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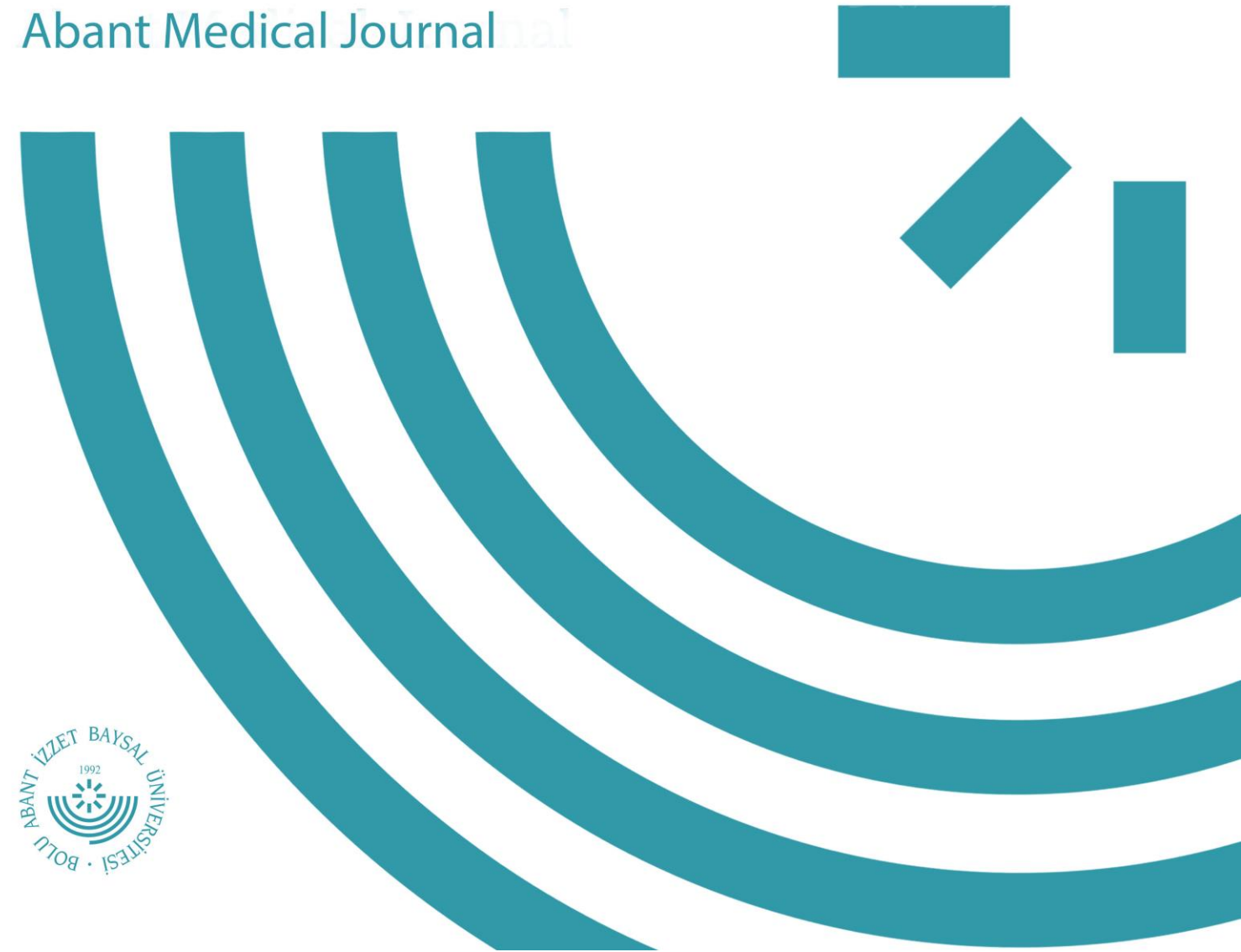

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Abant Tıp Dergisi

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The Effect of Physiotherapy on Pain, Functionality and Quality of Life Scores in Patients with Chronic Low Back Pain

Kronik Bel Ağrısı Olan Hastalarda Fizyoterapinin Ağrı, Fonksiyonellik ve Yaşam Kalitesi Puanlarına Etkisi

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Abstract

Objective: To evaluate whether physical therapy agents given in addition to medical treatment contribute to pain, functionality and quality of life in patients with chronic low back pain.

Materials and Methods: Patients diagnosed with chronic low back pain and planned for medical treatment (group 1, n: 30) and those who received physical therapy in addition to medical treatment (group 2, n: 30) were included in the study. Non steroid antienflamatuar drugs/myelexan selection and duration of use varied according to patients' comorbidities. Hot pack, transcutaneous electrical nerve stimulation and ultrasound were given as physical therapy agents. Patients were evaluated, as well as before and after treatment; Visual analogue scale, Oswestry disability index and short form 36 (SF-36) quality of life scale, lumbar range of motion, straight leg raising test (SLR) and finger-floor distance were evaluated.

Results: In both groups, a statistically significant improvement was achieved in all parameters, except the change in SLR and SF-36 general health perception score, compared to the pre-treatment period. However, SLR and SF-36 general health perception score changes improved significantly only in group 2 ($p<0.05$). More improvement was achieved in all parameters in the group with physical therapy than in the group with only medical treatment ($p<0.05$).

Conclusion: As a result, in our study; It has been shown that combined physical therapy agents added to medical treatment in chronic low back pain contribute to examination tests, general health perception and quality of life.

Keywords: Physical Therapy, Oswestry Disability Index, Short Form-36 Quality Of Life Questionnaire, Chronic Mechanical Low Back Pain.

&

Öz

Amaç: Kronik bel ağrılı hastalarda medikal tedaviye ek olarak verilen fizik tedavi ajanlarının ağrı, işlevsellik ve yaşam kalitesine katkıda bulunup bulunmadığını değerlendirmek.

Gereç ve Yöntemler: Kronik bel ağrısı tanısı almış ve ilaç tedavisi planlanan (grup 1, n:30) ve medikal tedaviye ek olarak fizik tedavi uygulanan (grup 2, n:30) hasta çalışmaya dahil edildi. Steroid olmayan antienflmatuvar ilaçlar/miyorelaksan seçimi ve kullanım süresi hastaların eşlik eden hastalıklarına göre değişiyordu. Fizik tedavi ajanları olarak sıcak paket, transkutanöz elektriksel sinir stimülasyonu ve ultrason verildi. Hastaların tedavi öncesi ve sonrası; görsel analog skala, Oswestry sakatlık indeksi, kısa form 36 (KF-36) yaşam kalitesi ölçeği, lomber eklem hareket açıklığı, düz bacak kaldırma testi (DBK) ve parmak-zemin mesafesi ile değerlendirildi.

Bulgular: Her iki grupta da DBK ve KF-36 genel sağlık algısı skorundaki değişim hariç tüm parametrelerde tedavi öncesine göre istatistiksel olarak anlamlı iyileşme sağlandı. Ancak DBK ve KF-36 genel sağlık algısı skorundaki değişimler sadece grup 2'de anlamlı olarak düzeldi ($p<0,05$). Fizik tedavi grubunda sadece medikal tedavi uygulanan gruba göre tüm parametrelerde daha fazla iyileşme sağlandı ($p<0,05$).

Sonuç: Sonuç olarak çalışmamızda; kronik bel ağrısında medikal tedaviye eklenen kombine fizik tedavi ajanlarının muayene testlerine, genel sağlık algısına ve yaşam kalitesine katkı sağladığı gösterilmiştir.

Anahtar Kelimeler: Fizik Tedavi, Oswestry Engellilik İndeksi, Kısa Form-36 Yaşam Kalitesi Anketi, Kronik Mekanik Bel Ağrısı.

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Introduction

Classically, low back pain is defined as muscle tension-stiffness between the lower costal border and the top of the inferior gluteal folds. It is one of the most common causes of pain and disability in society today. According to a study conducted in the United States, the annual treatment cost exceeds millions of dollars (1). Low back pain is classified as acute, subacute and chronic low back pain according to its duration. Acute pain is usually self-limiting and heals within 6-8 weeks. Only about 10% of these pains become chronic (2).

Chronic low back pain is difficult to manage. Medication, injection methods, physical therapy, exercise, back school and sometimes surgical methods are used in the treatment of chronic low back pain (3). In addition to medical treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants, non-pharmacological treatments such as transcutaneous electrical nerve stimulation (TENS), superficial heat and therapeutic ultrasound (US) can also be applied together (4-6).

The aim of physical therapy agents applied for chronic low back pain is to increase functionality and quality of life by providing symptomatic improvement by reducing pain, inflammation, muscular symptoms, muscle spasm and joint stiffness (7). In physiotherapy programs, superficial heating modalities (such as hot packs and infrared) and deep heating modalities (such as ultrasound, shortwave, and radar therapy), along with other physical therapy agents (such as analgesic currents), are among the most commonly used treatments. However, there are contradictions about the effectiveness of the physical therapy agents given. The contribution of single or combined use of physical therapy agents for chronic low back pain to medical treatment is still not fully known (5, 6, 8). Therefore, we aimed to determine whether combined physical therapy agents added to medical treatment contribute to pain, functionality and quality of life scores.

Materials and Methods

This study is prospective and includes a control group. Ethics committee approval was received for our study from Kayseri City Hospital Clinical Research Ethics Committee with decision number 221 dated November 21, 2020. The study was conducted in accordance with the Declaration of Helsinki criteria. Informed voluntary consent form was obtained from the participants. 102 patients who applied to our Physical Medicine and Rehabilitation Outpatient Clinic with mechanical low back pain between December 2020 and December 2021, whose complaint had been present for at least 3 months and whose treatment was planned, were examined. Demographic data of patients in both groups, before and after treatment; visual analogue scale (VAS), Oswestry disability index (ODI) and short form-36 (SF-36) quality of life scoring, lumbar range of motion (LROM), straight leg raise (SLR) and finger-floor distance (FFD)were evaluated. Data recording and examination were performed by another physical medicine and rehabilitation specialist before and after treatment (day 15).

Inclusion criteria for the study were as follows:

- Aged between 18 and 65 years
- Diagnosed with chronic mechanical low back pain, for which either medical treatment alone was planned or medical treatment combined with physical therapy was planned (patients were assigned to two treatment groups using the envelope method)
- Provided informed consent to participate in the study

Exclusion criteria for the study were as follows:

- Use of opioids, antidepressants, or antiepileptics (other than NSAIDs and myorelaxants) for medical treatment
- Non-mechanical causes of low back pain
- Contraindications to the application of physical therapy agents
- Presence of inflammatory or infectious diseases
- Advanced heart failure

- Plegia due to stroke, spinal cord injury, or traumatic brain injury
- History of malignancy
- Presence of a metal implant in the lumbar region
- Presence of a pacemaker.

The flow chart of our study is shown in Figure 1.

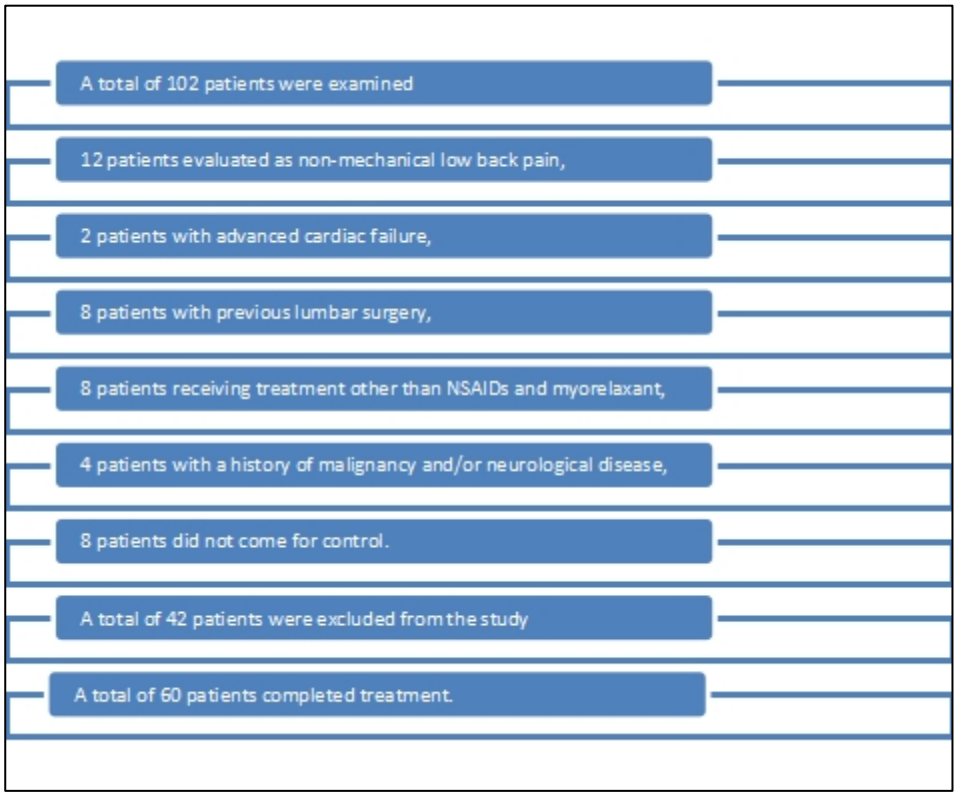


Figure 1. The flow chart of study

Patients who described chronic low back pain in their anamnesis were referred by the outpatient clinic physician. No imaging method was used to include the patients in the study. Using the envelope method, the patients were divided into two groups: Group 1, which received only medical treatment, and Group 2, which received medical treatment and physiotherapy. NSAIDs and myorelaxant were given to the group that received only medical treatment. NSAID/myelexan selection and duration of use varied according to patients' comorbidities (peptic ulcer, chronic renal failure, asthma, etc.). Physical therapy were given to the back area by physical therapy technician (hotpack 20 minutes as a superficial heater, US 1.5 watt/cm^2 8 minutes as a deep heater, TENS 100hz conventional 20 minutes). Additionally, pelvic tilt and abdominal isometric exercises were recommended for both groups (Lumbar stabilization exercises are a treatment that has been shown to be effective in chronic low back pain and were given to two groups in order not to deprive patients of this treatment during the research process) (9). A combined Chattanooga Intelect Advanced device was used for US and TENS in physical therapy.

TENS: TENS is applied transcutaneously using electrodes as an analgesic current. The electric current is gradually increased until the patient feels tingling. The application time is 15-30 minutes. The therapist follows the patient during the application. The intensity can be gradually increased. Patients with sensory deficits such as diabetes mellitus and neuropathy should be careful to avoid burns (10). In this study, conventional TENS was used as the TENS type. The application time was 20 minutes for each patient.

Hot packs: These promote muscle relaxation through vasodilation. It is wrapped in a towel before being placed on the affected area. They are typically reusable, moldable gel bags (11).

US treatment: The patient is placed in the prone position. Conductive gel is applied to the lumbosacral region after skin cleansing. US waves are transmitted to the lumbar region through the probe. US intensity (watt/cm2) is adjusted according to the patient's weight, additional disease and desired effect. It can be applied continuously or intermittently. While continuous use provides deep warming, the mechanical effects of intermittent US are utilized Application time is 6-10 minutes. The US probe is not applied fixedly to a certain point. The therapist should move the probe circularly during the application period (12). In this study, ultrasound intensity was applied as 1.5watt/cm², 8 minutes for each patient.

Visual analog scale (VAS): It is used to assess the severity of pain. The patient is asked to rate the pain on a scale of 0-10 or to select a scale of 0-10 on a marked paper. A score of 0 indicates no pain and a score of 10 indicates severe pain that can be felt (13).

Oswestry disability index (ODI): It is used to assess functional level. Turkish validity and reliability have been established (14). It is an index consisting of 10 items questioning function such as self-care, walking, sitting, traveling, etc., with each item scored between 0-5. The total score ranges from 0-100. 0-20 points indicate minimal, 20-40 points moderate, 40-60 points severe impairment. A score of 80-100 points corresponds to a bed-dependent level (15).

Short form-36 (SF-36) quality of life questionnaire: It is a form that evaluates quality of life. Turkish validity and reliability were performed by Demiral et al (16). It is a test consisting of 36 items that questions the quality of life in the last month. It has 8 subgroups (life energy, physical pain, physical functioning, mental health, social functioning, role inhibition due to emotional problems, role inhibition due to physical problems and general health) (17).

Straight leg raising (SLR): The patient is placed on his/her back. while the patient's knee is in extension, the leg is slowly flexed at the hip joint. If the patient feels pain in the back of the leg when the hip joint is flexed between 30-70 degrees, the test is positive. Although the SLR test is a guiding test for radiculopathy, it may give positive results in lumbar paravertebral muscle spasm and posterior longitudinal ligament sprain (18).

Finger-floor distance (FFD): While the patient is standing, the knees are extended, the soles of the feet are in full contact with the floor, and the hips and trunk are flexed forward. With the arms straight, the distance between the third finger of the hand and the ground is measured (19).

Statistical Analysis:

Pre-treatment and post-treatment values and intra-group changes were compared in both groups to evaluate whether physical therapy agents contributed to pain, functionality and quality of life. The suitability of the data for normal distribution was evaluated with histogram, q-q graphs and Shapiro-Wilk test. Homogeneity of variance was tested with the Levene test. In comparing clinical variables between treatment groups, the Pearson chi-square test was used for qualitative data and the Mann-Whitney U test was used for quantitative variables. To compare clinical variables before and after treatment, the McNemar-Bowker test was used for qualitative data and the Wilcoxon test was used for quantitative variables. The analysis of the data was evaluated using TURCOSA (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr) statistical software. $p<0.05$ level was considered significant. It could not be evaluated by power analysis before the study. However, in the post-power analysis, the change in VAS, ODI, FFD and SF-36 scores was found to be significant in the power analysis. In our study, the number of patients we included in the physical therapy and medical treatment groups was considered sufficient. Since there were differences between the two groups in some of the initial data, we compared the improvement after treatment compared to before treatment by calculating the difference.

Results

The mean age of the patients participating in the study was 41.43±11.52, and 48.3% of the patients were female and 51.7% were male. There was no significant difference in age, gender, body mass index, education level,

employment status, income level, smoking, physical activity duration (week/minute) and symptom duration (week/minute) in both groups (p>0.05) (Table 1).

Table 1.
Distributions of demographic data of patients in group 1 and group 2

Variable		Treatment groups			p value
		Group 1	Group 2	Total (n:60)	
Age (year)		42.53±12.91	40.33±10.03	41.43±11.52	0.464
Gender	**female**	14 (%46.79)	15 (%50)	29 (%48.3)	0.796
	male	16 (%53.3)	15 (%50)	31 (51.7)	
Body mass index (kg/m2)		27.23±4.47	26.76±5.31	26.99±4.87	0.713
Smoking (users)		4 (%13.3)	9 (%30)	13 (%21.7)	0.117
Physical activity duration (minute/week)		90 (67.5-172.5)	90 (60-180)	90 (62.5-180)	0.806
Symptom duration (month)		9 (7-24)	10.5 (6-24)	9 (6-24)	0.806

Group 1: Medical Treatment (n:30), Group 2: Physiotherapy (n:30), n: number of people

In both groups, statistically significant improvement was found in VAS, FFD, ODI, SF-36 sub-parameters (Physical Function Score, Physical Role Difficulty Score, Emotional Role Difficulty Score, Energy/Vitality Score, Mental Health Score, Social Functioning Score, Pain Score) compared to pre-treatment (p<0.001). Only SLR and SF-36 general health perception score score showed no statistically significant change (p>0.05) (Table 2, Table 3).

