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Hand Dominance in Fibromyalgia

Fibromiyaljide El Dominansı

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ABSTRACT Objective: To evaluate the handedness and its relationships with disease severity and functional outcomes related to fibromyalgia. **Material and Methods:** This cross-sectional study included 40 fibromyalgia patients aged 20-50 years and 40 healthy volunteers in the same age range as the control group. Data on the age, gender, height, weight, comorbidities, fibromyalgia diagnosis time, and treatments of the participants were recorded. Handgrip strengths with Jamar-type hand dynamometer, tip pinch strengths with pinch meter, and hand dexterities with the Nine-Hole Peg Test were evaluated for both hands of participants. The Edinburgh Handedness Inventory (with Geschwind scoring), Beck Depression Inventory, Beck Anxiety Inventory, and the Revised Fibromyalgia Impact Questionnaire were administered. **Results:** The right Edinburgh score (p<0.001) and Geschwind score (p=0.04) were significantly lower in the patient group. The number of non-right-handed (p=0.01) and ambidextrous (p=0.01) participants were significantly higher in the patient group. Ambidexterity was a statistically significant risk factor for fibromyalgia [OR%95CI: 6.02 (1.48-25.25), p=0.01]. The right Edinburgh score was negative, low-moderate correlated with fibromyalgia symptom severity score, and the Revised Fibromyalgia Impact Questionnaire -symptoms score (for both correlations; r=-0.36 p=0.02) **Conclusion:** Fibromyalgia may be associated with non-right-hand handedness. Right-handedness may be associated with more symptom severity in fibromyalgia.

Keywords: Fibromyalgia; functional laterality; ambidexterity; handedness

ÖZET Amaç: Fibromiyaljide el dominansının hastalık şiddeti ve hastalığa bağlı fonksiyonel sonuçlarla ilişkisini değerlendirmek. **Gereç ve Yöntemler:** Kesitsel tipteki bu çalışmaya 20-50 yaşlar arasında, 40 fibromiyalji hastası ve kontrol grubu olarak 40 sağlıklı gönüllü dâhil edildi. Yaş, cinsiyet, boy, ağırlık, komorbiditeler, fibromiyalji tanı süresi ve hastaların almakta oldukları tedavilere ilişkin veriler kaydedildi. Katılımcıların her 2 eli için Jamar tipi dinamometre ile el kavrama kuvvetleri, pinçmetre ile parmak ucu kavrama kuvvetleri, dokuz delikli tahta testi ile el becerileri değerlendirildi. Katılımcılara Edinburgh El tercihi anketi (Geschwind skorlamasıyla), Beck Depresyon anketi, Beck anksiyete anketi ve revize Fibromiyalji etki anketleri uygulandı. **Bulgular:** Sağ Edinburgh skoru (p<0.001) ve Geschwind skoru (p=0.04) hasta grubunda anlamlı olarak düşük izlendi. Sağ elli olmayan (p=0.01) ve ambidekster (p=0.01) katılımcı sayısı hasta grubunda anlamlı olarak daha yüksekti. Ambideksteritenin fibromiyalji için istatistiksel olarak anlamlı bir risk faktörü olduğu izlendi [RR%95GA: 6.02 (1.48-25.25), p=0.01]. Sağ Edinburgh skorunun fibromiyalji semptom şiddeti skoru ve revize fibromiyalji etki anketi skoru ile negatif yönde düşük-orta derecede korele olduğu izlendi (her 2 korelasyon için; r=-0.36 p=0.02). **Sonuç:** Fibromiyalji sağ el dışı el tercihi ile ilişkili görülmektedir. Sağ ellilik fibromiyaljide daha fazla semptom şiddeti ile ilişkili olabilir.

