyorken, naltrekson ise bulantı-kusma, baş ağrısı, baş dönmesi ve uykusuzluk gibi yan etkilere neden olabilir (8).

6- Fentermin/Topiramat Kombinasyonu

Fentermin, amfetamin türevi bir moleküldür; bu nedenle, NA ve DA geri-alımının inhibisyonu ve presinaptik salıverilmelerini arttırarak adrenerjik ve dopaminerjik nörotransmisyonu güçlendirir. Fentermin anorektik etkiyi, katekolaminerjik hipotalamik nörotransmisyonu arttırarak oluşturur. Periferdeki lipolitik etkisi de kilo vermeye katkı sağlar. Diğer amfetamin türevlerine göre bağımlılık yapıcı etkisi daha azdır. 1959 yılında obezite tedavisi için FDA tarafından onaylanmıştır. Avrupa ülkelerinde kardiyotoksik etkileri ve bağımlılık potansiyeli nedeniyle kullanılmamaktadır (4).

Fenterminin bağımlılık açısından oldukça güçlü etkili grupta (Uyuşturucu ile Mücadele Dairesi/Drug Enforcement Administration Sınıflandırmasına göre) olmasından dolayı kısa dönem kullanımı önerilir (5). İrritabilite, uykusuzluk, duygu-durum değişiklikleri, ağız kuruluğu, tremor, baş ağrısı, kan basıncı ve kalp atım hızı artışı, gastrointestinal yan etkiler gibi yaygın yan etkileri vardır. Kardiyovasküler hastalık hikayesi olanlar, hipertiroidizim, glokom, monoamin oksidaz inhibitörü kullananlarda kontrendikedir (9).

Topiramat ise epilepsi tedavisi ve migren proflaksisinde kullanılmak üzere geliştirilmiş bir sülfamat türevi monosakkarittir. Nöronlardaki voltaj bağımlı Na^{+} ve Ca^{+2} kanallarını ve AMPA/Kainat reseseptörlerini bloke ederek, GABA-A reseptör aktivitesini arttırarak ve karbonik anhidraz enzimini inhibe ederek etki gösterir. Kilo verme üzerindeki etkisiyle ilgili mekanizmalar kesin değildir. Periferde iskelet kasında insülin duyarlılığını arttırır ve 5′-adenozin monofosfat (AMP) ile aktive edilmiş protein kinaz (AMPK) ve asetil-koA karboksilazı aktive eder. Santral etkisi esas olarak hipotalamusta meydana gelir. Bu etkisi Leptin ile indüklenmiş JAK-STAT ve MAPK/ERK ve insülin ile uyarılmış insülin reseptörü substratı/ Akt/ forkhead box O1 yolu aktivasyonunu kuvvetlendirerek ortaya çıkar. Leptin ve insülin sinyalleri üzerindeki bu etkiler sonuçta POMC, tirotropin salgılayan hormon (TRH) ve kortikotropin salgılayan hormon (CRH) dahil olmak üzere anorektik peptitleri kodlayan genlerin

transkripsiyonunda bir artışa yol açar. Sıçanlarda AMPA reseptör uyarısıyla beslenmenin indüklendiği gözlemlenmiştir. Bu nedenle topiramatın AMPA reseptör inhibisyonu yaparak anorektik etki oluşturduğu düşünülebilir (4). Bunun yanında GABA aktivitesindeki artış da iştah baskılanmasında etkili olur (9).

Topiramatın reversibl kognitif disfonksiyon, metabolik asidoz, nefrokalsinozis ve parestezi gibi yan etkileri vardır. Kalp atım hızı, kan basıncı, elektrolitler ve kreatinin tedavi başında ve periyodik olarak tedavi sırasında özellikle doz artışı sırasında monitörize edilmelidir. (9).

Topiramat ve fentermin tek başına kullanıldığında istenilen oranda kilo kaybı sağlamadığı için kombinasyon şeklinde kullanılmaktadır. Kombinasyonun yan etkileri ise tek başlarına kullanıldıkları durumlardakilere benzerdir (4,9).