Table 2.
Analysis of changes in intra-group and inter-group evaluation parameters

Variable		Time of measurements		
		Before Treatment	Post Treatment	P value
Straight Leg Raise Test (Positive)	**Group 1**	13(43.3)	12(44.4)	0.999
	Group 2	20(66.7)	13(43.3)	**0.016**
Hand-finger-floor distance	**Group 1**	25.0(15.0-30.0)	15.0(10.0-20.0)	**<0.001**
	Group 2	22.5(15.0-42.5)	10.0(0.0-16.25)	**<0.001**
VAS	**Group 1**	9.0(8.75-9.25)	7.0(7.0-8.0)	**<0.001**
	Group 2	9.0(8.0-10.0)	5.0(4.0-5.0)	**<0.001**
ODI	**Group 1**	57.0(51.0-60.0)	46.0(37.5-52.0)	**<0.001**
	Group 2	56.0(44.0-64.5)	28.0(23.0-34.0)	**<0.001**

Group 1: Medical Treatment (n:30), Group 2: Physiotherapy (n:30), n: number of people, VAS: Visual analog scale, ODI: Oswestry disability index, p value indicates the significance level for comparison before and after treatment. Data are expressed as median (1st - 3rd quartile) or n (%). Statistically significant results are indicated in bold.

Table 3.
Analysis of changes in intra-group and inter-group SF-36 subparameter.

Variable		Time of measurements		P Value
		Before Treatment	Post Treatment	
SF-36 Physical Function Score	**Group 1**	42.5(38.75-57.5)	67.5(58.75-75.0)	**<0.001**
	Group 2	45.0(30.0-65.0)	80.0(70.0-85.0)	**<0.001**
SF-36 Physical Role Difficulty Score	**Group 1**	0.0(0.0-0.0)	50.0(25.0-50.0)	**<0.001**
	Group 2	0.0(0.0-62.5)	75.0(50.0-100.0)	**<0.001**
SF-36 Emotional Role Difficulty Score	**Group 1**	0.0(0.0-8.25)	33.0(33.0-44.25)	**<0.001**
	Group 2	0.0(0.0-62.5)	66.0(33.0-100.0)	**<0.001**
SF-36 Energy/Vitality Score	**Group 1**	40.0(35.0-50.0)	50.0(48.75-55.0)	**<0.001**
	Group 2	30.0(25.0-50.0)	60.0(50.0-61.25)	**<0.001**
SF-36 Mental Health Score	**Group 1**	44.0(36.0-52.0)	52.0(48.0-64.0)	**<0.001**
	Group 2	34.0(23.0-52.0)	66.0(55.0-72.0)	**<0.001**
SF-36 Social Functioning Score	**Group 1**	37.0(25.7-50.0)	50.0(50.0-50.0)	**<0.001**
	Group 2	37.0(25.0-50.0)	62.0(50.0-65.25)	**<0.001**
SF-36 Pain Score	**Group 1**	32.0(30.75-45.0)	45.0(45.0-55.0)	**<0.001**
	Group 2	22.0(22.0-45.0)	65.0(52.5-67.0)	**<0.001**
SF-36 General Health Perception Score	**Group 1**	65.0(25.0-65.0)	65.0(25.0-65.0)	0.798
	Group 2	45.0(23.75-65.0)	52.5(30.0-70.0)	**<0.001**

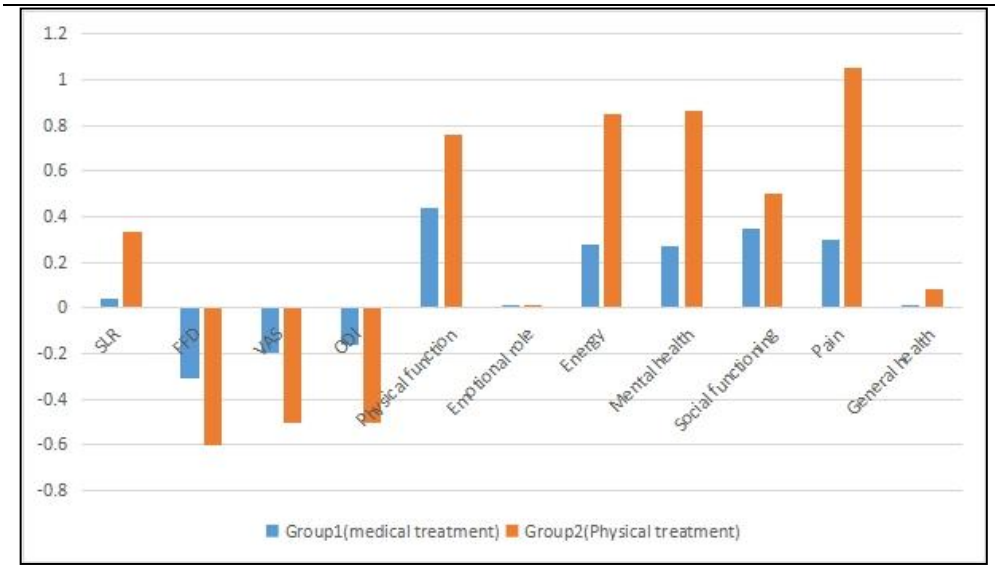
Group 1: Medical Treatment (n:30), Group 2: Physiotherapy (n:30), n: number of people, p value: indicates the significance level for comparison between treatment groups, p value indicates the significance level for comparison before and after treatment. Data are expressed as median (1st - 3rd quartile) or n (%), SF-36: Short form 36

Since there were differences between the two groups in some of the initial data, we compared the improvement after treatment compared to before treatment by calculating the difference. According to the difference analysis, greater improvements across all parameters were observed in the group receiving physical therapy compared to the group receiving only medical treatment (Table 4). Comparison of response to treatment with baseline measurements is presented in graph 1.

Table 4.
Analysis of Differences

Variable of Differences	Treatment Groups		P value
	Group 1	Group 2	
HFFD	-0.31(-0.50-(-0.17))	-0.60(-1.00-(-0.43))	**<0.001**
VAS	-0.20(-0.26-(-0.11))	-0.50(-0.55-(-0.44))	**<0.001**
ODI	-0.16(-0.23-(-0.11))	-0.50(-0.55-(-0.40))	**<0.001**
SF-36 Physical Function Score	0.44(0.19-0.67)	0.76(0.28-1.23)	**0.018**
SF-36 Physical Role Difficulty Score	0.00(-0.38-2.25)	0.00(0.00-0.00)	0.835
SF-36 Emotional Role Difficulty Score	0.00(0.00-2.03)	0.00(0.00-0.00)	0.359
SF-36 Energy/Vitality Score	0.28(0.08-0.50)	0.85(0.33-1.20)	**0.001**
SF-36 Mental Health Score	0.27(0.15-0.50)	0.86(0.30-1.89)	**0.001**
SF-36 Social Functioning Score	0.35(0.00-0.53)	0.50(0.35-1.01)	**0.010**
SF-36 Pain Score	0.30(0.00-0.68)	1.05(0.42-1.68)	**<0.001**
SF-36 General Health Perception Score	0.00(0.00-0.00)	0.08(0.00-0.21)	**<0.001**

Group 1: Medical Treatment (n:30), Group 2: Physiotherapy (n:30), n: number of people, VAS: visual analog scale, ODI: Oswestry disability index, HFFD: Hand-finger-floor distance, SF-36: short form 36, p value : indicates the significance level for comparison between treatment groups, p value indicates the significance level for comparison before and after treatment.



Graphic 1. Score compared to baseline measurements

SLR: Straight leg raising, FFD: Hand-Finger-floor distance, VAS: Visual analog scale, ODI: Oswestry disability index

Discussion

It has been shown that medical treatment and physical therapy agents provide significant improvement in pain and functional status in chronic low back pain. Since there was a difference between the two groups in some initial data, the difference between the two groups was calculated according to the calculation of the difference before and after treatment: significant improvement was achieved in all parameters except SLR and SF-36 general health perception score in both groups. More improvement was achieved in all parameters in the group where physical therapy was added. However, SLR and SF-36 general health perception score changes improved significantly only in group 2. In addition, this study showed for the first time that the change in SLR and SF-36 general health perception score improved significantly with the contribution of physical therapy agents, independent of medical treatment.

Physical therapy agents have long been used to treat chronic low back pain. These agents reduce chronic pain, inflammation, or tissue stiffness. It increases movement and recovery through vasodilation and neurostimulation. However, the effects of these agents are still debated (18). In addition, not only hot pack, TENS and US, but also interference, laser, extracorporeal shock wave therapy... many other physical therapy agents can be used in chronic low back pain (21). The application method, duration and dosage of physical therapy agents depend on the doctor's preference. For this reason, in our study, we included patients who received the same physical therapy agents for the same period of time. Although the role of physical therapy agents in reducing pain has been investigated in many studies (22); we came across a study that compared combined physical therapy agents in addition to medical treatment similar to ours. In this study, exercise therapy and paracetamol when necessary were applied to the control group, and combined physical therapy agents (hot pack, TENS, US) were applied to the study group in addition to these. The patients were evaluated using VAS, Oswestry Disability Index and Istanbul Low Back Pain Disability Index. Similar to our study, although there were statistically significant improvements in both groups, statistically significant greater improvements were found in the group that added combined physical therapy (23).

In addition, in our study, significant improvement was achieved in all parameters except SLR and SF-36 general health perception score in both groups. However, SLR and SF-36 general health perception score changes improved significantly only in group 2. This situation may be due to the fact that superficial and deep heating added to the medial treatment provided more effective relaxatıon of muscle spasm. The application of additional physical therapy agents to the patients in group 2, unlike group 1, may have increased patient satisfaction and caused a significant change in the SF-36 general health perception score.

Superficial heat applications such as hot packs accelerate tissue healing by reducing collagen elasticity and reducing muscle spasm through vasodilation, thus increasing the pain threshold (24). Despite studies reporting that TENS reduces pain intensity, improves disability, and reduces medication consumption in patients with chronic nonspecific low back pain (25); there are also studies showing that it does not reduce pain scores. In addition to studies showing that US added to the exercise program significantly improves function, lumbar joint range of motion and endurance (26); There are also studies indicating that the effectiveness of therapeutic US added to exercise is uncertain (5, 6).

In most studies, physical therapy agents were used as monotherapy +/- exercise. Evidence for physical therapy agents as monotherapy in chronic low back pain is insufficient in systematic reviews and meta-analyses (27, 28). Studies on the combined use of physical therapy agents are limited. The combined use of physical therapy agents in chronic low back pain has been shown in a limited number of studies to be more effective in controlling pain, joint range of motion and other symptoms than monotherapy (29, 30). In our study, consistent with these studies, further improvement was achieved in all parameters we measured with combined physical therapy agents added to medical treatment.

Chronic low back pain is often progressive and due to its resistant nature, has a poor prognosis and response to treatment. Apart from the NSAIDs and Myorelexans that we frequently use, long-term use of antiepileptics and antidepressants may be required in resistant cases (4). Studies have reported that despite the beneficial effects of medical treatments in chronic low back pain, caution should be exercised in long-term use due to their systemic side effects (31, 32). In our study, improvements were detected in VAS, ODI, LROM and FFD in the group that received only medical treatment. These improvements were greater in the group that received

combined physical therapy in addition to medical treatment. Therefore, combining medical treatments with physical therapy agents can not only improve general health perception but also prevent chronic drug use.

The strength of our study is the physicians who gave the treatments and the physicians who evaluated them before entering the treatment and those who evaluated them after leaving the treatment were different. Both groups were given medical treatment and exercise therapy. Unlike other studies, the effect of combined use of physical therapy agents rather than single use was examined. Unlike comparing two physical therapy agents that we frequently observe in the literature; physical therapy agents were compared with the group receiving medial therapy.

Our study had some limitations. First, we evaluated our patients before and after treatment. A longer follow-up period is needed to understand the effects of physical therapy in the future. Secondly, the number of patients in the groups could have been larger to sample the universe. Thirdly, while the same treatment was given to the patients in the physical therapy group; The medical treatments chosen between and within the groups may differ in both groups.

Conclusion

As a result, in our study; It has been shown that combined physical therapy agents added to medical treatment contribute to both the specific tests affected by chronic low back pain and the general health perception and quality of life. However, more research, especially systematic review and meta-analysis, is needed to more clearly evaluate the effectiveness of the combined use of physical therapy agents.

Ethics Committee Approval: The study was approved by the Kayseri City Hospital Clinical Research Ethics Committee (date: 21.11.2020 and decision number: 221).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

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The Long-Term Clinical Experience on PRES of A Tertiary Pediatric Neurology Center in Türkiye

Türkiye'de Bir Üçüncü Basamak Pediatrik Nöroloji Merkezinin PRES ile İlgili Uzun Dönem Klinik Deneyimi

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Abstract

Objective: This study evaluates the clinical and radiological characteristics, treatment approaches, and outcomes of pediatric patients diagnosed with Posterior Reversible Encephalopathy Syndrome (PRES) in a pediatric intensive care unit and hematology service.

Materials and Methods: A retrospective analysis was conducted on 32 pediatric patients diagnosed with PRES between 2015 and 2023. Patients were followed up for at least two years. Demographic data, clinical features, and radiological findings were collected. EEGs were performed during the acute period and in follow-ups longer than three months. MRIs were evaluated by a multidisciplinary team. Vital signs were closely monitored, and blood pressure and intracranial pressure were managed.

Results: Of the 32 patients, 9 were female (28%) and 23 were male (72%), aged between 26-214 months. The majority had undergone bone marrow transplantation (BMT), with 81% developing PRES post-transplant. Seizures were the most common symptom, occurring in 94% of cases. Antiseizure medication (ASM) such as levetiracetam and clonazepam were used for seizure management. MRIs showed T2-weighted hyperintense lesions in all patients. The primary underlying conditions included acute lymphoblastic leukemia (ALL), chronic renal failure (CRF), and thalassemia major. Hypertension was present in all patients.

Conclusion: The study highlights the high incidence of PRES in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and underscores the importance of early recognition and management of modifiable risk factors, particularly hypertension. Appropriate and timely intervention can significantly improve long-term outcomes for affected individuals. Further research is necessary to explore the pathophysiological mechanisms and optimize treatment strategies for PRES in pediatric populations.

Keywords: PRES, Hypertension, Chemotherapy, Bone Marrow Transplantation.

&

Öz

Amaç: Bu çalışma, pediatrik yoğun bakım ünitesi ve hematoloji servisinde Posterior Reversibl Ensefalopati Sendromu (PRES) tanısı konulan pediatrik hastaların klinik ve radyolojik özelliklerini, tedavi yaklaşımlarını ve sonuçlarını değerlendirmektedir.

Gereç ve Yöntemler: 2015-2023 yılları arasında PRES tanısı konulan 32 pediatrik hasta üzerinde retrospektif bir analiz yapıldı. Hastalar en az iki yıl boyunca takip edildi. Demografik veriler, klinik özellikler ve radyolojik bulgular toplandı. Akut dönemde ve üç aydan uzun takiplerde EEG'ler yapıldı. MR'lar multidisipliner bir ekip tarafından değerlendirildi. Hayati bulgular yakından izlendi ve kan basıncı ile kafa içi basınç yönetildi.

Bulgular: 32 hastanın 9'u kız (%28) ve 23'ü erkek (%72) olup, yaşları 26-214 ay arasında değişmektedir. Çoğunluğu kemik iliği nakli (BMT) geçirmiş olup, %81'i nakil sonrası PRES geliştirmiştir. Nöbetler en yaygın semptom olup, vakaların %94'ünde görülmüştür. Nöbet yönetimi için levetirasetam ve klonazepam gibi antinöbet ilaçlar kullanılmıştır. Tüm hastaların MR görüntülemelerinde T2-ağırlıklı hiperintens lezyonlar saptanmıştır. Eşlik eden hastalıklar arasında akut lenfoblastik lösemi (ALL), kronik böbrek yetmezliği (CRF) ve talasemi major bulunmaktadır. Tüm hastalarda hipertansiyon mevcuttur.

Sonuç: Çalışma, allojenik hematopoietik kök hücre nakli (HSCT) geçiren pediatrik hastalarda PRES'in yüksek insidansını vurgulamakta ve özellikle hipertansiyon gibi değiştirilebilir risk faktörlerinin erken tanınması ve yönetiminin önemini ortaya koymaktadır. Uygun ve zamanında müdahale, etkilenen bireyler için uzun vadeli sonuçları önemli ölçüde iyileştirebilir. Pediatrik popülasyonlarda PRES'in patofizyolojik mekanizmalarını keşfetmek ve tedavi stratejilerini optimize etmek için daha fazla araştırma gereklidir.

Anahtar Kelimeler: PRES, Hipertansiyon, Kemoterapi, Kemik İliği Transplantasyonu.

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Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical-radiological entity characterized by a constellation of neurological symptoms, including headache, altered mental status, visual disturbances, and seizures. First described in 1996, PRES is associated with vasogenic edema predominantly affecting the subcortical white matter of the posterior cerebral hemispheres, particularly in the parieto-occipital regions (1, 2). While the syndrome is typically reversible with appropriate management, delays in diagnosis or treatment may lead to irreversible neurological damage or even death.

PRES it is most reported in middle-aged adults, though pediatric cases are increasingly recognized, particularly in those undergoing chemotherapy or solid organ transplantation. From an epidemiological standpoint, PRES occurs across a wide demographic spectrum, though certain populations demonstrate a higher predisposition. Individuals with chronic kidney disease, autoimmune disorders, or those receiving immunosuppressive therapy are at elevated risk (3, 4).

The diagnosis of PRES is multifactorial, relying on clinical presentation combined with neuroimaging findings. Magnetic resonance imaging (MRI), particularly fluid-attenuated inversion recovery (FLAIR) sequences, remains the gold standard for detecting the characteristic parieto-occipital white matter hyperintensities indicative of vasogenic edema (5). Although initially thought to be exclusively reversible, permanent changes such as cytotoxic edema and infarction have been observed in some cases, highlighting the necessity of timely diagnosis and intervention (6, 7).

Supportive care, including seizure management and close monitoring of neurological status, forms the backbone of acute treatment. Most patients exhibit significant clinical and radiological improvement within days to weeks following appropriate therapy, but some may develop complications such as intracerebral hemorrhage or chronic epilepsy (8).

Given the diversity of clinical presentations and underlying triggers, the identification of PRES requires a high index of suspicion in at-risk populations. Further research into the pathophysiological mechanisms underlying PRES and the long-term outcomes of affected individuals is essential to improve diagnostic accuracy and therapeutic strategies, especially patients in childhood.