Anahtar Kelimeler: Fibromiyalji; fonksiyonel lateralite; iki el becerisi; el tercihi

Functional and structural hemispheric asymmetries are among the basic organizational principles of the human brain.[1–3] This results in the development of lateralization, one of the key features of human motor behavior.[1] Typically, the dominant hand movement is usually associated with strong activation of the contralateral hemisphere, while the non-dominant hand movement is associated with a bilateral activa-

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tion pattern.[4] In the presence of atypical cerebral motor lateralization, stronger right hemispheric activation is observed in left-handed use, and the bilateral activation pattern is more than normal in right-handed use.[4] The direction and typing of structural and behavioral asymmetries are mostly based on these contexts; about 90% of people are right-handed dominant, but the severity of dominance can vary.[3,5] Atypical lateralization, on the other hand, is an uncommon picture in the population, and it has been reported that approximately 10.6% of the population is left-handed dominant, and 9.3% is mixed dominant.[3,5]

It is not easy to directly evaluate brain lateralization.[6] Asymmetric hand use, known as handedness or hand dominance, which is accepted to reflect the asymmetry in the structural and functional organizations of the brain, is accepted as the most prominent finding of lateralization.[1,5-7] For this reasons, the evaluation of handedness is seen as an inexpensive, easy, and reliable measure reflecting brain lateralization.[6]

Handedness includes the concepts of hand preference and hand performance.[1] The term hand preference refers to the hand that plays the guiding and manipulating role while the other hand plays the supporting or stabilizing role.[1] Hand preference can vary according to its direction (right or left-handed) and degree (pure or mixed).[1] In the evaluation of hand preference, hand use in daily life is generally questioned by self-reported questionnaires (the most popular and frequently used one is the Edinburgh Handedness Inventory).[1] Manual dexterity or hand performance is assessed by motor performance tasks [(e.g., the nine-hole peg test)].[1] It is recommended to evaluate hand preference and hand performance together in the evaluation of handedness.[1,5]

Evaluating laterality changes in different psychiatric and neurodevelopmental diseases has recently been one of the popular perspectives of laterality studies.[2]

Fibromyalgia is a biopsychosocial disease model characterized by the experience of complex chronic widespread pain of unknown origin.[8,9] The course of fibromyalgia with nociplastic pain, the clinical picture often accompanied by mood and cognitive disorders, the association of biological and psychosocial factors with disease symptoms, and the fact that patients benefit from cognitive-behavioral treatment applications suggest that changes related to the central nervous system may be an important mechanism in this disease.[8,9] Indeed, some functional and structural changes (in white and gray matter) and changes in the connections between different brain areas have been reported in fibromyalgia patients.[8,10] In addition, the benefit of methods that modify brain connections, such as transcranial magnetic stimulation and antidepressant drug treatments, supports that functional connections in the brain may be impaired in the course of the disease.[8] The existence of these conditions related to central nervous system changes in fibromyalgia has brought to our mind the question of whether there are changes in structural and functional brain asymmetries, brain lateralization, and, therefore, handedness in fibromyalgia, similar to the previously mentioned psychiatric and neurodevelopmental diseases.

To our knowledge, there is no study in the literature evaluating brain lateralization or handedness in fibromyalgia. The aim of our study is to evaluate handedness, which is an indicator of brain lateralization, and its relationships with fibromyalgia disease severity and functional outcomes related to fibromyalgia in patients with fibromyalgia.

MATERIAL AND METHODS

STUDY DESIGN AND SAMPLE SELECTION

This cross-sectional study included 40 fibromyalgia patients aged 20-50 years, meeting the American College of Rheumatology (ACR) 2016 Fibromyalgia Diagnostic Criteria, and 40 healthy volunteers in the same age range as the control group.[11] Exclusion criteria were defined as being younger than 20 years of age, older than 50 years of age, having systemic, inflammatory, degenerative, and neurological diseases that may lead to loss of hand and finger grip strength and dexterity, and having a history of hand surgery or trauma in the last three months. Ethics committee approval and informed consent form were obtained for the study (Ethics Committee of Yenimahalle Training and Research Hospital, Ankara, Türkiye (date: March 04 2021, no: 2021-04-05). The principles of the Declaration of Helsinki were complied with.

