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Current Research and Reviews in Psychology and Psychiatry

Psikoloji ve Psikiyatride Güncel Araştırma ve İncelemeler





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Deneysel Morfin Bağımlılığının ve Morfin Çekilmesinin Mesane Düz Kas Kontraksiyonuna Etkisi

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ÖZ

Morfinin renal fonksiyonlar ve mesane üzerine etkileri araştırılmış olmakla birlikte morfinin uzun süreli kullanımı sonucu oluşan bağımlılık ve buna bağlı yoksunluk sendromunun mesane üzerinde farklı etki oluşturup oluşturmadığı henüz çalışılmamıştır. Bu çalışmanın amacı, morfin bağımlılığının ve morfin yoksunluğunun mesane düz kası üzerine olan etkisini araştırmaktır. Çalışmaya alınan yetişkin erkek Wistar-Albino ratlar (n:30) rastgele 3 gruba ayrıldı. Kontrol grubuna 7 gün boyunca 10 mg/kg %0.9 NaCl çözeltisi cilt altı yoldan enjekte edildi. Benzer şekilde, morfin ve morfin yoksunluğu grubuna ise 10 mg/kg morfin verildi. Son enjeksiyondan 2 saat sonra morfin yoksunluğu grubuna intraperitoneal yoldan 3 mg/kg nalokson verilirken, kontrol ve morfin gruplarına %0.9 NaCl verildi ve yarım saat boyunca hayvanların davranışları gözlemlendi. Sonrasında ise izole organ banyosunda gerimlerini kaydetmek amacıyla hayvanların mesaneleri ayrıldı. Morfin çekilmesi grubundaki sıçanlarda morfin yoksunluk davranışları gözlemlenmiştir. Grupların mesane kontraksiyonları incelendiğinde ise gerim değerleri arasında istatistiksel olarak anlamlı bir farklılık bulunmamıştır ($p>0.05$). Sonuç olarak, morfin bağımlılığı oluşturulmuş sıçanlarda yapılan çalışma sonucunda morfin bağımlılığı ya da morfin yoksunluğunun mesane kontraksiyonlarını etkilemediği görülmüştür.

Anahtar Kelimeler: İzole Organ Banyosu, Kontraktilite, Mesane, Morfin Bağımlılığı, Nalokson

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Effect of Experimental Morphine Dependence and Morphine Withdrawal on Bladder Smooth Muscle Contraction

ABSTRACT

Although the effects of morphine on renal functions and bladder have been investigated, it has not been studied yet whether the long-term morphine dependence and related withdrawal syndrome have a different effect on the bladder. Aim of the study is to investigate the effects of morphine addiction and morphine withdrawal on bladder smooth muscle. Adult male Wistar-Albino rats (n:30) included in the study were randomly divided into 3 groups. 10 mg/kg 0.9% NaCl solution was injected subcutaneously once a day for 7 days. 10 mg/kg morphine was injected subcutaneously once a day for 7 days in morphine and morphine-withdrawal group. After two hours of the last injections, 3 mg/kg 0.9% NaCl solution was injected intraperitoneally in both control and morphine groups, while 3 mg/kg naloxone for morphine-withdrawal group. Then the behavior of the animals was observed for thirty hours. Afterwards, the bladders were rapidly extracted and their tension was recorded in the isolated organ bath. Morphine withdrawal behaviors were observed in rats in the morphine withdrawal group. When the bladder contractions of the groups were examined, no statistically significant difference was found between the tension values ($p>0.05$). In summary the study carried out in rats with morphine addiction, it was observed that being addicted to morphine or being on morphine withdrawal did not affect bladder contractions.

Keywords: Isolated Organ Bath, Contractility, Bladder, Morphine Addiction, Naloxone

Sorumlu Yazar:

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GİRİŞ

Madde bağımlılığı, kişiler üzerinde olumsuz etkilerine rağmen, esrar, alkol, metamfetamin, morfin, nikotin gibi maddelerin tüketim için aranıp kullanılması ile karakterize kronik bir hastalıktır. Kullanımdan sonra kişi çoğunlukla alımı durdurmada problem yaşar ve madde almadığında yoksunluk belirtilerine sıklıkla anksiyete, disfori, irritabilite eşlik eder. Bağımlılığın ortaya çıkışında nörogelişimsel, genetik ve sosyal bileşenler mevcuttur (Kaya ve ark., 2019). Bağımlılığın nörobiyolojisinde mezolimbik sistem ve endojen opioid sistemi önemli bir rol oynamaktadır. Endojen opioid sistemindeki 3 ana opioid reseptörünün (μ , ν , δ), dopaminerjik, serotonerjik ve nöadrenerjik nöronlar aracılığıyla motivasyon, duygu durum ve stres kontrolü gibi alanlarda etkileri bulunmaktadır. Madde kullanımı ile artan dopaminerjik nörotransmisyon zevk alma ve hoşnutluğu, sonrasında ise o maddeye karşı şiddetli bir arzuya sebep olur (Akan ve ark., 2020). Bağımlılık, alınan maddenin beyindeki ödül merkezini etkileyerek keyif vermesi, bu nedenle de kişinin maddeyi tekrar almak istemesi ile oluşmaktadır. Karşılaştığı olumsuzluklara rağmen bağımlı olan kişi, kendi iradesi dışında bağımlısı olduğu maddeyi almaya devam etmektedir (Keifer ve Mann, 2005).

Genel olarak madde bağımlılığı, geçmiş dönemde kendisi için önemli olan başka davranışların yerine madde alımını daha önemli hale getiren bir sendrom olarak tanımlanmaktadır. Madde bağımlılığında temel özellikler, maddenin kullanımı, uyumu engelleyen yıkıcı doğası, davranış değişikliklerine sebep olması ve o maddeyle etkileşim sonrasında zamanla maddeye bağımlı kalmak şeklindedir (Dünya Sağlık Örgütü [DSÖ], 2009). Bağımlılık sınıflamaları içinde önemli bir yere sahip olan opioid kullanım bozukluğu ise kişilik bozuklukları ile birlikte seyreden ve erken ölüm nedenleri arasında sayılan, merkezi sinir sistemine (MSS) ait kronik tekrarlayıcı bir hastalık olarak tanımlanmaktadır. Bu durum morfin ve benzeri maddelerin uzun süreli kullanımı sonucunda gelişmektedir (Listos ve ark., 2019).

Opioidler etkilerini μ (mü), δ (delta) ve κ (kappa) opioid reseptörlerini uyararak etki göstermektedirler. Bu reseptörlerin uyarılmasıyla öfori, analjezi, sedasyon, diürez ve konstipasyon gibi etkiler görülebilmektedir. Araştırmalar sonucunda morfin ve diğer opioidlerin hem terapötik etkilerini hem de yan etkilerini genellikle μ opioid reseptörlerini uyararak gösterdikleri belirlenmiştir (Bender ve ark., 2014). Opioidlerin terapötik etkileri ve uzun süreli kullanımının bağımlılığa yol açması nedeniyle çeşitli doku ve organlar üzerine olan etkileri araştırılmaktadır. Renal fonksiyonlar ve mesane de bu araştırma alanlarından birisidir. Yapılan araştırmalar göstermiştir ki, opioidler renal fonksiyonları baskılamakta ve mesanenin tonusunu azaltmaktadır. Bu etkilerini parasempatik blokaj ile musculus detrusor vesicae kasının kasılmasını engelleyerek göstermektedirler. Bunun sonucu olarak da idrar birikmesine sebep olmaktadırlar. Morfin hipofiz bezinden ADH salınımını arttırmaktadır. Morfin kullananlarda bu sebepten dolayı idrar miktarlarında azalma olabilmektedir. Morfin vücutta bulunan bütün sfinkterlerde kasılma yapmakta ve özellikle mesane sfinkterinde yaptığı bu kasılma sebebiyle idrar retansiyonuna neden olmaktadır (Kranzler ve Ciraulo, 2013).

Bağımlılıkla ilgili özellikle böbreklerle metabolize edilen farmakolojik ajanlarla yapılacak tedavilerde renal fonksiyonlar son derece önemlidir. Morfinin renal fonksiyonlar ve mesane üzerine etkileri araştırılmış olmakla birlikte morfinin uzun süreli kullanımı sonucu oluşan bağımlılık ve buna bağlı yoksunluk sendromunun mesane üzerinde farklı etki oluşturup

oluşturmadığı henüz çalışılmamıştır. Bu çalışmada, morfin bağımlılığının ve morfin yoksunluğunun mesane düz kası üzerine olan etkisi araştırılmıştır.

YÖNTEM

Örneklem

Araştırmanın deneysel morfin bağımlılığı oluşturulması kısmı Necmettin Erbakan Üniversitesi Deneysel Tıp Uygulama ve Araştırma Merkezi'nde (KONÜDAM), mesane düz kas kasılma parametreleri deneyleri ise Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Fizyoloji Anabilim Dalı İzole Organ Laboratuvarı'nda yapılmıştır. Bütün deney gruplarında 250-350 gr ağırlığında yetişkin erkek Wistar-Albino ırkı sıçanlardan, rastgele 3 grup oluşturularak toplam 30 hayvan kullanılmıştır.

Veri Toplama Araçları

Modifiye Gellert ve Holtzman Skalası

Bu ölçek, morfin yoksunluğunun genel olarak derecelendirmesini sağlar: Yoksunluk sırasında bir dizi otonomik ve davranışsal değişiklikler derecelendirilir. Bu skalada, yoksunluk belirtisi olarak kilo kaybı (her %1 kayıp 1 puan), sıçrama sayısı (1-4 sıçrama 1 puan, 5-9 sıçrama 2 puan, 10 ve üzeri sıçrama 3 puan) ve vücut titreme sayısı (ıslak köpeğin silkinmesi hareketi) (1-2 titreme 2 puan, 3 ve üzeri titreme 4 puan) değerlendirilir. Ayrıca, ishal (2 puan), pitoz (2 puan), anormal duruş (3 puan) ve ereksiyon veya boşalma (ya da genital uyarılma) (3 puan) gözlenmesi halinde kaydedilir (Broseta ve ark., 2002; Gellert ve Holtzman, 1978).

İşlem

Çalışma, Necmettin Erbakan Üniversitesi Hayvan Deneyleri Yerel Etik Kurulu'nun 2021-051 sayılı kararı uyarınca gerçekleştirilmiştir. 'Guide for the Care and Use of Laboratory Animals' prensipleri doğrultusunda çalışmada hayvan hakları korunmuştur.

Araştırmada opioid bağımlılığı modeli olarak morfin bağımlılığı oluşturulmuştur. Hayvanlar 7 gün boyunca 22±1 oda sıcaklığında, 12 saat aydınlık/karanlık olacak şekilde ve sınırsız yem (ad-libitum) ile bir kafeste 3 ila 4 sıçan olacak şekilde barındırılmıştır.

Kontrol grubuna, 10 mg/kg serum fizyolojik (SF) (%0.9'luk NaCl çözeltisi) subkutan yol ile günde bir defa olarak 7 gün süresince enjekte edilmiştir. 7. günde saat 08.00'de son doz serum fizyolojik uygulamasından 2 saat sonrasında tek doz olarak 3 mg/kg serum fizyolojik intraperitoneal yol ile uygulanmıştır. Daha sonra hayvanların davranışları gözlenmiştir. Morfin grubuna, 10 mg/kg morfin subkutan yol ile günde bir defa olarak 7 gün süresince enjekte edilmiştir. 7. günde saat 08:00'de son doz morfin uygulamasından 2 saat sonrasında tek doz olarak 3 mg/kg SF periton içi yol ile enjekte edilerek hayvanların davranışları gözlenmiştir. Morfin yoksunluğu grubuna ise, 10 mg/kg morfin subkutan yol ile günde bir kez 7 gün enjekte edilmiştir. 7. günde saat 08:00'de son doz morfin uygulamasından 2 saat sonrasında tek doz olarak 3 mg/kg μ -opioid antagonisti olan nalokson periton içi yolla enjekte edilmiştir ve hayvanların davranışları gözlenmiştir.

Tüm gruplardaki hayvanlar nalokson ve SF enjeksiyonundan 1.5 saat önce ve enjeksiyonlardan 0.5 saat sonra tartılmıştır ve vücut ağırlık değişimleri belirlenmiştir. Bütün hayvanlar nalokson

ve SF enjeksiyonlarından hemen sonrasında 25 cm çapında ve 65 cm yüksekliğindeki pleksiglas şeffaf silindir gözlem kafeslerine alınmış ve hayvanların davranışları gözlenmiştir. Enjeksiyondan sonraki yarım saat (30 dk) boyunca gözlemlenip aşağıdaki tabloda verilen morfin yoksunluk davranış ve belirtileri manuel olarak skorlanmıştır. Projede morfin çekilmesi bulguları olarak Modifiye Gellert ve Holtzman skalası kullanılmıştır. Yoksunluk davranış skorları gruplar aralarında karşılaştırılmıştır. Elde edilen veriler tek yönlü varyans analiziyle değerlendirilmiştir.

Deney gruplarındaki tüm hayvanların mesaneleri sabah 09:00-10:30 arasında alınmıştır. Hayvanlara ketamin-ksilazin sedasyonundan sonra servikal dislokasyon uygulanıp mesaneler hızlı bir şekilde ayrılıp krebs solüsyonu içerisine alınmıştır. Mesanedeki doku artıklarının temizlenmesinden sonra, mesaneden 1,2 cm uzunluğunda, 2 mm genişliğinde ve 1 mm kalınlığında alınan şeritler her iki ucundan ipek ipliklerle bağlanarak bir ucu, içinde %95 O₂ ve %5 CO₂ ile gazlandırılan Krebs çözültisi bulunan haznenin tabanına, diğer ucu ise izometrik güç çevirgecine sabitlenip organ banyosuna vertikal olarak asılmış ve gerim 1000 mg olarak ayarlanmıştır.

Mesane şeritlerinin uygulamalarla elde edilen kasılmaları frekans ve gerim olacak şekilde izole organ banyosu sisteminde kaydedilmiştir. Mesane şeritlerinin izometrik gerim değişiklikleri üç kanaldaki güç değiştirici transdüser ile kaydedilmiştir. Dokular izole organ banyosuna asıldıktan sonra 15 dakikalık periyodlarla 45 dakika boyunca yıkama işlemi yapılarak anestezik ajanların etkisinin gitmesi beklenmiştir. Daha sonrasında spontan kasılmalar kaydedilmiştir. Mesane şeridinin asılmasından 1 saat sonra 0.001M adrenalin çözültisi hazneye eklenip kasılmalar indüklenmiştir. Adrenalin uygulamasından 15 dakika önce ve adrenalin uygulamasından sonra 15, 30 ve 45 dakika sonraki gerimleri manuel olarak kaydedilmiştir.

Verilerin Analizi

Sayısal değişkenler tanımlayıcı istatistik olarak ortalama ve standart sapma verilmiştir. Sayısal değişkenlerin analizinde genelleştirilmiş karma etki modelleri (generalized linear mixed effects models) kullanılmıştır. Post hoc karşılaştırmalar en küçük kareler ortalamaları karşılaştırılarak yapılmıştır ve bu karşılaştırmalarda Holm düzeltmesi kullanılmıştır. Analizler Jamovi 2.0 programı ile yapılmıştır. $p < 0.05$ değeri anlamlı kabul edilmiştir.

BULGULAR

Davranış Testleri Bulguları

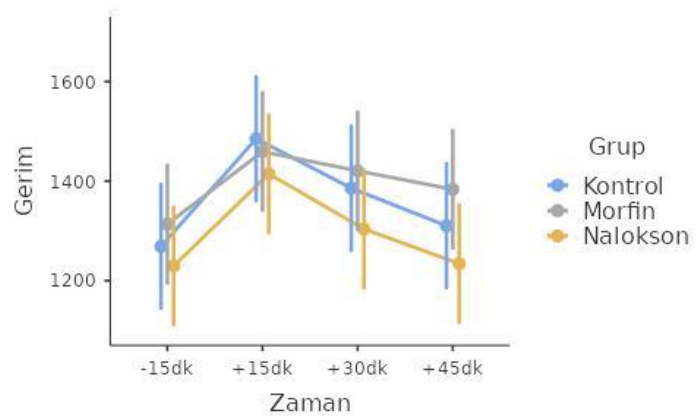
Grupların yoksunluk davranış skorlarına ait istatistikler Tablo 1.'de verilmiştir. Buna göre kontrol grubunun yoksunluk skoru 12.11 ± 2.47 iken, morfin grubunda bu değer 8.90 ± 2.77 olduğu görülmektedir. Morfin-nalokson grubunda ise bu skor 30.80 ± 5.27 'dir. Grupların yoksunluk skorları ANOVA testine göre incelendiğinde gruplar arasında anlamlı bir fark olduğu görülmüştür ($p < 0.001$). Bunun üzerine yapılan post hoc analizine göre bu anlamlı farkın kontrol-morfin nalokson grubu ($p < 0.001$) ve morfin-morfin nalokson grupları ($p = 0.004$) arasındaki kıyaslamalardan geldiği saptanmıştır. Kontrol-morfin grubunda ise anlamlı bir farkın olmadığı gözlenmiştir ($p = 0.171$).

Tablo 1. Deneyler Sonucunda Görülen Morfin Yoksunluk Bulguları (Ortalama ± Standart Hata Değerleri)

	Kontrol Grubu N=10	Morfin Grubu N=10	Morfin-Nalokson Grubu N=10	p
Ağırlık Kaybı (g)	10.11±2.80	5.20±3.16	10.70±3.68	0.06
Kaçma Girişimi	7.11±3.48	5.20±2.15	6.70±1.95	0.214
Silkelenme	0.00±0.00	0.00±0.00	1.90±1.20	1.0
Defekasyon	1.56±1.51	0.90±0.99	5.80±1.81	<0.001
Diş Çıtırdatma	0.67±1.00	0.30±0.48	4.90±2.02	<0.001
Yuvarlanma	0.00±0.00	0.10±0.32	0.30±0.48	0.636
Salya	0.00±0.00	0.00±0.00	0.90±1.10	1.0
Şahlanma	2.56±1.24	2.50±1.84	0.20±0.63	0.002
Süslenme	4.78±1.24	2.00±1.33	3.80±2.39	0.005
Göz Kısma	2.11±1.54	0.80±1.14	5.70±2.00	<0.001
Tıksırma	0.78±1.00	0.00±0.00	0.60±1.07	0.967
Anormal Postür	0.33±0.71	0.90±0.88	2.90±1.20	<0.001
Yoksunluk Skoru	12.11±2.47	8.90±2.77	30.80±5.27	<0.001

İzole Organ Banyosu Bulguları

Kayıt altına alınan gerim değerleri için karma etki modelinde grup – grup*zaman etkileri anlamlı bulunmamıştır (p=0.824). Gerim değerleri gruplar arasında anlamlı düzeyde değişmemektedir. Zaman ise anlamlı bulunmuştur (p<0.001). Mesanelere adrenalin uygulamasından 15 dakika sonrasındaki gerim değerlerinin adrenalin uygulamasından 15 dakika önceki gerim değerlerinin karşılaştırılması kontrol, morfin-nalokson ve morfin gruplarında farklı çıkmıştır (sırasıyla p<0.001, p<0.001 ve p=0.007). Adrenalin uygulamasından 30 dakika sonraki ve 15 dakika önceki mesane kontraksiyonları karşılaştırıldığında kontrol grubunda (p=0.04) ve morfin grubunda (p= 0.047) anlamlı bir fark olduğu gözlenmiştir. Morfin-nalokson grubunda ise bu fark görülmemektedir (p=0.167). Tüm gruplarda adrenalin uygulamasından 45 dakika sonraki ölçülen mesane kontraksiyonları ile adrenalin öncesi 15. dakikada ölçülen mesane kontraksiyonları arasında anlamlı bir fark oluşmadığı görülmüştür (p>0.05). Mesanelerin adrenalin ile indüklenmeden önce ve sonraki gerim değerleri Şekil 1.'de gösterilmektedir. Adrenalinle birlikte her grupta mesane kontraksiyonları 15 dakika boyunca artmış daha sonrasında azalmıştır.