Materials and Methods

Informed consent was obtained from the files of individuals included in this study. The ethics committee approval was obtained from the Human Research Ethics Committee of Akdeniz University Clinical Studies TBAEK-544 25.07.2024 and the study was planned and conducted in accordance with the Declaration of Helsinki.

The study included 32 patients who were clinically and radiologically diagnosed with PRES between 2015 and 2023, hospitalized in our pediatric intensive care unit and pediatric hematology service, and followed up for at least two years.

At least 2 (Elektroensefelography)EEGs were performed, the first EEG in the acute period and control EEG in follow-up longer than 3 months. MR imaging was performed at the time of diagnosis.

Demographic characteristics, clinical findings, electrophysiologic findings, and radiologic features were evaluated.

Vital signs were closely monitored and blood pressure and increased intracranial pressure were carefully managed in all patients. At the same time, patient heads were kept at 30-45 degrees, normal partial oxygen pressure was maintained, hypercapnia was avoided, electrolyte imbalance was corrected, seizure control was ensured and blood pressure values were kept within normal limits.

MRIs of all patients were evaluated by a pediatric neurologist, radiologist and intensive care physicians. Electroencephalogram (EEG) tests were performed using a Nihon Kohden Neurofax EEG-1200K device.

Results

Demographic and clinical characteristics of our patients are shown in Table 1. Of the 32 patients, 9 (28%) were female and 23 (72%) were male. Their ages ranged between 26-214 months.

The number of patients who underwent BMT was 21 (66%), and the number of patients who developed PRES after BMT was 17 (81%). Four patients had developed PRES before BMT. The number of patients with PRES and seizures after BMT was 15 (71%). The most common neurologic symptom was seizure, and 30 (94%) patients were consulted due to seizure, while 2 (6%) patients were consulted due to encephalopathy. Six (19%) patients had used antiepileptic drugs for less than 6 months, and 5 (83%) of these patients had no seizure recurrence. Eighteen patients used ASM for more than 6 months, and 8 (44%) of these patients had no seizure recurrence. There were 11 patients (34%) with 2 or more seizures. These 11 patients had seizures outside the acute phase. One patient needed multiple ASMs. There were 14 (44%) patients with normal EEG, 10 (31%) patients with cerebral dysfunction, and 3 (9%) patients with epileptic activity. Epileptiform activity was observed in all three patients, and it was focal. The types of seizures did not vary according to the existing clinical diagnosis.

Two patients had a pre-existing diagnosis of epilepsy before developing PRES. During follow-up, neurological sequelae were identified in only two patients: one with hearing loss (associated with chronic renal failure) and the other with polyneuropathy (associated with acute lymphoblastic leukemia). These sequelae were likely attributable to their underlying medical conditions rather than PRES itself.

Table 1.
Demographic and Clinical Characteristics of Our Cases

	n (%)
female	9 (28)
male	23 (72)
seizure	30 (94)
Case with BMT	21 (66)
PRES after BMT (Only cases with BMT)	17 (81)
Seizures in cases with PRES after BMT	15 (71)
≤6 months of ASM use	6 (19)
>6 months of ASM use	18 (56)
Number of seizures ≥2	11 (34)
ASM needs ≥2	1 (3)
EEG: no abnormalities	14 (44)
EEG: cerebral dysfunction	10 (31)
EEG: epileptic activity	3 (9)

In terms of antiepileptic drugs used, levetiracetam 21 (70%), clonazepam 6 (20%), oxcarbamazepine 3 (10%) and carbamazepine 1 (3%) were the most preferred antiepileptics. The main underlying diseases were ALL 6 (19%), AML 1 (3%), aplastic anemia 5 (16%) CRF (chronic renal failure) 8 (25%), CML 1 (3%), congenital neutropenia 1 (3%), chronic granulomatous disease 1 (3%), sickle cell anemia 2 (6%), severe combined immunodeficiency 1 (3%) and thalassemia major 6 (19%).

The highest blood pressure values measured after the development of PRES were above the 99th percentile for age in all patients (mean systolic blood pressure values: 145±19 mm Hg, mean diastolic blood pressure values: 94.1±9.9 mm Hg). Clinical presentation and etiology of the cases are shown in Table 2.

Table 2.
Clinical Presentation and Etiology of Cases

case	Age (mo*)	sex	underlying condition	clinical presentation	suspected etiology
1	78	m	aplastic anemia	seizure	chemotherapy hypertension
2	26	m	wilms tumor, CRF	seizure	hypertension
3	191	m	aplastic anemia, BMT	seizure	hypertension
4	146	m	relaps ALL	seizure	hypertension
5	144	m	ALL, BMT	seizure	hypertension
6	171	m	Thalassemia major, BMT	seizure	hypertension, GVHD
7	36	m	BMT, Renal tx	encephalopathy	hypertension
8	48	m	Aplastic anemia	seizure	hypertension
9	181	f	FSGS, RTx	seizure	hypertension
10	87	f	ALL	seizure	hypertension, chemotherapy
11	120	f	AML, BMT	seizure	hypertension, GVHD
12	120	f	congenital neutropenia	seizure	hypertension, chemotherapy
13	93	f	CRF-RTx	seizure	hypertension
14	131	f	ALL	seizure	hypertension
15	174	m	CML, BMT	seizure	hypertension, GVHD
16	211	m	Sickle cell anemia, BMT	seizure	hypertension
17	73	m	SCID, BMT	seizure	hypertension, GVHD, chemotherapy
18	70	f	Chronic granulomatous disease, BMT	seizure	hypertension, GVHD, chemotherapy
19	190	e	CRF	seizure	hypertension
20	154	m	ALL, BMT	encephalopathy	hypertension
21	134	f	ALL	seizure	hypertension
22	96	m	aplastic anemia, BMT	seizure	hypertension
23	57	m	Nefrotic syndrome	seizure	hypertension

24	106	f	thalassemia major, BMT	seizure	hypertension, GVHD
25	214	m	Sickle cell anemia, BMT	seizure	hypertension
26	142	m	aplastic anemia, BMT	seizure	hypertension
27	151	m	thalassemia major, BMT	seizure	hypertension
28	152	m	thalassemia major, BMT	seizure	hypertension, GVHD, chemotherapy
29	186	m	CRF-RTx	seizure	hypertension
30	145	m	CRF	seizure	hypertension
31	146	m	Thalassemia major, BMT	seizure	hypertension
32	95	m	Thalassemia major, BMT	seizure	hypertension

*mo: months, BMT: Bone marrow transplantation, ALL: acute lymphoblastic leukemia, CRF: chronic renal failure, RT: renal transplantation, GVHD: graft versus host disease

Imaging Findings

All patients (100%) exhibited hyperintense lesions in the parieto-occipital regions on T2-weighted and FLAIR sequences in magnetic resonance imaging (MRI). These findings were consistent with the characteristic radiological features of PRES. The distribution and intensity of the lesions reflected the typical pattern of vasogenic edema. Additionally, similar hyperintense lesions were observed in other regions, such as the frontal lobes, cerebellum, and brainstem, in some patients. These findings suggest that PRES is not limited to the parieto-occipital regions but may involve more widespread areas. The consistency of imaging findings supports the use of MRI as the gold standard for diagnosing PRES. Early identification of these radiological features can reinforce clinical suspicion, enabling timely initiation of treatment and potentially improving long-term neurological outcomes for patients.

Discussion

Our study confirms the high prevalence of PRES in pediatric patients undergoing allogeneic HSCT and highlights the significant clinical burden of seizures in this population. Early recognition and management of PRES, with a focus on controlling modifiable risk factors such as hypertension, early recognition and management are essential to improving patient long-term outcomes.

The data show that 94% of patients experienced seizures, with 34% experiencing recurrent episodes. This high prevalence of seizures is consistent with the well-established clinical presentation of PRES, where seizures are one of the most common manifestations. The high incidence of PRES observed in this cohort, particularly among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), aligns with previous studies that highlight HSCT as a significant risk factor for the development of PRES (9, 10). In this study, 81% of the patients who underwent allogeneic HSCT developed PRES. This finding supports existing evidence suggesting that HSCT patients, especially those receiving high doses of immunosuppressive agents such as cyclosporine or tacrolimus, are at elevated risk due to endothelial damage and impaired cerebral autoregulation (11). These results underscore the importance of close neurological monitoring in this patient population, particularly during the immediate post-transplant period.

When compared to other studies, the demographic characteristics of this cohort, particularly the male predominance (72%), may reflect a higher male representation in the overall HSCT population or gender-related differences in susceptibility to PRES. Previous literature has reported mixed findings on gender distribution in PRES, with some studies suggesting a slight female predominance due to the association with

pregnancy-related conditions like pre-eclampsia. However, in the context of HSCT, gender-related immunological or pharmacological factors might contribute to the increased prevalence in males in pediatric ages observed here.

All patients demonstrated characteristic MRI findings of hyperintense lesions in the parieto-occipital regions on T2-weighted and FLAIR sequences, which is consistent with the classic radiological features of PRES (12). This uniformity in imaging findings reinforces the utility of MRI as a diagnostic tool in suspected cases of PRES, especially in post-HSCT patients presenting with seizures and altered mental status. The involvement of the parieto-occipital regions in all patients within this cohort may suggest a predilection of these regions for vasogenic edema in PRES, though other studies have also identified additional regions, such as the frontal lobes, cerebellum, and brainstem, in some cases (3). Future research could explore the correlation between specific radiological patterns and clinical outcomes to improve prognostication.

The findings from this study carry significant clinical implications, particularly for high-risk patient populations. A proactive approach is essential for integrating these insights into clinical practice. Early identification and close monitoring of risk factors, such as hypertension and immunosuppressive therapy in post-HSCT patients, are critical for preventing the development of PRES. Tight blood pressure control and careful adjustment of immunosuppressive drug dosages can serve as effective strategies to mitigate risk. Furthermore, implementing more aggressive antiepileptic treatment protocols in patients prone to seizures may help prevent recurrence and related complications. These measures have the potential to reduce both acute morbidity and long-term neurological sequelae, ultimately improving patient outcomes.

The high incidence of recurrent seizures despite anticonvulsant therapy underscores the need for vigilant neurological monitoring and potentially more intensive seizure management in patients at risk of PRES. Additionally, the elevated incidence of PRES following HSCT highlights the importance of early recognition of modifiable risk factors, such as uncontrolled hypertension or high-dose immunosuppressive therapy, which could facilitate timely interventions to reduce risk. Preventive strategies, including strict blood pressure management and judicious use of immunosuppression, should be prioritized in high-risk patients (13, 14).

One limitation of this study is the relatively small sample size, which may limit the generalizability of the findings. Furthermore, the retrospective nature of the data collection may introduce bias in the reporting of clinical features or treatment outcomes. Future studies with more significant, prospective cohorts are necessary to validate these findings and to explore additional factors, such as long-term outcomes, the role of specific immunosuppression agents, and the impact of different seizure management strategies.

Further research is needed to better understand the pathophysiology of PRES in the context of HSCT, particularly for the role of immunosuppression agents, endothelial dysfunction, and cerebral auto-regulation. Additionally, studies should explore whether early intervention strategies, such as preemptive anti-hypertensive therapy or alternative immunosuppression regimens, could reduce the incidence of PRES in high-risk populations.

During the follow-up of our patients, sequelae were observed in only two cases (one with hearing loss—CRF, and the other with polyneuropathy—ALL), which were thought to be related to their underlying conditions. Long-term follow-up studies are also required to assess the potential for permanent neurological sequelae in patients who experience PRES after HSCT.

Ethics Committee Approval: The study was approved by the Human Research Ethics Committee of Akdeniz University Clinical Studies (decision number: TBAEK-544, date: 25.07.2024).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

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M.S.Y., Ö.Y.K., Ş.H.; Critical Review: S.A., F.D., Ş.G., M.S.Y., Ö.Y.K., Ş.H. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Dynamic Thiol / Disulfide Homeostasis in Patients with Nasal Polyps and The Effects of Smoking on Homeostasis Parameters

Nazal Polipli Hastalarda Dinamik Tiyol / Disülfid Homeostazi Ve Sigaranin Homeostaz Parametreleri Üzerine Etkileri

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Abstract

Objective: The aim of this study is to investigate dynamic thiol/disulfide homeostasis as an oxidative stress marker in nasal polyposis (NP) patients and the effects of smoking on homeostasis parameters in these patients.

Materials and Methods: A total of forty NP patients and 36 healthy volunteers participated in the current study. Participants were categorized into two groups: 20 smokers and 20 non-smokers. Erel and Neşelioğlu developed an automated method to analyze thiol-disulfide homeostasis parameters in samples of serum from the participants. Groups were compared. Each parameter related to thiol/disulfide homeostasis—native thiol (SH), total thiol (ToSH), disulfide (SS), SS/SH (%), SH/ToSH (%), and SS/ToSH (%)—was evaluated separately.

Results: There were notable differences across the groups relating markers associated with thiol-disulfide balance. Total Thiol (ToSH) µmol/L (p=0.005), Native Thiol (SH) µmol/L (p=0.001), and SH/ToSH (%) levels were lower in patients with nasal polyps than the control group, and disulfide (SS) (p=0.001), SS/NT (%) (p=0.001), and SS/ToSH (%) levels were statistically significantly higher than the control group (p=0.001). Total Thiol (ToSH) and Native Thiol (SH) µmol/L levels were lower in the smoker group, while SS/NT% levels were higher, but the differences were not statistically significant (p > 0.05).

Conclusion: In NP patients, thiol/disulfide homeostasis shifts towards disulfide formation because of native thiol oxidation. Also, parameters of Thiol/disulfide homeostasis can serve as new oxidative stress markers in nasal polyps.

Keywords: Nasal Polyp, Oxidative Stress, Smoking, Thiol/Disulfide Homeostasis.

&

Öz

Amaç: Bu çalışmanın amacı, nazal polipozis (NP) hastalarında bir oksidatif stres belirteci olarak dinamik tiyol/disülfid homeostazını ve sigaranın bu hastalardaki homeostaz parametreleri üzerindeki etkilerini araştırmaktır.

Gereç ve Yöntemler: Çalışmamıza 40 NP hastası ve 36 sağlıklı gönüllü birey dahil edildi. Hasta grubu kendi içerisinde 20'si sigara içen ve 20'si sigara içmeyen hasta olarak 2 gruba ayrıldı. Tüm katılımcıların serum örneklerinde tiyol-disülfit homeostazisi parametreleri Erel ve Neşelioğlu tarafından geliştirilen yeni otomatik ölçme yöntemi ile analiz edildi ve guruplar arasında karşılaştırıldı.

Bulgular: Tiyol-disülfid dengesine bağlı belirteçler açısından gruplar arasında belirgin farklar gözlemlenmiştir. Total tiyol (ToSH) µmol/L (p=0,005), native tiyol (SH) µmol/L (p=0.001) ve SH/ToSH (%) düzeyleri, nazal polipli hastalarda kontrol grubuna göre daha düşük bulunmuş, disülfid (SS) (p=0,001), SS/NT (%) (p=0,001) ve SS/ToSH (%) düzeyleri ise kontrol grubuna kıyasla istatistiksel olarak anlamlı derecede yüksek bulunmuştur (p=0,001). Total Thiol (ToSH) ve Native Thiol (SH) µmol/L düzeyleri sigara içen grupta daha düşük, SS/NT% düzeyleri ise daha yüksek bulunmuş, ancak bu fark istatistiksel olarak anlamlı olmamıştır (p > 0,05).

Sonuç: NP hastalarında, tiyol/disülfid homeostazı, native tiyol oksidasyonu nedeniyle disülfid oluşumuna doğru kaymaktadır. Ayrıca, tiyol/disülfid homeostaz parametreleri, nazal poliplerde yeni oksidatif stres göstergeleri olarak kullanılabilir.

Anahtar Kelimeler: Nazal Polip, Oksidatif Stres, Sigara Içme, Tiyol/Disülfid Homeostazı

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Introduction

Nasal polyp (NP) is a chronic condition associated with inflammation of the nasal or paranasal sinus mucosa. The source of this condition is still unclear and is the most common cause of nasal mass. The prevalence in the community varies between 2-4% (1). Chronic rhinosinusitis (CRS) is linked to disorders, such as cystic fibrosis (CF), allergic rhinitis (AR), bronchial asthma, and primary ciliary dyskinesia. NPs, which are edematous soft tissue masses that develop due to the nasal or paranasal sinus mucosa as a result of susceptibility to infection and vascular reorganization caused by mucosal inflammation, can expand and overflow into the nasal passage, producing symptoms like post-nasal drip, nasal congestion, headache, and runny nose. They also lead to secondary complaints such as decreased quality of life, snoring, CRS, and olfactory dysfunction

Extensive research has been conducted on the potential causes of NP, a condition with an unknown origin. Furthermore, histologic and pathophysiologic studies indicate that the process is multifactorial. Inflammation is thought to be a major factor. Therefore, free oxygen radicals and oxidative stress are some of the etiologic causes investigated (2,3).

The oxidative balance is the balance between reactive oxygen species (ROS generated in cells during normal physiological processes, and antioxidants, which eliminate them. Oxidative stress is an imbalance favoring ROS, characterized by insufficient endogenous defense systems in the cell and the accumulation of free oxygen radicals (4).

There are several parameters, some oxidants and some antioxidants, used to indicate oxidative stress in the body (5). Thiols, one of the antioxidant parameters, are organic compounds made up of sulfur and hydrogen atoms with a sulfhydryl (-SH) group attached to the carbon atom, also called mercaptan. Organic compounds containing thiol groups are important for defending against oxidative stress because of their reducing abilities. There are many thiol molecules in plasma (6).

Thiols interact with free radicals to inhibit ROS-induced harm to cells and tissues. FRs cause the oxidation of amino acid thiol groups containing sulfur and disulfide bonds through the above reaction. Disulfide bonds can be transformed into thiols through reduction. This is how the balance between thiol and disulfide compounds is preserved in cells and tissues. This helps regulate the antioxidant defense system, enzyme activities, detoxification, apoptosis, and intracellular signal transduction mechanisms. Decreased thiols and increased disulfide content result in decreased clearance of ROS products. Increased disulfide levels adversely affect protection against oxidation and redox products, leading to functional and structural abnormalities in various organs and systems. This increases the frequency of cellular damage and apoptosis (7).

Cigarette smoke contains more than 4000 chemicals, including tobacco-specific N-nitrosamines, polynuclear aromatic hydrocarbons, and aromatic amines. These chemicals are highly carcinogenic and can also cause oxidative stress by inducing the formation of free radicals. This redox imbalance can cause toxic effects that damage all elements of cells, especially proteins, lipids, and nucleic acids. Oxidative stress is considered to be significant in the advancement of various diseases. Previous research suggests that the acute and chronic effects of smoking may weaken antioxidant defense systems, which may ultimately lead to long-term pathologies. (8,9)

No existing study has evaluated the impact of TDH and smoking on homeostasis parameters in NP patients. The current study was conducted with the aim of exploring the impact of TDH as oxidative stress marker in the pathophysiology of NP as well as the impacts of smoking on parameters of homeostasis.