DATA COLLECTION

Information about the age, gender, height, weight, and comorbidities of the participants included in the study was recorded. In addition, information about the duration of fibromyalgia diagnosis and pharmacological and non-pharmacological treatments for fibromyalgia were also recorded in the patient group.

Handgrip strengths with Jamar-type hand dynamometer, tip pinch strengths with pinch meter, and hand dexterities with the Nine-Hole Peg Test (NHPT) were evaluated for both hands of all participants.[12,13] The Edinburgh Handedness Inventory (EHI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were administered to all participants.[14-16] In addition, the ACR 2016 Fibromyalgia Diagnostic Criteria were questioned in the patient group, and the Revised Fibromyalgia Impact Questionnaire (FIQR) was applied.[11,17]

OUTCOME PARAMETERS

The handgrip and tip pinch strengths: The handgrip strength and tip pinch strength of the participants were measured using the Jamar-type hand dynamometer (Baseline, White Plains NY 10602, USA.) and pinch meter (Baseline, White Plains NY 10602, USA.) available in our clinic. The handgrip strengths were measured with shoulders in adduction and neutral rotation, elbows in 90-degree flexion, and forearms and wrists in a neutral position, while the tip pinch strengths were measured by squeezing a pinch meter between the thumb and index finger.[12,18] Participants took a deep breath and then applied gripping force with maximal force while exhaling. In the analysis, the average of the three measurements made with an interval of five minutes was taken as the basis for the analysis.[12]

NHPT: NHPT was used to evaluate the hand dexterity of the participants.[13] This test consists of a square area and nine holes in this area, nine cylinders suitable for these holes, and a storage box. Participants quickly took the nine cylinders from the storage box and placed them in the holes, and after placing all the cylinders, they put the cylinders back in the storage box one by one. In the evaluation of the test, the time elapsed during these operations was measured in seconds with a chronometer, and shorter times were considered to indicate better hand dexterity.[13]

EHI: It is a questionnaire developed by Oldfield in 1971 to evaluate handedness.[14] The Turkish reliability study of the questionnaire was conducted in 2019 by Atasavun Uysal et al. and the validity and reliability study was conducted by Tuna in 2021.[19,20] This inventory questions individuals' hand use in 10 different activities of daily living (writing, drawing, throwing, using scissors, brushing teeth, using a knife, using a spoon, using a broom, lighting a match, opening a box). In the inventory, there are two boxes for each activity questioning the use of the right and left hand. Only the right or left hand is always used for the specified activity; if the other hand is not used at all, both boxes for the used hand are checked. Generally, if the right or left hand is used for the specified activity, one of the boxes for the used hand is checked. If the specified activity is performed using both hands, one of the boxes on both the right and the left is checked. Right, and left-hand scores are calculated by counting the boxes checked for right and left-hand use.[14,19,20] In addition, Geschwind scoring was also used in our study. In this scoring, always right-handed activities are scored as +10, usually right-handed activities as +5, ambidextrous activities as 0, usually left-handed activities as -5, and always left-handed activities as -10. The total score ranges from -100 to +100.[19,21] In accordance with the Turkish reliability study, in our study, participants with a total score below -40 were grouped as left-handed, those between -40 and 40 (including these values) as ambidextrous, and those above 40 as right-handed.[19]

BDI: It is a scale developed by Beck et al. in 1961 to evaluate the level and severity of depressive symptoms.[15] The Turkish validity and reliability study was conducted by Hisli in 1989.[22] The scale consists of 21 questions in a 4-point Likert structure, where each question is scored between 0 and 3. In our study, those with a scale score of 9 and below were considered those without depression, and those with a score above nine were considered those with depression.[15]

BAI: It is a scale developed by Beck et al. in 1988 to determine the frequency of anxiety symptoms experienced by individuals.[16] The Turkish validity and reliability study was performed by Ulusoy et al. in 1998.[23] The scale consists of 21 questions in a 4-point Likert structure, where each question is

scored between 0 and 3. Higher scores indicate more severe anxiety. In our study, those with a scale score of 7 and below were considered those without anxiety, and those with a score above seven were considered those with anxiety.[16]