Şekil 1. Mesanelerin Adrenalin ile İndüklenmeden Önce ve Sonraki Gerim Değerleri

TARTIŞMA

Opioidler analjezi tedavisinde kullanılmakta olan en etkili ajanlardır. Ancak sürekli olarak kullanılmaları halinde bağımlılık ve tolerans, bırakıldıklarında ise yoksunluk sendromu gelişmesine neden olabilmektedirler. Opioid bağımlılığının ve yoksunluğunun etkilediği mekanizmalar arasında düz kasların bulunduğu farklı çalışmalar bulunmaktadır. Bu çalışmada, gruplar üzerinde iki aşamalı uygulama gerçekleştirilmiştir. İlk olarak deney hayvanlarında morfin bağımlılık modeli uygulanıp hayvanlar bağımlı hale getirilmiştir. İkinci aşamada ise mesane kontraksiyonları in vitro ortamda incelenmiştir. Morfin bağımlılığının oluşup oluşmadığının belirlenmesi için Gellert ve Holtzman Davranış Skorlaması uygulanmıştır.

İzole sıçan mesanesinde morfinin etkilerini saptamak için yapılmış bir çalışmada akut morfin uygulamasının izole sıçan mesanesinin asetilkoline (Ach) tepkisini artırdığı belirlenmiştir. Akut morfinin etkileri tedavi edilmemiş ve kronik olarak morfin ile tedavi edilmiş sıçanlardan alınan mesane dokularında test edilmiş ve morfin her iki deney grubunda da Ach'a karşı geliştirilmiş tepkiyi indüklemiştir fakat artan bu tepkiler iki deney grubu karşılaştırıldığında farklılık göstermemiştir. Kronik morfin tedavisi uygulanmış sıçanlar üzerinde mesanenin nörolojik tepkileri incelendiğinde test edilen her frekansta (0.1-50 Hz.) kasın elektriksel stimülasyona verdiği yanıtı değiştirmedeği görülmüştür. Organ banyosu haznesine eklenen naloksonun varlığı da bu etkiyi değiştirmemiştir. Tüm bunlar izole sıçan mesanesinde opioid reseptörlerinin bulunmadığını ve morfinin nöroefektör kavşağı üzerinde doğrudan etkisinin olmadığını göstermektedir (Acevedo ve ark, 1986).

Carpenter'ın (1986) yapmış olduğu çalışmada morfin sülfat içeren paletler sıçanlara subkutan yerleştirilip yedinci günde çıkartılmıştır ve miksiyonları incelenmiştir. Morfin sülfat (5 mg/kg) uygulamasının miksiyon işlemini başlatmak için hacim eşliğini artırdığı gözlemlenmiştir. Morfinin terapötik dozunun sıçan mesanesi üzerinde spazmojenik etkisinin olmadığı gözlenmiş olup morfinin idrar retansiyonuna neden olduğu gözlemlenen deneylerde bu etkide aşırı aktif bir üretral sfinkterin etkili olduğu bulunmuştur.

Başka bir çalışmada yapılan gözlemler, spinal opioid mekanizmalarının mesane fonksiyonunun nörojenik kontrolünde rol oynadığı ve intratekal uygulanan opioid ilaçların μ ve δ opioid reseptörlerini içeren spinal mekanizmalar tarafından mesane motilitesinin inhibisyonuna aracılık ettiği hipotezini desteklemiştir. Morfinin intratekal uygulamasının mesane aktivitesini inhibe ettiği, ancak bunun başlangıçta daha yavaş ve omuriliğin servikal ve torasik bölgelerine lumbo-sakral bölgelere göre uygulama yapıldığında daha yüksek dozlar gerektirdiği gözlemlenmiştir. Bu, morfinin başlıca etkilerinin distal omurga bölgelerine lokalize olabileceğini düşündürmüştür. İntravenöz morfin için spinal lokus, intravenöz morfin tarafından üretilen mesane motilitesinin inhibisyonunu tersine çeviren dozlarda intravenöz nalokson uygulamasının etkisinin olmaması ile daha da desteklenmiştir (Dray ve Metsch, 1984). Başka bir çalışmada ise izole mesanenin morfin stimülasyonuna verilen depresif tepkilerinin ileumda olduğundan daha az aktif olduğu ve ilaca toleransın ve bağımlılığının ortaya çıkmadığı bulunmuştur. Yine aynı çalışmada morfinin, elektrik stimülasyonu ile uyarılan kobay ve sıçan mesanelerinin kasılmalarının boyutunu azalttığı gözlemlenmiştir ancak mesane preparatlarında morfine bağımlılık gösterilememiştir (Fennessy ve ark., 1969).

Postoperatif analjezide yaygın olarak kullanılmakta olan morfinin sıçanlarda mesane kasılmalarını inhibe ettiği gösterilmiştir (Kontani ve ark., 1989). Yapılan bir başka çalışmada spinal opioid mekanizmaların mesane fonksiyonunun nörolojik kontrolünde yer alıp almadığı incelenmiş ve basınç dönüştürücü kullanarak mesane basınçları kaydedilmiştir. İntratekal morfin uygulamasının sıçanlarda izometrik olarak kaydedilen spontan mesane kasılmalarını inhibe ettiği gözlemlenmiş olup bu etkinin morfinin dozuna bağlı olduğu belirtilmiştir. İntratekal nalokson uygulanması ile morfinin bu etkisi tersine çevrilmiştir. Bu gözlemler sonucunda spinal opioid mekanizmaların mesane fonksiyonunun nörolojik kontrolünde yer aldığı bulunmuştur (Dray ve Metsch, 1984).

Zhou ve arkadaşlarının (2016) yapmış olduğu bir çalışmada ise izole Guinea domuzu mesanesine kümülatif olarak tienorfin, buprenorfin, morfin ve nalokson eklenmiştir ve kasılmalar izole organ banyosunda kaydedilmiştir. Sonuçlara göre tienorfin ve buprenorfinin, 1.0 ila 32.0 μM konsantrasyonda A_{50} (1 μM) tarafından indüklenen izole mesane kasılmaları üzerinde hiçbir etkisi olmazken, 100 μM konsantrasyonda inhibitör etki göstermişlerdir ve bu konsantrasyonda tienorfin buprenorfinden daha zayıf inhibitör etki göstermiştir. Morfin ve nalokson kümülatif olarak uygulandığında morfin 3.2 mM'da nalokson ise 320 μM 'da mesane kontraksiyonlarını artırmıştır. Yine aynı çalışmada Guinea domuzlarının mesanesindeki μ opioid reseptörünün mRNA seviyelerini belirlemek için ve frontal kortekse kıyasla opioid reseptörlerini analiz etmek için RTqPCR yapılmıştır ve mesanedeki μ reseptörünün mRNA seviyeleri frontal korteksteki ile aynı olduğu sonucuna ulaşılmıştır. Morfinin (2 mg/kg, intravenöz) sıçan mesanesinin eşik basıncını artırabileceği ve idrara çıkma aralıklarını uzatabileceği gösterilmiştir (Shimizu ve ark., 2000).

Yukarıda belirtilen çalışmalar ve bulgular söz konusu olmakla birlikte morfin bağımlılık modeli oluşturulmuş sıçanlarda mesane kontraksiyonlarının incelenmesi üzerine daha önce yapılmış bir çalışma bulunmamaktadır. Sonuç olarak mevcut çalışmada nalokson uygulanan grupta morfin yoksunluğu olduğu gözlemlenmiş ancak morfin bağımlılığının ya da nalokson ile morfin çekilmesi uygulamasının mesane kontraksiyonlarını etkilemediği görülmüştür. Bu bağlamda morfin bağımlılığı ve yoksunluğunun mesane ve diğer düz kaslar üzerine olan etkileriyle ilgili daha fazla araştırmaya ihtiyaç olduğu görülmektedir.

Sınırlılıklar: Araştırmamızın birkaç kısıtlılığı bulunmaktadır. Çalışmamızda morfin ve nalokson uygulamaları subkutan yolla yapılmıştır. Deneysel bağımlılık ve yoksunluğun oluşmasında intratekal yoldan yapılan uygulamalar daha etkili olabilir. Bir diğer kısıtlılık, araştırmamızda histopatolojik inceleme yapılmamıştır. Bundan sonraki çalışmalarda, çeşitli genetik inceleme yöntemleriyle MSS'ye kıyasla mesanedeki μ opioid reseptörünün mRNA düzeylerini tespit etmek suretiyle mesanedeki μ opioid reseptör aktivitesi hakkında daha net bilgiler edinmek mümkün olabilir.

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Relations of Cyber Bullying Sensitivity to Perceived Social Support and to Parent and Peer Attachments in High School Students¹⁻²

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ABSTRACT

Growing evidence has shown the importance of cyberbullying sensitivity in preventing cyberbullying in adolescence. Yet, limited research has examined the relations of cyberbullying sensitivity to perceived social support as well as to attachment with parents and peers. The aim of this study was to examine the relations of cyberbullying sensitivity to sociodemographic characteristics, internet usage characteristics, perceived social support, and parental and peer attachment in high school students. The present study was a cross-sectional school survey to which a total of 831 adolescents were admitted (505 males and 326 females; mean age, 16.13 years). The adolescents completed some forms and scales, including a Personal Information Questionnaire, the Cyber Bullying Sensitivity Scale (CSS), the Multidimensional Perceived Social Support Scale (MPSSS), and the Parent and Peer Attachment Inventory (IPPA). The resulting findings showed that 74.6% of participants had daily internet access. In this context, it was found that household rules for internet use were less strict among those participants who were comparatively older or were attending higher classes. It was also determined that students with high social support and parental attachment scores spent less time on the internet. Girls' scores for CSS, friend support, and peer attachment were found higher than those found in the boys. A positive correlation was established between the CSS scores and the MPSSS and IPPA scores. Social support and attachment

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scores of the group with a reportedly better school achievement were found significantly higher than those found in other groups. Gender, family income, and family support were determined as the predictive factors with respect to cyberbullying sensitivity. In conclusion, social support and positive communication with parents and peers may be effective factors in preventing the risks of problematic internet use and of exposure to cyberbullying in adolescence.

Keywords: Adolescent, Attachment, Cyber Bullying, Perceived Social Support, Sensitivity

Lise Öğrencilerinde Siber Zorbalık Duyarlılığının Algılanan Sosyal Destek ve Ebeveyn ve Akarana Bağlanma ile İlişkisi

ÖZ

Artan kanıtlar, ergenlik döneminde siber zorbalığın önlenmesinde siber zorbalık duyarlılığının önemini göstermiştir. Bununla birlikte, sınırlı sayıda araştırma, siber zorbalık duyarlılığı ile algılanan sosyal destek ve ebeveynler ve akranlarla bağlanma arasındaki ilişkileri incelemiştir. Bu çalışmanın amacı, lise öğrencilerinde siber zorbalık duyarlılığı ile sosyodemografik özellikler, internet kullanım özellikleri, algılanan sosyal destek ve ebeveyn ve akarana bağlanma arasındaki ilişkiyi incelemektir. Bu çalışma, 831 ergen (505 erkek ve 326 kadın; ortalama yaş, 16.13 yıl) ile yapılan kesitsel bir okul anket çalışmasıdır. Ergenler, Kişisel Bilgi Anketi, Siber Zorbalık Duyarlılık Ölçeği, Çok Boyutlu Algılanan Sosyal Destek Ölçeği ve Ebeveyn ve Akran Bağlanma Envanteri'ni içeren form ve ölçekleri doldurmuştur. Bulgular, katılımcıların %74,6'sının her gün internet erişimine sahip olduğunu göstermiştir. Katılımcıların yaş ve sınıf düzeyi arttıkça evde internet kullanımına ilişkin kural/kısıtlamanın azaldığı bulunmuştur. Sosyal destek ve ebeveynle bağlanma puanları yüksek olan öğrencilerin internette daha az zaman geçirdikleri belirlenmiştir. Kızların siber zorbalık duyarlılık puanları, arkadaş desteği puanları ve akarana bağlanma puanları erkeklerden daha yüksek bulunmuştur. Siber zorbalık duyarlılık puanları ile sosyal destek ve bağlanma puanları arasında pozitif bir korelasyon bulunmuştur. Okul başarısının daha iyi olduğunu bildiren grubun sosyal destek ve bağlanma puanları anlamlı olarak daha yüksek bulunmuştur. Cinsiyet, aile geliri ve aile desteği siber zorbalık duyarlılığını yordayıcı faktörler olarak tespit edilmiştir. Sonuç olarak, ergenlik döneminde problemlerli internet kullanımı ve siber zorbalığa maruz kalma risklerini önlemede sosyal destek ve ebeveyn ve akranlarla olumlu iletişim etkili faktörler olabilir.

Anahtar Kelimeler: Siber Zorbalık, Ergen, Bağlanma, Algılanan Sosyal Destek, Duyarlılık

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INTRODUCTION

Adolescence is a period when there is a tendency to engage in risky behaviors. Brain maturation continues during adolescence, and significant changes are detected in brain structure and function during this period (Vijayakumar et al., 2018). Therefore, it is known that this age group is particularly vulnerable and cannot fully perceive the connection between their behaviors and their consequences (Ang, 2015). Impulsivity, sensation seeking, thrill seeking, depression, and other individual differences also contribute to risk taking that resist standard risk-reduction interventions during adolescence (Reyna & Farley, 2006). With limited contextual cues and relative anonymity of the online environment, adolescents tend to be more disinhibited and to engage in more high-risk behaviors (Ang, 2015). Thus, the online environment seems to be the basis for increasing risks, including cyberbullying.

Cyberbullying is generally defined as deliberate and repeated aggressive activities inflicted toward an individual or a specific group of individuals through the use of electronic technologies (Guo, 2016; Tokunaga, 2010; Vaillancourt et al., 2017). With the widespread use of digital technologies in adolescents, the traditional form of aggression has been replaced by cyberbullying in recent years (Jimenez, 2019). According to a 2019 national representative survey of 4,972 middle and high school students aged 12 to 17 in the United States, 37% of adolescents reported being cyberbullied once in their lifetime (Patchin, 2019). In a previous study conducted in seven European countries, the cyber victimization rate was found to be 13.3-37.3 in the adolescent age group (Athanasidou et al., 2018).

Exposure to cyberbullying has been found to be more stressful, and render more serious consequences compared to traditional bullying (Hellfeldt et al., 2020). Previous studies show that cyberbullying is related to serious mental health concerns including depression, anxiety, self-esteem problems, emotional distress, substance use, school absenteeism, and suicidal behavior in adolescents. On the other hand, perpetrators of cyberbullying are more likely to report increased substance use, aggression, and delinquent behaviors (Bannink et al., 2014; Field, 2018; Vaillancourt et al., 2017).

Various factors such as previous cyberbullying behavior, access to internet, duration of internet use, adolescents' ability to use technology, age, family management and social relationships are important factors affecting the exposure to cyberbullying or becoming a victim (Athanasidou et al., 2018; Foody et al., 2019; Kowalski et al., 2014). Among these, the factors related to parents and peers seem important based on the social and developmental characteristics of adolescence. Developing a positive parent-adolescent emotional bond, as early as possible, as well as maintaining positive peer relationships and perceived friend support are particularly important in adolescents' development. (Ang, 2015; Foody et al., 2019).

The prevention of cyberbullying and elimination of its negative effects are of great importance for the health of adolescents. One common strategy to prevent cyberbullying is to provide information for youth, parents, and school personnel on what constitutes cyberbullying and on how to avoid being a victim (Espelage & Hong, 2017). Sensitivity is one of the solutions to cope with anxious stimuli, and it can be viewed as a means through which any threatening stimulus can be avoided, and awareness can be increased (Krahé et al., 2011). Cyberbullying behaviors can be perceived as a threat by individuals, and they can protect themselves against

this threat by increasing their sensitivity (Cassidy et al., 2013; Hinduja & Patchin, 2010). Accordingly, cyberbullying sensitivity may serve to avoid those behaviors that otherwise may cause the subject to become the victim of bullying during the use of cyber devices, to gain awareness of the existence of such threats, as well as to take precautions and keep a high level of attention to distinguish the stimuli that may pose a threat (Tanrikulu et al., 2013).

A key component in the social environment of adolescents is the presence or absence of social support, which can be defined as the individual's perception of being cared for, valued, and included in his or her social environment, including the family, peers, and other significant people (Saylor & Leach, 2009). It has been suggested that a strong social support perceived by adolescents and positive relationships of adolescents with their parents and peers would reduce the risk of online victimization (Foody et al., 2019; Livingstone et al., 2015; Ronis & Slaunwhite, 2019). Therefore, social support and secure attachment turn out to be important factors in the development of cyberbullying sensitivity in adolescents. In this context, though, there are a limited number of studies focusing on the relationship between cyberbullying sensitivity and adolescents' perceived social support and their attachment to their parents and peers. In short, all the considerations above encouraged us to conduct the present study, through which we examined the relations of cyberbullying sensitivity to socio-demographic characteristics, internet usage habits, perceived social support and attachment to parents and peers in high school students.

METHOD

The present study is a cross-sectional school survey, which we carried out using the relational survey model. We obtained the ethical permission for this study from the Health Sciences Ethics Committee of Ankara University, under serial number 02-40 of 29/01/2018. This study was approved by the Provincial Directorate of National Education and conducted in line with standard procedures for the protection of human participants.

Participants and Procedures

Our sample was selected using the disproportionate cluster sampling method. The sample of this study consisted of students from high schools, for which permission was obtained from the Provincial Directorate of National Education. The exclusion criteria from the study included the presence of history of seeking assistance from judicial authorities due to previous child abuse, the presence of traditional bullying or cyberbullying, and the failure of parents in signing the consent form.

First, consent forms were sent to the parents of the participating students, and the interviews were conducted only once the consent forms were received. Written and verbal information about the purpose of the research was given to the students by the researcher and the instructions were explained accordingly. After this procedure, the students were asked to fill in the form and scales. The forms and scales used in the study were given to the participants in the same file and at the same time. Data were collected from 884 students attending four different high schools in Cerkezkoy, Tekirdag, Turkey, in the fall semester of the 2018-2019 academic year. After excluding survey packets with missing data, the final data of 831 participants (505 females and 326 males) were analyzed.

Measurement Tools

Personal Information Form

A separate questionnaire was used to collect demographic information about the participants in the study. This questionnaire included questions about participants' school, grade, age, gender, parents' education and occupation status, monthly income of families, school achievements as perceived by participants, internet access frequency, daily average time spent on the internet, and the purpose of using the means to access the internet.

Cyberbullying Sensitivity Scale (CSS)

The CSS scale, which includes questions to determine whether or not the questioned student is aware of the risks of the internet environment, consists of 13 items and a single factor. It is filled as "No" (1 point), "Sometimes" (2 points) and "Yes" (3 points) and scored accordingly. As reported by Tanrikulu et al. (2013), the scale is a structure that explains 46.65% of the total variance, whereas the confirmatory factor analysis and fit values for this emerging structure confirm the model (Chi-square $\chi^2 / sd = 3,220$, RMSEA = .082). They further reported that the internal consistency coefficients of the scale were found between .83 and .90, and that the split-half-test reliability coefficients were between .75 and .84. In addition, they found that the item-total correlations of the scale ranked between .42 and .63 for the integrated group, and all the differences between the averages of the 27% lower-upper groups were significant. The lowest score that can be obtained from the scale is 13 and the highest score is 39, with high scores indicating a high sensitivity to cyberbullying. (Tanrikulu et al., 2013).

Multidimensional Scale of Perceived Social Support (MPSSS)

The purpose of the scale developed by Zimet et al. (1988) is to evaluate the adequacy of perceived social support. The validity and reliability study of the revised form of that scale in Turkey was conducted in 2001 (Eker et al., 2001). They reported that Cronbach Alpha internal consistency coefficients were calculated as .80 and above for the sub-dimensions and the entirety of the scale. The scale consisted of 12 items of 7 Likert type and had 3 sub-dimensions: support from family, friends, and a special person.

The Inventory of Parent and Peer Attachment (PPAI) Short Form

This inventory was created by Armsden and Greenberg (1987) to measure the commitment of young people to their parents and peers. The short form of the inventory, developed by Raja et al. (1992), consists of 24 7-point Likert-type items. The inventory contains two parallel forms: peer attachment and parent attachment. It also comprises items representing factors that promotes feelings of attachment, namely: (1) trust, (2) communication, and (3) alienation. It was adapted into Turkish by Günaydın et al. (2005), and both mother and father forms were found to have high internal consistency coefficients among questioned university students (Cronbach $\alpha = .88$ and .90, respectively). Bayraktar et al. (2009) studied the features of the mother, father, and peer forms of the scale on high school students and found that the reliability coefficients of the forms were sufficient (peer form .73, parent forms .84).