Materials and Methods

Selection of Study Groups and Study Design

Patients diagnosed with nasal polyposis and a control group suitable for the demographic characteristics of the patients were included in the study. The study was prospectively conducted. All patients and the healthy control group provided verbal and written signed informed consent forms after being fully informed. The approval of the Bolu Abant İzzet Baysal University Ethics Committee, dated 13/07/2021 and numbered 2021/175, were obtained for the study.

Inclusion Criteria

The current study included 40 patients in total aged between 18 and 65, without systemic disease but with complaints of nasal congestion and were diagnosed with nasal polyposis. Patients were categorized into two groups: 20 individuals who smoke and 20 individuals who do not smoke. Thirty-six healthy volunteers, matched in age and sex, and without any complaints, were included in the control group all of whom were non-smokers.

Exclusion Criteria

Patients below 18 and over 65 years, those with additional systemic diseases (except asthma) such as hypertension, diabetes mellitus, thyroid hormone disorder, hyperlipidemia, active upper respiratory tract infection, chronic liver and kidney disease, those who are pregnant or breastfeeding, those who have used systemic steroids, antihistamines, and leukotriene receptor antagonists for any reason in the last three months, those with asthma in exacerbation, and those receiving antioxidant replacement.

The Lund Kennedy scoring system, determined endoscopically, was used to assess the severity of nasal polyp disease. A 4 mm rigid 0-degree endoscope (Karl-StorzVR GmBH & Co., Tuttlingen, Germany) was used for endoscopic examination.

Biochemical Examination

Blood samples were obtained from participants after an 8-hour fasting, between 08:00 and 10:00 AM. Patient and healthy control group samples were collected in a yellow-capped gel tube (biochemistry tube) and then transported to the laboratory. Following clotting, blood samples were centrifuged at 1500g for fifteen minutes to isolate the serum. The serum was moved to an Eppendorf tube and placed in a cooler at -80 °C for storage, following the appropriate storage conditions, until the analysis day. Serum samples were thawed on the study day, and thiol-disulfide homeostasis parameters were analyzed. This method consists of two steps: the first step involves determining the levels of native thiol (NT) using DTNB [5,5'-dithiobis-(2-nitrobenzoic) acid]. The second step, on the other hand, involves dynamic and reducible disulfide bonds (-S-S) being reduced to free functional (reactive) thiol groups (-SH) with sodium borohydride (NaBH4). Excess NaBH4 is disposed of by reacting it with formaldehyde. The total thiol (TT) groups, which include both NaBH4-reduced and native thiols, are measured by reacting them with DTNB [5,5'-dithiobis-(2- nitrobenzoic) acid]. The dynamic disulfide (SS) amount can be calculated by taking fifty percent of the concentrations of native thiol and total thiol differences. For measuring the native thiol (SH), total thiol (ToSH), and disulfide (SS) values, and other relevant parameters, determined by calculating the redox potential (Thiol Oxidation-Reduction Ratio, SS/SH%), oxidized thiol ratio (SS/ToSH%), and reduced thiol ratio (SH/ToSH%), this new method can be applied.

Parameters of tynamic thiol/disulfide homeostasis, an oxidative stress indicator, and their ratios, were compared between patients with nasal polyps and healthy volunteers.

The effect of smoking on these parameters was also evaluated.

Statistical Analysis

SPSS 22.0 for Windows packaged program was utilized for the statistical analysis. Furthermore, descriptive statistical methods were utilized. Kruskall Wallis Test was employed for comparisons involving three or more groups, while the Independent Sample T test was used to compare the groups. For analyzing the qualitative data, the Pearson Chi-Square test was utilized. The Pearson Correlation test was utilized for assessing the correlation of the measurements. Significance was assessed at p-values of less than 0.01 and 0.05.

Results

While 52.6% (n = 40) of participants were in patient group, 47.4% (n = 36) were in the control group. Within the patient group, 50.0% (n = 20) did smoke, and the remaining 50.0% (n = 20) were non-smokers. In the patient group, 67.5% (n = 27) were male and 32.5% (n = 13) were female. In the control group, 63.9% (n = 23) were male and 36.1% (n = 13) were female. The average age of the patient group was 46.60±10.55 years, and the mean age

of control group was 44.14±10.84 years. There was no significant difference between the groups in terms of age and gender (p > 0.05).

Total Thiol (ToSH), µmol/L measurement (p = 0.005; p<0.01), and there were differences between groups in terms of Native Thiol (SH), µmol/L measurements (p = 0.001; p<0.01). The values in the control group increased.

Disulfide (SS), µmol/L measurement (p=0.001; p<0.01) and SS/NT% measurement (p=0.001; p<0.01) of patient and control groups were statistically significantly different. (p=0,001; p<0,01). The values in the patient group increased (Table 1).

Table 1.

Evaluation of Laboratory Measurements According to Patient Group and Control Group

	Patient Group (n=20)		*Control Group (n=36)*		
	Mean±Sd	**Min-Max (Median)**	**Mean±Sd**	**Min-Max (Median)**	**[a]p**
Total Tiyol (ToSH), µmol/L	446.36±82.51	146.98-567.88 (460.53)	497.22±68.6	327.3-600.82 (514.59)	***0.005****
Nativ Tiyol (SH), µmol/L	383.14±78.16	106.93-508 (399.33)	442.94±69.23	280.45-588.91 (456.71)	***0.001****
Disülfit (SS), µmol/L	31.61±5.17	20.03-44.31 (31.3)	27.14±5.48	5.96-36.34 (27.37)	***0.001****
SS/SH, %	8.63±2.37	5.75-18.73 (7.87)	6.31±1.65	1.01-10.36 (6.23)	***0.001****
SH/ToSH,%	0.85±0.03	0.73-0.9 (0.86)	0.89±0.03	0.83-0.98 (0.89)	***0.001****
SS/ToSH,%	0.07±0.02	0.05-0.14 (0.07)	0.06±0.01	0.01-0.09 (0.06)	***0.001****

Sd: Standard deviation, [a]Independent Sample T Test, **p<0.01.

The comparison of the patient and the control groups revealed that the SH/ToSH% measurements were statistically significantly different (p = 0.001; p<0.01). The values in the control group increased (Table 1).

The comparison between groups revealed that SS/ToSH% measurement were statistically significantly different (p=0.001; p<0.01). The values in the patient group increased (Table 1).

Evaluation of Laboratory Measurements Based on Patient Groups: Smokers and Non-Smokers is given in the Table 2.

The comparison of all groups revealed that Total Thiol (ToSH), µmol/L measurement had statistically significant difference (p=0.005; p<0.01). The level was elevated in the control group than both the smoking and non-smoking patient groups (Table 3).

According to the comparison of all groups, Native Thiol (SH) µmol/L measurement had a statistically significant difference (p = 0.001; p<0.01). The levels elevated in the control group than both groups of smokers and non-smokers (Table 3).

According to the comparison of all groups, disulfide (SS) µmol/L measurement was statistically significantly different (p = 0.001; p<0.01). The levels elevated in non-smokers than both the control and the smoking patient groups (Table 3).

According to the comparison of all groups, the SS/NT% measurement was statistically significantly different (p = 0.001; p<0.01). The levels elevated in smokers than both the control group and the non-smokers (Table 3).

Table 2.

Evaluation of Laboratory Measurements According to Smoking and Non-Smoking Patient Groups

	Smoking Patient Group (n=20)		*Non-Smoking Patient Group (n=20)*		[a]p
	Mean±Sd	**Min-Max (Medyan)**	**Mean±Sd**	**Min-Max (Medyan)**	
Total Tiyol(ToSH), µmol/L	437.87±95.16	146.98-559.86 (455.29)	454.85±69.03	281.98-567.88 (469.6)	***0.522***
Nativ Tiyol (SH), µmol/L	376.03±88.88	106.93-494.58 (394.77)	390.25±67.33	237.6-508 (401.54)	***0.572***
Disülfit (SS), µmol/L	30.92±5.37	20.03-44.31 (30.73)	32.3±5.01	22.19-41.4 (31.96)	***0.406***
SS/SH,%	8.78±2.87	6.55-18.73 (7.83)	8.49±1.79	5.75-12.16 (8.45)	***0.701***
SH/ToSH,%	0.85±0.04	0.73-0.88 (0.86)	0.86±0.03	0.8-0.9 (0.86)	***0.750***
SS/ToSH,%	0.07±0.02	0.06-0.14 (0.07)	0.07±0.01	0.05-0.1 (0.07)	***0.741***

Sd: Standard deviation, [a]Independent Sample T Test.

According to the comparison of all groups, the SH/ToSH;% measurement was statistically significantly different (p = 0.001; p<0.01). These values elevated in the control group (Table 3).

According to the comparison of all groups, the SS/ToSH;% measurement was statistically significantly different (p = 0.001; p<0.01). These values decreased in the control group (Table 3).

Table 3.

Evaluation of Laboratory Measurements by Groups

	Smoking Patient Group (n=20)		*Non-Smoking Patient Group (n=20)*		*Control Group (n=36)*		[a]p
	Mean±Sd	**Min-Max (Medyan)**	**Mean±Sd**	**Min-Max (Medyan)**	**Mean±Sd**	**Min-Max (Medyan)**	
Total Tiyol(ToSH), µmol/L	437.87±95.16	146.98-559.86 (455.29)	454.85±69.03	281.98-567.88 (469.6)	497.22±68.6	327.3-600.82 (514.59)	***0.009****
Nativ Tiyol (SH), µmol/L	376.03±88.88	106.93-494.58 (394.77)	390.25±67.33	237.6-508 (401.54)	442.94±69.23	280.45-588.91 (456.71)	***0.002****
Disülfit (SS), µmol/L	30.92±5.37	20.03-44.31 (30.73)	32.3±5.01	22.19-41.4 (31.96)	27.14±5.48	5.96-36.34 (27.37)	***0.001****
SS/SH, %	8.78±2.87	6.55-18.73 (7.83)	8.49±1.79	5.75-12.16 (8.45)	6.31±1.65	1.01-10.36 (6.23)	***0.001****
SH/ToSH,%	0.85±0.04	0.73-0.88 (0.86)	0.86±0.03	0.8-0.9 (0.86)	0.89±0.03	0.83-0.98 (0.89)	***0.001****
SS/ToSH,%	0.07±0.02	0.06-0.14 (0.07)	0.07±0.01	0.05-0.1 (0.07)	0.06±0.01	0.01-0.09 (0.06)	***0.001****

Sd: Standard deviation, [a]Kruskall Wallis Testi, *p<0.01.

A substantial negative connection was found between the Lund Kennedy score and Disulfide (SS) µmol/L measurement at 32.3% level (r = -0.232; p = 0.042; p<0.05). This relationship between Lund Kennedy Scoring and Laboratory Measurements is given in Figure 1 and Table 4.

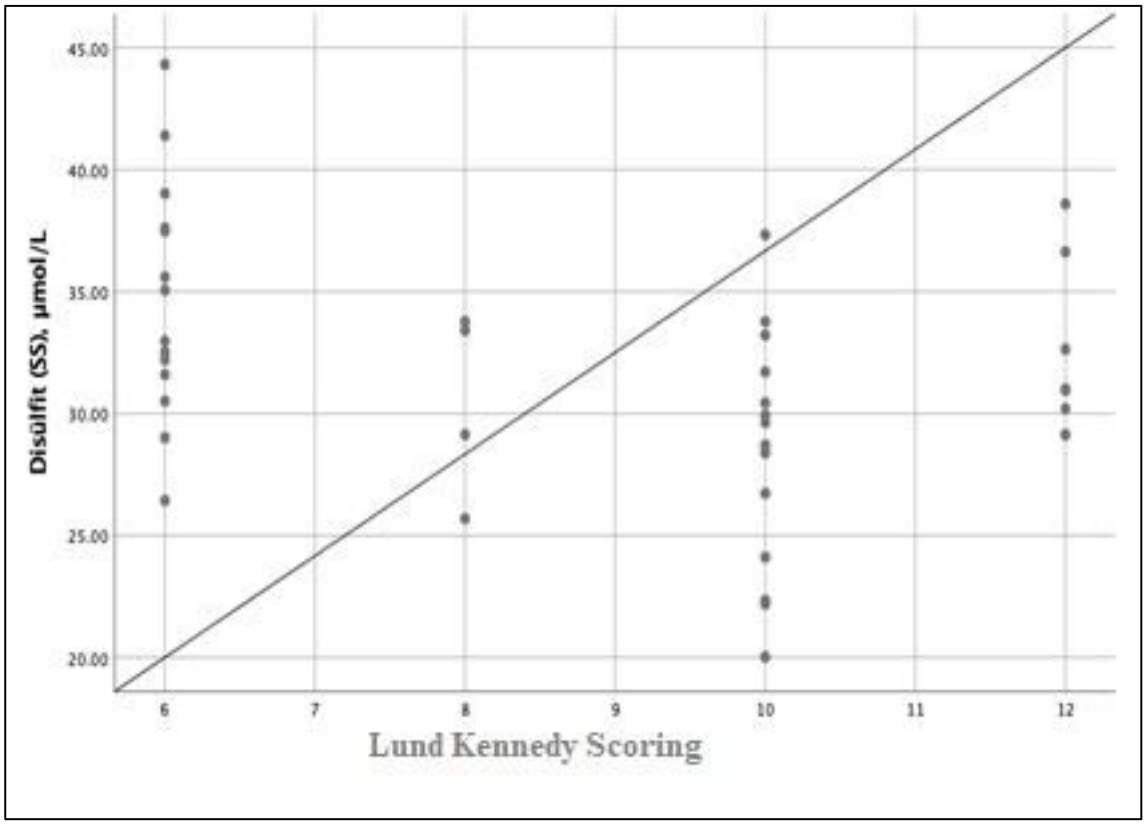

Figure 1. Relationship Between Lund Kennedy Scoring and Disulfide (SS), µmol/L Measurement

Table 4.
Relationship between Lund Kennedy Scoring and Laboratory Measurements

		Lund Kennedy Scoring
Total tiyol(ToSH), µmol/L	***r***	-0.170
	p	**0.293**
Nativ tiyol (SH), µmol/L	***r***	-0.137
	p	**0.399**
Disülfit (SS), µmol/L	***r***	-0.323
	p	**0.042***
SS/SH, %	***r***	-0.010
	p	**0.951**
SH/ToSH, %	***r***	0.022
	p	**0.895**
SS/ToSH, %	***r***	-0.022
	p	**0.895**

r=Pearson Correlation, *p<0.05.

Discussion

Nasal polyps are a complex pathological condition, particularly associated with the effects of oxidative stress, which may play a significant role in the development and severity of the disease. The levels of alpha-tocopherol, ascorbic acid, retinol, reduced glutathione, beta-carotene, glutathione peroxidase, superoxide dismutase (SOD), and the combination of malondialdehyde and thio-barbituric acid as peroxidation products were measured in plasma in Dagli et al.'s study comparing 31 patients with NP with 19 control patients with turbinate hypertrophy and septal deviation. A comparison with the control group, blood antioxidant levels decreased, and oxidant levels of malondialdehyde thio-barbituric were significantly increased in the patient group with NP (10). Bozkuş et al. conducted a study comparing 38 patients with NP to 35 controls with septal deviation and middle turbinate hypertrophy. The researchers evaluated the TAS (total antioxidant capacity), TOS (total oxidative burden), and OSI (oxidative stress index) in samples of serum and tissues. Levels of TAS in serum and tissue samples were notably reduced, whereas OSI and TOS levels increased in NP patients in comparison to the control group (11). The studies offer compelling evidence that oxidative stress affects the development of NP and suggest that antioxidants may mitigate tissue damage induced by SR in NP.

There are many antioxidant and oxidant parameters used to study oxidative stress in the body 7). Recent studies suggest that measurement of thiol levels in serum may indirectly reflect antioxidant defense. It has been found that under oxidative stress, thiol levels should decrease, and disulfide levels should increase. Bozdemir et al. showed the involvement of oxidative stress in the development of mucosal inflammation in CRS patients without polyps by analyzing TDH parameters, which serve as an indicator for oxidative stress. CRS patients had significantly lower total thiol μmol/L levels and native thiol μmol/L than the control group ($p<.001$). The results of disulfide (SS) and SS/NT measurements in the groups showed no statistical difference. These results suggest that there is a thiol depletion in CRS, thus altering homeostasis in the direction of oxidation, possibly as a consequence of the inflammatory process of the disease (12).

According to the study conducted by Sevil et al., there was no statistically significant difference in the levels of total thiol of patients with CRS with NP and patients with CRS without NP ($p > 0.05$). There was a significant difference between CRS with NP and CRS without NP in %SH/TT, %SS/TT, %SS/SH, SS, and SH ($p<0.05$). Comparing the patient groups within themselves, it was observed that the SH level was higher in CRS without NP, whereas the SS level was higher in CRS with NP. While no significant difference was detected between CRS patients without NP and the control group in terms of %SS/TT, %SS/SH, %SH/TT, SS, and SH ($p>0.05$), there was a statistically significant difference ($p<0.05$) in CRS patients with NP and the control group in terms of %SS/TT, %SS/SH, %SH/TT, SS, and SH. The CRS group with NP had lower levels of TT and SH compared to the control group ($p<0.05$). According to these results, dynamic SH/SS homeostasis is changed towards SS creation as a consequence of SH oxidation in CRS patients (13).

Our initial hypothesis in this study was that dynamic TDH parameters would vary between the NP group and the control group, as we intended to evaluate the effect of oxidative stress on the NP and dynamic TDH parameters development. Each parameter related to TDH, native thiol (SH), total thiol (ToSH), disulfide (SS), SS/SH (%), SH/ToSH (%), and SS/ToSH (%) were evaluated separately. According to the results of our hypothesis analysis, there is a significant difference between the groups in parameters related to thiol-disulfide balance. Total Thiol (ToSH) μmol/L measurement ($p=0.005$; $p<0.01$), Native Thiol (SH) μmol/L measurement ($p=0.001$; $p<0.01$), and SH/ToSH% measurement show statistically significant differences, and these values in the NP group were lower compared to the control group. Disulfide (SS) μmol/L ($p = 0.001$; $p<0.01$), SS/NT% ($p = 0.001$; $p<0.01$), and SS/ToSH% ($p = 0.001$; $p<0.01$) showed statistically significant differences, and these values in the NP group evaluated compared to the control group.

Görgülü et al. aimed to examine the impact of smoking on the formation of NP. In the study, the serum cotinine levels, serum total IgE levels, and absorption levels were compared between 60 patients who underwent ESC (18 non-smokers and 42 smokers) and a control group of 50 individuals (both smokers and non-smokers). The results of this study revealed that smoking cessation, as one of the environmental factors influencing the etiopathogenesis in NP patients, and the prevention of exposure to cigarette smoke are important protective factors in preventing NP formation and protecting against recurrence (14)

In a research conducted by Solak et al., the native thiol, disulfide, and total thiol serum levels, and a comparison was made between the ratios of disulfide/total thiol, disulfide/native thiol, and native/total thiol

in 84 smoker patients and 86 non-smokers healthy volunteers. Smokers had decreased levels of total, native, and native/total thiols compared to control group, but increased levels of disulfide, disulfide/total thiol, and disulfide/native thiol. The results suggested that smoking may lead to oxidative stress and disrupt the balance of thiol/disulfide levels towards the disulfide side in comparison to the healthy group (15).