ACR 2016 Fibromyalgia Diagnostic Criteria: It is a set of diagnostic criteria developed for the diagnosis of fibromyalgia and created as a result of the revision of previously used diagnostic criteria.[11] It consists of two parts, the widespread pain index (WPI) and the symptom severity scale (SSS).[11]

In the evaluation of the widespread pain index, areas of continuous pain in the last seven days are marked in five body areas (upper left, upper right, lower left, lower right, axial) and 19 body regions (both jaws, shoulder, upper arm, lower arm, , hip, upper leg, lower leg, and neck, upper back, lower back, chest, abdomen). Each region counts as one point. The total score ranges from 0 to 19. For a diagnosis of widespread pain, pain must be present in at least 4 out of 5 body areas (jaw, chest, and abdominal pain are not considered in the widespread pain group by themselves).[11]

The symptom severity scale assessment consists of two parts. In the first part, patients score the severity of their fatigue, waking unrefreshed, and cognitive symptoms in the last week between 0 and 3. In the second part, patients score symptoms of headache, lower abdominal pain or cramping, and depression in the past six months (0=none, 1=yes). The total score ranges from 0 to 12.[11]

In the evaluation of the Fibromyalgia Severity Scale (FSS), WPI and SSS scores are collected. The total score ranges from 12 to 31. A higher score indicates greater disease severity. The total score must be greater than 12 for a diagnosis of fibromyalgia.[11] WPI ≥7 and SSS score ≥5, or WPI=4-6 and SSS score ≥9 suggest a diagnosis of fibromyalgia.[11]

FIQR: It is a questionnaire developed by Bennett et al. in 2009 to evaluate functional limitations and disability due to fibromyalgia.[17] The Turkish validity and reliability study of the questionnaire was conducted by Ediz et al. in 2011.[24] The questionnaire, which consists of 21 questions in total, consists of three parts: function, overall impact, and symptoms. The answers to each question are marked on a scale from 0 to 10. The total score is calculated by summing the results by dividing the score of the first section by three, the score of the second section by one, and the score of the third section by two. Higher scores indicate a more fibromyalgia-related disability.[17,24]

STATISTICAL ANALYSIS:

SPSS (IBM, Armonk, NY, ABD) version 20 program was used for statistical analysis. The suitability of numerical variables to normal distribution was examined visually (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests), homogeneity of variances using Levene's test. In descriptive statistics, numerical variables were expressed as mean and standard deviation, and categorical variables were expressed as numbers and percentages. In the comparison of numerical data between groups, when the parametric test conditions were met, the independent groups' t-test was used, and when the parametric test conditions were not met, the Mann-Whitney U test was used. The chi-square test was used for the comparison of categorical data between groups. Pearson correlation analysis (two-tailed) was used for the variables that both fit a normal distribution, and the Spearman test (two-tailed) was used for the variables at least one of which was not normally distributed. Possible risk factors for fibromyalgia and anxiety were analyzed by logistic regression analysis, and the Hosmer-Lemeshow test was used to evaluate model fit. The statistical significance level for the analysis was accepted as p=0.05.

RESULTS

BASELINE CHARACTERISTICS

The patient and control groups were similar in terms of age, gender distribution, height, weight, and presence of systemic disease (p>0.05). There were two participants diagnosed with arrhythmias, six diabetes mellitus (DM), eight hypertension (HT), one asthma, two heart valve disease, and two ulcerative colitis in the patient group; one arrhythmia, two asthma, five DM, six HT, two hyperlipidemia, and two hypothyroidism in the control group.

In the patient group, there were three patients received treatment with acupuncture, 22 exercises, five massages, 11 physical therapy applications, two balneotherapy, two cupping therapies, one local injection treatment within the scope of non-pharmacological treatments; nine duloxetine, seven pregabalin, six non-steroidal anti-inflammatory drugs within the scope of pharmacological treatments.