Data Analysis

The data of the study were analyzed using the SPSS 20.0 (Statistical Package for the Social Sciences) statistical package program. Skewness and kurtosis values of all variables were examined, and the data were observed to show a normal distribution. Descriptive characteristics of the sampling and measurement tools were given first. Chi-square tests were conducted to evaluate the relationships between sociodemographic variables and internet usage habits. Pearson Correlation Analysis was performed to determine the relationship between research variables. The internal consistency coefficients of the scales used in the study were calculated by the Cronbach Alpha method. Independent groups' T test and one-way analysis of variance (ANOVA) were used to determine whether the research variables changed according to the sociodemographic characteristics and internet usage habits. Bonferroni test was applied as a post-hoc multiple comparison test to find out from which groups the difference originated. The hierarchical regression analysis was used to determine the variables that predict the sensitivity to cyber bullying. Statistical significance level was accepted as $p < 0.05$.

RESULTS

Sociodemographic Characteristics and Internet Usage Habits

The descriptive statistics regarding the sociodemographic characteristics and internet usage habits of participants are shown in Table 1. Participants' ages and grades varied between 14 and 19 years (mean 16.13 ± 1.13) and 9th and 12th grades, respectively. A total of 385 participants (46.3%) stated that their perceived school achievement was moderate.

Most of their mothers reported themselves to have an education level corresponding to primary school or below and were not working. Most of their fathers had a secondary or high school degree and were working.

It was determined that 620 participants (74.6%) could access the internet every day. A total of 235 participants (28.3%) were reported to spend more than 3 hours a day on the internet. 262 participants (31.5%) reported a rule or restriction on internet use at home (Table 1).

Table 1. Sociodemographic Characteristics and Internet Usage Habits of the Participants

Sociodemographic Characteristics	N (%)	Internet Usage Habits	N (%)
Gender		Internet access frequency	
Girl	505 (60.8)	Once or less in a week	85 (10.2)
Boy	326 (39.2)	2-6 days in a week	126 (15.2)
Age		Every day	620 (74.6)
≤ 15 years	284 (34.2)	Duration of daily internet usage	
16-17 years	457 (55)	0-30 min	151 (18.2)
≥ 18 years	90 (10.8)	30-59 minutes	124 (14.8)
Grade		1-2 hours	175 (21.1)
Grade 9	234 (28.2)	2-3 hours	146 (17.6)
Grade 10	209 (25.2)	More than three hours	235 (28.3)
Grade 11	203 (24.4)	Rules/restrictions on home internet use	
Grade 12	185 (22.3)	Present	262 (31.5)
Mother's status		Absent	569 (68.5)
Alive	822 (98.9)	Internet access device	
Dead	9 (1.1)	Smart phone	460 (55.4)
Mother's education		Computer	51 (6.1)
Primary school or less	467 (56.2)	Tablet	7(0.8)
Secondary-high school	341 (41)	Smart phone and computer	183 (22)
University or higher	23 (2.8)	Smart phone and tablet	31 (3.7)
Mother's occupation		Computer and tablet	2 (0.2)
Working	268 (32.3)	All	97 (11.8)
Not working	563 (67.7)	Place to access the internet	
Father's status		Home	713 (74)
Alive	801 (96.4)	Internet café	48 (5)
Dead	30 (3.6)	School	38 (3.9)
Father's education		Friend's computer	24 (2.5)
Primary school or less	302 (46.4)	Other	140 (14.6)
Secondary-high school	475 (57.2)	Purpose of internet use	
University or higher	54 (6.4)	Using social networking sites	689 (15.2)
Father's occupation		Sending e-mail	147 (3.2)
Working	757 (91.1)	Searching for information	644 (14.2)
Not working	74 (8.9)	Preparing homework or lecture	742 (16.3)
Family's monthly income		Playing online games	263 (5.8)
Low	295 (35.5)	Playing offline games	190 (4.2)
Moderate	300 (36.1)	Chatting	605 (13.3)
High	236 (28.4)	Surfing shopping sites	312 (6.9)
Perceived school success		Making website design	37 (0.8)
Very good	90 (10.8)	Reading the news	199 (4.4)
Average	668 (80.4)	Streaming TV, video or music	663 (14.6)
Bad	73 (8.8)	Other	51 (1.1)

The Relationships of Sociodemographic Characteristics to Internet Usage

Table 2 shows the relationships between sociodemographic variables and internet usage habits. It was statistically determined that the household rules for internet use were less strict among those participants who were comparatively older or were attending higher classes.

Table 2. Relationships Between Sociodemographic Variables and Internet Usage Habits

	Internet Access Frequency			P	Duration of Daily Internet Usage					P	Rules/Restrictions on The Internet Use at Home		P
	Once a week or less	2-6 days a week	Every day		0-30 min	30 min - 1-hour	1-2 hours	2-3 hours	More than three hours		Present	Absent	
Gender													
Girl	10.3	12.3	77.4	<i>.247</i>	20	15.4	19.7	15.8	29.1	<i>.171</i>	31.9	68.1	<i>.785</i>
Boy	10.1	19.6	70.2		15.3	14.1	23.3	20.2	27.1		31	69	
Age													
≤ 15 years	12.7	17.2	70.1	<i>.180</i>	17.6	18	21.8	19	23.6	<i>.251</i>	43	57	<i>.000</i>
16-17 years	8.5	13.8	77.7		18.4	13.1	20.4	17.1	31		25.6	74.4	
≥ 18 years	11.1	15.6	73.3		18.9	14.4	22.2	15.6	28.9		25.6	74.4	
Grade													
Grade 9	11.7	17.8	70.5	<i>.359</i>	17.5	18.8	23.5	18.4	21.8	<i>.142</i>	47	53	<i>.000</i>
Grade 10	9.6	15.8	74.6		19.1	15.3	15.8	17.7	32.1		30.1	69.9	
Grade 11	7.4	11.3	81.3		17.8	13.8	18.7	18.2	31.5		25.6	74.4	
Grade 12	9.7	14.1	76.2		18.4	10.8	26.5	15.7	28.6		20.0	80.0	
Mother status													
Alive	9.6	15.2	75.2	<i>.000</i>	17.6	15	21.3	17.6	28.5	<i>.015</i>	31.5	68.5	<i>.907</i>
Dead	66.7	11.1	22.2		66.7	11.1	0	11.1	11.1		33.3	66.7	
Mother education													
Primary school or low	13.3	15.6	71.1	<i>.104</i>	21.2	16.7	19.5	17.3	25.3	<i>.071</i>	27.6	72.4	<i>.012</i>
Secondary-high school	10.1	13.7	76.2		16.9	12.0	24.0	18.3	28.8		37.2	62.8	
University or higher	9.7	12	78.3		20.0	16.0	16.0	24.0	24.0		26.1	73.9	
Mother occupation													
Working	7.8	13.4	78.7	<i>.457</i>	16.4	11.2	22	16.4	34	<i>.053</i>	30.2	69.8	<i>.577</i>
Not working	10.4	15	74.6		19	16.7	20.6	18.1	25.6		32.1	67.9	
Father status													
Alive	9.9	14.7	75.4	<i>.000</i>	17.7	14.6	21.3	18	28.3	<i>.000</i>	31.3	68.7	<i>.537</i>
Dead	20	26.7	53.3		30	23.3	13.3	6.7	26.7		36.7	63.3	
Father education													
Primary school or low	14.2	14.2	71.6	<i>.133</i>	23.2	16.6	19.5	18.8	21.9	<i>.018</i>	27.2	72.8	<i>.088</i>
Secondary-high school	10.4	14.8	74.8		14.3	14.3	22.1	17.1	32.2		32.6	67.4	
University or higher	9.1	17.6	73.3		24.1	11.1	20.4	14.8	29.6		39	61	
Father's occupation													
Working	9.5	14	76.5	<i>.000</i>	18.0	14.4	20.5	18.2	28.9	<i>.164</i>	31.8	68.2	<i>.541</i>
Not working	17.6	27	55.4		20.3	20.3	27	10.8	21.6		28.4	71.6	
Family monthly income													
Low	18	18.3	63.7	<i>.000</i>	24.7	18	18.6	16.3	22.4	<i>.000</i>	33.6	66.4	<i>.472</i>
Moderate	7	17.7	75.3		16	16	23	19	26		29	71	
High	4.7	8	87.3		12.7	9.7	21.6	17.4	38.6		32.2	67.8	
Perceived school success													
Very good	13.3	12.2	74.4	<i>.287</i>	26.7	14.4	24.4	14.4	20	<i>.000</i>	43.3	56.7	<i>.045</i>
Average	9.9	16.3	73.8		18.1	15.9	20.1	18.4	27.5		30.1	69.9	
Bad	9.6	8.2	82.2		8.2	6.8	26.0	13.7	45.2		30.1	69.9	

Participants whose parents were alive reported more internet access and a longer duration of daily internet usage. The participants whose mothers were university graduates or higher reported less internet usage rules/restrictions at home than other participants. The participants whose fathers were middle or high school graduates were the ones who spent the most time online. Adolescents with working fathers had higher frequency of internet access than others. Internet access frequency and duration of daily internet usage of high-income participants were found to be higher than it was found in other income groups.

It was observed that those who described their school achievement as bad had longer time spent on the internet, and less internet rules in their home as compared to others.

Descriptive Statistics and Correlations of Measurement Tools

Table 3 shows descriptive data for each scale and its sub-scales. The correlations among research variables are shown in Table 4. There were positive and significant correlations among the variables. Most importantly, cyberbullying sensitivity was determined to be positively correlated with both MPSSS scores and IPAA scores.

Table 3. Descriptive Statistics on Measurement Tools

	Minimum	Maximum	Mean	Standard Deviation	Internal Consistency Coefficient
1. Cyberbullying Sensitivity Scale (CSS)	17	39	32.34	4.80	0.78
2. Multidimensional Perceived Social Support Scale (MPSSS)-Total	21	84	61.73	14.20	0.84
2.1. Family subscale	4	28	22.23	5.63	0.81
2.2. Friend subscale	4	28	21.57	5.73	0.82
2.3. A special person subscale	4	28	17.94	8.08	0.89
3. Inventory of Parent and Peer Attachment (IPPA)					
3.1. Parent Attachment Scale (PAS)	23	84	64.85	12.84	0.81
3.1.1. Trust subscale	8	28	23.26	4.80	0.65
3.1.2. Communication subscale	5	28	20.33	4.99	0.54
3.1.3. Alienation subscale	4	28	21.26	5.66	0.66
3.2. Peer Attachment Scale (PeerAS)	30	84	62.36	10.90	0.72
3.2.1. Trust subscale	9	28	22.69	4.49	0.61
3.2.2. Communication subscale	5	28	18.58	5.58	0.50
3.2.3. Alienation subscale	6	28	21.10	4.95	0.52

Table 4. The Correlations Between Research Variables

Variable	(1)	(2)	(2.1)	(2.2)	(2.3)	(3.1)	(3.1.1)	(3.1.2)	(3.1.3)	(3.2)	(3.2.1)	(3.2.2)	(3.2.3)
1. CSS	1												
2. MPSSS-Total	.14***	1											
2.1. FS	.18**	.69***	1										
2.2. FrS	.08*	.62***	.30***	1									
2.3. SpS	.06	.80***	.31***	.27***	1								
3.1.PAS-Total	.12***	.51***	.70***	.20***	.27***	1							
3.1.1. PT	.10**	.46***	.63***	.20***	.24***	.84***	1						
3.1.2. CP	.13***	.47***	.64***	.19***	.23***	.84***	.62***	1					
3.1.3. AP	.08*	.36***	.50***	.11**	.20***	.82***	.51***	.49***	1				
3.2. PeerAS-Total	.09*	.51***	.32***	.64***	.22***	.38***	.28***	.33***	.34***	1			
3.2.1. PeerT	.09**	.46***	.28***	.62***	.17***	.26***	.26***	.25***	.16***	.82***	1		
3.2.2. CPeer	.07*	.42***	.20***	.57***	.20***	.21***	.16***	.26***	.12**	.78***	.54***	1	
3.2.3. APeer	.05	.32***	.26***	.32***	.15***	.41***	.24***	.26***	.50***	.74***	.40***	.29***	1

* $p < .05$; ** $p < .01$; *** $p < .001$

CSS: Cyberbullying Sensitivity Scale; MPSSS: Multidimensional Perceived Social Support Scale; FS: Family subscale; FrS: Friend subscale; SpS: A special person subscale; PAS: Parent Attachment Scale; PT: Parent trust subscale; CP: Communication with parent subscale; AP: Parental alienation subscale; PeerAS: Peer Attachment Scale; PeerT: Peer trust subscale; CPeer: Communication with peer subscale; APeer: Peer alienation subscale.

Comparison of Research Variables in Terms of Sociodemographic Characteristics and Internet Usage Habits

Independent groups t-test results to determine whether the participants' scale scores change according to sociodemographic variables and internet usage habits are shown in Table 5.

The CSS scores of the girls were found higher than the boys ($t=6.17, p<.001$). Further, the scores of friend support, total peer attachment, peer trust and peer communication of the girls were found higher than they were found in the boys ($t=2.24, p<.05$; $t=3.36, p<.01$; $t=2.82, p<.01$; $t=3.83, p<.001$, respectively). On the other hand, the boys had higher parent trust scores than the girls ($t=-3.05, p<.01$).

Both MPSSS total scores and family support scores of the participants who reportedly had household rules for internet use were found to be significantly higher ($t=2.00, p<.05$ and $t=2.38, p<.05$; respectively).

The results of ANOVA performed to determine whether the study variables differed according to sociodemographic characteristics and internet usage habits are shown in Table 6. Post hoc test results are presented below.

Total MPSSS scores, friend support scores, total peer attachment scores and peer trust scores of the 9th grade students were found higher than the scores of the 12th grade students (respectively; $p<.05, p<.01, p<.05$ and $p<.05$).

Table 5. Comparison Results of Research Variables in Terms of Sociodemographic Characteristics and Internet Usage Habits By T-Test

	Girls	Boys	<i>t</i>	Mother alive	Mother dead	<i>t</i>	Father alive	Father dead	<i>t</i>	Working mother	Non-working mother	<i>t</i>	Working father	Non-working father	<i>t</i>	Internet rule present	Internet rule absent	<i>t</i>
CSS	33.2±4.4	31.1±5.1	6.17***	32.3±4.8	32.9±4.3	-0.38	32.3±4.8	32.5±4.7	-0.18	32.4±4.80	32.3±4.81	0.03	32.3±4.8	32.6±4.5	-0.58	32.6±4.8	32.2±4.8	1.14
MPSSS-Total	61.9±14.2	61.4±14.2	0.61*	61.8±14.2	59.2±14.2	0.53	61.9±14.0	57.2±18.0	1.42	61.2±14.3	62.0±14.2	-0.75	61.9±14.0	60.1±16.1	0.92	63.2±13.7	61.1±14.4	2.00*
FS	22.2±5.8	22.3±5.4	-0.13	22.2±5.6	21.4±5.7	0.42	22.3±5.6	20.3±5.9	1.79	21.9±5.8	22.4±5.5	-1.18	22.4±5.5	21.3±6.6	1.32	22.9±5.3	21.9±5.7	2.38*
FrS	21.9±5.6	21.0±5.9	2.24*	21.6±5.7	21.3±5.9	0.06	21.6±5.6	19.9±7.4	1.25	21.5±6.1	21.6±5.6	-0.31	21.6±5.7	21.4±6.1	0.30	21.7±5.2	21.5±5.9	0.62
SpS	17.8±8.3	18.1±7.8	-0.45	17.9±8.1	16.3±8.1	0.60	18.0±8.1	16.9±8.6	0.68	17.8±8.2	18.0±8.0	-0.26	18.0±8.1	17.5±8.5	0.51	18.5±7.6	17.7±8.3	1.46
PAS-Total	64.2±13.4	65.9±11.9	-1.93	64.9±12.9	60.4±11.8	1.13	65.0±12.8	60.3±13.9	1.83	65.4±13.1	64.6±12.7	0.80	65.1±12.6	62.2±14.7	1.62	65.6±12.6	64.5±13.0	1.13
PT	22.9±5.1	23.9±4.3	-3.05**	23.3±4.8	21.2±4.6	1.35	23.3±4.7	21.0±5.9	1.15	23.5±4.8	23.2±4.8	0.90	23.4±4.8	22.3±5.0	1.73	23.5±4.7	23.2±4.9	0.86
CP	20.2±5.2	20.5±4.7	-0.81	20.4±5.0	18.7±4.0	1.24	20.3±5.0	20.1±4.5	0.25	20.5±5.1	20.3±5.0	0.56	20.4±4.9	19.6±5.6	1.14	20.7±4.5	20.2±5.2	1.47
AP	21.1±5.7	21.5±5.6	-1.08	21.3±5.7	20.6±4.2	0.50	21.3±5.6	19.2±6.1	1.93	21.4±5.6	21.2±5.7	0.53	21.4±5.5	20.3±6.8	1.29	21.4±5.8	21.2±5.6	0.58
PeerAS-Total	63.4±11.0	60.8±10.6	3.36**	62.3±10.9	66.0±7.3	-1.49	62.5±10.9	60.1±10.1	1.23	62.0±11.3	62.6±10.7	-0.73	62.4±11.0	62.4±10.2	-0.01	62.7±10.3	62.2±11.2	0.65
PeerT	23.0±4.5	22.1±4.5	2.82**	26.7±4.5	24.0±4.2	-0.93	22.7±4.5	21.9±4.7	0.90	22.5±5.0	22.8±4.2	-0.83	22.6±4.5	23.2±4.3	-0.97	23.0±4.2	22.6±4.6	1.35
CPeer	19.1±4.5	17.8±4.6	3.83***	18.6±4.6	19.4±3.3	-0.80	18.6±4.6	17.6±4.1	1.27	18.4±4.7	18.7±4.5	-0.76	18.6±4.6	18.7±4.3	-0.15	18.7±4.1	18.5±4.8	0.53
APeer	21.3±4.9	20.8±5.1	1.20	21.1±5.0	22.6±3.4	1.30	21.1±5.0	20.6±4.9	0.61	21.1±4.8	21.1±5.0	-0.14	21.2±4.9	20.6±5.2	0.90	21.0±4.9	21.1±5.0	-0.26

Mean ± SD; Student T test: * $p < .05$; ** $p < .01$; *** $p < .001$

CSS: Cyberbullying Sensitivity Scale; MPSSS: Multidimensional Perceived Social Support Scale; FS: Family subscale; FrS: Friend subscale; SpS: A special person subscale; PAS: Parent Attachment Scale; PT: Parent trust subscale; CP: Communication with parent subscale; AP: Parental alienation subscale; PeerAS: Peer Attachment Scale; PeerT: Peer trust subscale; CPeer: Communication with peer subscale; APeer: Peer alienation subscale.

Total MPSSSS scores, friend support scores, total peer attachment scores and peer alienation scores of the participants aged 18 years or above were found to be lower than the scores of both the other age groups (for total MPSSSS scores, $p < .01$ and $p < .05$, respectively; for the friend support scores, $p < .01$ and $p < .05$, respectively; for the total peer attachment scores, both $p < .01$; for peer alienation scores, both $p < .05$). On the other hand, the participants aged 18 years or above had lower peer trust scores than those aged 15 years or below ($p < .05$).

Total MPSSSS scores, family support scores and special person support scores of the group whose mother was a secondary school or high school graduate were found significantly higher than the scores of other groups (all $p < .001$). The parental attachment total scores, parent trust scores and parent communication scores of the group whose mothers graduated from secondary school or high school were found higher than the scores of other groups ($p < .05$, $p < .05$ and $p < .01$, respectively). The group whose father was a secondary school or high school graduate had higher total MPSSSS and family support scores than other groups ($p < .05$ and $p < .01$, respectively).