7-Metformin

Metformin Tip 2 diyabetes mellitus tedavisinde 20 seneyi aşkın süredir kullanılan bir ajandır. Obezitede monoterapi olarak onaylanmamıştır ancak özellikle tip 2 diyabet gibi ko-morbiditesi olan hastalarda tedaviye eklenebilir (14). Metformin hepatik glukoneogenezi inhibe ederken, kas ve karaciğer gibi periferdeki dokularda insülin bağımlı glukoz alımını arttırır (9). Metformin kullanımı ile yağsız dokuda az miktarda değişiklik olurken yağ kütlesinde azalma meydana gelir. Egzersiz ile metformin birlikte kullanıldığında AMPK uyarılması artar. Ayrıca gastrointestinal sistemde tahriş oluşturarak gıda alımını azaltarak kilo kaybına katkıda bulunabilir (15).

Gaz ve diyare gibi gastrointestinal yan etkileri vardır. Metformine bağımlı laktik asidoz nadir görülse de ciddi bir durumdur (9).

8-Metreleptin

FDA tarafından genetik sebepli obezite için onaylanmış ilaçlardan birisidir. Çocuklarda ve yetişkin hastalarda kullanılır. Leptinin enjekte edilebilen rekombinant formudur. Leptin geninde mutasyon olup leptin eksikliği olan konjenital jeneralize lipodistrofisi olan kişilerde kullanılır ve metabolik düzelme sağlar (3, 9, 16). Hiperglisemi ve hipertriglisemiyi iyileştirir, hepatik yağlanmayı azaltır (3). Ciddi kilo kaybı, hiperfajide belirgin iyileşme ve açlık derecesinde azalma ortaya çıkarır (9). Metreleptine karşı antikor oluşumu metreleptin ile tedavi sürecinde kilo alımına ve efikasite kaybına neden olabilir. Bu yüzden metreleptin konjenital leptin eksikliği olan obezite dışında kontrendikedir.

En yaygın yan etkileri ise baş ağrısı, hipoglisemi, kilo kaybı ve karın ağrısıdır (3).

9-Setmelanotid (RM-493)

Metreleptin gibi FDA tarafından genetik sebepli obezite tedavisi için onaylanmış ilaçlardan birisidir. Setmelanotid, α-MSH' nin 8 aminoasitli siklik peptid yapısında analoğudur. Endojen MC4R ligandıdır (17). POMC, leptin reseptörü (LEPR) ve prohormon konvertaz 1 (PCSK1) genlerinde mutasyon olduğunda ve Prader- Willi sendromu, Bardet-Biedl sendromu, Alström sendromu olan obez hastalarda kullanılır (3, 16). Beyindeki melanokortin reseptör agonistleri gıda alımını, tokluğu düzenlemeye yardımcı olur ve insülin duyarlılığını etkiler (3). MC4R yolağı setmelanotid ile direkt aktive olarak açlık hissini azaltır. Enerji alımını azaltarak ve enerji tüketimini arttırarak kilo kaybı sağlar (17).

Yan etkileri ağız kuruluğu, enjeksiyon yerinde lokalize cilt indurasyonu ve nevüslerde koyulaşmadır (9).

B- Obezitede Tedavisinde Araştırılan Diğer Seçenekler

1-Semaglutid

Halihazırda kullanılmakta olan GLP-1R agonisti liraglutide göre daha uzun ömürlü ve en yeni GLP-1R agonistidir. Yakın zamanda Avrupa, Japonya ve Kuzey Amerika'da tip 2 diyabet için kullanım onayı almıştır. Semaglutid haftada bir kullanılabildiği için uzun dönemde kullanım kolaylığı sağlayarak tercih sebebi olabilir. Obez yetişkinlerde kan şekeri, HbA1c seviyelerini düzenler. Enerji

alımını azaltarak ve tokluğu arttırarak belirgin kilo kaybı sağlar. Bu nedenle tedavide umut vadetmektedir (3, 18, 19).

Semaglutid yan etki profili olarak diğer GLP-1 agonistlerine benzer. Hipoglisemik yan etkisi azdır. En yaygın yan etkileri bulantı, gazdır (3).

2-Oksitosin

Oksitosin hipotalamus tarafından üretilen salgılanmak üzere hipofizde depolanan bir hormondur. Aynı zamanda over, testis, timus, böbrek ve kalp dahil olmak üzere çeşitli periferik organlarda da sentezlenebilmektedir (20). Overektomize edilmiş sıçanlarla yapılmış bir çalışmada oksitosin enjeksiyonunun besin alımında azalma, kilo kaybı sağladığı gösterilmiştir. Aynı zamanda viseral ve subkutan yağ kütlesinde ve adiposit boyutunda azalma sağlamıştır (21). Oksitosinin haz yolakları ve homeostatik yolaklar üzerinden gıda tüketimini düzenlemesinin dışında periferde insülin rezistansında iyileşme, lipoliz ve yağ asidi β oksidasyonu üzerinde etkili olduğu görülmüştür (22, 23).