The baseline characteristics of the patient and control groups are presented in Table 1.

COMPARISONS BETWEEN PATIENT AND CONTROL GROUPS IN TERMS OF OUTCOME PARAMETERS

It was observed that the handgrip strengths of the right and left hands were significantly lower in the patient group compared to the control group (both right and left hands $p<0.001$). NHPT durations in the right and left hands were significantly longer in the patient group compared to the control group (both right and left hands $p<0.001$). There was no statistically significant difference between the patient and control groups in terms of right and left tip pinch strengths (for right-hand $p=0.21$, for left-hand $p=0.18$).

The right Edinburgh score was significantly lower in the patient group compared to the control group ($p<0.001$). The Geschwind score was also found to be significantly lower in the patient group compared to the control group ($p=0.04$). There was no statistically significant difference between the patient and control groups in terms of the left Edinburgh score ($p=0.53$).

The number of non-right-handed participants in the patient group was significantly higher than in the control group (13 participants in the patient group and 4 participants in the control group, $p=0.01$). The number of right-hand dominant participants was found to be significantly lower in the patient group compared to the control group ($p=0.01$), and the number of ambidextrous participants was significantly higher in the patient group compared to the control group ($p=0.01$). There was no statistically significant difference between the patient and control groups in terms of the number of left-hand dominant patients.

TABLE 1: Baseline characteristics of the patient and control groups.

	Patients group (n=40)	Control group (n=40)	p value
Age-year*	37.5±10 (20-50)	33.7±9.6 (20-50)	0.08
Gender-n (%)			
Female	33 (82.5)	29 (72.5)	0.28
Male	7 (17.5)	11 (27.5)	
Height-cm*	164.3±8.2 (151-184)	167.2±9.4 (155-198)	0.15
Weight-kg*	70.1±13.5 (50-103)	66.3±16.6 (43-102)	0.11
Presence of systemic disease -n (%)			
No	27 (67.5)	27 (67.5)	1
Yes	13 (32.5)	13 (32.5)	
Fibromyalgia diagnosis time-month*	62.1±54.3 (5-180)	-	-
Presence of any treatment for fibromyalgia -n (%)			
No	4 (10)		
Yes	36 (90)		
Presence of non-pharmacological treatment-n (%)			
No	9 (22.5)		
Yes	31 (77.5)		
Pharmacological treatment-n (%)			
No	21 (52.5)	-	-
Yes	19 (47.5)		
ACR 2016 Fibromyalgia Diagnostic Criteria*			
FSS	19.3±5.2 (12-31)	-	-
WPI	11.3±4 (5-19)		
SSS	8±2.2 (5-12)		
FIQR scores*			
FIQR-T	37.7±17.6 (6.8-71.8)	-	-
FIQR-F	30.4±18.1 (0-72)		
FIQR-OI	6.8±5.1 (0-20)		
FIQR-S	40.9±18.6 (8-76)		

*Data are expressed as mean±standard deviation (minimum-maximum value); **Statistical significance level p=0.05; ACR:American College of Rheumatology; FSS: Fibromyalgia severity scale; WPI: Widespread pain index; SSS: Symptom severity scale; FIQR: The Revised Fibromyalgia Impact Questionnaire; FIQR-T: The Revised Fibromyalgia Impact Questionnaire total score; FIQR-F: The Revised Fibromyalgia Impact Questionnaire function score; FIQR-OI: The Revised Fibromyalgia Impact Questionnaire overall impact score; FIQR-S: The Revised Fibromyalgia Impact Questionnaire symptoms score.

Beck Anxiety score was found to be significantly higher in the patient group compared to the control group ($p=0.03$). Although the Beck Depression score was higher in the patient group compared to the control group, the difference between the groups was not statistically significant ($p=0.1$). In addition, although the number of patients with depression and anxiety was higher in the patient group compared to the control group, the difference between the groups was not statistically significant (for both depression and anxiety, $p=0.06$).

Descriptive statistics on outcome parameters and comparisons between groups are presented in Table 2.