Table 6. Comparison of Research Variables with ANOVA In Terms of Sociodemographic Characteristics and Internet Usage Habits

	Grade		Age		Mother education groups		Father education groups		Monthly income groups		Perceived school achievement		Internet access frequency		Duration of daily internet usage	
	F	p	F	p	F	p	F	p	F	p	F	p	F	p	F	p
CSS	0.403	.751	.534	.586	2.715	0.067	1.563	0.210	6.279	.002	2.280	.103	0.275	0.260	1.369	0.243
MPSSS-Total	3.200	.023	5.065	.007	12.187	0.000	4.217	0.015	3.555	.029	7.937	.000	1.393	0.249	1.917	0.065
FS	2.070	.103	1.926	.146	10.390	0.000	5.099	0.006	0.411	0.693	9.944	.000	1.251	0.287	4.692	0.001
FrS	5.848	.001	8.683	.000	1.818	0.163	0.906	0.405	1.297	0.274	.076	.927	2.278	0.103	2.095	0.080
SpS	0.843	.471	1.323	.267	9.845	0.000	1.987	0.138	4.566	.011	6.873	.001	0.177	0.838	0.851	0.493
PAS-Total	0.216	.885	.940	.391	4.265	0.014	0.914	0.401	1.884	0.153	7.481	.001	1.537	0.216	4.923	0.001
PT	0.648	.584	.805	.448	4.140	0.016	0.889	0.412	0.787	0.456	4.216	.015	0.712	0.491	4.843	0.001
CP	0.515	.672	.821	.440	6.492	0.002	2.239	0.107	0.041	0.960	8.015	.000	0.649	0.523	5.041	0.001
AP	0.064	.979	.449	.638	0.609	0.544	0.117	0.890	4.799	.008	2.889	.061	2.376	0.094	2.118	0.077
PeerAS-Total	3.199	.023	5.650	.004	0.450	0.638	0.649	0.523	2.116	0.121	.623	.536	1.296	0.274	1.154	0.330
PeerT	3.277	.021	4.059	.018	1.494	0.225	0.462	0.630	1.563	0.210	.256	.774	2.091	0.124	0.794	0.529
CPeer	2.195	.087	2.834	.059	0.099	0.906	0.157	0.854	1.161	0.314	1.624	.198	3.628	.0270	1.493	0.202
APeer	1.423	.235	3.708	.025	0.171	0.842	0.663	0.515	2.760	0.64	.200	.819	0.494	0.610	2.860	.0230

CSS: Cyberbullying Sensitivity Scale; MPSSS: Multidimensional Perceived Social Support Scale; FS: Family subscale; FrS: Friend subscale; SpS: A special person subscale; PAS: Parent Attachment Scale; PT: Parent trust subscale; CP: Communication with parent subscale; AP: Parental alienation subscale; PeerAS: Peer Attachment Scale; PeerT: Peer trust subscale; CPeer: Communication with peer subscale; APeer: Peer alienation subscale.

The CSS score of the low-income group was found significantly higher than the score of the high-income group ($p < .01$). The MPSSS score, special person support score and parent alienation score of the high-income group were found higher than the scores of the moderate-income group ($p < .05$, $p < .05$ and $p < .01$, respectively).

The peer communication scores of the group who had daily internet access were found higher than in those who had less frequent internet access ($p < .05$).

Family support scores, total parental attachment scores, parent trust scores and parent communication scores of the group who spent more than 3 hours a day on the internet was found significantly lower than the scores of the groups who spent less time on the internet (all $p < .01$). On the other hand, the group who spent 30 minutes–1 hour daily on the internet had higher peer alienation scores than the group who spent more than 3 hours ($p < .01$).

Total MPSSS scores, family support scores, special person support scores, total parent attachment scores, parental trust scores and parent communication scores of the group that reported better school achievement were found to be statistically significantly higher than those of other groups.

Variables Predicting Cyberbullying Sensitivity

Table 7 shows the variables predicting cyberbullying sensitivity in the hierarchical regression analysis. The demographic variables to predict the cyberbullying sensitivity were gender and average monthly income. These two demographic variables accounted for 5% of the total variance ($F_{15-815} = 3.769$, $p < .001$). The third variable that predicts the sensitivity to cyberbullying was the family subscale of the MPSSS. Including this variable to the equation increased the total variance explained to 8% ($F_{18-812} = 4.889$, $p < .001$).

Table 7. Variables Predicting Cyberbullying Sensitivity

Variable	B	Beta	R	R ²	Adjusted R ²	F
Grade	.08	.02				
Gender	-1.89	-.19***				
Age	.09	.02				
Mother education	-.41	-.05				
Mother status	.48	.01				
Mother occupation	-.31	-.03				
Father education	-.24	-.03	.26	.06	.05	3.769***
Father status	.32	.01				
Father occupation	.10	.01				
Average monthly income	-.54	-.09*				
Internet access frequency	.42	.06				
Duration of daily internet usage	-.14	-.04				
Rules on home internet use	-.36	-.04				
Perceived school success	.03	.01				
Family support	.13	.16**				
Friend support	.01	.02	.31	.10	.08	4.889***
A special person support	.01	.02				
Parent trust	.01	.01				
Parent communication	.02	.02				
Parent alienation	.01	.00				
Peer trust	.02	.02	.31	.10	.07	.104
Peer communication	-.01	-.01				
Peer alienation	-.02	-.02				

* $p < .05$; ** $p < .01$; *** $p < .001$

DISCUSSION

This study examined the effect of perceived social support and attachment on the adolescents' internet usage habits and cyberbullying sensitivity. It was reported that an increasing use of internet among adolescents led to concerns with respect to an increasing risk of problematic internet use (Boniel-Nissim & Sasson, 2018). In our study, it was determined that 74.6% of students with an average age of 16.3 years used the internet every day and 67% among them used the internet more than 1 hour a day. Since the scores of cyber bullying and cyber victimization increased with an increase in the duration of internet usage (Uludaşdemir et al., 2019; Athaniosou et al., 2018), children spending a long time online need to be carefully monitored for these risks.

Firstly, the effects of various variables on the internet usage habits have been discussed. It is known that the education level of parents has an important effect in preventing cyber problems and problematic internet use in adolescents (Laftman et al., 2013; Athaniosou et al., 2018). In our study, it was found that the father's working status and a higher income level of the family were positively associated to the increased frequency of internet access and to the increased average daily internet usage time. The fact that families with higher socioeconomic status have easy access to internet and digital technologies can facilitate their guidance in this regard.

Rules regarding internet use at home and providing parental control are important in preventing problematic internet use (Elsaesser et al., 2017). However, it was determined that 68.5% of our study population did not have internet rules or restrictions at home and it was also found that household rules/restrictions on internet use decreased with an increase in the age and class of the participants. It was further found that participants with highly educated mothers experienced fewer internet usage rules/restrictions at home. Our results were in line with previous studies suggesting that parents with low socioeconomic and educational attainment are highly ambivalent and anxious about digital media and have a more restrictive attitude towards digital devices (Livingstone et al., 2015).

Previous research shows that cyberbullies generally have lower academic performance (Tokunaga, 2010; Guo & Wang, 2020). In our study, we found that those with lower school achievement were spending more time on the internet and had less internet rules at home, and that these children had lower social support and attachment scores. This may show the effect of an inadequate parental support along with lower academic achievement on the problematic internet use and thus on the cyberbullying risk.

According to previous studies, a healthy parent-child attachment is effective in preventing problematic internet use, and in fact, the time spent on the internet reportedly decreases as the time the students spend with their family members increases (Lei & Wu, 2007; Elsaesser et al., 2017). Boniel-Nissim & Sasson (2018) indicated that poor parent-child communication increased problematic internet use behaviors. As an important finding in our study, it was observed that students who showed more attachment to their parents and had family support were spending less time on the internet. This shows the importance of family support and secure connection in preventing problematic internet use. On the other hand, the low peer communication and high peer alienation scores of the students who accessed the internet less

frequently in our study pointed out the importance of internet in establishing peer relationships. As a matter of fact, it is seen today that it is almost a necessity for adolescents to maintain social relations with their friends over the internet (Kowalski et al., 2014, Gorrese & Ruggieri, 2012).

Secondly, those variables with an effect on cyberbullying sensitivity have been discussed. As an important finding, adolescents in our study had high sensitivity scores against cyberbullying, indicating that individuals were aware of cyberbullying. In a study examining the differences between countries in terms of perceived violence of cyberbullying through various scenarios, it was found that Turkish students perceived all scenarios more severely than those adolescents in other countries (Palladino et al., 2017). The authors of that study argued that due to the recent increase in awareness of cyberbullying, Turkish students have developed a higher sensitivity to threats such as cyberbullying.

In line with previous studies (Aktürk, 2015; Gündüz et al., 2021, Şentürk & Bayat, 2016), female students had higher cyberbullying sensitivity scores than males in our study. The high sensitivity of girls to cyberbullying can be explained by their previous experiences of cyberbullying and by the fact that they are warned by their parents more frequently about the dangers of the cyber world.

Furthermore, adolescents with low socioeconomic levels had both lower family support and attachment scores in our study, in compliance with previous studies (Saylor & Leach, 2009). However, these adolescents were found to be more susceptible to cyberbullying. In this context, the family income was found to be an important variable that predicts the cyberbullying sensitivity. Inadequate family support, poor family relationships and limited internet access may be observed in students from lower socioeconomic levels, and the risk of getting their already-limited internet access blocked by their families in case of any problems in the internet environment may cause these students to be more careful.

Parental support and good relationships with parents and friends are one of the factors that prevent adolescents from becoming victims of cyberbullying and play a role in solving the problem in adolescents exposed to cyberbullying (Elsaesser et al., 2017, Boniel-Nissim & Sasson, 2018, Hellfeldt et al., 2020). Similarly, positive correlations were found in our study between social support and cyberbullying sensitivity and parental attachment, and the family support subscale was identified as an important variable that predicts cyberbullying sensitivity. Strong attachment to parents is of great importance in preventing pathological internet use and reducing the risk of cyberbullying.

Healthy relationships of adolescents not only with their families, but also with their peers reduce the risks of bullying, whereas cyberbullying victims mostly seek social support from their peers (Burton et al., 2013; Livingstone et al., 2015). In our study, adolescents who were strongly attached to their peers had high cyberbullying sensitivity. This finding shows the importance of healthy relationships with peers and of friend support in preventing and coping with cyberbullying.

Limitations: This study has some limitations. First, a cross-sectional study was conducted. It was therefore only possible to measure the study variables at a given time and their evolution could not be followed. Second, the study included only the students from a single city, and the

findings obtained reflected only the personal views of this sample. Future research should be conducted to investigate cyber bullying sensitivity in a larger population with different socioeconomical characteristics.

Conclusion: A higher cyberbullying sensitivity in adolescents of our study reflects that the students perceive their online exposure to bullying behaviors as a threat, even if they spend a lot of time on the internet. It was observed that the students' internet usage habits are affected by various sociodemographic characteristics and these features may cause differences in cyberbullying sensitivity, social support, and parental and peer attachment status. The fact that adolescents with higher perceived social support and strong attachment to parents and peers spent less time on the internet and had higher sensitivity to cyberbullying points out the importance of social support and attachment in preventing cyberbullying. Positive attachment between parents and adolescents and perceived strong social support from family and friends will reduce problematic internet use among adolescents and thus the risk of cyberbullying. Therefore, in order for the cyber bullying prevention strategies to become effective, they should encompass multiple systems such as the family, the peers, and the school.

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The Relationship Between Attachment Styles and Willingness to Cooperate with Robots: Mediating Effects of Nursing Students' Belief About Human Nature and Trust in Robots

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ABSTRACT

Organizations providing healthcare services adopt modern technologies to improve the quality of the services they offer. Deploying the human-robot cooperation process in organizations is a challenge and organizations need to prepare their employees for the process. A single individual characteristic may be a variable that affects an employee's adoption process. To learn whether individual characteristics affect this process, this paper examined how nursing students' attachment styles have an effect on the human-robot cooperation process and whether beliefs about human nature have a mediation effect on how nursing students perceive robots. The study investigated how trust in robots affects attachment styles and the willingness to cooperate with robots. Nursing students filled out paper-based surveys in classrooms. Data were analyzed via Pearson product-moment correlations and PROCESS macro. The mediation hypotheses were supported with significant results. In human-robot cooperation, the human operator's character may affect the entire process. Therefore, studies are needed to focus on the effects of individual factors on the adoption of these technologies.

Keywords: Attachment Styles, Human-Robot Interaction, Human Nature, Robots, Trust

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Bađlanma Stilleri ile Robotlarla İşbirliđi Yapma İsteđi Arasındaki İlişki: Hemşirelik Öğrencilerinin İnsan Doğasına İlişkin İnançları ve Robotlara Güvenlerinin Aracı Etkileri

ÖZ

Sađlık hizmeti sunan kuruluşlar, sundukları hizmetin kalitesini artırmak için modern teknolojileri edinmektedir. Organizasyonlarda insan-robot işbirliđi sürecini sađlamak zorlu bir aşamadır. Bu kuruluşların çalışanlarını bu sürece hazırlaması gerekir. Kişilik özellikleri bu teknolojileri benimseme sürecini etkileyen bir deđişken olabilir. Bu çalışmada, bazı bireysel özelliklerin bu süreci etkileyip etkilemediđini öğrenmek için, hemşirelik öğrencilerinin bađlanma stillerinin nasıl bir etkiye sahip olduđunu ve insan doğasına dair inancın insanların robotlara dair algısı üzerinde aracılık etkisinin olup olmadığını incelenmiştir. Robotlara duyulan güvenin bađlanma stillerini ve robotlarla işbirliđi yapma istekliliđini nasıl etkilediđi de araştırılmıştır. Hemşirelik öğrencileri sınıflarda anketleri doldurmuştur. Veriler, Pearson çarpım-moment korelasyon katsayısı ve PROCESS makro ile analiz edilmiştir. Aracılık hipotezleri desteklenmiştir. İnsan-robot işbirliđinde, bireyin karakteri tüm süreci etkileyebilir. Bu nedenle, bu teknolojilerin benimsenmesinde bireysel faktörlerin etkilerine odaklanmak için yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bađlanma Stilleri, İnsan-Robot Etkileşimi, İnsan Doğası, Robotlar, Güven

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INTRODUCTION

Healthcare technologies are essential in terms of improving the speed and quality of services provided. Thanks to robots that can be used in the healthcare sector, the workload of caregivers may be reduced and the quality of life of patients may be increased. In particular, the workload of nurses may be reduced if robots do the repetitive and time-consuming tasks (Kuo et al., 2008).

Robot use in the healthcare sector has not yet progressed to the desired level (Carayon, 2006); but research and development projects are growing rapidly (International Federation of Robotics, 2019). Effective interaction between humans and robots is essential to increasing the use of robots for nursing tasks (Zhao et al., 2014). Human behavior is an important factor in the context of the service robot's ability to complete nursing tasks efficiently (Zhao et al., 2014). Communication between people and service robots is important to ensure cooperation (Zhao et al., 2014).

In order to use robots in healthcare applications, they must have the ability to interact socially with people (Kuo et al., 2008). The purpose of healthcare robots is not to replace nurses or other medical professionals, but to assist and collaborate with human users (Kuo et al., 2008). Successful outcomes may be achieved when human and robot capabilities are combined by providing human and robot cooperation. Robots have advanced sensors, computational skills, and the ability to perform repetitive tasks without fatigue in a short time. People have cognitive skills, situational awareness, and effective decision-making skills (Li et al., 2013). Therefore, with effective interaction, tasks may be accomplished with maximum efficiency.

The healthcare industry includes interpersonal relationships from various professions, as well as relationships with patients and their families (Leiter et al., 2015). The robots that will be added to this network of relationships are not alive like humans and animals, but they appear to be more alive than inanimate beings and have the capacity to communicate (Collins et al., 2013). They are therefore worthy of examination from a different perspective than other technological products; because they may have the potential to influence the social context in which they are involved.

New research may lead to understanding of potential challenges that may arise and to earlier development of solutions. For example, understanding how the characteristics of human users influence the human-robot cooperation process as a predictor may be effective in uncovering the potential success of people who are expected to work cooperatively with robots. Also, studies may be designed to predict the potential challenges driven by individual characteristics and potential ways to overcome them. For this purpose, the focus is on nursing students who will become an important share of the healthcare sector's human resources. This paper linked students' attachment styles and to their belief about human nature, their trust in robots and their willingness to cooperate with robots. Thus, this paper has pointed out that some personality traits of people who are expected to work with robots in the healthcare sector may also be taken into consideration.

Adult Attachment

A theory to develop effective social relationships in both social psychology and developmental psychology is attachment (Leiter et al., 2015). Attachment theory is an interpersonal development theory that maintains that infants' interaction with caregivers affects their relationships throughout life (Bowlby, 1969). Bowlby (1969) examined the basic process of attachment; while Ainsworth (1985) investigated how attachment-seeking efforts led to successful and unsuccessful attachment formation (Harms, 2011). Ainsworth measured the baby's reactions when left alone by the caregiver for a while and when the caregiver returned. She called this technique a "strange situation". According to attachment theory, individuals expect comfort and safety from an attachment figure from birth (Bowlby, 1969). The caregiver's responsiveness affects the individual's self-worth and his / her trust in others (Bowlby, 1969). The individual develops a working model about themselves and other people, depending on whether he or she is consistently taken care of in situations where he or she is experiencing stress. For example, individuals who consistently receive support may form a secure attachments, whereas individuals who do not consistently receive support may form insecure attachments (Hazan & Shaver, 1990).

Internal working models include one's basic beliefs about himself/herself and other people, and these beliefs affect an individual's relationships throughout his or her life (Bowlby, 1988). Attachment styles can be conceptualized into two dimensions: avoidance of intimacy and anxiety over abandonment (Bowlby, 1969). In cases where both dimensions are low, people have a secure attachment; because they have a positive working model both for themselves and for other people. These individuals are comfortable in interpersonal relationships and they have high self-efficacy, and believe that other people will support them in case of need (Mikulincer & Florian, 1995).

Individuals with high anxiety about abandonment have a negative perception of themselves. They constantly need to be close to others and are very sensitive to rejection (Mikulincer & Florian, 1995). Individuals with high avoidance of intimacy have a negative perception of other people. They have little trust in people. They don't believe people will be around when they need them. They also do not want other people to depend on them (Miller, 2007).

Adult Attachment involves four attachment style based on the combination of these two dimensions being high or low (Griffin & Bartholomew, 1994). The secure attachment style is related to one's self-confidence and trust in other people. These individuals had warm and accepting parents in childhood. The preoccupied attachment style is associated with a feeling of worthlessness, low anxiety, and high avoidance. In childhood, they had emotionally unpredictable parents (sometimes they were warm and accepting, sometimes withholding and overprotective). Fearful attachment style is associated with high anxiety and high avoidance. These individuals want intimacy; but because of fear of rejection, they avoid close relationships and have had rejecting, overly critical and uncaring parents in childhood. The dismissing attachment style is associated with low anxiety and high avoidance. In childhood, they have physically and emotionally undemonstrative parents.

Adults with a secure attachment style are confident in seeking and receiving support from other people in times of stress (Pines, 2004). Securely attached individuals show more risk-taking

and exploring behaviors because they trust their partners (Fraley & Shaver, 2008). Securely attached individuals are more likely to cope with change than insecure ones (Mikulincer et al., 1993). Insecure people place greater emphasis on autonomy and control (Collins et al., 1996).

Hazan and Shaver (1990) investigated the effect of attachment theory on workplace behavior. According to them, attachment theory may help to understand social relationships in the workplace and related emotions. Many studies show that attachment styles shape behaviors, attitudes, and emotional responses in the workplace (Harms, 2011; Richards & Schat, 2011). Attachment theory previously focused on the type of response to stress, coping mechanisms, individual differences in emotions, thoughts, and behaviors in interpersonal relationships (Mikulincer and Florian, 1995). Recently, however, this theory has been applied to the interpersonal relationships at the workplace (Leiter et al., 2015). Adult attachment styles are effective in measuring the quality of relationships adults have with other people (Collins & Read, 1990). This includes the relationships in work-life (Leiter et al., 2015) and the social relationships that individuals have in the workplace affect their well-being (Day & Leiter, 2014).

According to the research, securely attached employees experience higher satisfaction with their work and enjoy their colleagues (Hazan & Shaver, 1990). Anxious/ambivalent individuals are concerned about being rejected by their colleagues and also expect approval from their colleagues. Avoidant employees prefer to work alone so they don't have to socialize. Colleagues evaluated securely attached employees more likable than insecure ones; and while they evaluated dismissive employees as defensive, they evaluated preoccupied individuals as more anxious (Kobak & Sceery, 1988). Styles other than secure attachment are categorized as insecure (Meredith et al., 2011).

Trust in Robots

Relationships with other people are at the heart of human existence. People are born into relationships and spend their lives in relationships (Berscheid & Peplau, 1983). From the relationship between a child and his/her caregiver to the relationship between players on a football team, trust is one of the most fundamental factors for a relationship to be preserved (Ullman & Malle, 2018). For example, colleagues must trust each other to cooperate among themselves (Leiter et al., 2015).

People relate not only to other people but also to non-human beings (de Graaf, 2016). Studies have been conducted on the extent to which information from interpersonal relationships may reflect the situation on human-robot interaction (Eyssel & Hegel, 2012). Studies show that humans interact with computers (Reeves & Nass, 1996) and robots (Kerepesi et al., 2006) as they interact with other people. This tendency increases the likelihood of people making emotional ties to artificial beings (Krämer et al., 2011). Factors affecting interpersonal relationships may similarly affect a person's trust in the machine (Muir, 1987). Thus, to adopt and use robot technology, effective communication must be established between the user and the machine (Desai et al., 2009).