We compared the smoking group with NP with the group of non-smoking in our study. The results of laboratory measurements were as follows: Total Thiol (ToSH) and Native Thiol (SH) μmol/L measurements were numerically lower in the smoker group, while SS/NT% measurements were numerically higher; however, they were not statistically significantly different ($p > 0.05$). The absence of statistical significance in our findings may be due to the small sample size.

The Lund Kennedy scoring system is a widely used method for assessing the severity of nasal polyposis (NP). It evaluates the extent of nasal polyp involvement based on the findings from endoscopic examination, considering factors such as the location, size, and number of polyps present in the nasal cavity and paranasal sinuses. In our study, attempting to assess the relationship between the disease severity and oxidative stress, we found a significant negative relationship between the Lund Kennedy score used in the evaluation of NP disease severity and Disulfide (SS), μmol/L measurement at 32.3% level ($r = -0.232$; $p = 0.042$; $p<0.05$). Typically, an increase in oxidative stress is expected to correlate with a rise in disease severity, and therefore, a positive correlation is anticipated. However, the sample size in our study may have contributed to the emergence of this inverse correlation.

As far as we know, no study has assessed the impact of dynamic TDH and smoking on the parameters related to the homeostasis of NP patients. The current study investigated the effect of dynamic TDH as an indicator for oxidative stress in the pathophysiology of NP as well as the effects of smoking on parameters related to homeostasis.

It was limited by the small number of cases. Our study may have been inadequate in representing larger groups due to the fact that patients were selected according to certain exclusion criteria and 40 patients in total were assessed, potentially impacting the results.

In conclusion, each parameter related to thiol/disulfide homeostasis—native thiol (SH), total thiol (ToSH), disulfide (SS), SS/SH%, SH/ToSH%, and SS/ToSH%—was evaluated separately in our study, aiming to explore the effect of dynamic TDH as an indicator of oxidative stress in the pathophysiology of NP and the impact of smoking on hemostasis parameters. We found significant differences between the groups in our hypothesis analysis regarding indicators associated with thiol-disulfide balance. These results suggest that TDH is shifted towards SS formation caused by SH oxidation in NP patients. These results suggest that oxidative stress may be important for NP.

Ethics Committee Approval: The study was approved by the Bolu Abant İzzet Baysal University Ethics Committee (date: 13.07.2021 and decision number: 2021/175).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

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The Case of Lichen Planus Pigmentosus Inversus Associated With SARS-Cov-2 Vaccine (Sinovac): A Rare Entity

SARS-CoV-2 Aşısı (Sinovac) ile İlişkili Liken Planus Pigmentozus İnversus: Nadir Bir Olgu

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Abstract

COVID-19 vaccines may cause the onset or exacerbation of inflammatory skin diseases. However, the relationship between COVID-19 vaccines and immune-mediated skin diseases is still not fully known. Lichen planus pigmentosus inversus is a rare variant of lichen planus and, unlike lichen planus pigmentosus, this form frequently affects people with white skin. It occurs in intertriginous areas such as the groin and axillae and 90% of patients have axillary involvement. There are cases of lichen planus reported after COVID-19 vaccines, and this is the first case of lichen planus pigmentosus inversus after SARS-CoV-2 vaccine (Sinovac). Additional studies are needed to demonstrate this relationship.

Keywords: Covid -19, Dermoscopy, Dermatoscopy, Lichen Planus Pigmentosus, Vaccine.

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Öz

COVID-19 aşıları inflamatuvar deri hastalıklarının başlamasına veya alevlenmesine neden olabilir. Bununla birlikte, COVID-19 aşıları ile immün aracılı deri hastalıkları arasındaki ilişki hala tam olarak bilinmemektedir.

Liken planus pigmentosus inversus, liken planusun nadir görülen bir varyantı olup liken planus pigmentozusun aksine, bu form sıklıkla beyaz tenli kişileri etkiler. Kasık ve koltuk altı gibi intertriginöz bölgelerde ortaya çıkar ve hastaların %90'ında aksiller tutulum mevcuttur.

COVID-19 aşıları sonrası bildirilen liken planus olguları mevcut olup, bu vaka inaktif COVID-19 aşısı (Sinovac) sonrası ortaya çıkan liken planus pigmentosus inversusu bildiren ilk vakadır. Bu ilişkiyi ortaya koymak için ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Covid -19, Dermatoskopi, Pigmente Liken Planus, Aşı.

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Introduction

Coronavirus disease 2019 (COVID-19) vaccines may cause the onset or exacerbation of inflammatory skin diseases such as lichen planus, psoriasis, and bullous pemphigoid. However, the relationship between COVID-19 vaccines and immune-mediated skin diseases is still unknown (1). Here, we present a case of lichen planus pigmentosus inversus (LPPI) that occurred 1 week after the second dose of Sinovac vaccine.

Case Presentation

A 60-year-old female patient was admitted to our outpatient clinic with the complaint of a brown patch that started in the right axilla and then appeared in the left axilla, 1 week after the second dose of the Sinovac vaccine. Upon dermatological examination, there was a brown patch in both axillae, more common in the left axilla (Figure 1a, b). There was no oral mucosa or nail involvement. The patient had no known comorbidities, and no abnormalities were detected in routine laboratory tests and hepatic serology. In dermoscopic examination; perifollicular grey-brown dots were present, perifollicular dot detected in wood mode (Figure 1c, d). The histopathological examination of the left axilla incisional biopsy revealed a lichenoid inflammatory infiltrate with melanin leakage (Figure 1e). Histopathology was consistent with LPPI based on these findings. Tacrolimus 1% ointment and methylprednisolone aceponate ointment were prescribed to the patient.

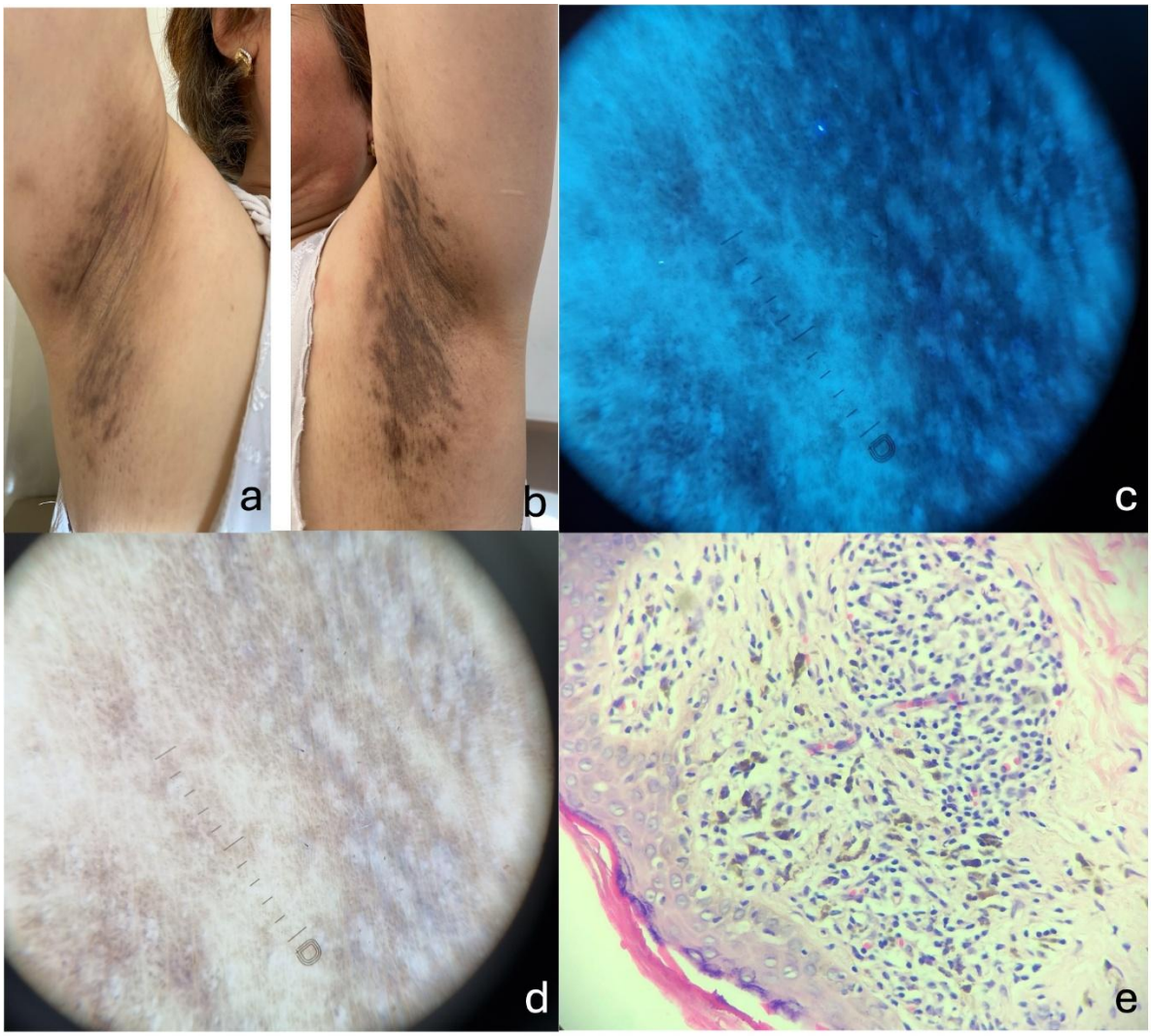

Figure 1.
(a,b) Brown patch in both axillae, more common in the left axilla
(c) Perifollicular dot detected in wood mode (Dermlite-5®, x10 magnification)
(d) Perifollicular grey-brown dots (Dermlite-5®, x10 magnification, polarized mode)
(e) Orthokeratotic hyperkeratosis, basal vacuolar degeneration, melanin incontinence in the superficial dermis and band-like chronic inflammation. (Hematoxylin-Eosin x400)

Discussion

Lichen planus pigmentosus inversus is a rare variant of lichen planus (2). Unlike lichen planus pigmentosus (LPP), which predominantly affects individuals with darker skin tones and is commonly observed in sun-exposed areas, LPPI is more frequently encountered in light-skinned individuals and characteristically involves intertriginous and flexural regions, such as the axilla and groin, which are typically non-sun-exposed (3). Axillary involvement is present in 90% of patients (2).

Histopathologically, it is characterized by pigment incontinence, vacuolar degeneration and keratinocyte apoptosis in the basal cell layer, and a band-like lymphohistiocytic lichenoid infiltrate in the dermis (4). Dermoscopy of LPPI reveals three distinct patterns. The diffuse pattern is characterized by homogenous, structureless brownish areas, likely corresponding to epidermal pigmentation. The dotted pattern consists of blue-gray-brown dots and globules, presumably representing dermal melanophages. The mixed pattern, as the most complex presentation, combines features of both patterns, indicating concurrent epidermal and dermal pigmentary alterations (5).

All vaccines activate the immune system, triggering a certain level of inflammation, which can result in various skin reactions (6). It is thought that the COVID-19 vaccine induces a Th1 response and leads to increased levels of cytokines such as IL-2, TNF-α and IFN-γ, which play a central role in the development of LP (7). Although the exact etiology of LPP is unknown, it is thought to be a lichenoid reaction to many agents, such as viral infections, vaccines, trauma, and ultraviolet exposure (8). LP has been described after different vaccines (hepatitis B, influenza, rabies, and combination vaccines) and more recently COVID-19 vaccines. A single case of lichen planus occurring after Sinovac vaccine has been reported. Since the pathogenesis of LPPI is similar to classical LP, it is not surprising that LPPI can also be elicited by COVID-19 vaccines (7).

Thus far, three cases of LPPI following COVID-19 vaccination have been reported in the literature. Sun et al. described a case that developed two weeks after the first dose of the Oxford-AstraZeneca vaccine, with disease exacerbation following the second dose. Edek et al. reported another case in which skin lesions appeared one week after the third dose of the Pfizer-BioNTech vaccine, followed by nail involvement two weeks later. Similarly, Gil-Quiñones et al. reported an LPPI case emerging two weeks after the second dose of the Oxford-AstraZeneca vaccine (7,9,10). These reports suggest a potential temporal association between COVID-19 vaccination and the onset or exacerbation of LPPI.

Our case is the LPPI reported after inactivated vaccine (Sinovac) vaccination. Additional studies are needed to clarify this relationship.

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A Rare Case of Familial Hemiplegic Migraine with Reversible Motor Weakness and Aphasia

Güç Kaybı ve Afazi ile Seyreden Nadir Bir Ailevi Hemiplejik Migren Vakası

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Abstract

A case presenting with unilateral motor weakness, speech disturbance, and migraine-like headache, accompanied by normal cranial imaging, diagnosed as familial hemiplegic migraine (FHM), is presented to emphasize its rarity and the importance of differential diagnosis.

A 44-year-old male patient presented with unilateral weakness in the right arm and leg, lasting approximately one day, along with speech impairment characterized by motor aphasia. The patient reported migraine-like throbbing headaches accompanied by photophobia and phonophobia, with episodes recurring every 3-5 years and triggered by stress. His medical history included thyroid surgery and smoking (20 pack-years), and a family history of similar episodes in the mother and uncle. Neurological examination revealed motor aphasia and right extremity muscle strength of 4/5, but no other pathological findings. Laboratory results, EEG, and cranial magnetic resonance imaging (MRI) were normal. During hospitalization, enoxaparin and lamotrigine were initiated due to prolonged symptoms. The symptoms gradually improved within 2-3 days, with complete resolution observed by the third day.

In patients presenting with migraine-like attacks accompanied by unilateral motor weakness and speech disturbances, familial hemiplegic migraine should be considered, especially when imaging and laboratory findings are unremarkable. Recognition of this rare diagnosis is crucial to avoid unnecessary investigations and treatments.

Keywords: Case Report, Familial Hemiplegic Migraine, Migraine.

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Öz

Tek taraflı motor zayıflık, konuşma bozukluğu ve migren benzeri baş ağrısı ile birlikte normal kraniyal görüntüleme bulgularının eşlik ettiği ve ailevi hemiplejik migren (FHM) olarak tanı alan bir vaka, bu nadir durumun ve ayırıcı tanının önemini vurgulamak amacıyla sunulmaktadır.

44 yaşındaki erkek hasta, yaklaşık bir gün süren sağ kol ve bacakta tek taraflı güçsüzlük ile motor afazi ile karakterize konuşma bozukluğu şikayetleriyle başvurdu. Hasta, stresle tetiklenen ve 3-5 yılda bir tekrarlayan, fotofobi ve fonofobi ile birlikte görülen migren benzeri zonklayıcı baş ağrılarından bahsetti. Tıbbi geçmişinde tiroid cerrahisi ve 20 paket-yıl sigara öyküsü, ayrıca annesi ve amcasında benzer atak öyküsü olduğu öğrenildi. Nörolojik muayenede motor afazi ve sağ ekstremitelerde 4/5 kas gücü saptandı ancak başka patolojik bulguya rastlanmadı. Laboratuvar sonuçları, EEG ve kraniyal manyetik rezonans görüntüleme (MRI) normaldi. Hastanede yatışı sırasında, uzamış semptomlar nedeniyle enoksaparin ve lamotrijin tedavisi başlandı. Semptomlar 2-3 gün içinde kademeli olarak iyileşti ve üçüncü gün sonunda tamamen düzeldi.

Tek taraflı motor zayıflık ve konuşma bozuklukları ile birlikte migren benzeri ataklarla başvuran hastalarda, görüntüleme ve laboratuvar bulguları normal olduğunda ailevi hemiplejik migren düşünülmelidir. Bu nadir tanının tanınması, gereksiz tetkik ve tedavilerden kaçınılması açısından hayati öneme sahiptir.

Anahtar Kelimeler: Vaka Raporu, Ailevi Hemiplejik Migren, Migren.

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Introduction

Hemiplegic migraine (HM) is a subtype of migraine with aura accompanied by reversible motor weakness. It frequently begins in childhood or early adulthood. Its prevalence is approximately 0.01%. It is three times more common in women than men (1).

It is divided into familial and sporadic forms, with the familial form referred to as familial hemiplegic migraine (FHM) (2). A family history is observed in 18% of patients with hemiplegic migraine. It follows an autosomal dominant (AD) inheritance pattern. In half of the families, a mutation in the CACNA1A gene located on chromosome 19p13, encoding the pore-forming alpha-1A subunit of voltage-gated P/Q-type calcium channels, is found. In approximately 15% of cases, a mutation in the ATP1A2 gene located on chromosome 1q23, encoding the alpha-2 subunit of the sodium/potassium pump, has been identified. In about 20% of cases, no genetic localization has been determined (3-6). Differential diagnoses include epilepsy (Todd's paresis), transient ischemic attack, stroke, metabolic disturbances, infections, and rare syndromes (Table 1).

Table 1.
Familial Hemiplegic Migraine Differantial Diagnosis

Condition	Distinguishing Features
Transient Ischemic Attack	Sudden onset, typically in older adults, risk factors (e.g. hypertension, atrial fibrillation), symptoms last <24h, imaging may show vascular changes
Stroke	Persistent deficits, positive neuroimaging, not fully reversible
Epilepsy (Todd's Paresis)	Preceding seizure activity, EEG abnormalities, rapid resolution of weakness
Metabolıc Disorders (e.g. Hypoglycemia)	Altered mental status, blood test abnormalities
Meningitis/Encephalitis	Fever, neck stiffness, altered consciousness, CSF abnormalities
Mitochondrial disorders (e.g. MELAS)	Lactic acidosis, stroke-like episodes, family history, elevated serum lactate

This case highlights familial hemiplegic migraine and the need to consider it during differential diagnosis.

Case

A 44-year-old male patient presented to our clinic with complaints of unilateral weakness in the arm and leg lasting approximately one day and speech disturbance (inability to fully articulate words), which began around age 15. It was learned that his complaints were accompanied by throbbing, unilateral headaches with photophobia and phonophobia. The headaches, lasting about one day, gradually decreased, and the attacks recurred once every 3-5 years. The headaches were triggered by stress. The patient's past medical history included thyroid surgery and a 20 pack-year smoking history. In the family history, it was noted that his mother and uncle had experienced similar episodes.

On neurological examination, the patient was conscious with motor aphasia, and the muscle strength of his right extremities was 4/5. Routine laboratory values were unremarkable. EEG findings were within normal limits, and electrocardiography (ECG) was normal. Previous etiological investigations for stroke performed at

an external center under the preliminary diagnosis of transient ischemic attack were within normal limits. Cranial magnetic resonance imaging (MRI) was evaluated as normal.