Kronik kullanımda kardiyovasküler yan etkiler ve hiponatremi riski açısından değerlendirilmesi gerekir. Daha nadir olarak baş ağrısı ve mide bulantısına neden olabilir (23).

3-Bromokriptin

Bromokriptin, Amerika'da FDA tarafından glukoz toleransı ve insülin sensitivitesi üzerindeki olumlu etkilerinden dolayı tip 2 diyabet tedavisi için onaylanmış dopamin 2 reseptör agonistidir (24). Santral sinir sisteminde mezolimbik ve hipotalamik dopaminerjik sinyalleri modüle ederek kilo üzerinde etkili olur (25). Bununla birlikte periferik dokularda dopamin, insüline duyarlı dokularda glikoz alımını ve yağ dokusunda lipit metabolizmasını doğrudan modüle ettiği için de kilo kaybı sağlayabilir (26). Bromokripin uygulamasının serum leptin seviyelerini düşürmesi ve leptin rezistansında iyileşme sağlaması, bromokriptinin obezite tedavisi için bir seçenek olmasını sağlamaktadır (27).

4-Resveratrol

Resveratrol üzerinde en çok çalışımış olan polifenolik bileşiklerden birisidir. Anti inflamatuar, yaşlanma karşıtı, kansere karşı koruyucu, kardiyovasküler sistem üzerinde olumlu etkilerinin yanında hücresel fonksiyonları ve genel metabolik sağlığı iyileştirme gibi obezite için fayda sağlayabilecek etkileri ile de ön plana çıkmaktadır (28). Leptin reseptörü geninde mutasyon olan genetik spontan tip 2 diyabet hastası db/db farelerle yapılan bir çalışmada 10 hafta %0,4 oranında resveratrol içeren diyet ile beslenme sonucu BAT aktivasyonu ve beyaz yağ dokusunun (WAT) kahverengileşmesinde artışla glikoz homeostazını iyileştirici etki görülmüştür (29). Ayrıca, resveratrol, "bağırsak florası yağ dokusu"(gut microbiota adipose tissue) aksını düzenleyerek enerji tüketimini artırır. Glikoz ve lipit metabolizmasını düzenler. Bu sayede bağırsak florasının bileşimini düzenleyebilir (30). Tüm bu etkiler göz önüne alındığında resveratrol obezite tedavisi için etkili olabilir.

5-β3 adrenerjik reseptör agonistleri

β3-adrenoseptörler, insanlarda WAT ve BAT'ta iskelet kasında eksprese edilir. Enerji ve glukoz homeostazının sağlanmasında rol oynarlar. β_3-adrenerjik reseptör agonistleri ise subkutan WAT ve özellikle BAT'ta yoğun olarak bulunan, termojenezde etkili olan ayrıştırıcı protein-1(UCP1)'in gen ekspresyonunu arttırarak termojenik ve insülin duyarlaştırıcı etkinlik gösterirler (11, 31, 32). Subkutan ve epididimal beyaz yağ dokusunu azalmasını sağlarlar. Ayrıca diyabetik hayvan modellerinde hiperglisemiyi belirgin şekilde iyileştirdikleri gösterilmiştir (11).

β_3-adrenerjik reseptör agonisti ilaçlardan bazıları (L-796,568) insan çalışmalarında başarısız olmuştur, ancak yeni bir β_3-adrenerjik reseptör agonisti olan mirabegron insanlarda BAT termojenezini ve istirahatteki metabolik hızı arttırdığı için obezitede potansiyel bir terapötik ajan olarak görülmektedir (11).

6-Velneperit

Nöropeptit Y (NP Y) güçlü bir oreksijenik peptitdir. Etkilerinin hipotalamik NP Y

reseptörleri üzerinden gösterir. Besin alımını arttırır ve enerji tüketimini azaltır. Velneperit (S-2367) ise NP Y reseptörlerinin, Y5 reseptör alt tipinin antagonistidir. İştah azaltarak ve tokluk hissi sağlayarak beslenmeyi kontrol eder. Faz 2 klinik çalışmalarda velneperit ortalama bir kilo kaybı sağlamıştır (33). Fakat kilo kaybı sağlamada yetersiz kalmasından dolayı klinik deneyler sonlandırılmıştır (34).