Trust is a key factor in our daily interactions. Being able to collaborate with others depends on it (Wu et al., 2016). Automation has led modern society to a major process of change (Yerdon

et al., 2017). Robots have also begun to do things that require trust (Ullman & Malle, 2018). Therefore, various studies have been conducted to measure and theoretically examine human trust in robots (Yang et al., 2017). In human-machine interaction, trust is how much the user trusts the machine's decisions, actions, and suggestions. People's trust in human-robot interaction is very effective in their cooperation (Haring et al., 2013). In the meta-review, Hancock et al. (2011) concluded that trust is necessary to achieve the goals of human and robot as a team. Trust is a pattern that can be interpreted according to context. In particular, as the success of the work to be carried out with the robot becomes critical, the trust becomes more important (Kessler et al., 2017; Wu et al., 2016).

Overuse or underuse of automation is closely related to trust (Parasuraman & Riley, 1997). Unauthorized trust in automation can be fatal (Parasuraman & Riley, 1997). The fact that operators do not realize this even when automation behaves incorrectly is an example of misuse by over trusting the system. Disuse is that operators do not allow automation to do their job due to a lack of trust in the automation system. People may over trust robotic systems even though these systems make mistakes (Borenstein et al., 2017; Robinette et al., 2016). Therefore, to match the intentions of the designer and the user of the robot, the trust element must be calibrated appropriately (Lee & See, 2004). Calibrating trust ensures the correct use (Parasuraman & Riley, 1997).

The trust between humans and robots may be affected by the character of the human user, environmental factors and the character of the robot (Billings et al., 2012; Xu & Dudek, 2016). For the efficient distribution of tasks between the operator and autonomous machines, human trust in the machine is one of the design issues (Xu & Dudek, 2016). Trust directly affects the autonomy given to robots (Erebak & Turgut, 2019; Sheridan and Hennessy, 1984).

The Hypotheses

The majority of researchers agree that culture has some clear characteristics (Cohen, 2009). First, culture arises from adaptive interactions between humans and the environment. Second, there are shared elements in the culture. Third, culture is transferred from period to period, from generation to generation. Kluckhohn and Strodtbeck (1961) argued that there were some common problems shared by all people, that there were various alternatives to solving these problems, but that the solution preferred by each society was related to the culture of that society. One of these problems is what is human nature? Good, evil, or a mixture of both? Taking into account individual influences, the internal working model developed by Bowlby (1988) may affect the formation of the idea of human nature. In Bowlby's theory, individuals' perception of negative or positive others constitutes an important part of the attachment. Therefore, the attachment style of people may weaken or strengthen the idea of the nature of human beings, which is a cultural phenomenon, albeit to varying degrees.

Culture is also important at the individual level (Matsumoto et al., 1999). Two individuals living in the same country may have different cultural characteristics (McCoy et al., 2005). That is, national culture may affect the individual, but it may not determine its purely cultural characteristics (Lee et al., 2007). Trust in robots may also vary by culture (Li et al., 2010; Yerdon et al., 2017). Studies have shown that trust varies in individualist or collectivist cultures (Hui & Triandis, 1986). Some theorists define social trust as a desire to trust others (Whiteley,

2000). These levels of social trust vary from country to country (Schmitt-Beck, 2008). Social trust is an adhesive that keeps people together in a society and promotes cooperation (Beilmann & Lilleoja, 2015).

The complexity and human-like nature of the relationship between humans and robotic technologies indicate the importance of psychological factors in human-robot relationships. Robots are expected not only to do their tasks but also to adapt to their social environment (de Graaf, 2016). In the future, robots are expected to take part in various social environments. These include houses, nursing homes, hospitals, and schools. Today, human-robot relationships are being shaped by taking advantage of human-to-human relationships. This may allow people to build more meaningful relationships with robots (de Graaf, 2016).

Social responses to human interaction with robots have been reported in many studies (Kahn Jr. et al., 2013; Kerepesi et al., 2006). Due to some social clues, people treat these beings differently and want to connect with them emotionally (Scheutz, 2011). Given all these studies, the attachment styles of individuals may affect the belief in the nature of the human being due to the negative/positive other perception in internal workings. The belief in human nature may also affect trust in robots because of individuals' human-like attributions to robots. Therefore, the following hypothesis was created:

Hypothesis 1: The belief about human nature has a mediation effect on the relationship between attachment styles and trust in robots.

Since robots have social characteristics and humans attribute human-like characteristics to robots, humans may see robots as part of the negative/positive others group specified in attachment theory. Therefore, the effect of attachment style may determine whether to trust others, robots. Besides, since trust in robots is essential to cooperate with them, trust in robots may have a mediation effect on the relationship between attachment styles and the willingness to cooperate with robots. Therefore, the following hypothesis was created:

Hypothesis 2: Trust in robots has a mediation effect on the relationship between attachment styles and the willingness to cooperate with robots.

METHOD

Participants and Procedures

A total of 374 nursing students answered paper-based surveys (Total number of nursing students in the university was 460). We explained the purpose of the research and received informed consent from the students and asked them to respond to surveys in the classroom in the beginning of the courses. It took them about 15 minutes to fill out the questionnaires. The mean age of the students was 21 years ($SD = 2$). See Table 1 for other demographic information. Ethical permission for this study was obtained from the Human Research Ethics Committee of Erzincan Binali Yıldırım University with the date of 16/01/2019 and protocol number 01/04.

Table 1. Demographic Data

		Frequency	%
Class Standing	Freshman	104	27.8
	Sophomore	106	28.3
	Junior	68	18.2
	Senior	96	25.7
	Total	374	100.0
Gender	Female	252	67.4
	Male	122	32.6
	Total	374	100.0

Measurement Tools

Adult Attachment Styles

The scale, which was created by combining various scales by Griffin and Bartholomew (1994), contains 30 items and measures the attachment styles of individuals and some dimensions related to attachment. It was adapted to Turkish by Sümer and Güngör (1999). This study was based on the model of Hazan and Shaver (1990). This model has three attachment styles: secure style (items 10, 13, 15, 23, and 30), ($\alpha = .40$), dismissing style (items 1, 12, 24, and 29), ($\alpha = .45$) and anxious/ambivalent style (items 4, 11, 18, 21, and 25), ($\alpha = .66$). To illustrate the styles, one item in the scale for secure style was “I am comfortable depending on other people”, one item for the dismissing style was “I find it difficult to depend on other people” and one item for the anxious/ambivalent style was “I want to merge completely with another person”. Students scored their responses using a 6-point Likert-type scale (1 = not at all like me, 6 = very much like me). There is no consensus on whether an attachment is inherently categorical or dimensional since attachment styles have a certain effect on each person (Ravitz et al., 2010). If the standard and acceptable cutoff points are determined, categories may be obtained from dimensional scales (Ravitz et al., 2010). The three styles in the attachment model used in this study were accepted as dimensional, not categorical. A confirmatory factor analysis (CFA) was executed to confirm the compliance of the scale. After removing items 10, 15 and 30 from secure attachments style, the three-factor structure of the scale indicated acceptable fit indices, [$\chi^2 / df = 2.529$, CFI = 0.91, GFI = 0.95, RMSEA = 0.064, and SRMR = 0.062], ($\alpha = .73$).

The Belief About Human Nature

We used the 6-item human nature sub-scale of the Cultural Perspectives Questionnaire-CPQ4, developed by Maznevski and Distefano (1995), to learn students’ beliefs about human nature. It was adapted to Turkish by Basım (1998). Students responded using a 6-point Likert-type scale (1 = strongly disagree, 6 = strongly agree). An example of an item on the scale was “You should be suspicious of everybody”. A high score indicates that the respondent perceived human nature as more evil. As a result of the CFA, acceptable goodness of fit indices were observed for this one-factor structure, [$\chi^2 / df = 3.014$, CFI = 0.98, GFI = 0.98, RMSEA = 0.073 and SRMR = 0.033], ($\alpha = .77$).

Trust in Robots

The Checklist for Trust between People and Automation developed by Jian, Bisantz, and Drury (2000) was used to measure trust in robots. There are 9 items on the scale and it was adapted to

Turkish by Erebak and Turgut (2019). Students responded using a 6-point Likert-type scale ranging from 1 (strongly disagree) to 6 (strongly agree). An example of an item in the scale was “I am suspicious of robots’ intent, action, or output”. The CFA showed that one-factor scale had acceptable goodness of fit indices, [$\chi^2 / df = 2.673$, CFI = 0.95, GFI = 0.97, RMSEA = 0.067 and SRMR = 0.037), ($\alpha = .71$).

The Willingness to Cooperate with Robots

Two items were developed by the authors to measure students’ willingness to cooperate with robots in the future. In the first step, three behavior experts were asked to report independently to develop items for cooperation with robots. The reports were examined and categorized according to similarity by the researchers. The authors organized two discussion rounds to complete the final wordings of the items. Afterward, two psychologists commented on the comprehensibility of the items. The means and standard deviations of the items indicated adequate variability. Internal consistency was provided. The first item was “I would like to cooperate with the robots in the future” and the other item was “I can easily cooperate with robots while performing my job in the future”. Students responded using a 6-point Likert-type scale ranging from 1 (strongly disagree) to 6 (strongly agree). An explanatory factor analysis (EFA) was performed to examine the structure of the items, [(KMO = 0.5), (Barlett’s Sphericity: $\chi^2 = 519.698$, Df = 1, $p < .001$)]. According to the EFA results, a single factor was obtained and all factor loadings were above .90. This one-factor accounted for 93% of the total variance ($\alpha = .93$). Since, the most appropriate reliability coefficient for a scale containing two items is the Spearman-Brown coefficient which also equals to 0.93 (Eisinga et al., 2013).

RESULTS

A Shapiro-Wilk test was used to test for normality on the dependent variables such as trust to robots and cooperation with robots; and that indicated that the data was normally distributed. According to the Pearson product-moment correlation results, all three attachment styles correlated with each other as moderate positive. While there was a moderate positive relationship between the belief about human nature and dismissing attachment style, a positive but weak relationship with other attachment styles was found. Also, there was a weak and positive relationship between attachment styles and trust in robots, but there was no relationship between attachment styles and the willingness to cooperate with robots. There was a weak and positive relationship between the belief about human nature and trust in robots and the willingness to cooperate with robots (see Table 2).

Table 2. The Correlations of the Variables

	1	2	3	4	5	6	7
1 Secure Style	-	.517**	.445**	.315**	.242**	.081	-.082
2 Dismissing Style		-	.338**	.444**	.238**	.030	-.054
3 Preoccupied Style			-	.296**	.131*	.095	-.133*
4 Human Nature				-	.255**	.108*	-.045
5 Trust in Robots					-	.506**	.006
6 WillCoopRob						-	.054

Note. ^a Human Nature: The belief about human nature. ^b WillCoopRob: The willingness to cooperate with robots. ^c **Correlation is significant at the 0.01 level (2-tailed). ^d *Correlation is significant at the 0.05 level (2-tailed).

PROCESS macro was used (Hayes, 2017) to test the simple mediation hypotheses. By selecting the fourth model, this paper analyzed attachment styles as predictor variables, the belief about human nature as a mediator, and trust in robots were outcome variables. According to the results, the belief that human nature is evil showed a partial mediation effect for dismissing and secure attachment style, while it showed a full mediation effect for preoccupied attachment style (see Table 3).

Table 3. The Mediation Effect of the Belief about Human Nature

Independent Variable	Point Estimate	SE	Bootstrapping Percentile 95% CI	
			Lower	Upper
Secure Style	Direct Effects			
	0.1157	0.0336	0.0497	0.1817
	Indirect Effects			
Dismissing Style	0.0402	0.0151	0.0138	0.0735
	Direct Effects			
	0.1413	0.0506	0.0419	0.2408
Preoccupied Style	Indirect Effects			
	0.0752	0.0258	0.0247	0.1268
	Direct Effects			
	0.0502	0.0432	-0.0347	0.1351
	Indirect Effects			
	0.0576	0.0177	0.0253	0.0955

Note. ^a Bootstrap sample size = 5.000. ^b Dependent variable: Trust in robots.

This paper also analyzed attachment styles as predictor variables, trust in robots as a mediator, and the willingness to cooperate with robots as outcome variables. According to the results, the dismissing attachment style had a direct but negative effect on the willingness to cooperate with robots, while with the partial mediation effect of trust in robots it had a positive indirect effect on the willingness to cooperate with robots. Trust in robots had the effect of full mediation in the relationship between preoccupied and secure attachment style and the willingness to cooperate with robots (see Table 4).

Table 4. The Mediation Effect of Trust in Robots

Independent Variable	Point Estimate	SE	Bootstrapping Percentile 95% CI	
			Lower	Upper
Secure Style	Direct Effect			
	-0.0531	0.0563	0.0497	-0.0531
	Indirect Effect			
Dismissing Style	0.1526	0.0366	0.0138	0.1526
	Direct Effect			
	-0.1644	0.0792	0.0419	-0.1644
Preoccupied Style	Indirect Effect			
	0.2169	0.0554	0.0247	0.2169
	Direct Effect			
	0.0462	0.0704	-0.0347	0.0462
	Indirect Effect			
	0.1026	0.0400	0.0253	0.1026

Note. ^a Bootstrap sample size = 5.000. ^b Dependent variable: The willingness to cooperate with robots.

DISCUSSION

A more complex approach is required to plan the process of adapting robots with social characteristics to healthcare applications since people exhibit different behaviors when interacting with robots with human body form in comparison to other technological products. Moreover, considering the characteristics of employees, it can be expected that human-robot interaction in organizations may be influenced by many variables. Therefore, the ability of robots to operate at the most effective level depends on how well organizations are prepared for this process. An important part of this preparation is a better understanding of the employee side of the employee-robot interaction.

Personality is one of the most fundamental factors in understanding human behavior (Li et al., 2014). Additionally, the attachment style of the individual is an integral part of the individual's personality (Ainsworth, 1985). As assistive social robotics develops, people are more likely to form attachment-like bonds with robots (Collins et al., 2013). Individual factors affect various organizational outcomes as well as technology adaptation. With the involvement of robots in the work-life, the effects of these individual factors may increase even more. In this study, it is examined whether attachment styles, which are important variable that affecting nursing students' relationships with other people, reflect their trust in robots and their willingness to cooperate with them.

In the first hypothesis, it is suggested that the belief about human nature would have a mediation effect on attachment styles (secure, dismissing, and preoccupied) and the relationship to trust in robots since it is related to people's perception of other people and because people make human-like attributions to robots. This hypothesis was supported by the three-attachment style. Dismissing and secure attachment style had a direct effect on trust in robots as well. The direct effect of both the belief that human nature is evil and dismissing and a secure attachment style on trust in robots is consistent with studies on how people attribute human-like characteristics to robots (see Erebak, 2019; Eyssel & Hegel, 2012; Kahn Jr et al., 2013; Scheutz 2011; Kerepesi et., 2006). It is also noteworthy that all three attachment styles are in a positive correlation with the belief about human nature. This may indicate that culture affects the belief about human nature. Individuals with dismissing attachment style, who have positive self and negative others model in the context of attachment, have a stronger relationship with the belief that human nature is evil than others. Moreover, in the preoccupied style, which has a negative self and positive others model, the result that the belief that human nature is evil has a full mediation effect may point out that culture may be more determinative in individuals with this style.

Trust affects decisions in risky and uncertain situations (Park et al., 2008). Trust affects the extent to which a person will allow a robot to behave autonomously (Desai et al., 2009). In other words, the less the individual trusts the robot, the more he/she interferes with the work of the robot (De Visser et al., 2006). In addition, traditionally, robots are built to function in a specified place and for a specified task. However, people may work with more complex machines with the development of collaborative robots (cobots) (Palmarini et al., 2018). Therefore, employees interacting with robots must be flexible and innovative (Kagermann et al., 2013). Thus, the second hypothesis was supported that one's character could be effective in

the process of cooperation with the robot, and that trust in robots may play a mediation role in this relationship. The effect of trust in robots on the character of the individual (see Billings et al., 2012) and the support of trust in robots to the process of cooperation with robots are consistent with previous studies (see Borenstein et al., 2017; Robinette et al., 2016; Parasuraman and Riley, 1997; Wagner, 2009; Wu et al., 2016). Furthermore, the results, the direct negative effect of the dismissing attachment style on the willingness to cooperate is positively mediated by the trust in robots, and trust in robots had the full mediation effect between the secure and preoccupied styles and cooperation willingness, may emphasize that trust in robots is an important factor in human-robot interaction in the context of attachment theory.

In this study, no specific robot type was specified. However, when presenting certain types of robots to participants, these relationships may vary. For example, as the level of anthropomorphism of the robot increases, the degree of human trust in them may change. People may attribute more human-like characteristics to robots. Moreover, the willingness to collaborate with robots may also vary on a mission-by-task basis. Depending on the characteristics of the task (for example, it is repetitive, monotonous), individuals' approaches may change. Therefore, more specific connections can be achieved through studies that include these variables.

When adapting robotic technologies to healthcare organizations, it should also be taken into account which professional group the robot will work with and with whom. In this study, it is revealed that the attachment styles of nurses of next years may affect this process. For example, robots may be paired with a human operator. When choosing this human operator, the attachment style of the nurse may be learned and what kind of challenges the individual may face may be calculated based on personality traits. Also, it is possible to investigate what kind of human-like characteristics can be attributed to robots in the culture of the employees of the organization.

Conclusion: Healthcare organizations have great potential in using robotic technologies in their service applications. Therefore, the potential of cooperation with robots in the service offered by professional groups should be explored specifically for healthcare organizations. In this way, efficient and efficient service quality may be achieved with robotic technology. In this study, this paper contributed to the insight into how adult attachment styles of nursing students who will work in the healthcare sector in the coming years may affect their potential to cooperate with robots. This paper emphasized that individual characteristics and culture may influence on how one perceives robots. With the contribution of new studies, organizations may take action by taking into account the effects of individual factors on the human-robot cooperation process and may foresee potential challenges.

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Do Individual Selective Serotonin Reuptake Inhibitors Used During Pregnancy Show Any Differences in The Risk of Neonatal and Childhood Outcomes: An Overview

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ABSTRACT

This review summarizes current data on the risk of neonatal and childhood outcomes associated with maternal use of individual selective serotonin reuptake inhibitors (SSRIs) during pregnancy. Research articles and meta-analyses published in English language and curated in PubMed between January 2005 and April 2020 were screened. Based on limited available data, compared to others, slightly higher risks associated with individual SSRIs are as follows: paroxetine for preterm birth, escitalopram for low birth weight, sertraline and paroxetine for spontaneous abortion, fluoxetine for persistent pulmonary hypertension and fluoxetine and paroxetine for poor neonatal adaptation syndrome. Sertraline for persistent pulmonary hypertension and sertraline and paroxetine for autism spectrum disorders may be relatively safer compared to the other SSRIs. The current evidence is inadequate for definitive conclusions. Further multicenter comparative studies are urgently needed.

Keywords: Antidepressants, Pregnancy, Preterm Birth, Low Birth Weight, Spontaneous Abortion

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Gebelikte Bireysel Kullanılan Seçici Serotonin Geri Alım İnhibitörleri Yenidoğan ve Çocukluktaki Riskler Açısından Farklılık Gösteriyor Mu: Genel Bakış

ÖZ

Bu derleme, hamilelik sırasında seçici serotonin geri alım inhibitörlerinin (SSRI'lar) annede bireysel kullanımıyla ilişkili yenidoğan ve çocukluktaki sonuçların risklerine ilişkin mevcut verileri özetlemektedir. Ocak 2005 ile Nisan 2020 arasında İngilizce ve PubMed'de yayınlanan araştırma makaleleri ve meta-analizler tarandı. Sınırlı mevcut verilere göre, diğerlerine kıyasla, bireysel SSRI'larla ilişkili biraz daha yüksek riskler şu şekildedir: erken doğum için paroksetin, düşük doğum ağırlığı için essitalopram, spontan düşük için sertralin ve paroksetin, kalıcı pulmoner hipertansiyon için fluoksetin ve zayıf yenidoğan adaptasyon sendromu olanlar için fluoksetin ve paroksetin. Kalıcı pulmoner hipertansiyon için sertralin ve otizm spektrum bozuklukları için sertralin ve paroksetin diğer SSRI'lara kıyasla nispeten daha güvenli olabilir. Mevcut kanıtlar kesin sonuçlar için yetersizdir. Daha fazla çok merkezli karşılaştırmalı çalışmalara acilen ihtiyaç vardır.