During hospitalization, enoxaparin was started, and due to the prolonged attack symptoms, lamotrigine was initiated. The symptoms gradually improved within 2-3 days. Initially, improvement in hemiparesis was observed within a few hours. By the end of the first day, word articulation started, although the patient had

Discussion

HM was first described by Clark in 1910, who emphasized that the clinical presentation of recurrent motor weakness and headache could be due to migraine (7). Later, additional case series were reported, expanding the clinical understanding of the condition. According to the 2013 classification of the International Headache Society, HM is diagnosed based on migraine with aura criteria, at least two attacks, reversible motor weakness, and the presence of at least one symptom of visual, sensory, or speech disturbances, each aura symptom lasting longer than 5 minutes but less than 24 hours. In familial cases, the presence of at least one first- or second-degree relative with a similar history is diagnostic (8).

Clinical data indicate that HM frequently begins between the ages of 10-15 (1). Our patient's symptoms began at a similar age. Migraine is the most common type of chronic episodic headache. Childhood migraine prevalence ranges between 3-10.6% (9). The clinical presentation in children can vary widely and may occur at any age. In pediatric migraine, focal neurological findings, particularly hemiplegia, may accompany headache attacks. Hemiplegic migraine is diagnosed based on unilateral weakness during migraine attacks (10).

Neurological deficits typically last 15-60 minutes in most cases. Attacks usually begin in childhood, adolescence, or early adulthood. Diagnosis may be delayed in the absence of a family history (10). Hemiplegic migraine attacks can also be accompanied by fever, lethargy, confusion, ataxia, hemianopia, sensory symptoms, seizures, and loss of consciousness. While neurological deficits usually resolve completely after the attack, they may occasionally persist (10).

Familial hemiplegic migraine was first described by Whitty et al. in 1953 (11). Pathophysiological mechanisms of migraine may involve genetic mutations, neurogenic inflammation, neuropeptides, altered neurophysiology, brainstem activation, and cortical spreading depression. Cortical spreading depression activates the trigeminal nucleus caudalis, leading to dilation of extracerebral circulation, particularly the meningeal arteries, causing headaches (12).

Genetic testing was not performed in this case due to limited availability of genetic analysis in the local clinical setting and the absence of progressive or atypical features that would have altered the management approach. Nevertheless, the clinical picture and the clear autosomal dominant inheritance pattern strongly supported the diagnosis.

The diagnosis of HM is one of exclusion, confirmed by history and routine biochemical, hematological, lumbar puncture, and imaging studies (13). Bradshaw et al. described HM cases in 1965, noting weakness lasting less than an hour in 58% of patients (14). In our case, weakness lasted several hours.

Acute neurological deficits in HM typically resolve quickly, with EEG showing focal slowing during acute episodes, recurrent attacks in the history, and family history supporting the diagnosis. The aura and headache characteristics in our case were consistent, with both visual aura and aphasia present as symptoms. Acute neurological deficits resolved rapidly. Imaging findings in diffusion-weighted MRI (DWI) and ADC sequences may appear normal or hyperintense, while T2-weighted images may show edema resulting from vasogenic causes (5,15). Cranial MRI in our case was normal.

Mild head trauma or angiography can trigger headaches (4). Increased perfusion may be detected in angiography, but caution is necessary as it may worsen clinical findings. Diffuse, severe, throbbing headaches occurring after contrast administration resolve spontaneously within 72 hours (8). Our patient had no history of trauma or interventional procedures such as angiography

Differential diagnoses include epilepsy (Todd's paresis), transient ischemic attack or stroke, metabolic abnormalities (hypercapnia, hypoglycemia, hyponatremia, hypocalcemia), liver or kidney failure, antiphospholipid syndrome, meningitis, and encephalitis (19).

HM is known to be associated with episodic cerebellar ataxia (EA) in 50% of cases. EA type 2 is acetazolamide-responsive paroxysmal cerebellar ataxia, with inheritance linked to similar mutations on chromosome 19. Nonsense mutations cause HM, while frameshift mutations result in EA type 2. The presence of cerebellar ataxia as part of the HM clinical spectrum is not surprising (20). Permanent neurological deficits, including ataxia and cerebellar dysfunction, are observed in 20% of familial cases (21). Nystagmus occurs transiently in 75% and ataxia in 40% of cases (13).

Another diagnosis to consider in differential diagnosis is alternating hemiplegia. This rare condition involves recurrent hemiplegic attacks that may affect one or both sides of the body, accompanied by autonomic changes, nystagmus, ocular motor palsy, and cognitive dysfunction.

Conclusion

The patient was diagnosed with familial hemiplegic migraine based on diagnostic criteria, the absence of pathological findings in imaging and biochemical tests, autosomal dominant inheritance, and the exclusion of other diseases in the differential diagnosis.

This case highlights the importance of considering familial hemiplegic migraine in patients presenting with recurrent motor symptoms and negative neuroimaging, especially when a family history is present.

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Animal Experimental Models Used in The Study of Psychiatric Diseases

Psikiyatrik Hastalıkların Araştırılmasında Kullanılan Hayvan Deneyi Modelleri

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Abstract

Animal experimental models used for modelling psychiatric diseases and treatments are an indispensable tool. But it is impossible to construct a single animal model which demonstrates every aspect of a psychiatric disease. Thus, partial models are preferred. The validity of models is examined for construct, face and prediction dimensions. This evaluation is used together with the similarity with human disease and is of vital importance in terms of obtaining findings that will contribute to clinical applications. Learned helplessness, forced swim tests and tail suspension test are traditional tools for modelling depression with good predictive but limited construct validity so research shifted away from them. In depression research, animal models focusing on basic formations such as anhedonia comes to the fore. Chronic mild stress (CMS) protocol is used to create anhedonia and dependent variables like sucrose preference, intracranial self-stimulation reward (ICSS) and progressive ratio reward are used to measure the anhedonia with good face and predictive validity. Anxiety models include high plus maze, operant conflict test and social interaction paradigms best used to determine drugs anxiolytic effects. Modeling schizophrenia is challenging because of the complexity of positive, negative, and cognitive symptoms that make the disease a uniquely human thought disorder. Pharmacological manipulations like dopaminergic or glutamatergic agents, neonatal brain lesion models, and genetic manipulation techniques have been developed in this area. Prepulse inhibition (PPI), latent inhibition, and working memory tests, while not fully valid, provide results similar to humans. Addiction research utilizes animal models that reflect the stages of binge/intoxication, withdrawal, and craving. Measurements of intracranial self-stimulation threshold (ICSS) measurements, conditioned place preference (CPP), and stress-induced reinstatement are used to demonstrate how substance use escalates, how reward thresholds change, and why relapse occurs. These methods demonstrate strong predictive validity and provide experimental settings for testing new pharmacological interventions. In general, animal models provide an irreplaceable opportunity for investigating the neurobiological and behavioral mechanisms for psychiatric illness. Despite their partial validity, these models are indispensable for investigating etiology, identifying therapeutic targets, and guiding clinical research. Future studies with improved model designs and incorporating genetic and environmental factors will increase the applicability to complex psychiatric conditions.

Keywords: Animal Models, Psychiatry, Schizophrenia Models, Depression Models, Addiction Animal Models.

&

Öz

Hayvan modelleri, psikiyatrik bozuklukların oluşumunu anlamada ve deneysel müdahaleler yapmada önemli rol oynamaktadır. Ancak psikiyatrik hastalıkların tüm klinik özelliklerini hayvanlarda sergileyen kapsamlı modeller oluşturmak mümkün değildir. Bunun yerine, araştırmalarda depresyon, anksiyete, şizofreni ve bağımlılık gibi bozuklukların belirli semptom kümelerine odaklanan kısmi modeller kullanılmaktadır. Depresyon araştırmalarında hayvan deneyleri kronik hafif stres paradigmasıyla modellenir. Bu modelde depresyonun bağımlı değişkenleri ise intrakraniyal öz uyarım, sakkaroz tercihi ve progresif oranlı pekiştireç tepkisi ölçümleridir. Her değişken geçerlilik ve güvenilirlik açısından farklılık gösterse de, anhedoni ve motivasyonel eksiklikler hakkında geçerli ölçümler sunar. Anksiyete modellerinde ölçümler; yükseltilmiş artı labirent, operant çatışma testi ve sosyal etkileşim değerlendirmeleri gibi testler aracılığıyla gerçekleştirilir. Sıklıkla ilaçların anksiyolitik etkilerini belirlemede kullanılırlar. Ancak bu ölçümler genellikle panik bozukluk veya PTSD gibi belirli alt tipler yerine yalnızca yaygın anksiyeteyi yansıtır. Şizofreniyi modellemek, hastalığın insana özgü bir düşünce bozukluğu olması dolayısıyla; pozitif, negatif ve bilişsel semptomların karmaşıklığı nedeniyle güçtür. Bu alanda farmakolojik manipülasyonlar (örn.; dopaminerjik veya glutamaterjik ajanlar), neonatal beyin lezyonu modelleri ve genetik yaklaşımlar geliştirilmiştir. Prepulse inhibisyon, latent inhibisyon ve çalışma belleği testleri, tam görünüş geçerliliği sunmamakla birlikte insanlardaki bulgulara benzer sonuçlar sunmaktadır. Bağımlılık araştırmaları, aşırı tüketim/entoksikasyon, yoksunluk ve aşerme evrelerini yansıtan hayvan modellerinden faydalanır. İntrakranyel self stimülasyon eşik ölçümleri, şartlandırılmış yer tercihi ve stres kaynaklı yeniden madde arayışı gibi ölçümler, madde kullanımının nasıl arttığını, ödül eşiklerinin nasıl değiştiğini ve nüksetmenin neden meydana geldiğini göstermede kullanılır. Bu yöntemler güçlü prediktif geçerlilik gösterir ve yeni farmakolojik müdahaleleri test etmek için deney ortamı sağlar. Genel olarak, hayvan modelleri psikiyatrik hastalıkların altında yatan nörobiyolojik ve davranışsal mekanizmalara ışık tutmada yeri doldurulamaz bir alan sunar. Bu modeller geçerliliklerinin kısmi olmasına rağmen; hastalık etyolojisini araştırmak, terapötik hedefleri belirlemek ve klinik araştırmalara rehberlik etmek için elimizdeki iyi birer araçtır. Model tasarımlarını iyileştirerek ve genetik ve çevresel faktörleri entegre ederek; gelecekteki çalışmalar bu modellerin karmaşık psikiyatrik durumlara uygulanabilme gücünü artıracaktır.

Anahtar Kelimeler: Psikiyatride Hayvan Modelleri, Bağımlılık Modelleri, Şizofreni Modelleri, Depresyon Modelleri.

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Introduction

Animal Experimental Models Used in The Study of Psychiatric Diseases

Animal Model Definitions Associated with Psychiatric Disorders

Animal models are experimental paradigms developed to study specific phenomena observed in humans. Complete animal models encompassing the entire syndrome of psychiatric disorders are conceptually or practically impossible. Although there is no single animal model that reflects the entire clinical picture of the syndrome in the case of addiction, anxiety, or depression, there are partial models that focus on specific elements of these disorders (1). Incorporating issues such as comorbidity, polysubstance use, and child abuse into animal studies is also challenging.

The fact that psychiatric disorders are defined on the basis of a complex and ever-changing classification and include many subtypes and different etiologies makes holistic models difficult in practice. Therefore, approaches that model only certain symptoms of the disorder may be more useful in terms of face, construct and predictive validity (1).

Assessing the Validity of Animal Models

Validity of animal models are generally evaluated across three dimensions (Table 1). The most critical concept in animal models in the field of addiction is construct validity. This refers to the interpretability and explanatory power of the animal model; it also looks at whether the model is consistent with different criteria or known conditions. A procedure is considered to be construct valid if it provides meaningful relationships between observable data (e.g., reward threshold) and a theoretical construct (e.g., the concept of reward) (2). In terms of construct validity, the model and the controlling variables are expected to produce similar results in both the model and the target disorder. This is usually tested with common experimental manipulations (3).

Table 1.

Validity assesment aspects of animal models of psychiatric disorders

1. **Construct Validity:**
    - The degree to which the model reflects the basic biological, genetic or neurophysiological processes of the psychopathological condition in question is evaluated
2. **Predictive Validity:**
    - It is examined whether the animal model responds to the same treatment methods or drugs that are effective in humans. For example, an antidepressant used in a depression model is expected to be effective.
3. **Face Validity:**
    - It is assessed whether the model exhibits behavioral or physiological characteristics similar to symptoms seen in humans. For example, in anxiety models, the presence of fear or avoidance behaviors is important.

Face validity is based on the similarity of animal syndromes to human conditions, but mimicking all human symptoms is usually limited (4). Predictive validity is assessed by the capacity of the model to make accurate predictions about the clinical condition (4).

Animal Models of Depression: Measurements of Reward and Motivation

Introduction and Definitions

Depression is a common and important public health problem and risk factors include genetic and stress-related factors. Traditional animal models used to assess the efficacy of antidepressant drugs consist of a series

of tests that offer high efficiency and ease of use. These tests include antagonism of reserpine-induced behavioral changes (depletion of dopamine, serotonin, and norepinephrine) and potentiation of the effects of substances such as tryptophan(serotonin), apomorphine(dopamine), or yohimbine(norepinephrine) with behavioral measures such as the forced swim test. Such tests are widely used to study the mechanisms of action of antidepressant drugs.

In non-pharmacological depression modeling approaches; various models such as forced swim test, learned helplessness, olfactory bulbectomy have been traditionally used. Today, there is a tendency towards "endophenotype-like" criteria rather than these broad models. Modeling of core depressive symptoms such as reward deprivation(anhedonia) has gained importance due its excellent validity across all three dimentions. Chronic mild stress (CMS) is frequently used to examine the impairment in reward motivation. Here, the main dependent variables are sucrose consumption/preference, intracranial self-stimulation reward (ICSS), and progressive ratio reinforcement for natural reward.

Chronic Mild Stress: A Model for Depression

Rats are exposed to various mild stressors such as they deprived of food and water, constant lighting, tilted cages, cold environment, noise or stroboscopic light for 5–6 weeks. As a result, symptoms associated with depression such as decreased sexual behavior, sleep disturbances, immune and HPA axis dysregulation are observed. Below are the measurement tools to examine depression induced by the chronic mild stress in animals (5) (Table 2).

Table 2.

Behavioral Assessments for Depression in Animals

- Intracranial Stimulation Award (ICSS)
- Sucrose Intake/Preference
- Progressive Ratio Reward

Intracranial Stimulation reward (ICSS)

ICSS offers several advantages over natural rewards: It directly stimulates reward circuits and the extent to which the subject rewards himself can be measured directly (frequency or current intensity). In animals subjected to chronic mild stress, an increase in threshold values in the ventral tegmental area (i.e., a decrease in reward sensitivity) has been observed. The use of antidepressants for 14-21 days can reverse the depressive-like state by lowering this threshold again (5).

Sucrose Intake/Preference

Sucrose is a naturally rewarding substance for rodents. A decrease in sucrose preference is seen as a reflection of anhedonia. In rats with chronic mild stress, sucrose preference typically decreases. This can reversed by antidepressant drug treatment (5).

Progressive Ratio Reward

This method is used to measure the "relative strength" or motivational value of a reward. It does not always give consistent results in the chronic mild stress model; sometimes the response rate does not change or may even increase. In contrast, when depression is modeled with psychostimulant withdrawal, a significant decrease in progressive rate responding is seen (6).

Validity of Animal Models of Depression

As can be seen, the three measures of reward deprivation discussed in this review differ significantly in terms of sensitivity, reliability, and construct validity. Brain stimulation reward provides a reliable and sensitive method for measuring reward deprivation that occurs in substance withdrawal, consistent with reward deprivation described in humans. Neuropharmacological validation of brain stimulation reward has shown that agents that lower thresholds increase reward value in humans, whereas agents that raise thresholds generally elicit dysphoric responses in humans, supporting construct validity (5). With more limited data,

progressive ratio rewarding appears to produce reductions in thresholds for natural rewards associated with substance abstinence, which is consistent with data on brain reward thresholds (7).

However, the sucrose preference model, although widely used, is much less reliable and valid. While some studies associates decrease in consumption with weight loss, others contradict (8). Decreases in sucrose consumption are often not observed during substance abstinence or at all in humans. As a result, many studies have found no changes in sucrose consumption and/or preferences. In fact, humans experiencing episodes of major depression report an increased "craving" for sweets, the opposite of rats exposed to chronic mild stress. However, sucrose consumption after chronic mild stress has predictive validity for antidepressant treatments, which is one reason why sucrose consumption/preferences are increasingly popular in the literature (8). Another reason for the widespread use of sucrose consumption/preference is probably that it is easier to measure.

Anxiety Animal Models

Introduction

Anxiety can be an adaptive emotion in the face of threat, but it can also be disabling when it becomes excessive. Clinically, subtypes such as generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) have been identified. Most animal models aim to examine specific anxiety-like states rather than reflect the full range of symptoms in humans.

Animal Models of Generalized Anxiety Disorder

Animal models of anxiety disorders are listed in Table 3.

Table 3.
Animal Models of Anxiety

Operant Conflict Test
Elevated Plus Maze
Defensive Retreat
Defensive Embedding
Social Interaction
CO_2 inhalation
Schedule-induced polydipsia

Operant Conflict Test

In this widely used test, positive reinforcement (food, water) is sometimes combined with punishing stimuli (electric shock). For example, the Geller-Seifter test (9) and the Vogel conflict test (10) are frequently used. They exhibit high specificity in detecting anxiolytic drugs that target the GABA receptor. However, training for these tests takes time and factors such as the effect of the drug on feeding motivation cannot always be clearly separated (8).

Elevated Plus Maze

It is a plus-shaped maze platform usually 50 cm above the ground. Closed Arms are surrounded by high walls and give the animals a sense of a safer space (11). Open arms have no borders and the feeling of being in an open space can increase anxiety (11). The test assumes that animals naturally experience a conflict between curiosity about new environments and seeking safety.

GABA agonists generally increase exploration in open arms, whereas inverse agonists decrease it. It is popular because it is easy to administer, but it may not always reflect specific types of anxiety such as panic (8).

Defensive Retreat

The time the animal hides in a dark compartment placed in a bright area is recorded. Benzodiazepines shorten the hiding time; adrenergic drugs may increase it. It is thought to reflect agoraphobia. In addition, the effects of CRF agonists/antagonists can be examined in this model and the stress response can be evaluated.

Defensive Burying

It is a test based on rodents burying objects they consider disturbing in sawdust. Benzodiazepines reduce this behavior, and CRF can strengthen it. Similar behavior can be triggered with neutral objects (e.g. glass marbles) (12). It has been suggested that this test has face validity for specific phobias or obsessive-compulsive traits (13).

Social Interaction

Here, the duration of mutual social behavior of two male rats (or mice) in a novel environment is measured. High light or novelty suppresses social interaction and increases anxiety-like behavior. GABA agonists, opioids, and some serotonergic drugs can increase social interaction in a bright environment. Antidepressants are generally ineffective (except for long-term use) (14).