7-Davalintide (AC2307)

Amilin, pankreasta β hücrelerinden insülin ile birlikte salgılanan bir hormondur. Besin alımını azaltır, gastrik boşalmayı yavaşlatır ve postprandiyal glukagon sekresyonunu azaltır (35). Area postrema üzerinden SSS'ye ulaşarak santral olarak beslenme kontrolünde de etkili olur. Amilin, oreksijenik nöropeptidlerin ekspresyonunu azaltarak enerji homeostazında etkili olur. İnsanlarda amilin reseptör subtipleri, kalsitonin reseptörü ve reseptör aktivitesini modifiye eden proteinlerle kompleks halindedir (3).

Amilin mimetik peptid olan davalintidin (AC2307) hayvan çalışmalarında gıda alımını ve vücut ağırlığını azalttığı ve metabolik aktiviteyi arttırdığı gösterilmiştir (3). Obez ve yüksek kilolu bireylerde subkutan davalintide ve plasebonun kilo değiştirici etkisinin karşılaştırıldığı faz 2 çalışması ise tamamlanmıştır (36). Ancak klinik çalışmalar sonucu beklenen etki görülmediği için etkileri arttırmak için amilin resepörleri ve kalsitonin reseptörlerinin ilişkisi göz önünde bulundurularak kombinasyon seçeneklerine yönlenilmiştir (37).

8-Glukoz-bağımlı insülinotropik polipeptid (GIP) analogları

Gastrik inhibitör peptit olarak da adlandırılan glukoz bağımlı insulinotropik polipeptid, ince bağırsakta entero endokrin K hücreleri tarafından salgılanır. Pankreastaki β hücreleri üzerindeki GIP reseptörlerine direkt etki ederek insülin salınımını uyarır (38).

Deneysel hayvan çalışmalarında obez/diyabetik kemirgenlerde GIP reseptör agonizması ve antagonizmasının her ikisinin de glisemik kontrolü iyileştirdiği görülmüştür. Aynı zamanda insanlarda ve hayvanlarda GIP reseptör aktivasyonu ve inhibisyonu farklılık göstermektedir (39).

GIP etkinliğindeki farklılıklar ve tip 2 diyabetli kişilerde GIP'in insülinotropik etkisinin zayıflamasından dolayı obeziteye karşı tedavi yaklaşımlarında GIP/GLP-1 reseptörleri dual agonistleri kullanımına yönlenilmiştir. Bu sayede GLP-1R agonistlerinin kullanımında sınırlayıcı olan gastrointestinal yan etkiler azalabilir ve terapötik etkinlik iyileşebilir (40).

9-Beloranib

Beloranib, doğal bir kimyasal bileşik olan fumagillinin bir analoğudur. Kanser tedavisi için anjiogenez inhibitörü olarak üretilmiştir (3). Metionin aminopeptidaz-2 (MetAP2) inhibisyonu yaparak etki eder. MetAP2 inhibisyonu ile yağ biyosentezi azalır, yağ oksidasyonu ve lipoliz artar (41). Obez hayvan modellerinde beloranib ile besin alımının azaldığı, kilo kaybı sağlandığı ve yağ kütlesini azalttığı gösterilmiştir (42). Faz 2 klinik çalışmalarda ise doza bağlı kilo kaybı gözlemlenmiştir. Buna bağlı olarak bel ve kalça çevresinde de azalma gözlemlenmiştir. Kolesterol, C- reaktif protein seviyelerinde ve sistolik kan basıncında iyileşmeler sağlanmıştır (41). Ancak Prader-Willi sendromuna bağlı obezitede beloranib faz 3 klinik çalışmaları 2 hastada pulmoner emboli nedeniyle ölüm meydana gelmesinden dolayı durmuştur (3, 43).

10-Tesofensin

Tesofensin, yeni triple monoamin geri-alım inhibitörüdür. DA, NA ve serotonin geri-alımını inhibe eder (44). Diyete bağlı obez olan sıçanlarla yapılmış bir çalışmada iştahta ve besin alımında azalma sonucu kilo kaybı gözlemlenmiştir. Bu etki altındaki mekanizma ise α1 adrenoreseptörler ve dopamin 1 reseptörlerinin indirekt olarak uyarılmasıdır (45, 46). Aynı zamanda tesofensin toplam yağ kütlesinde ve plazma kolesterol seviyelerinde düşüş de sağlamıştır (47).