Anahtar Kelimeler: Antidepresanlar, Gebelik, Erken Doğum, Düşük Doğum Ağırlığı, Spontan Abortus

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INTRODUCTION

Antidepressants are widely used for the treatment of many psychiatric diagnoses, especially depression and anxiety disorders. Epidemiological studies suggest that pregnant women are increasingly prescribed antidepressants (Dankner et al., 2018; Meunier et al., 2013; Munk-Olsen et al., 2012). Although the prevalence rate for the use of antidepressants during pregnancy is reported very differently in different geographical regions, a recent meta-analysis demonstrated a relatively frequent international use with about 4.0% (Molenaar et al., 2020). Pharmacotherapy in the treatment of some pregnant patients is clinically inevitable and the safety of antidepressants for the fetus or newborns is an important coercive factor in their selection during treatment. Despite low absolute risks, safety concerns related to the use of antidepressants during pregnancy continue due to controversial results reported in the literature.

One of the risks that is immediately associated with the use of antidepressants during pregnancy is the development of congenital malformation in the infant. However, other neonatal and childhood outcomes such as preterm birth, low birth weight and autism spectrum disorders are both frequent and important for long-term health. For example, preterm birth, which is frequently seen in the general population, is associated with 70% of neonatal deaths and up to 75% of neonatal morbidity (Wen et al., 2004). Moreover, meta-analyses have suggested that preterm birth and low birth weight negatively affect cognitive and academic performance in children (Aarnoudse-Moens et al., 2009; Allotey et al., 2018). On the other hand, available studies, systematic reviews or meta-analyses examining the relationship between antidepressants and neonatal outcomes are mostly focused on the use of general antidepressants or a class of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants rather than specific individual antidepressants. The current paper aimed to present current data on the effects of specific SSRIs used in pregnant women on birth outcomes other than congenital malformations.

Methods

English language papers published in the PubMed electronic database between January 2005 and May 2020 were screened. The search words used were as follows: pregnancy, antidepressant, SSRI, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, neonatal outcome, birth outcome, preterm birth, low birth weight, spontaneous abortion, persistent pulmonary hypertension, autism spectrum disorders, attention-deficit/hyperactivity disorder and poor neonatal adaptation syndrome. Clinical studies and meta-analyses but not reviews, case reports, letters to editor and experimental studies were included in this review.

1. Preterm Birth

Preterm birth is one of the major issues in perinatal health. It is defined as birth of the baby before 37 weeks of gestation (Tucker & McGuire, 2004). The prevalence rate of preterm birth estimated to be 5-10% in the general population (Frey & Klebanoff, 2016; Sharifi et al., 2017; Wen et al., 2004). Preterm birth could be triggered by multiple factors including infections, inflammation, uteroplacental ischaemia or haemorrhage. Gestational hypertension, intrauterine growth restriction, periodontal disease and a history of previous preterm birth are some risk factors (Goldenberg et al., 2008). Maternal use antidepressants during pregnancy appears to be

another risk factor for preterm birth. Meta-analyses have demonstrated that the prevalence of preterm birth in women exposed to SSRI antidepressants is 1.43-1.83 fold higher compared to the controls (Biffi et al., 2020; Eke et al., 2016; Huang et al., 2014).

Several studies have examined the relationship between maternal use of individual SSRIs and the risk of preterm birth in the infants. The reported prevalence of preterm birth in pregnant women using paroxetine was 8.7-20.0% (Costei et al., 2002; Diav-Citrin et al., 2008), fluoxetine was 4.1-14.3% (Chambers et al., 1996; Diav-Citrin et al., 2008), citalopram was 11% (Tucker & McGuire, 2004) and escitalopram was 11% (Klieger-Grossmann et al., 2012). This prevalence was 4-10% in the comparison groups including women unexposed to SSRIs. Simon et al. (Simon et al., 2002) revealed that perinatal outcomes with the use of sertraline, paroxetine and fluoxetine were similar. In a meta-analysis by McDonagh et al. (McDonagh et al., 2014), it was found that risk of preterm birth with citalopram or escitalopram was not significantly different from fluoxetine, paroxetine and sertraline. A more recent meta-analysis by Eke et al. (Eke et al., 2016) has suggested that women who used paroxetine had a similar risk of preterm birth to those who used fluoxetine (odds ratios=2.07 vs 1.91, respectively).

2. Low Birth Weight

Low birth weight is defined as birth below 2500 g and affects about 10% of infants. (Xu et al., 2014; Yonkers et al., 2014). Older maternal age, low economic level, disturbances in blood pressure and maternal anemia are the main risk factors for low birth weight (Figuerideo et al., 2018; Yadav & Lee, 2013). The relationship between low birth weight and maternal use of antidepressant during pregnancy is currently unclear due to the controversial study results (Grzeskowiak et al., 2012; Hayes et al., 2012).

The prevalence rate of low birth weight in infants exposed to fluoxetine and escitalopram was 11.5% and 9.9%, respectively, which was significantly higher compared to the controls (Chambers et al., 1996; Klieger-Grossmann et al., 2012). Klieger-Grossmann et al. (2012) also reported that the risk of low birth weight with maternal use of escitalopram was significantly higher than other antidepressants. The difference in mean birth weight between escitalopram and other antidepressants was 370 g. The mean birth weight in newborns exposed to fluoxetine was reported to be 160 g lower when compared to controls (Chambers et al., 1996). Other authors have reported that compared to the control non-exposed groups, the mean birth weight was lower by 180 g in paroxetine group and 100 g in citalopram group (Grigoriadis et al., 2018; Tucker & McGuire, 2004).

3. Spontaneous Abortion

The spontaneous termination pregnancy is an accepted definition of spontaneous abortion (Yonkers et al., 2014). Epidemiological studies indicate that spontaneous abortion is observed in 6-11% of pregnant women in the general population (Hemels et al., 2005; Kjaersgaard et al., 2013). Its occurrence is particularly frequent secondary to congenital malformations. Therefore, spontaneous abortion is considered as one of the important indicators of embryotoxic effects of medications (Ellfolk & Malm, 2010).

The prevalence rate of spontaneous abortion in pregnant women exposed to specific SSRIs were reported as follows: 10-11.8% with fluoxetine, 11% with citalopram, 15% with

escitalopram, and 9.1% with paroxetine (Chambers et al., 1996; Diav-Citrin et al., 2008; Klieger-Grossmann et al., 2012; Sivojelezova et al., 2005). In a study by Diav-Citrin et al. (Diav-Citrin et al., 2008), the risk for fluoxetine (but not paroxetine) was significantly higher compared to the controls. On the other hand, Nakhai-Pour et al. (Nakhai-Pour et al., 2010) found that significantly elevated risk of spontaneous abortion was associated with paroxetine (n=84, odds ratio = 1.75) but not fluoxetine (n=22, odds ratio = 1.44), citalopram (n=19, odds ratio = 1.55), sertraline (n=28, odds ratio = 1.33) and fluvoxamine (n=5, odds ratio = 2.19); although the sample size was small in the study. Using a sample of 22,061 pregnancies exposed to antidepressants, Kjaersgaard et al. (2013) study reported that no individual SSRI could be related to spontaneous abortion. The risk ratios reported by these authors were 1.04 for fluoxetine, 1.43 for citalopram, 1.45 for paroxetine, 1.16 for sertraline and 1.65 for escitalopram, when compared to non-exposed women. The authors also analyzed the risk ratio in those patients with a diagnosis of depression and reported that the risk ratio for each of the SSRIs above was reduced around 1.00.

4. Persistent Pulmonary Hypertension

Persistent pulmonary hypertension in the newborn is characterized by elevated pulmonary vascular resistance that causes hypoxemia (Sharma et al., 2015). Its incidence rate is reported to be 1.8/1000 live births (Masarwa et al., 2019). Persistent pulmonary hypertension can lead to severe hypoxemia, cardio-pulmonary instability and mortality (Sharma et al., 2015; Yonkers et al., 2014). Asphyxia and meconium aspiration are the most common causes for persistent pulmonary hypertension. Premature birth, smoking, obesity, septicemia and cardiac malformation are the other risk factors (Occhiogrosso et al., 2012; Sharma et al., 2015; Yonkers et al., 2014). However, recent meta-analyses have suggested that maternal use of SSRI antidepressants during pregnancy is associated with an increased likelihood of persistent pulmonary hypertension in newborns (Grigoriadis et al., 2014; Masarwa et al., 2019; Ng et al., 2019).

Persistent pulmonary hypertension was reported to be observed in 0.35-1.9% of newborns exposed to sertraline in-utero. This prevalence rate was 0.39-1.1% for paroxetine, 0.27-0.8% for fluoxetine, 0.33% for citalopram and 0.18% for escitalopram (Chambers et al., 2006; Kieler et al., 2012). Källén and Olausson (2008) noted that while 15% of the patients used fluoxetine, 4 (36.4%) of 11 women who had infants with persistent pulmonary hypertension reported an exposure to fluoxetine during pregnancy. In this study, the use of paroxetine, sertraline and citalopram had similar weight in the study sample and in the patients whose infants had persistent pulmonary hypertension. A single published meta-analysis has reported pairwise comparison of individual SSRI antidepressants. Masarwa et al. (2019) reported that among SSRIs, sertraline was found most likely to have lowest risk for persistent pulmonary hypertension. When pairwise comparisons were considered, fluoxetine appeared to have a higher odds ratio compared to paroxetine, sertraline and escitalopram. Additionally, the odds ratio was lower for escitalopram than citalopram.

5. Autism Spectrum Disorders

Autism spectrum disorders are neurodevelopmental conditions that can cause persistent and severe impairment in social communication and interactions (Baxter et al., 2015; Modabbernia

et al., 2017). Autism spectrum disorders are observed in 7.6 per 1000 individuals and is associated with physical, mental, functional and other neurodevelopmental disorders (Baxter et al., 2015; Lord et al., 2018). Advanced maternal age, preterm birth, low birth weight, maternal infections, meconium aspiration and maternal diabetes are some of the risk factors for autism spectrum disorders (Lord et al., 2018; Modabbernia et al., 2017). In addition, it has been suggested that maternal use of SSRI antidepressants during pregnancy may increase the risk of autism spectrum disorders in the offspring (Andalib et al., 2017; Kaplan et al., 2016; Man et al., 2015).

Results of studies analyzing the effects of specific SSRIs on the risk of autism spectrum disorders are mixed. Victorin et al. (2017) reported that the risk of autism spectrum disorders in children of mothers using citalopram and escitalopram during their pregnancy was significantly higher compared to children of mothers who did not use these drugs (prevalence rate: 2.6%, relative risk =1.71). However, this risk did not retain statistical significance when maternal depression or anxiety disorders were considered. On the other hand, Brown et al. (2017) noted a lower hazard ratio of 1.76 for citalopram compared to other SSRIs (reported hazard ratios were 2.93 for fluoxetine, 2.48 for sertraline and 2.12 for paroxetine). In a study by Bérard et al. (2016), the hazard ratio for autism spectrum disorders was highest with the use of fluvoxamine (7.30) and fluoxetine (4.99) and lowest with sertraline (0.45). The hazard ratios for citalopram and paroxetine reported by these authors were 2.23 and 1.99, respectively. A recent meta-analysis (Halvorsen et al., 2019) that included data from Viktorin et al. (2017) and Brown et al. (2017) has demonstrated that maternal use of citalopram but not fluoxetine, sertraline and paroxetine, during pregnancy were associated with elevated risk of autism spectrum disorders in children. However, this meta-analysis included results of inverse probability of treatment-weighted analysis instead of crude analysis from by Brown et al. (Brown et al., 2017). The inverse probability of treatment-weighted analysis revealed very lower hazard ratios for paroxetine and fluoxetine compared to the crude analysis, which may have affected results of the meta-analysis by Halvorsen et al. (Halvorsen et al., 2019).

6. Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder that affects 7.2% of children (Thomas et al., 2015). Genetic, biological and environmental factors such as low birth weight, smoking during pregnancy, exposure to alcohol in utero, infections, maternal stress and drug use during pregnancy play a role in its pathogenesis (Biederman, 2005; Sciberras et al., 2017). The available evidence suggests that antenatal use of SSRI antidepressants by the mother increased the risk of attention-deficit/hyperactivity disorder in children by 1.33-1.50 folds (Halvorsen et al., 2019; Jiang et al., 2018). However, to date, no study examining the effect of use of specific SSRIs by the mother on attention-deficit/hyperactivity disorder in the child has been published in the literature (Uguz, 2018).

7. Poor Neonatal Adaptation Syndrome

Poor neonatal adaptation syndrome is seen in newborns following prolonged in utero exposure to drugs (Klinger & Merlob, 2008). The prevalence of this syndrome in newborns exposed and unexposed to SSRIs is about 30% and 5%, respectively (Kieviet et al., 2013; Lattimore et al., 2005). The etiology is unclear; however, a role of withdrawal or toxicity of the drugs in the

symptoms of this syndrome has been suggested. (Kieviet et al., 2013). Poor neonatal adaptation syndrome consists of central nervous system (e.g., restlessness, tremor, sleep disturbances, lethargy, agitation, weak cry, weak sucking and hypertonicity/hypotonicity), autonomic (e.g., temperature instability and excessive sweating), respiratory (tachypnea, dyspnea) and gastrointestinal (e.g., vomiting, diarrhea and feeding problems) symptoms (Kieviet et al., 2013; Klinger & Merlob, 2008). Poor neonatal adaptation syndrome is generally mild, of short duration, self-limiting without treatment, and rarely needs admission to a neonatal care unit (Kieviet et al., 2013).

Two meta-analyses reported a 4 - 5-fold increased risk of poor neonatal adaptation syndrome in newborns of women who were prescribed serotonergic antidepressants (Grigoriadis et al., 2013a; Lattimore et al., 2005). Poor neonatal adaptation syndrome was reported in 17.2-31.5 % of infants with exposure to fluoxetine and 20.4 % of infants with exposure to paroxetine (Chambers et al., 1996; Diav-Citrin et al., 2008). In a retrospective cohort study, it was reported that infants antenatally exposed to citalopram, sertraline and fluoxetine had similar prevalence rates of poor neonatal adaptation syndrome (Forsberg et al., 2014). On the other hand, Sanz et al. (2005) reported that out of 93 cases of SSRI-induced neonatal withdrawal syndrome, 64 were associated with paroxetine, 14 with fluoxetine, 9 with sertraline and 7 with citalopram. The authors concluded that paroxetine might have an elevated risk of neonatal withdrawal syndrome compared to other SSRIs.

DISCUSSION

Principal factors in pharmacological treatment of psychiatric disorders during the perinatal period are efficacy and safety of the psychotropic drugs. The efficacy of a particular drug in the psychiatric disorder specific to the patient can be retrieved from her history. However, if the patient experiences the symptoms during pregnancy, safety data on medications obtained from the literature are important. On the other hand, similar to non-perinatal patients, it is expected that clinical improvement in symptoms and adverse events secondary to the use of each antidepressant may vary between pregnant patients. Moreover, clinical features of psychiatric conditions such as severity, comorbidity, impairment in social, occupational and family relationship are not equal in all patients. It has been suggested that psychiatric conditions are associated with increased risk of preterm birth, low birth weight in infants, as well as autism spectrum disorders and attention-deficit/hyperactivity disorder in children (Grigoriadis et al., 2018; Grigoriadis et al., 2013b; Grote et al., 2010; Kaplan et al., 2017; Man et al., 2018). Therefore, an individualized risk-benefit evaluation should be carried out prior to a decision on which medication will be administered (Cuomo et al., 2018).

According to the limited number of available studies, the prevalence rate of preterm birth in women using paroxetine appears to be slightly higher compared to fluoxetine, citalopram and escitalopram; however, comparative studies and meta-analyses revealed that difference between these SSRIs did not reach statistical significance. Current evidence suggests that among SSRIs maternal use of escitalopram is associated with the highest risk of low birth weight, although the reported prevalence rate is similar to the general population. No published study to date has examined the effects of sertraline and fluvoxamine on the risk of low birth weight. There is also no clear evidence suggesting a statistically significant elevated risk of the

use of an individual SSRI with spontaneous abortion. Nevertheless, two studies (Kjaersgaard et al., 2013; Nakhai-Pour et al., 2010) imply that compared to exposure to sertraline or fluoxetine, risk ratio/odds ratio for spontaneous abortion appear to be slightly higher in women using paroxetine or citalopram/escitalopram. Both studies, however, lack statistical comparative analysis. The available data suggest that the risk of persistent pulmonary hypertension may be lowest with sertraline and highest with fluoxetine. Although current study results regarding the risk of autism spectrum disorders with maternal use of individual SSRIs are controversial, relatively consistent results imply that sertraline and paroxetine to be slightly safer than other SSRIs. Lack of published studies prevents any firm comment on the risk of attention-deficit/hyperactivity disorder in children with maternal antenatal use of individual SSRIs. Finally, based on the current evidence, paroxetine and fluoxetine may be more disadvantaged SSRIs with regard to poor neonatal adaptation syndrome in newborns. Overall, lowest risk of negative outcomes appears to be associated with sertraline while the highest risk is associated with fluoxetine. If these comments are confirmed by further studies, SSRIs with relatively higher risk than the others should be used with caution and at the lowest possible dose.

Ideally, studies on the safety of SSRIs in pregnant women should have a prospective controlled observational design that includes treated and non-treated patient groups who have matched diagnosis and severity of depression and anxiety disorders. However, such a design has ethical and legal difficulties. This dilemma is an important reason why current scientific evidence is mostly based on electronic health registry databases and retrospective studies. The available studies are insufficient in completely excluding the effects of maternal depression and anxiety disorders, although some authors have considered them as confounders in their analyses. Data from several studies related to autism spectrum disorders (Viktorin et al., 2017) and spontaneous abortion (Kjaersgaard et al., 2013) suggest the importance of underlying maternal depression. Population based register database studies have relatively large samples of individual antidepressants, although the data on how many women took the medication as prescribed is unclear. However, these studies mostly include data on classes of antidepressant rather than individual drugs (Grigoriadis et al., 2013c). Additionally, most available studies do not assess the possible effects of the daily dose of antidepressants used. The range of therapeutic daily dose of antidepressants may vary by 4-fold, which can theoretically cause greater fetal exposure. Several studies have suggested that high daily dose of SSRIs can dramatically increase the risk of preterm birth (Roca et al., 2011; Suri et al., 2007). The relationship between other neonatal outcomes and dosing is unclear (Uguz, 2016). In addition to these limitations, the paucity of studies investigating effects of individual SSRIs on neonatal and childhood outcomes is another problem in interpreting the results. Current meta-analyses including individual SSRIs are based on very few studies. Nevertheless, the availability of studies with relatively large sample size and a prospective observational design is a considerable advantage (Diav-Citrin et al., 2008; Klieger-Grossmann et al., 2012; Sivojelezova et al., 2009).

CONCLUSION

Owing to small number of studies with relatively small sample sizes and methodological limitations, the available scientific evidence is inadequate to convincingly determine which individual SSRI used in pregnancy has greater increased risk of neonatal or childhood outcomes

compared to others. Despite the limitations, the current review concludes that individual SSRIs which are slightly more disadvantaged than others for each outcome are as follows: paroxetine for preterm birth, escitalopram for low birth weight, sertraline and fluoxetine for spontaneous abortion, fluoxetine for persistent pulmonary hypertension, citalopram/escitalopram, fluoxetine and fluvoxamine for autism spectrum disorders, and fluoxetine and paroxetine for poor neonatal adaptation syndrome. However, multicenter comparative studies with large sample sizes that include data on the use of individual SSRIs are urgently needed to reach reliable and definitive conclusions for clinicians.

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Endoplazmik Retikulum Stresinin Psikiyatrideki Yeri¹

Mustafa KARAAĞAÇ² 

ÖZ

Psikiyatrik hastalıkların etyolojisinde bugüne kadar hücre içi çeşitli patofizyolojik mekanizmalar araştırma konusu olmuştur. Endoplazmik retikulum, hücre içinde bulunan ve bazı önemli homeostatik süreçlerde yer alan bir organeldir. Endoplazmik retikulum stresi, çeşitli uyarılar sonucunda bu homeostatik mekanizmalarda meydana gelen değişimleri ifade etmektedir. Endoplazmik retikulum stresi bugüne kadar birçok hastalık için araştırma konusu olmuştur. Bu derlemede, psikiyatrik hastalıkların oluşumunda endoplazmik retikulum stresinin etkisinin güncel literatür verileri doğrultusunda tartışılması, olası patofizyolojik mekanizmaların aydınlatılması ve yeni tedavi seçeneklerinin geliştirilmesi hususlarında yapılacak çalışmalara ışık tutması amaçlanmıştır.