Animal Models of Other Anxiety Disorders

There is no single model with general validity for panic disorder, obsessive-compulsive disorder, and PTSD. Panic attacks can be modeled in rats by CO2 inhalation or lactate, CCK-4 or doxapram infusion. Since panic disorder also include fear of panic attacks with avoidance panic related cues; Vogel conflict test (10) can be used to measure anxiety and this model may reflect CO2-induced panic symptoms in humans. However, unlike humans' rodents do not voluntarily inhale CO2 deeply, so mechanical lung applications on rodents may be a solution for a better panic disorder model.

One proposed model for obsessive-compulsive disorder is "schedule-induced polydipsia," observed in rats exposed to intermittent food intake. Food offered in small amounts and at intervals triggers excessive drinking behavior in response to hunger stimuli. SSRIs reduce excessive drinking after 14–21 days. However, benzodiazepines may increase this behavior, while CRF may decrease it (12), which may have results that may be inconsistent with OCD (13).

Protocols that include various repeated shocks, developed for PTSD but there is no specific pharmacological treatment the biological pathomechanisms of PTSD are still far from being understood, so it is difficult to define exact conditions of construct validity (15).

Validity of Animal Models of Anxiety

Many of these models are aimed at identifying effective drugs for generalized anxiety disorder and have good predictive and face validity in this direction. On the other hand, additional models are needed for panic disorder, OCD, phobia, and PTSD. The lack of pharmacological treatments, especially in the areas of PTSD and specific phobia, makes model development even more difficult.

Another limiting factor is that anxiety requiring treatment in the clinic is seen in patients with high "trait anxiety", whereas animal tests are based on the "state anxiety" (16). Nevertheless, these tests can be considered valid to the extent that they reflect clinical pathology. Genetically high anxiety animal lines or genetic manipulations may allow this distinction to be examined more clearly in the future.

It is also difficult to distinguish different anxiety subtypes in animal models (16). In the case of panic disorder and generalized anxiety disorder, it is not clear whether the two syndromes have separate biological bases (8). While the high-concentration CO2 inhalation test has been used in the differential diagnosis of panic disorder and generalized anxiety disorder in humans, it loses its reliability because rodents do not voluntarily inhale CO2 deeply. More valid panic disorder models can be developed by overcoming this limitation through an alternative method such as the use of a mechanical lung. Factor analysis can separate the behavioral measurements into basic factors such as "anxiety," "exploration," and "locomotor activity" (16).

Schizophrenia

Schizophrenia has been considered very difficult to model in animals due to the human-specific aspects of thought, perception, and language. Currently, classifications offer consensual criteria for a set of possibly overlapping disorders (17, 18). In this framework, schizophrenia includes three main symptom clusters:(1) Negative symptoms (social withdrawal, alogia, apathy, restricted affect), (2) Positive symptoms (hallucinations and delusions), and (3) Cognitive impairments (problems in attention, memory, planning and abstract thinking, disorganization of speech and perception) (17-19). The disease mostly occurs in the 20s; however, prodromal symptoms such as mild sensory, motor and social dysfunctions may be observed at an earlier stage.

Schizophrenia is often considered a neurodevelopmental disorder. What is known about its etiology and pathophysiology is limited, the role of environmental factors (e.g. traumatic life events, substance use, chronic stress) in the development of schizophrenia is remains controversial (20).

All schizophrenia animal models are heuristic tools, due to our incomplete understanding of underlying mechanisms. Pharmacological models disrupt dopaminergic and glutamatergic pathways. Neonatal brain lesion models in rodents aim to mimic developmental brain disorders. Genetic models are based on the manipulation of genes thought to be involved in disease etiology (21).

Behavioral Reflection of Schizophrenia Symptoms

In animal models, not all symptoms of schizophrenia appear simultaneously, as they do in patients (21). In these models, specific behavioral tests are used to investigate how experimental interventions trigger certain symptoms. However, none of the tests are specific to schizophrenia; most are general behavioral paradigms used in other disorders (21).

Cognitive Symptoms

Attention, working memory, executive functions, and declarative memory are frequently impaired in schizophrenia. Since these dysfunctions are not specific to humans, they are easier to study in animals.

Prepulse Inhibition (PPI)

In schizophrenia, patients may not be able to filter sensory information and exposed to excessive stimulation. The PPI paradigm, which regulates the startle reflex, measures the suppression of the response caused by a stronger stimulus by a weaker stimulus. PPI is reduced in schizophrenic patients and in individuals without psychosis who are taking dopamine agonists (22). This impairment can be partially corrected with antipsychotics. Although it is a popular and translational test from an animal model (21), low PPI are not specific nor diagnostic (22).

Latent inhibition

Latent inhibition (LI) is an information filtering concept which refers to reduced attention given to a previously encountered stimulus that was neither important nor reinforcing. Absence of this effect has been linked to the cognitive overload that occurs when patients with schizophrenia pay attention to unimportant stimuli, resulting in an inability to sustain attention. Amphetamine impairs LI in humans (23), whereas antipsychotics enhance it (24). Animal models offer good face and construct validity.

Working Memory and Executive Functions

Working memory is the ability to remember and process information for a short time. Executive functions include higher-level cognitive processes such as planning, decision making, error correction, and attention. These functions are performed by the prefrontal cortex. Impairments on working memory and executive function tests are common in schizophrenia. Working memory and cognitive flexibility can be measured in animal models with tests such as hole-finding, radial arm maze, or Morris water maze (8). Similarly, “attentional set-shifting” tasks have been developed in animals, similar to the Wisconsin Card Sorting Test in humans. Animals with impaired prefrontal cortex function often have difficulty with these “interdimensional attention shift” tests.

Positive Symptoms

It is not possible to directly measure hallucinations or delusions in animals (23). Therefore, "similar" behaviors related to positive symptoms, are examined. For example, increased motor activity (open field test) can be observed in animal models of psychomotor agitation when placed in a new environment. Increased locomotor activity response to psychostimulants can also used as a tool for psychomotor agitation (21).

Negative Symptoms

Ventral hippocampus lesions, DISC1 and NRG1 gene mutations, ketamine infusion and early social isolation are used to create negative symptoms in animals (16). These symptoms can be evaluated using social interaction tests such as the frequency of contact with a stranger, friendly approach and aggressive behavior of the animals (21).

Since the negative symptoms of schizophrenia (anhedonia, social withdrawal, etc.) can also be seen in depression, their association with schizophrenia must be confirmed by demonstrating the ineffectiveness of antidepressant treatments on these symptoms.

Animal Models of Schizophrenia

Animal models of schizophrenia are listed in Table 4.

Table 4.

Behavioral assessments in Schizophrenia Animal Models

Cognitive symptoms
Attention
• Prepulse Inhibition (PPI) • Latent inhibition
Executive functions:
Working memory
• Holeboard • Y-maze • Radial arm maze
Behavioral flexibility
• Extinction of operant behaviors • Morris water maze • Attentional set shift
Positive symptoms
• Open field test • Psychostimulant induced locomotor activity test
Negative symptoms
• Anhedonia • Affective behaviors • Social withdrawal

Pharmacological Models

The first models are based on psychostimulants (amphetamine, methylphenidate) or dopamine agonists(apomorphine) (21). These drugs increase locomotor activity, causing impairments in tests such as PPI and latent inhibition, which are alleviated by antipsychotics (21). It is thought that dopamine excess may be related to the positive symptoms of schizophrenia in particular; however, causal evidence is limited (21).

On the other hand, substances such as NMDA receptor antagonists PCP and ketamine cause psychosis-like symptoms in healthy individuals and increase symptom severity in schizophrenia patients (21). This suggests that glutamate hypofunction may also play a role in schizophrenia. Subchronic PCP administration impairs working memory in animals, which can be partially corrected with atypical antipsychotics (e.g. clozapine) (25). PCP also suppresses social behavior; these effects are more pronounced after chronic use and can be reversed with clozapine, while typical antipsychotics cannot correct this (25).

Neurodevelopmental Models

Epidemiological data have shown that factors such as early pregnancy complications, birth trauma, perinatal hypoxia and prematurity may increase the risk of schizophrenia. In this context, the "neurodevelopmental hypothesis" has been developed. Lipska and Weinberger developed a rat model in which the ventral hippocampus was bilaterally lesioned after in 7th day of life (26). These lesions affect the pathways to the prefrontal cortex, and while normal or mild effects are observed until adolescence, dopaminergic hypersensitivity, increased locomotor response, impaired PPI, working memory deficits and latent inhibition disorders are observed in adulthood (26).

Genetic Models

Human genetic studies have identified many loci and genes thought to be associated with schizophrenia. For example, mutations in the DISC1("disrupted in schizophrenia 1") gene have been linked to certain phenotypes in animals, such as ventricular enlargement and cognitive impairment (27). The G72/G30 locus in the human genome is another candidate; however, these genes may not have an exact counterpart in rodents (8). However, there are studies showing that transgenic mice can exhibit schizophrenia-like behaviors, such as PPI impairment and symptoms that can be improved by antipsychotics (28).

Although schizophrenia is thought to have a hereditary basis, a genomic variant or combination with full penetration has not yet been identified. The fact that the disease is seen in 50% of homozygous twins supports the genetic predisposition, but it also strengthens the view that environmental factors, epigenetic mechanisms, and spontaneous genomic events are at least as effective as genetic factors. In this context, complex gene-environment interactions must also be considered to understand the etiology and pathophysiology of schizophrenia. Although it is not possible to directly examine such interactions in humans, controlled studies on environmental variables can be conducted in modern animal research facilities. Indeed, environmental factors such as urban birth, prenatal viral infections, perinatal oxidative stress, or exposure to cannabinoids during adolescence, which have been shown to affect the rate of schizophrenia in retrospective human studies (29), have also been shown to have significant effects on schizophrenia-related behaviors in rat models (30).

Animal Models of Addiction

Addiction is defined as a disorder ranging from impulsivity to compulsivity and is examined in a three-stage cycle according to DSM-IV criteria:(1) binge/intoxication, (2) withdrawal, and (3) preoccupation/craving (18). Although the first experimental studies in this area focused on the initial positive reinforcement effects of more addictive substances, the primary area of investigation in recent years has been on the motivational changes that develop in the context of addiction (31). Animal models of addiction are listed in Table 5.

Table 5.

Behavioral assessments in animal models of addiction
Intoxication phase
Self-administration
Intracranial self-stimulation (ICSS)
Conditional place preference (CPP)
Drug Discrimination
Genetically selected animal models
Patterns of drug taking despite punishment
Deprivation
Intracranial self-stimulation
Conditioned place aversion
Disrupted operant schedules
Drug discrimination
Measures of anxiety
• Elevated plus maze
• Defensive burying
Preoccupation/Craving
Drug-induced renewal
Cue-induced renewal
Cue induced renewal without extinction (relapse)
Stress-induced renewal
Second Degree Reinforcement Schedules
Protracted abstinence
Conditioned withdrawal

Animal Models of The Intoxication Phase

These models are organized to parallel the DSM-IV addiction criteria for the three stages of addiction (18). For an animal model, it is necessary to objectively define and reliably demonstrate the conditions under which a particular behavior is a symptom of a substance use disorder. Drug reinforcement does not necessarily lead to addiction (e.g., social drinking) because in humans the behavior being modelled can occur in both pathological and normal situations and still have predictive validity. Yet in humans drinking alone has great predictive validity for the binge/intoxication stage of addiction (32), and it is difficult to imagine addiction without drug reinforcement.

Intracranial Stimulation Reward (ICSS) models

As mentioned above in depression models, animals perform a variety of tasks to self-stimulate reward circuts. Drugs of abuse lower ICSS thresholds, and the extent to which drugs reduce ICSS thresholds is strongly correlated with their abuse potential (33).

Conditional Place Preference (CPP) models

CPP is a Pavlovian conditioning paradigm. The animal's preference for environments paired with the drug indicates the positive reinforcement of the substance. Similarly, aversive situations can be measured as place aversion (34).

Drug Discrimination models

In this model, the internal(interoceptive) cues that drugs cause in subjects act as discriminative stimuli that determine which response the animal will give. With this method, it is possible to examine the similarity of a new substance to a known addictive substance with a good predictive validity (35).

Intravenous and Oral Self-administration Models

Animals can learn to self-administer drugs that reward the brain, especially the dopaminergic system, without becoming addicted. Drugs that exhibit positive reinforcement effects, as measured by lowered brain stimulation reward thresholds and conditioned place preference, particularly in models of continuous self-administration, have a large overlap with drugs with high abuse potential in humans. Performance on a progressive ratio schedule can be related to the following principle from the DSM-IV addiction criterion: "Excessive time spent on activities required to obtain the substance" (18). Oral self-administration models are almost always framed around alcohol because of the apparent face validity.

The two-bottle cage drinking option is one of the most widely used paradigms to study ethanol consumption in rodents. In its simplest form, animals are provided access to two water bottles, one containing plain tap water and the other containing ethanol, for 24 hours per day. Daily consumption is measured by the weight change of bottle over a 24-hour period. In this model, the choice of two bottles is sometimes measured by filling both bottles with water and measuring the animal's operant conditioning. In the drinking in the dark model (36), mice can be made to voluntarily consume high doses of alcohol only when alcohol consumption is restricted during day hours. It can be observed that much higher doses of alcohol are consumed as available time is shortened (36).

Genetically Selected Animal Models

In the study, also known as the "Indiana University Rat Lines", high and low alcohol preference strains of rats were genetically selected. The observation that rats in the high alcohol preference strains voluntarily preferred to maintain blood alcohol levels in the range of 50–200 mg% suggests that these rat models have parallels with genetic hypotheses about risky alcohol intake in humans (37).

Patterns of Drug Taking Despite Punishment

In addiction, compulsive use is prominent. In some models, aversive stimuli given simultaneously with the drug reduce substance seeking in non-addicted animals, but seeking is not suppressed in animals with long-term drug intake (38).

Summary of Animal Models of the Intoxication Phase

These methods are reliable tools for understanding the neurobiological basis of acute reinforcing effects and compulsive substance-seeking behaviors during the intoxication phase of the addiction cycle. Although substance addiction is suggested to involve maladaptive mechanisms that go beyond the short-term effects of drugs, examination of positive reinforcing effects provides an important framework for understanding the long-term effects of these mechanisms on motivation.

Drug use disorder is a disease that progresses with periods of intense use and the preferred substance can change. An advantage of intoxication phase models is that they are suitable for designing different operant models with a trained animal. Tests can be performed with the same subject for weeks and dose-effect analyses can be created for different substances. In addition, results can be verified by applying pharmacological manipulations with standard reference compounds (35).

The advantage of the ICSS measurement for studying substance effects on motivation and reward is that behavioral threshold measurements are quantitative (across stimulus frequency and duration) and consistent

over long periods of time. Furthermore, the ICSS technique has high specificity in predicting the abuse potential of drugs; no false-positive results have been recorded to date.

The conditioned place preference (CPP) model stands out with its high sensitivity to low doses, suitability for examining positive and negative reinforcement effects, and allowing drug effects to be tested in sober conditions.

Models such as drug taking despite punishment with progressive ratio schedules have face and construct validity. Literature shows that individuals who meet addiction criteria exert more effort to obtain the substance and their behavioral repertoire narrows around substance seeking and use (18). In rat models of drug seeking despite punishment and progressive ratio paradigms suggest the role of dopamine systems in the reinforcing effects of cocaine in rats (31).

Animal Models of The Deprivation Stage

Withdrawal from chronic drug use is often characterized by reactions that are the opposite of the acute and initial effects of the substance. Many of the physical symptoms that occur during withdrawal from drugs such as alcohol and opioids in animals can be easily quantified, thus providing an important indicator for studying the neurobiological mechanisms of addiction (39). Standardized rating scales have been developed for opiate, nicotine, and alcohol withdrawal. However, measuring the motivational aspects of withdrawal is more relevant for understanding the counter adaptive mechanisms that drive addiction. The measures are discussed below and they are highly sensitive in identifying the motivational aspects of drug withdrawal (35).

Animal models that have examined motivational withdrawal effects include operant mechanisms, conditioned place aversion, intracerebral self-stimulation (ICSS), elevated plus maze, and drug discrimination. Some reflect the general bad feeling of withdrawal, while others reveal more specific components (8).

Threshold Increase in ICSS

Withdrawal from all major drugs after chronic use increases ICSS thresholds, meaning reward sensitivity decreases.

Conditioned Place Avoidance Response (CPA)

The aversive stimulus effects of withdrawal can be measured by conditioned place aversion, a variant of CPP. One method used in opioid addiction is to induce withdrawal by administering low dose naloxone. Although naloxone alone produces place aversion in nondependent rats, the threshold dose required to produce place aversion in dependent rats is significantly reduced. Place aversion has also been observed in induced nicotine withdrawal and acute spontaneous ethanol withdrawal.

Anxiety-Like Responses

Anxiety-like behaviors that increase with drug withdrawal can be assessed with height avoidance (elevated plus maze) or defensive burying tests.

Drug Self-administration in Long-Term dependent Animals

An important feature of the development of addiction is the increase in frequency and quantity of use over time, which is also a DSM-IV diagnostic criteria (18). Extended access models have frequently seen a transition from initial use to higher doses. Recently, animal models of prolonged drug self-access and models of drug self-administration during withdrawal in dependent animals are useful for understanding the transition from drug use to addiction. In rats with induced alcohol dependence, it was observed that ethanol intake was approximately doubled after the withdrawal period and the animals were able to maintain blood alcohol levels of 100-150mg% for 12 hours (8). This phenomenon, called the "withdrawal effect," has been observed in mice, rats, monkeys, and social drinkers.

Overview of Deprivation Phase in Animal Models

The motivational effects of withdrawal in humans (dysphoria, anhedonia elements, loss of motivation, anxiety, and irritability) are also observed in these animal models. Increase in ICSS thresholds has high predictive value, impairment in operant responding indicates at least a general state of discomfort, while drug

discrimination provides a sensitive and powerful method for comparing other drug's withdrawal states. Acamprosate and naltrexone have been shown to be more effective in reducing alcohol intake in addicted rats.

In models of prolonged use, an increase in breaking point (the point at which the subject stops trying when no new reward is received) of the progressive ratio reward for substances such as cocaine, methamphetamine, heroin, and nicotine means that the motivation to seek the substance or the reward of the substance increases.

As more data emerge to explain the neurobiological basis of negative mood in animals and as comparisons with similar negative mood in humans are made, the construct validity of these models will be strengthened. Increased drug consumption with prolonged use has been replicated in many times and has been linked to mechanisms of cross-system tolerance and reward allostasis.

Multiple variables used to understand the motivational effects of withdrawal may provide a framework for identifying overlapping neurobiological bases. Finally, the reinforcing properties of drugs may also change with addiction (8). Evidence from behavioral measures (response impairment, reward threshold change, conditioned place aversion) suggests that addiction alone may lead to an aversive motivational state (40).

Animal Models of The Preoccupation/Craving Stage

The most important feature of addiction is that it follows a chronic and relapsing course. In animals, "relapse" has been studied in three ways:(1) drug-priming induced renewal, (2) cue-based renewal, and (3) stress-induced renewal (41).