Bir klinik çalışmada ise tesofensin ile lipit oksidasyonunda artış olduğu görülmüştür. Toplam enerji tüketiminde bir değişiklik saptanmamasına rağmen, uykudaki enerji tüketimi anlamlı olarak daha fazla bulunmuştur. Bu sonuçlar tesofensinin metabolik hızda küçük bir artışla birlikte besin alımını azaltarak kilo kaybı sağladığını desteklemektedir (48).

Sempatomimetik etkinliğinden dolayı istenmeyen yan etkiler için metoprolol ile kombine kullanımı açısından Prader-Willi sendromu ve hipotalamik yaralanmaya bağlı obezitede Faz 2 klinik çalışmalar yapılmaktadır (36).

C- Anti-Obezite Aşıları (Ghrelin, Gip, Somatostatin, Adiposit, Adenovirus 36)

Aşılama; obezite tedavisinde ve önlenmesinde alternatif bir yaklaşımdır. Aşı geliştirmede öncelikli hedef iştahı stimüle eden ghrelin, somatostatin gibi peptitleri baskılamaya veya besin absorbsiyonunu engellemeye yöneliktir.

Ghrelin aşısı diyete bağlı obez farelerde enerji tüketimini arttırmış ve viseral ve subkutan yağ dokusunda azalma sağlamıştır (49).

Sıçanlarda GIP aşılaması sonucunda diyete bağlı obeziteye karşı koruma sağlanmıştır. Bazal metabolik hızdaki artışa bağlı olarak enerji tüketimi artmış ve yağ birikimi azalmıştır. Otoimmun reaksiyon gelişimi olmaması da olumlu bir sonuçtur (50).

Diyete bağlı obez farelerle yapılmış somatostatin aşısı çalışmasında besin tüketiminde değişiklik olmadan kilo kaybı gözlemlenmiştir (51).

Obezite aşırı yağ birikimi ve yağ doku disfonksiyonu ile ilişkili bir hastalık olduğu için adipositlere karşı aşı etkili bir yaklaşım olabilir. 13 kişilik ortalama VKİ'si 26,3 kg/m^2 olan küçük bir grupla domuz yağ dokusundan elde edilmiş adiposit aşısı ile yapılmış bir klinik çalışmada kilo üzerinde ve VKİ'de belirgin bir değişiklik görülmezken bel çevresinde azalma ve lipit profilinde iyileşme gözlemlenmiştir. Bunun yanında sistolik ve diyastolik kan basınçları etkilenmemiş ve karaciğer alanin aminotrasnferaz (ALT), aspartat aminotransferaz (AST) enzimlerinde değişiklik gözlenmemiştir (52).

Adenovirus 36'nın primatlarda adipoziteyi arttıp kilo alımına neden olduğu gösterilmiştir (53). Ayrıca makrofajların yağ doku içinde infiltrasyonunu arttırarak inflamasyona neden olur (54). İnsanlarla adenovirus 36 aşısıyla yapılan başka bir çalışmada ise, erken dönemde kilo kaybı sağlanamamış olsa da kilo alımına karşı koruyucu bir etki ve pro-inflamatuar sitonkinlerin salınımında azalma görülmüştür (55).

Obezite patogenezi göz önünde bulundurulduğunda genetik, cinsiyet, yaş gibi değiştirilemeyen kişisel faktörler ve diyet, yaşam tarzı, ko-morbid hastalıklar gibi değiştirlebilir faktörlere göre tedavi planlanması gereken bir hastalıktır. Tedavi süreci bireysel olarak şekillendirilmelidir. Bu nedenle günümüzde kullanılan ilaçların yanında patogenezde yer alan faktörlere spesifik ilaç seçenekleri araştırılmaktadır. Son çare olarak, obezitede ilaçla tedavi seçeneklerinin uzun dönemdeki istenmeyen yan etkileri ve uyunç sıkıntıları nedeniyle aşı seçenekleri de önem kazanmaktadır. Ancak, her türlü kesin ve araştırılma aşamasında olan tedavi seçeneklerine rağmen yine de obezite son yıllarda artarak büyüyen ciddi bir sağlık sorunu olarak kalmaktadır.

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