Anahtar Kelimeler: Endoplazmik Retikulum, Stres, Psikiyatri

The Role of Endoplasmic Reticulum Stress in Psychiatry

ABSTRACT

Various intracellular pathophysiological mechanisms have been the subject of research in the ethology of psychiatric diseases so far. The endoplasmic reticulum is an organelle located inside the cell and involved in some essential homeostatic processes. Endoplasmic reticulum stress refers to the changes that occur in these homeostatic mechanisms due to various stimuli. Endoplasmic reticulum stress has been the subject of research for many diseases until today. This review aims to discuss the effect of endoplasmic reticulum stress in the formation of psychiatric diseases in line with current literature data, illuminate possible pathophysiological mechanisms, and shed light on the studies to be done on the development of new treatment options.

Keywords: Endoplasmic Reticulum, Stress, Psychiatry

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GİRİŞ

1. Endoplazmik Retikulum

ER ökaryotik hücrelerde endomembran sisteminde yer alan protein sentezinin düzenlenmesi, proteinlerin modifikasyonu ve katlanması, fosfolipidlerin ve steroidlerin sentezi ve dağılımı, translokasyon ve hücredeki kalsiyum dengesi gibi süreçler için gereken önemli bir organeldir (Imai ve ark., 2016; Zanotto ve ark., 2017). ER sitoplazmanın önemli bir bölümünde yer alan uzun tübüller aracılığı ile moleküllerin sitoplazma içerisinde geniş alanlara taşınmasını sağlar (Palade ve Porter, 1954).

ER klasik olarak ribozom içeren endoplazmik retikulum (DER) ve ribozom içermeyen endoplazmik retikulum (GER) olarak ikiye ayrılmıştır (English ve ark., 2009). Yüksek miktarda protein salgılayan hücreler GER açısından zenginken, steroid sentezleyen hücrelerde ve kas hücrelerinde bol miktarda DER bulunur. Birçok hücrede, GER ve DER uzamsal olarak ayrılmış bölgelerde yer almazken hepatositler ve nöronlar gibi bazı hücrelerde, GER ve DER farklı hücresel alanlarda bulunur (Borgese ve ark., 2006). DER morfoloji açısından daha karmaşık, tübüler ağı ve daha fazla sayıda dallanma noktası içermesi ile GER'den farklıdır. Ksenobiyotik metabolize edici enzimler de öncelikli olarak DER'de bulunur (Orrenius ve Ericsson, 1966).

ER homeostazını bozan durumlarda, “ER Stresi” olarak adlandırılan hücresel bir durum meydana gelir. ER stresine hücresel yanıt, stresin üstesinden gelmek ve ER homeostazını geri kazanmak için uyumsal mekanizmaların harekete geçmesini içerir (Hetz, 2012).

1.1. Endoplazmik Retikulum Stresi ve Katlanmamış Protein Cevabı (UPR)

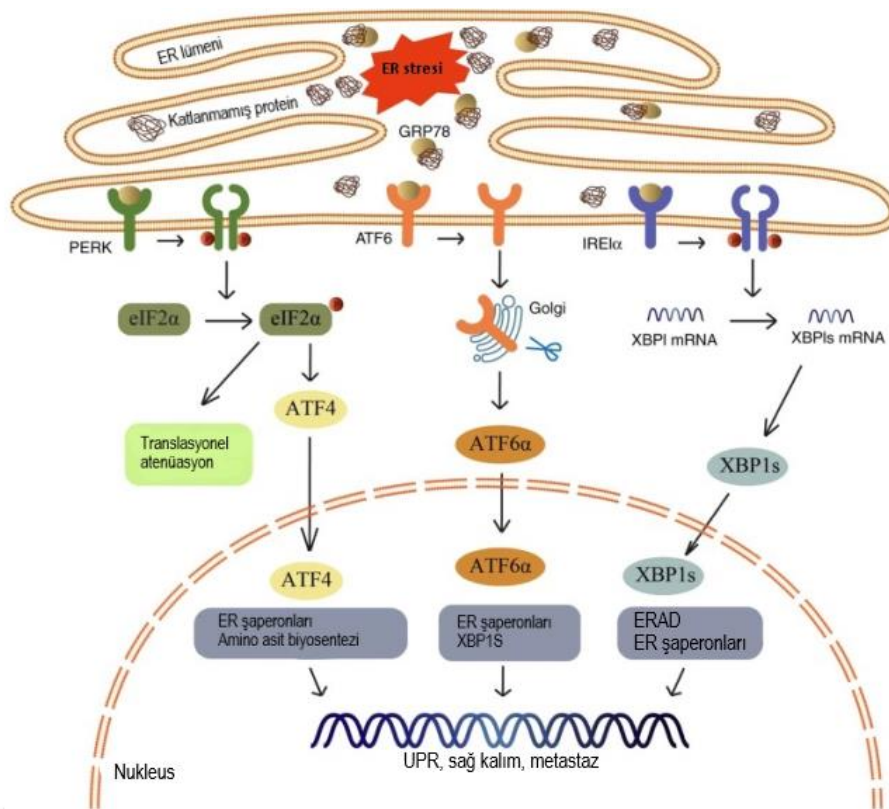
ER stresi, hücrenin iç veya dış faktörlerle uyarılması sonrasında homeostatik morfolojide ve ER'nin fonksiyonunda meydana gelen moleküler ve biyokimyasal değişiklikleri ifade etmektedir. ER stresi sonucunda proteinlerin işlenmesi ve taşınması bozulmakta ve ER'de büyük miktarlarda katlanmamış veya yanlış katlanmış proteinler birikmektedir. Hücrelerde, ER stresini hafifletmek ve normal ER fonksiyonun korumak için tedbirler alınmaktadır. Hücrenin hayatta kalması, ER stres tepkisinin çözülmesi ve normal proteinlerin üretilmesiyle mümkündür (Oakes ve Papa, 2015). Eğer bu katlanmamış proteinler salınırsa, spesifik apoptotik mekanizmalar aktive olur (Shore ve ark., 2011).

ER lümenindeki protein katlanma durumu, genel olarak katlanmamış protein yanıtı (UPR) olarak bilinen bir dizi evrimsel olarak korunan sinyal yolu ile sürekli olarak denetlenmektedir (Cox ve Walter, 1996; Sidrauski ve Walter, 1997). ER protein katlama kapasitesi aşıldığında veya uygun şekilde katlanamayan işlevsiz proteinler biriktiğinde (ER stresi), UPR aktive edilir, böylece hücre homeostazını geri kazanmak için organelin katlanma kapasitesi düzenlenir. UPR'nin görevi, ER'de protein katlanma dengesini korumaktır. İlk olarak, UPR, genel protein sentezini geçici olarak azaltarak ER'deki protein yükünü azaltır (Harding ve ark., 2000). İkincisi, ER hacmini endomembran biyosenteziyle genişletir (Bommiasamy ve ark., 2009; Sriburi ve ark., 2004). Üçüncüsü, şaperonların ve foldazların upregüle edilmesiyle ER katlama kapasitesini artırır (Acosta-Alvear ve ark., 2007; Lee ve ark., 2003). Dördüncüsü, ER ile ilişkili degradasyon (ERAD) ve ER-faji sisteminin upregüle edilmesiyle ER protein devir kapasitesini artırır ve böylece ER'de biriken yanlış katlanmış proteinler veya tüm organelin hasarlı

kısımları ortadan kaldırılır (Bernaes ve ark., 2006; Travers ve ark., 2000). Son olarak, eğer halen homeostaz sağlanamazsa, UPR organizmanın yararına hatalı hücreleri ortadan kaldıran apoptoz mekanizmalarını başlatır (Lin ve ark., 2007).

Tüm bu mekanizmalar, ER’de protein birikimine verilen cevaplardır ve protein sentezinin azaltılması, protein degradasyonunun desteklenmesi ve protein katlanmasına yardımcı olan moleküler şaperonların artırılması ile ER stresi hafifletilir.

Protein kinaz R-benzeri ER kinaz (PERK), inositol gerektiren enzim 1 α (IRE1 α) ve aktive edici transkripsiyon faktörü 6 (ATF6), UPR’yi başlatan önemli transmembran proteinleridir (Bettigole ve Glimcher, 2015). Strese maruz kalmayan hücrelerde, bu proteinler GRP78’e bağlanarak inaktif bir durumda tutulmaktadır (Korennykh ve Walter, 2012). ER stresi tespit edildiğinde, UPR sinyal yolu aktifleşir ve GRP78 bu üç molekülden ayrılarak katlanmamış proteinlere bağlanır (Şekil 1.) (Casas, 2017).



Şekil 1. ER Stresinin Mekanizması. Çeşitli fizyolojik koşullar protein katlanma işlemini bozabilir ve sonuç olarak ER stresi olarak adlandırılan, ER’de katlanmamış ve yanlış katlanmış proteinlerin birikmesine neden olabilir (“Role of endoplasmic reticulum stress in depression”, Mao, J. (2019).

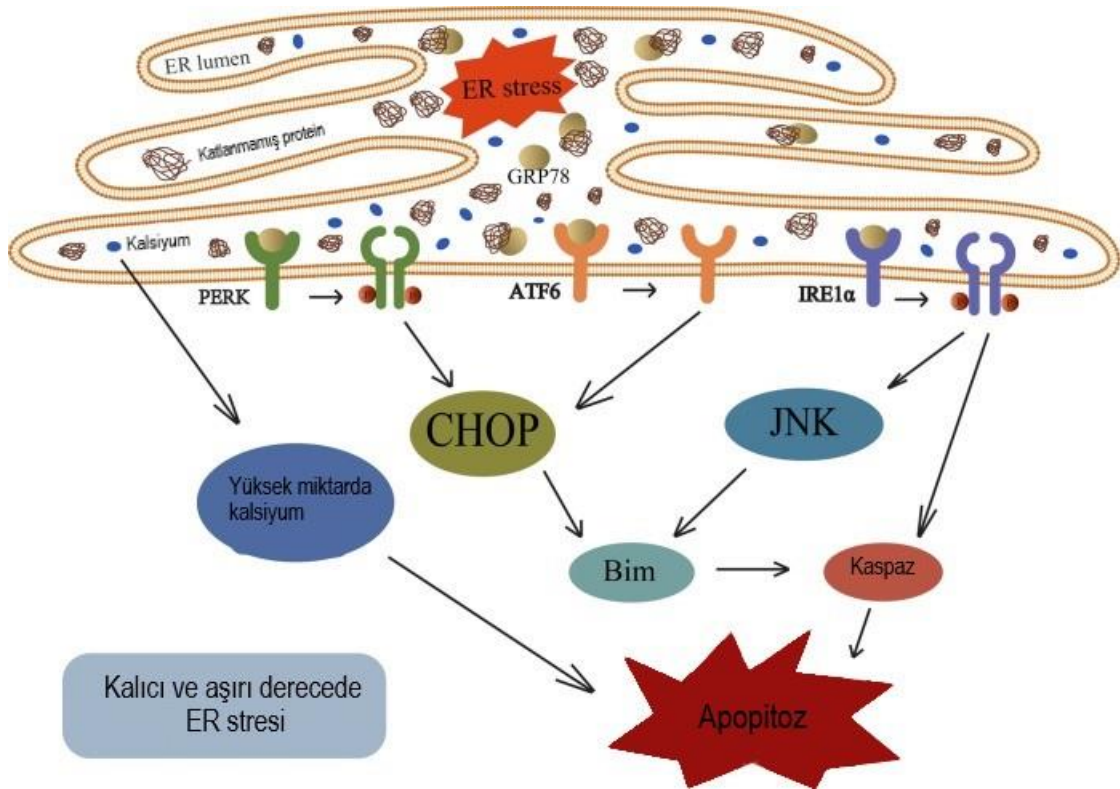
Molecular Medicine Reports, 20(6), 4774-4780 makalesinden izin dahilinde alınmış ve Türkçeleştirilmiştir. Telif hakkı Molecular Medicine Reports dergisine aittir, (2019).

PERK, GRP78’den ayrıldıktan sonra otofosforilasyon ve kendi aktivasyonunu başlatmak için homodimerize olur (Harding ve ark., 2000). PERK’in aktive olması ile ökaryotik translasyon başlatıcı faktörü 2 α ’nın (eIF2 α) fosforilasyonu tetiklenmekte, bu da ATF4 gibi çoklu transkripsiyon faktörlerinin ekspresyonunu aktive etmektedir (Harding ve ark., 2000). Fosforile olmuş eIF2 α aktivitesi, stresin erken safhalarında inhibe edilerek hücredeki çoğu proteinin sentezi ve translasyonu yavaşlatılır ve ER’deki katlanmış protein yükü azaltılır. Ek olarak,

ATF4, amino asit metabolizmasını, indirgenme-yükseltgenme reaksiyonlarını ve protein sekresyonunu düzenleyerek koruyucu bir rol oynamaktadır (Carrara ve ark., 2015). Stres cevabının süresi ve yoğunluğu arttıkça, aktifleştirilmiş ATF4, pro-apoptotik CCAAT / arttırıcı bağlayıcı protein-homolog proteinin (CHOP) ekspresyonunu indüklemektedir (Han ve ark., 2013).

IRE1 α , serin/treonin kinaz ve endonükleaz alanı içeren bir transmembran proteindir (Yang ve ark., 2016). IRE1 α 'nın GRP78'den ayrılmasını takiben, IRE1 α , intrasitoplazmik kısmının homodimerizasyonu ve fosforilasyonu ile kendi kendini aktive eder, böylece çevresindeki endonükleaz kısmının allosterik aktivasyonu sağlanır (Carrara ve ark., 2015). Aktive edilmiş IRE1 α , ATF6 tarafından uyarılarak, X-box bağlayıcı protein 1'in (XBP1) mRNA'sındaki 26-bazlık intronu eşleştirir ve eşlenmiş mRNA, kararlı durum transkripsiyon faktörü XBP1'i kodlamak için translasyonel çerçeve kaymasına uğrar (Lee ve ark., 2003). Transkripsiyon faktörü XBP1, sadece GRP78 ve CHOP genlerinin transkripsiyonunu indüklemez, ayrıca ER homeostazisini sağlamak için ER degradasyonunu artıran α mannosidaz benzeri 1 (EDEMI) yoluyla ERAD mekanizmasını aktive etmektedir (Papaioannou ve ark., 2018; Wu ve ark., 2015). Bu nedenle, XBP1, ER homeostazisini düzenlenmesi için hayati bir rol oynamaktadır (Mao ve ark., 2019b).

Stressiz durumda, ATF6 ER'de zimojen olarak bulunmaktadır. ER stresi meydana geldiğinde, GRP78'den ayrılarak golgiye taşınmaktadır. ATF6'nın omurgalılarda, ATF6p ve ATF6a olmak üzere iki homoloğu vardır. Bu homologlar ER stresi ile membrandan ayrılan sitoplazmik transkripsiyon faktör alanlarına sahip tip II transmembran proteinleridir. ATF6 α transkripsiyon faktörü golgi aparatına geldiğinde, sırasıyla lümenal bölgesinin ve transmembran bağlantı noktasının kaldırıldığı S1P ve S2P (site 1 ve site 2 proteazları) tarafından işleme uğrar (Haze ve ark., 1999; Ye ve ark., 2000). XBP1 ile birlikte ATF6 α da, GRP78 gibi transkripsiyonunu aktive eder ve bu sayede ER stresini azaltıp ve hücrenin hayatta kalmasını sağlamak için koruyucu etkilerini gösterir (Shoulders ve ark., 2013). PERK ve IRE1'den farklı olarak, ATF6, ER'de proteinin yüklenmesini önlemez. Daha ziyade, ER hacmini ve protein işleme ve bozunma kapasitelerini arttırmaktadır (Adachi ve ark., 2008; Bommasamy ve ark., 2009). Bu transdüksiyon yolları, negatif geri besleme yoluyla ER stresine karşı koymak için birlikte çalışmakta, katlanmamış proteinlerin miktarını azaltmakta ve hücrenin hayatta kalmasını sağlamaktadır (Oakes ve Papa, 2015). Bu mekanizmalar başarısız olduğunda, kalıcı UPR sinyalleri kronik ER stresini indüklerken, apoptozu indüklemek için sitoplazmaya büyük miktarlarda kalsiyum salınmaktadır (Shore ve ark., 2011). UPR, CHOP, JNK'ler, proapoptotik Bcl-2 benzeri protein 11 ve kaspazların aktivasyonunun ardından apoptoz yoluyla hücre ölümüne neden olmaktadır (Hiramatsu ve ark., 2015) (Şekil 2.).



Şekil 2. ER'nin işlevi ciddi şekilde bozulduğunda, apoptozu indüklemek için büyük miktarda kalsiyum sitoplazmaya salınır. UPR ayrıca CHOP, JNK'ler, Bim ve kaspazlar aracılığıyla apoptotik sinyalleri tetikler ("Role of endoplasmic reticulum stress in depression", Mao, J. (2019). *Molecular Medicine Reports*, 20(6), 4774-4780 makalesinden izin dahilinde alınmış ve Türkçeleştirilmiştir. Telif hakkı Molecular Medicine Reports dergisine aittir, 2019).

UPR mekanizması, hücrelerin ve dokuların fizyolojik durumuna uyum sağlamak için mevcut olan duruma ve hücre tipine özgü bir şekilde koordine edilmektedir. UPR hem hayatta tutucu hem de proapoptotik yolları indüklediğinden, nöropatolojiler, kanser, diyabet, ateroskleroz ile bakteriyel ve viral enfeksiyonlar da dahil olmak üzere çok sayıda hastalığın oluşumunu etkileyebilecek ölüm kalım kararlarının merkezinde bulunur (Bi ve ark., 2005).

1.2. Endoplazmik Retikulum Stresi ve Psikiyatri

Psikiyatrik rahatsızlıkların birçoğunun patofizyolojisi tam olarak aydınlatılamamıştır. Literatür verisi incelendiğinde, bu boşluğu tamamlamak için çok sayıda araştırmalar yapılmıştır. Kronik hafif strese (KHS) maruz kalan sıçanlar veya fareler depresyon modelleri olarak yaygın bir şekilde kullanılmaktadır (Hill ve ark., 2012). Bir çalışmada, KHS'ye maruz kalan farelerdeki depresif davranışların ER stresi ile ilişkili olduğu ve altta yatan mekanizmanın yetersiz ATP sentezi ve nöronal apoptoz veya ölüme yol açan aşırı aktif oksidasyon ve ER stresi olduğu ileri sürülmüştür (Y. Liu ve ark., 2011). Bir başka çalışmaya göre ise, sıçanlarda KHS ile indüklenen depresyon tablosu, hipokampal hidrojen sülfür (H₂S) üretiminin bozulmasından kaynaklanmakta ve bu da sırasıyla GRP78, CHOP ve kaspaz-12 ekspresyonunu artırarak hipokampal ER stresine yol açmaktadır (Tan ve ark., 2015).

Yakın zamanlı yapılan çalışmalarda, kronik kısıtlama stresi (KKS) sonucunda kemirgenlerde bilişsel bozukluk ve anksiyete/depresyon benzeri davranış geliştiği gösterilmiştir. Jangra ve ark. tarafından yapılan bir çalışmaya göre, honokiol (Çin'de *Magnolia officinalis*'in kabuğundan

izole edilen geleneksel bir tedavi) farelerin hipokampüsünde GRP78 ve CHOP artışını önleyerek bilişsel bozukluğu ve depresif belirtileri ortadan kaldırmaktadır (Jangra ve ark., 2016). Ayrıca, KKS uygulanan farelerde, hipokampusta GRP78 ve CHOP seviyelerinin, prefrontal kortekste ise CHOP ekspresyon seviyelerinin, kontrol grubuyla karşılaştırıldığında arttığı bulunurken; Sodyum fenilbutirat (ER stres inhibitörü) ve edaravone (serbest radikal temizleyicisi) bu genlerin yüksek ekspresyonunu azaltmakla birlikte, bilişsel eksiklikleri ve depresif belirtileri düzeltmektedir (Jangra ve ark., 2017).

GRP78, ATF6, XBP1 ve CHOP gen ekspresyon seviyelerinin de kronik kısıtlama stresine maruz kalan sıçanların striatumunda arttığı gösterilmiştir. Bu bulgu ER stresinin depresyon gelişiminde rol aldığını göstermektedir (Pavlovsky ve ark., 2013).