Drug-priming Induced renewal

Injecting a small dose of the drug into animals whose drug seeking has been extinguished will cause the drug seeking behavior to dramatically increase again (8).

Cue Based renewal

The auditory, visual, etc. cues associated with the drug alone can rekindle the old "lever" or "button" pressing behavior (42).

Cue induced renewal without extinction(relapse)

In humans, relapse can occur when drug cues are exposed in everyday life without overt "extinction," and in the laboratory, drug seeking increases dramatically in animals when cues are given after "forced remission" (42).

Stress induced renewal

Stress and anxiety are among the most common triggers for relapse in humans, and in animals, stressors such as electric shock, starvation, cold, social defeat, and yohimbine reactivate extinguished drug-seeking behavior (43).

Second Order Reinforcement Schedules

It refers to two-stage complex reinforcement systems in which a neutral stimulus becomes the reinforcer of another neutral stimulus. Second-order reinforcement schedules are a complex system formed by combining two different reinforcement programs.

Animals are trained to associate a repetitive stimulus, initially neutral, with a drug—for example, a tone is played every time a lever is pulled 10 times, followed by 100 sounds and then the drug is administered.

These setups examine how animals can sustain neutral behaviors at extremely high intensity in anticipation of drug availability. This approach allows for modeling drug seeking behaviors absence of the drug (44).

Protracted Abstinence

Even if physical and motivational withdrawal symptoms disappear, an individual who has reached a level of addiction can quickly reverse to their previous level of addiction when they start using the substance again. In animal models, when access to the substance is provided again weeks after the cessation of chronic alcohol or opioid use, tolerance develops much more rapidly and use above previous doses can be observed in a short time (8, 45).

Overview of Animal Models of Addiction

Overall, many of these models have good predictive validity for at least a particular stage of the addiction cycle. The motivational effects of withdrawal are examined by ICSS threshold elevation and anxiety measures. Cue, drug, or stress-induced renewal models are used in the craving phase. Important parallels have been demonstrated between animal findings and human relapsing behavior.

These models provide insight into mechanisms in addiction, from changes in the reward system to negative affect and exaggerated responses to stress.

Conclusion

Animal models are experimental tools designed to investigate and better understand phenomena observed in humans. Due to inherent species differences; these models are not intended to fully replicate complex human mental disorders such as schizophrenia, depression, anxiety or addiction. Instead, their aim is to demonstrate and experiment with key features of diseases leading the development of partial models.

The limitations of animal models of schizophrenia are related to our incomplete understanding of the pathophysiology of the disease. Most of the genes associated with schizophrenia thought to exert their effects primarily through prefrontal cortex. However, many of the susceptibility gene mutation models fail to demonstrate penetrance, possibly because animal prefrontal cortex is not as developed as that of humans. Despite this challanges, pharmacological (dopamine/glutamate) and neurodevelopmental lesion approaches can be applied with behavioral tests that partially reflect positive, negative and cognitive symptoms (locomotor activity, PPI, latent inhibition, social withdrawal and executive function tests).

Addiction models are also partial models and each reflect the stages of intoxication, withdrawal, and craving. They offer high face and predictive validity for respective stages. However, construct validity remains the weakest aspect of such models.

Approaches that focus on reward deprivation in depression (e.g. intracranial self-stimulation, progressive ratio response) or those with strong predictive validity for anxiety (elevated plus maze, conflict tests, etc.) are commonly used. These models have remained at the forefront because of their widespread application in drug development studies.

In modeling depression and anxiety disorders, paradigms focused on the monoamine hypothesis have been extensively utilized, while many other factors involved in the etiology of these disorders (such as inflammation, apoptosis, cytokine-mediated stress pathways, growth factors, genetic and epigenetic factors and nutrition) have not been adequately modeled. Incorporating these factors could be pivotal for improving construct validity in anxiety models. In addition, resilience to neurotic disorders is at least as important as predisposing factors, yet it has received very little attention. Future studies should therefore focus on models of pathophysiology. Shared genetic and epigenetic markers between humans and animals could serve as promising targets for future interventions.

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GSTT-1 ve GSTM-1 Gen Delesyonlarının Mide Kanseri Gelişim Riski Üzerine Etkisi

The Effect of GSTT-1 and GSTM-1 Gene Deletions on Gastric Cancer Development Risk

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Öz

GİRİŞ ve AMAÇ: Mide kanseri tüm dünyada en sık görülen kanserlerden olup erken tespiti ve risk faktörlerinin kontrolü en etkin korunma yöntemi olmaktadır. Değişik genlerin spesifik varyant alellerine bağlı genetik yatkınlık çevresel maruziyetin etkisini modifiye edebilmektedir. Bu çalışmada GSTT-1 ve GSTM-1 gen delesyonlarının mide kanseri üzerindeki etkileri araştırılmıştır.

YÖNTEM ve GEREÇLER: Bu çalışmaya, Ankara Üniversitesi Tıp Fakültesi Genel Cerrahi Kliniğine Mide Adenokanseri tanısı alan 61 hasta vaka grubu olarak, endoskopi ünitesine üst Gastrointestinal sistem endoskopisi yaptırmak için başvuran 61 hasta kontrol grubu olmak üzere toplamda 122 hasta dahil edildi. Vaka ve kontrol grubuna ait parafin doku örnekelerinden sıvı DNA izole edildi. Sıvı formdaki DNA'lardan PCR yapılarak GSTT-1 ve GSTM-1 gen delesyonu durumuna bakıldı.

BULGULAR: Vaka grubunda tümöral ve normal dokuların GSTT-1 ve GSTM-1 gen delesyonu durumuna göre karşılaştırılmasında anlamlı bir fark ortaya çıkmadı. Vaka grubu tümöral ve normal dokularının GSTT-1 ve GSTM-1 gen delesyonu durumu ile kontrol grubu GSTT-1 ve GSTM-1 gen delesyonu durumu arasında anlamlı bir fark ortaya çıkmadı.

TARTIŞMA ve SONUÇ: Bu çalışmada GSTT-1 gen delesyonu ya da GSTM-1 gen delesyonu ile mide kanseri arasında anlamlı bir ilişki bulunamamıştır.

Anahtar Kelimeler: Mide kanseri, Gen delesyonu, GSTT-1, GSTM-1

Abstract

INTRODUCTION: Gastric cancer is one of the most common malignancies worldwide, and early detection and controlling risk factors are best effective preventative methods. Genetic susceptibility due to specific variant alleles of different genes can modify the effect of environmental exposure. In this paper effects of GSTT-1 and GSTM-1 gene deletions on gastric cancer were evaluated.

METHODS: One-hundred and twenty-two patients were included the study. Sixty-one patients those were treated in Ankara University Department of General Surgery and included in case group, 61 patients those were performed upper gastrointestinal system endoscopy included in control group. Liquid DNA was isolated from parraffin blocks and GSTT-1 and GSTM-1 gene deletions were evaluated in both groups.

RESULTS: There were no significant difference between normal and tumor tissue in the case group in terms of GSTT-1 and GSTM-1 deletions. Also in comparison of GSTT-1 and GSTM-1 gene deletion status, there were no significant difference between control group and case group.

DISCUSSION and CONCLUSION: In this study, no relationship was found between GSTT-1 or GSTM-1 gene deletions and gastric cancer.

Keywords: Gastric cancer, gene deletion, GSTT-1, GSTM-1

GİRİŞ

Mide kanseri dünyada en sık görülen gastrointestinal sistem kanserlerinden biridir (1,2). Düşük survi oranları göz önüne alındığında mide kanseri risk faktörlerinin belirlenmesi ve önlenmesi önem arz etmektedir. Mide kanserinin gelişiminde çevresel faktörlerin yanında genetik faktörlerin de rol oynadığı çalışmalarda gösterilmiştir (3-8).

Glutatyon S transferaz gen ailesi çevresel karsinojenlere karşı hücrelerin korunmasında rol oynamaktadır (9,10). GSTT1 ve GSTM1 gen delesyonlarının mide kanseri gelişimi arasındaki ilişki bazı çalışmalarda ortaya konmuş olmakla birlikte literatürde çelişkili veriler mevcuttur (11-15). Bu çalışmada mide kanseri olgularının tümör dokusu, tümör olmayan mide dokusu ve sağlıklı kontrol grubundaki kişilerden alınan mide dokusu örneklerindeki GST gen delesyon durumu araştırılmıştır.

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GEREÇ ve YÖNTEMLER

Bu çalışma Ankara 2 Nolu Klinik Araştırmalar Etik Kurul Başkanlığı'nın 19 Ekim 2009 tarih ve 02-03 Sayılı onayı ile yapılmıştır. Çalışmaya Ankara Üniversitesi Tıp Fakültesi Genel Cerrahi kliniğinde Ocak 2008- Ocak 2010 tarihleri arasında mide adenokarsinomu tanısı ile ameliyat edilen 61 hasta (Vaka grubu) ile dispeptik şikayetler nedeniyle yine aynı kliniğin endoskopi ünitesinde üst gis endoskopisi yapılan 61 hasta kontrol grubu olmak üzere toplam 122 hasta dahil edildi. Tüm olgulardan aydınlatılmış onam formları alındı ve çalışmaya katılan hastalara anket formu doldurduldu.

DNA İzolasyonu

Tümör DNA'sını elde etmek için rezeksiyon materyalinden rutin inceleme için hazırlanmış olan tümörlü parafin bloklardan 10 µ kalınlığında parafin kesitler alındı. İşaretlenen boyalı preparatlara denk gelen boyasız kesitlerin deparafinizasyonu sonrasında mikroskop altında tümör diseksiyonu yapıldı. Takiben diseksiyon materyali DNA ekstraksiyonunun gerçekleşeceği DNA ekstraksiyon buffer içine alındı. Ekstraksiyon buffer daha önce tanımlanan şekilde hazırlandı. Blokta az sayıda tümör hücresi bulunması durumunda ise lazer mikrodiseksiyon ile elde edilen hücrelerden 'QIAamp DNA FFPE T tissue kit (Qiagen) ile DNA ekstraksiyonu gerçekleştirildi. Yukarıda tanımlanan yöntemler ile mide tümörlü hastaların rezeksiyon materyallerindeki tümörsüz sahadan alınan örneklerden ve kontrol grubundan alınan örneklerden DNA ekstrasyonu yapıldı.

Polimeraz zincir reaksiyonu (PCR)

Bu çalışmada PCR tekniği ile GSTT1 ve GSTM1 gen delesyonları için seçilen bölgenin amplifikasyonu gerçekleştirildi. GSTT1 ve GSTM 1 gen delesyonlarının belirlenmesi için yapılan polimeraz zincir reaksiyonlarında son konstantrasyonları 10pmol/µl olacak şekilde primerler kullanıldı. GSTT1 geninin delesyonunu göstermek amacı ile yapılan PCR tekniği için amplifikasyonda forward 5' TCCTTACTGGTCCTCACATCT - 3 reverse: 5'-GTGTGGCAGCATAAGCAGGACT-3' primer çiftleri kullanıldı. GSTM1 geninin delesyonunu göstermek amacı ile de forward: 5'-GAA GGT GGC CTC CTC CTT GG-3' reverse: 5'-AATTCTGGATTGTAGCAGAT-3' primer çiftleri kullanıldı.

İstatistiksel Analiz

Verilerin analizinde SPSS 23.0 paket program kullanıldı. Sayısal değişkenlerin karşılaştırılmasında ki-kare, sürekli değişkenlerin karşılaştırılmasında ise Student-t testi kullanıldı. Tümör dokusu ve sağlıklı dokulardaki GSTT1 ve GSTM dağılımları arasındaki farkın saptanması için Mc-Nemar testi kullanıldı. Tüm testler için $p<0.05$ değeri anlamlı olarak kabul edildi.

Olguların klinik ve demografik özellikleri tablo 1'de gösterilmiştir. Adenokanser tanısı alan hastalarda tümörlü dokular ile normal dokular arasında GSTT1 ve GSTM1 delesyonları açısından bir fark saptanmadı ($p=1.00$, $p=1.00$). Vaka grubunun tümörlü dokuları ile kontrol grubunun dokuları karşılaştırıldığında GSTT1 ve GSTM1 delesyonu açısından anlamlı fark bulunamadı ($p=0.823$ ve $p=0.856$). Vaka grubunun normal dokuları ile kontrol grubu dokuları arasında GSTT1 ve GSTM1 delesyonu açısından anlamlı fark bulunamadı ($p=1.00$ ve $p=1.00$). Vaka ve kontrol grubundaki hastalar cinsiyet açısından ayrı ayrı değerlendirildiğinde GSTT1 ve GSTM1 delesyonları açısından anlamlı fark saptanmadı. Sigara kullanımı ile GSTT1 ve GSTM1 delesyonları arasında istatistiksel olarak anlamlı farklılık saptanmadı ($p=0.975$). (Tablo 2).

TARTIŞMA

Çalışmamızda GSTT1 ya GSTM1 gen delesyonları ile mide kanseri arasında anlamlı bir ilişki saptanmamıştır. GST gen delesyonu ile ilgili yapılan çalışmaların çoğunda analizler periferik kan örnekleri alınarak yapılmıştır (13-15). Diğer

çalışmalardan farklı olarak bu çalışmada genetik analizler mide dokusundan yapılmıştır. Ayrıca genetik polimorfizmin yanı sıra yaşam tarzı, beslenme alışkanlığı ve sigara kullanma gibi faktörler de analiz edilmiştir. Torre ve arkadaşları tarafından yapılan meta-analizde periferik kan örneklerinden yapılan analizde GSTM1 delesyonu ile mide kanseri arasından anlamlı ilişki saptanmıştır. Yine bu çalışmada sigara kullanan hastaların GSTM1 eksikliğinin mide kanseri riskinin yaklaşık 3 kat arttığı bildirilmiştir (16). Ricerio ve arkadaşlarının yayınladığı bir meta-analizde GSTM1 ve mide kanseri arasında Asya ve Avrasya populasyonunda pozitif korelasyon saptanırken, Avrupa ve Amerika populasyonunda korelasyon saptanmamıştır (17). Bu meta-analiz etnik faktörlerin de mide kanseri gelişimi üzerinde etkili olabileceğini göstermektedir. Ülkemizde yapılan bir çalışmada Tamer ve arkadaşları GSTM1 delesyonunun mide kanseri riskini arttırdığını ileri sürmüşlerdir (18). Bizim çalışmamızda GSTM1 delesyonu ile mide kanseri arasında bir ilişki saptanmamıştır.

GSTT1 delesyonu ile ilgili literatürde çelişkili sonuçlar bulunmaktadır. Uzakdoğu ülkelerinden yapılan bazı çalışmalarda GSTT1 delesyonunun mide kanseri gelişiminde rol oynamadığı bildirilmiş iken karşıt görüş bildiren çalışmalar da mevcuttur (19-22). Tamer ve arkadaşları iki farklı bölgeden hastaların dahil edildiği çalışmasında GSTT1 delesyonu ile mide kanseri arasında ilişki gösterememiştir (18). Bizim çalışmamızda GSTT1'in mide kanseri gelişimi üzerine bir etkisi olmadığı sonucuna varılmıştır. Çalışmalar arasındaki bu çelişkili sonuçlar bölgesel ve etnik faktörlerin gen delesyonları ve kanser gelişimi üzerine etkili olduğunu düşündürmektedir.

Çalışmamızda mide kanseri ile kahve tüketimi arasında anlamlı ilişki bulunmuş olup bu bulgu literatür verileri ile de uyumludur (23,24). Ancak fazla sayıda hasta içeren populasyon bazlı çalışmalarda kahve tüketiminin mide kanseri riskini arttırmadığı bildirilmiştir (25,26).

Çalışmamızın belirtilmesi gereken birtakım kısıtlılıkları mevcuttur. İlk olarak çalışmamızda denek sayısı görece olarak az olup daha yüksek olgu sayısı içeren çalışmalar istatistiksel olarak farklılık gösterebilir. Ayrıca tümör yerleşim yeri, tümörün derecesi ve evresi ile gen delesyonları arasındaki ilişki çalışılmamış olup çalışmanın limitasyonları olarak kabul edilebilir.

Sonuç

Bulgularımız GSTT1 ve GSTM1 gen delesyonlarının mide kanseri üzerine etkili olmadığını göstermektedir. Benzer çalışmalarda gen delesyonu özellikle sigara içimi ile değerlendirildiğinde anlamlı sonuçlara ulaşılmıştır. Çalışmalar arası farklılıklar etnik ve coğrafik değişiklerin mide kanseri gelişiminde etkili olması nedeniyle olabilir.

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Tablo 1. Grupların demografik ve klinik özellikleri

	Vaka	**Kontrol**	**P değeri**
Yaş (ortalama±SS)	60.46 ±10.2	41.79 ±13.5	p<0.01
Cinsiyet			
Erkek	42 (%68.9)	25 (%41)	p<0.01
Kadın	19 (%31.1)	36 (%59)	
Sigara			
İçiyor	26 (%42.6)	33 (%54.1)	
İçmiyor	26 (%42.6)	16 (%26.2)	p<0.162
Ex-smoker	9 (%14.8)	12 (%19.7)	
Alkol			
Yok	33 (%54.1)	35 (%57.4)	*
Nadiren	22 (%36.1)	25 (%41)	
Haftada bir	5 (%8.2)	0 (%0)	
Sık	1 (%1.6)	1 (%1.6)	
Tütsülenmiş gıda			
Yok	3 (%4.9)	4 (%6.6)	
Nadiren	39 (%63.9)	46 (%75.4)	p=0.240
Sık	19 (%31.1)	11 (%18)	
Kahve			
Yok	26 (%42.6)	21 (%34.4)	
Nadiren	13 (% 21.3)	31 (%50.8)	P<0.01
Sık	22 (% 36.1)	9 (% 14.8)	
Çay			
Yok	4 (%6.6)	1 (%1.6)	*
Nadiren	1 (% 1.6)	2 (%3.3)	
Sık	56(% 91.8)	58 (% 95.1)	

Tablo 2. Çalışma gruplarındaki GSTT1 ve GSTM1 delesyonları

	Normal doku (Vaka grubu)	**Tümör Dokusu (Vaka grubu)**
GSTT1 delesyonu (n)		
Var	12	13
Yok	49	48
Toplam	61	61
GSTM1 delesyonu (n)		
Var	29	30
Yok	32	31
Toplam	61	61
	Normal doku (Kontrol grubu)	**Tümör Dokusu (Vaka grubu)**
GSTT1 delesyonu (n)		
Var	12	13
Yok	49	48
Toplam	61	61
GSTM1 delesyonu (n)		
Var	29	31
Yok	32	30
Toplam	61	61
	Normal doku (Kontrol Grubu)	**Normal doku (Vaka grubu)**
GSTT1 delesyonu (n)		
Var	12	12
Yok	49	49
Toplam	61	61
GSTM1 delesyonu (n)		
Var	29	30
Yok	32	31
Toplam	61	61

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