Lipopolisakkarit, merkezi veya periferik uygulamadan sonra kemirgenlerde anksiyete ve depresyon benzeri davranışlara neden olan bir endotoksindir (Lawson ve ark., 2013). Sıçanlarda lipopolisakkarit uygulamasından sonra hipokampusta, GRP78 mRNA ekspresyonunun belirgin şekilde artması, UPR'nin, lipopolisakkarite bağlı gelişen davranış anomalilerinde rol oynadığını düşündürmektedir (Jangra ve ark., 2016). Sosyal yenilgi stresine duyarlı farelerde, amigdala GRP78, CHOP ve kolin asetiltransferaz ekspresyonunda önemli bir artış ile ilişkili olarak depresyon benzeri davranışlar görülmektedir (Huang ve ark., 2013). Liu ve arkadaşları, sosyal yenilgi stresinden sonra farelerin hipokampüsünde GRP78 ve XBP1 ekspresyonunun önemli ölçüde arttığını bulmuşlardır (Liu ve ark., 2019). Ayrıca, kronik sosyal yenilgi stresi, hipokampustaki PERK-eIF2 α sinyal yolunu aktive ederek ve BDNF ekspresyon seviyelerini azaltarak farelerde depresyon benzeri davranışlara ve bellek bozukluğuna yol açabilir (Li ve ark., 2019).

Sharma ve arkadaşları, hipokampusta PERK ekspresyonunun inhibe edilmesinin, farelerde hipokampal bağımlı belleği güçlendirdiğini ve ters/geri döndürülebilir bellek bozulmasını geri çevirebildiğini göstermiştir (Sharma ve ark., 2018). Bu bulgu, hipokampusun Cornu Ammon 1 bölgesindeki PERK ekspresyon seviyelerini düzenleyerek bilişsel işlevlerin iyileştirilebileceğini düşündürmektedir. Ek olarak, kortikosteronun plazma seviyeleri ile GRP78, GRP94, ATF6, XBP1, ATF4 ve CHOP'u kodlayan genlerin ekspresyonunun, öğrenilmiş çaresizliğe sahip olan sıçanların hipokampüsünde arttığı ve dolayısıyla depresyon tablosunun aşırı dirençli ER stresi ile ilişkili olabileceğini düşünülmektedir (Timberlake ve Dwivedi, 2016).

Endoplazmik retikulum stresinin ruhsal hastalıklardaki yeri bazı insan çalışmalarında da araştırılmıştır. Behnke ve arkadaşları, insanlarda ER stresinin depresyonun patofizyolojisi üzerindeki etkisini araştırmak için psikiyatrik rahatsızlığı olan hastaların postmortem beyin dokularında GRP78, GRP94 ve kalretikülinin ekspresyon düzeylerini ölçmüşlerdir. İntihar nedeniyle ölen MDB'li hastaların temporal kortekslerinde, intihar dışı ölümleri olan MDB hastalarına veya diğer gruplara göre GRP78, GRP94 ve kalretikülinin seviyelerinin daha fazla olduğu bulunmuştur (Behnke ve ark., 2016).

Başka bir çalışmada ise, intihar nedeniyle yaşamını yitiren bipolar bozukluk veya şizofreni hastalarının bazılarında, bu proteinlerin ekspresyon seviyelerinde bir farklılık saptanmamıştır (Bown ve ark., 2000) Ayrıca, reaktif oksijen türevlerinin üretildiği ve oksidatif stresin merkezi

bir mekanizması olan ksantin oksidaz aktivitesinin, rekürren depresyonu olan hastaların temporal lob dokusunda arttığı gösterilmiştir (Harrison, 2002; Michel ve ark., 2010).

Ek olarak, GRP78, EDEM1, CHOP ve XBP1'in ekspresyon seviyelerinin analiz edildiği bir çalışmada, MDB'li hastalarda kontrol grubuna göre GRP78, EDEM1, CHOP ve XBP1 düzeyleri anlamlı olarak daha yüksek saptanmıştır (Nevell ve ark., 2014)

Bipolar Bozuklukta gözlenen hücresel işlev bozukluklarının altında yatan mekanizmalarda ER stresinin yeri tam olarak aydınlatılamamıştır. Çoğu çalışmada, bipolar bozukluklu bireylerden elde edilen hücre kültürlerinde, ER stresini indükleyen ajanlara karşı bozulmuş bir yanıt gösterilmiştir. Bipolar bozuklukta özellikle CHOP ifadesi ve XBP1 uçbirleştirmesinin, ER stresinin indüklenmesinden sonra bozulmuş olduğu görülmüştür (Hayashi ve ark., 2009; Pfaffenseller ve ark., 2014; Rieger ve ark., 2015). Bipolar bozukluk hastalarının B-lenfositlerinde yapılan ufuk açıcı bir çalışmada, So ve arkadaşları Thapsigargin ve tunikamisin indüklemesiyle XBP1 ve CHOP genlerinin ekspresyonunun azaldığını bildirmiştir (So ve ark., 2007).

Farklı bir çalışmada, sağlıklı kontroller, lityuma cevap veren hastalar ve lityuma yanıt vermeyen hastalarda periferik lökositlerdeki RNA dizileri incelenmiştir. Yapılan gen analizi sonucunda, Bipolar bozuklukta lityuma klinik cevabın ER stresini düzenleyen bir gen ağı tarafından modüle edildiği gösterilmiştir (Breen ve ark., 2016). Bu bulgular, Bipolar bozuklukta hücrelerin ER stresine karşı kompensatuar mekanizmalarının yetersiz kaldığını ve dolayısıyla stresli koşullar altında hayatta kalmalarını sınırladığını göstermektedir (Kakiuchi ve ark., 2009).

XBP1 (X-box bağlayıcı protein) geninde -116C/G polimorfizminin ilişkisi, daha önce ilaç kullanmamış şizofreni hastalarında gözlenmiştir (Kakiuchi ve ark., 2004). Ek olarak, serebellumdaki azalmış HSP70 seviyelerinin şizofrenideki bilişsel işlev bozukluğa neden olması muhtemeldir (Leonidas, 2012).

SONUÇ VE ÖNERİLER

Günümüzde çoğu psikiyatrik hastalığın etyolojisi yeteri kadar anlaşılabilmemiştir. Yukarıda tartışılan veriler, endoplazmik retikulum stresinin ruhsal rahatsızlıkların gelişiminde önemli bir yeri olabileceğini göstermektedir. Gelecekte bu mekanizmanın işleyişinin tam olarak aydınlatılması için çalışmalara ihtiyaç duyulmakla beraber, yeni ve etkin tedavi seçeneklerinin geliştirilmesi için umut vaat etmektedir.

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Nöropsikiyatrik Bir Tablo: Deliryöz Mani Olgu Sunumu

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ÖZ

Bilinç bulanıklığı, oryantasyonda bozulma, gün içerisinde dalgalı seyir gibi deliryum belirtileri, mani, katatoni ve/veya psikoz semptomları ile birlikte görüldüğünde deliryöz mani akla gelmelidir. Deliryöz maninin klinik prezantasyonu saatler ve günler içerisinde başlayıp hızlı progresyon gösterir. Burada 65 yaş kadın hastanın geçirmiş olduğu subakut-kronik dönem serebrovasküler olay sonrası konfüzyon ve oryantasyon bozukluğu nedeniyle nöroloji servisinde tetkik edilirken mani belirtilerinin ortaya çıkışı ve tedavi süreci ele alınmaktadır. Nöroloji ve psikiyatri branşlarının işbirliği ile deliryöz mani tanısı koyulan hastaya birkaç saat içerisinde EKT uygulanmış ve ilk EKT'den itibaren dramatik yanıt gözlenmiştir. Daha önce bipolar bozukluk öyküsü olmayan hastaya EKT sonlandırıldıktan sonra duygudurum düzenleyici olarak valproik asit başlanmıştır. Hasta halen bipolar bozukluk yönünden remisyonda olup düzenli olarak takip ve tedavisine devam etmektedir. Nadir görülen deliryöz mani tablosu nöropsikiyatrik bir tablo olup, tedavi edilmediğinde ölümcül olabileceğinden klinisyenlerin bu konuda dikkatli olmaları gerekmektedir.

Anahtar Kelimeler: Deliryöz Mani, Serebrovasküler Olay, Katatoni, Psikoz, Deliryum, Mani

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A Neuropsychiatric Manifestation: A Case Report of Delirious Mania

ABSTRACT

Delirious mania should be considered when symptoms of delirium such as blurred consciousness, disorientation, and fluctuating course during the day are accompanied by symptoms of mania, catatonia, and/or psychosis. The clinical presentation of delirious mania begins within hours and days and progresses rapidly. Here, the appearance of mania symptoms and the treatment process of a 65-year-old female patient while being examined in the neurology service due to confusion and disorientation after a subacute-chronic period cerebrovascular accident are discussed. With the cooperation of neurology and psychiatry branches, ECT was applied to the patient who was diagnosed with delirious mania within a few hours, and a dramatic response was observed from the first ECT. After ECT was terminated, valproic acid was started as a mood stabilizer in the patient who had no history of bipolar disorder before. The patient is still in remission in terms of bipolar disorder and continues to be followed up and treated regularly. Clinicians should be careful in this regard, as delirious mania, which is rare, is a neuropsychiatric condition and can be fatal if left untreated.

Keywords: Delirious Mania, Cerebrovascular Event, Catatonia, Psychosis, Delirium, Mania

Sorumlu Yazar:

Zakire Kübra AKSOY

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GİRİŞ

Deliryöz mani, akut başlangıçlı, deliryum, mani ve psikoz semptomları ile karakterize, tedavi edilmediği takdirde ölümcül olabilen nöropsikiyatrik bir sendromdur (Detweiler ve ark., 2009; Fink, 1999; Melo ve Serra, 2020). Patofizyolojisi tam olarak bilinmemesi nedeniyle bu klinik tablo herhangi bir sınıflandırma sistemi içerisinde yer almamaktadır (Can ve ark., 2015). Bu durum tanı koyulmasını güçleştirmektedir. Deliryöz maninin klinik prezantasyonu saatler ve günler içerisinde başlayıp hızlı progresyon gösterir. Klinik olarak deliryum tablosunda görülen oryantasyonda bozulma, bilinçte dalgalanma, bilişsel fonksiyonlarda bozulma ve manide görülen grandiyözite, irritabilite, uyku ihtiyacında azalma, konuşmada artış, dezorganize konuşma, psikomotor aktivite artışı, dezorganize düşünce, fikir uçuşmaları, cinsel istekte artış gibi semptomlar birlikte görülür. Katatoni ve psikoz semptomları da sıklıkla eşlik eder (Jacobowski, 2013). Nadir olduğu düşünülse de son raporlar deliryöz maninin tüm akut mani vakalarının %15'ini oluşturabileceğini öne sürülmektedir (Jacobowski ve ark., 2013).

Her ne kadar deliryöz mani için belirlenmiş bir tedavi kılavuzu bulunmamaktaysa da Karmacharya ve arkadaşlarının 2007 yılında 16 hasta ile yaptıkları bir çalışmada hastalara uygulanan elektrokonvülsif tedavi (EKT), tipik ve atipik antipsikotik ve benzodiyazepin tedavileri karşılaştırdıklarında, en etkin tedavi yönteminin EKT olduğunu göstermişlerdir (Arsan ve ark., 2021; Karmacharya ve ark., 2008). EKT'nin yapılamadığı durumlarda yüksek doz benzodiazepinler kullanılması önerilmektedir (Karmacharya ve ark., 2008).

Bu olguda nöroloji servisinde iken deliryöz mani tablosu gelişen bir hastanın tanı ve tedavi süreci sunulmuştur. Nadir görülen, tanı koyulmasında güçlük yaşanan ve ölümcül olabilen bir durum olduğundan klinik önemine dikkat çekmek amaçlanmıştır.

OLGU

65 yaşında kadın hasta, ilkökul mezunu, ev hanımı nöroloji kliniğinde yatmakta iken ajitasyon ve agresyon nedeniyle psikiyatriden konsültasyon istendi. Bir ay önce aort kapak replasmanı ve by-pass operasyonu yapılan, 20 gün önce taburcu olan hastanın 20 gündür uykusunda bozulma olduğu öğrenildi. Hastanın acil servise başvurusundan 1 hafta önce başlayan çok konuşma, sürekli eskilerden bahsetme, uyku ihtiyacında azalma (gece 2-3 saat), yemek yememe şikayetlerinin olduğu bildirildi. Hastanın “ben öldüm, dilim küçüldü, gözüm görmüyor, cennette geziyorum, çocuğum vardı, göturdüler, sesi geliyor, ben bilirim, benim söylediklerimi yapacaksınız, ben sizin babanız yerineyim” şeklinde garip söylemlerinin olduğu ifade edildi. Yakınları ilaç vermeye çalıştığında “beni zehirleyeceksiniz, öldüreceksiniz” diyerek ilaçlarını almadığı, son birkaç gündür ise konuşmasında azalma olmakla birlikte sadece “Allah Allah” şeklinde tekrarlamalarının olduğu öğrenildi. Hastanın bilincinde dalgalanma, konuşmasında azalma, uykuya meyil, bulantı kusma şikayetleri olması üzerine yakınları tarafından acil servise müracaat ettiği anlaşıldı. Acil serviste difüzyon manyetik rezonans görüntüleme ve beyin bilgisayarlı tomografinin çekildiği, difüzyon manyetik rezonans görüntüleme de sol parietal lob posterior superiorda kortekste subkortikal alanı etkileyen difüzyon kısıtlanması göstermeyen lezyonların olduğu ve akut ödem enfarkt ile uyumlu olabileceği tespit edildi. Beyin bilgisayarlı tomografi de ise “Akut intrakranial kanama izlenmediği” rapor edildi. Ardından hastanın nöroloji konsültasyonunda yapılan muayenesinde bilincinin konfüze olduğu, konuşma hızı ve miktarı azalmış olduğu, kooperasyonun minimal kısıtlı olması dışında patolojik bulgu

saptanmadığı şeklinde tamamlandığı öğrenildi. Hastada subakut-kronik dönem infarkt düşünülerek iskemik serebrovasküler olay ön tanısıyla ileri tetkik ve tedavi amacıyla nöroloji servisine yatırılıp yapıldığı bilgisine ulaşıldı. O esnada yapılan kan tetkiklerinde trigliserit ve LDL yüksekliği ve HDL düşüklüğü dışında patolojik bulgu saptanmamıştı. Kontrastlı kranial manyetik rezonans görüntüleme yapıldığında, “Sol paryetal lob posterior korteksi ve subkortikal beyaz cevheri etkileyen, kontrast tutmayan infarkt alanı görülmektedir. Sol frontalde milimetrik boyutta birkaç adet infarkt alanı mevcuttur” şeklinde yorumlandığı anlaşıldı. Hasta iskemik serobrovaküler olay etyolojisi açısından kardiyo-lojiye danışıldığında ise iskemik serobrovaküler olay açısından kardiyak etyoloji saptanmadığı öğrenildi. Kranial beyin anjiografisinde ve boyun bölgesi arterlerine yönelik anjiografide boyun ve sol karotis bifurkasyonunda %70-80 darlık saptanmıştı. Hastaya girişimsel nöroradyoloji tarafından taburculuk sonrası operasyon planlanmış, dahiliye tarafından hiperlipidemi nedeniyle diyet ve atorvastatin ile kontrol önerilmişti.

Yatışının üçüncü gününde, 00.30 saatlerinde anlamsız bir şekilde bağırıp çağırma, pencereden atlamak isteme, saldırganlık olması üzerine hastaya aralıklı olarak 2 ampul diazepam intravenöz, yarım ampul haloperidol intramusküler, lorazepam 2.5 mg sublingual verilmiş olmasına rağmen hastanın ajitasyon ve eksitasyonunda azalma olmaması nedeniyle psikiyatri konsültasyonu istendi. Yapılan ruhsal durum muayenesinde, genel görünümü düşküdü, bilinç konfüzeydi, oryantasyon yer ve zaman ekseninde bozulmuştu. Yeterli kooperasyon kurulamamaktaydı. Duygulanım disforikti. Konuşma anlamsızdı, ara ara bağırma eşlik ediyordu. Davranışta psikomotor eksitasyon hali vardı. Öne arkaya sallanma şeklinde stereotipi mevcuttu. Görsel halüsinasyon ve grandiyöz hezeyan tariflendi. Uyku ihtiyacında azalma mevcuttu. Hastada ön planda deliryöz mani düşünöldü. İvedi bir şekilde elektrokonvülsif tedavi hazırlığı yapıldı, 4 saat içerisinde EKT yapıldı. Etkin bir şekilde nöbet (132 mc ile 48 saniye) geçiren hastanın ilk EKT sonrası yapılan ruhsal durum muayenesinde bilinç açık, oryante ve koopereydi. Duygulanım ötimikti. Konuşma hızı ve miktarı olağandı. Hezeyan tariflenmedi. Algıda patoloji saptanmadı. Davranış normoaktifti. Uyku ritmi ve iştah normale dönmüştü. Gün aşırı iki seans daha EKT yapılan hastanın remisyonda olduğuna kanaat getirilerek EKT sonlandırıldı. İdame tedavisi olarak valproik asit 500 mg 1*1 başlandı. Hasta klinik tam iyilik hali ile taburcu edilmiş olup takip ve tedavisi psikiyatri ve nöroloji kliniklerinde devam etmektedir. Psikiyatri kliniğine ayda bir olmak üzere iki kez gelmiş olup iki aylık süreçte remisyonadadır.

TARTIŞMA VE SONUÇ

Olgumuz bilinç bulanıklığı, oryantasyon bozukluğu nedeniyle tetkik edilmekte iken hastada mani semptomlarından konuşmada artış, uyku ihtiyacında azalma, grandiyözite, distraktabilite, irritabilite, psikotik semptomlardan perseküsyon, nihilistik hezeyanlar, görsel ve işitsel halüsinasyonlar ve katatonik belirtilerden stereotipi, psikomotor eksitasyon, negativizm ortaya çıktı. Deliryum, geç başlangıçlı bipolar bozukluk, kısa psikotik atak ayırıcı tanıda yer aldı. Deliryuma eşlik eden mani, psikoz ve katatoni belirtilerinin aynı tabloda yer alması nedeniyle ön planda deliryöz mani düşünöldü. Tipik antipsikotiklerle ajitasyonun yatışmaması, benzodiazepinlere yanıtız ve oldukça gürültülü bir tablo oluşu nedeniyle birinci basamak tedavi olarak EKT yapıldı. İlk EKT’den itibaren itibaren deliryöz mani tablosunun düzelmesi, 3 seans EKT sonrası tam remisyona girmesi tanıyı destekler nitelikteydi.

Pompey ve Januel katatoni için, deliryöz maniye de içecek olan beş aşamalı bir tedavi protokolü önermektedir: birinci aşama, semptomaya yol açtığından şüphelenilen ilaçları kesmek; ikinci aşama, altta yatan fiziksel hastalık durumlarını değerlendirmek ve tedavi etmek (standart biyokimya analizi, idrar ilaç taraması, EEG, merkezi sinir sistemi görüntülemesini içerir); üçüncü aşama, 2.5 mg lorazepam denemesi; 1 saat sonra katatonik belirtileri değerlendirme; kısmi veya tam yanıt ile, 6 gün boyunca 3 mg/gün ile başlama, ardından dozu azaltma; dördüncü aşama lorazepam'a yanıt vermeyebilecek %20'lik kısım için EKT'yi uygulama; malign katatoniden şüpheleniliyorsa ve/veya otonomik instabilite varlığında doğrudan EKT uygulanması şeklindedir (Pompey ve Januel, 2002).

Deliryöz mani tedavisinde EKT kullanımının, prognozu önemli ölçüde iyileştirdiği bildirilmektedir (Lee ve ark., 2012). Deliryöz mani vakalarının çoğu EKT'ye yanıt vermiştir ve malign vakaların çoğunluğunda 2-12 EKT tedavisi tercih edilmektedir (Fink, 1999; Fox ve Bostwick, 1997; Karmacharya ve ark., 2008; Van Den Eede ve ark., 2005). Bazı araştırmacılar gün aşırı EKT'yi (Fox ve Bostwick, 1997) önerirken, diğerleri iyileşmeyi hızlandırmak için günlük EKT tedavilerini önermektedir (Fink, 1999; Fink ve Taylor, 2001).

Sonuç olarak, klinisyenler açısından deliryöz manie eşlik eden mani semptomlarının olması, psikoz ve katatoni belirtilerinin eşlik etmesi halinde deliryöz maninin akılda tutulması ve ivedilikle tedavi edilmesi, bu konuda EKT'nin mutlaka bir tedavi olarak dikkate alınması önem arz etmektedir.

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