TABLE 2: Descriptive statistics on outcome parameters and comparisons between groups.

	Patient group (n=40)	Control group (n=40)	p value
Handgrip strength-kg*			
Right	14.6±8 (2-35)	23.8±10.6 (5-55)	**<0.001****
Left	13.8±9 (1-40)	21.7±10.6 (8-60)	**<0.001****
Tip pinch strength-kg*			
Right	6.5±3.3 (2-17)	7.1±2.9 (2.5-17.5)	0.21
Left	6.4±3.4 (1-17)	7.2±2.9 (4-16)	0.18
NHPT duration-sec*			
Right	20.3±4.4 (13-35)	16.6±2.4 (12-23)	**<0.001****
Left	22±5.5 (13-38)	18.2±2.8 (13-25)	**<0.001****
Edinburgh score*			
Right	12.8±2.5 (3-17)	14.3±3.1 (2-20)	**<0.001****
Left	3±3.6 (0-17)	2.3±2.5 (0-10)	0.53
Geschwind score*	49.7± 29.4 [(-70)-85]	60.2±25.2 [(-40)-100]	**0.04****
Laterality group -n (%)			
Right-handed	27 (67.5)	36 (90)	**0.01****
Ambidextrous	12 (30)	3 (7.5)	**0.01****
Left-handed	1 (2.5)	1 (2.5)	NA
BDI score*	10.6±8.2 (0-32)	7.8±7.3 (0-30)	0.10
Presence of depression-n (%)			
No	21 (52.5)	29 (72.5)	0.06
Yes	19 (47.5)	11 (27.5)	
BAI score*	12.5±8.9 (0-42)	9.6±11.5 (0-54)	**0.03****
Presence of anxiety-n (%)			
No	11 (27.5)	19 (47.5)	0.06
Yes	29 (72.5)	21 (52.5)	

*Data are expressed as mean±standard deviation (minimum-maximum value); **Statistical significance level p=0.05; NHPT: Nine hole peg test; BDI: The Beck Depression Inventory; BAI: The Beck Anxiety Inventory.

CORRELATIONS BETWEEN OUTCOME PARAMETERS

Correlations İn The Control Group

It was observed that there were no statistically significant relationships between Geschwind score, right and left Edinburgh scores, with handgrip strengths, tip pinch strengths, NHPT durations, and BAI and BDI scores (p>0.05).

Correlations between outcome parameters in the control group are presented in Table 3a.

Correlations İn The Fibromyalgia Group

It was observed that there was a moderately significant negative correlation between the left Edinburgh score with the right tip pinch strength (r=-0.42 p=0.006). There were no statistically significant correlations between the left Edinburgh score with right and left-hand grip strengths, right and left-hand NHPT durations, left tip pinch strength, BAI, and BDI scores (p>0.05).

No statistically significant correlations were observed between the Geschwind score and right Edinburgh scores with handgrip strengths, tip pinch strengths, NHPT durations, BAI, and BDI scores (p>0.05).

Correlations between outcome parameters in the patient group are presented in Table 3b.

Correlations İn Terms Of Outcome Parameters Related To Fibromyalgia

It was observed that there were negative, low-moderate significant correlations between the right Edin-

TABLE 3a: Correlations between variables in the control group.

	Edinburgh score-right	Edinburgh score-left	Geschwind score	BDI score	BAI score
Handgrip strength-right	r:-0.15	r:-0.003	r:-0.07	**r:-0.43**	**r:-0.45**
	p:0.36	p:0.98	p:0.65	**p:0.005***	**p:0.004***
Handgrip strength-left	r:-0.17	r:0.13	r:-0.13	**r:-0.59**	**r:-0.53**
	p:0.28	p:0.42	p:0.41	**p<0.001***	**p<0.001***
Tip pinch strength-right	r:-0.03	r:-0.10	r:-0.02	**r:-0.39**	**r:-0.36**
	p:0.83	p:0.53	p:0.90	**p:0.01****	**p:0.02****
Tip pinch strength-left	r:-0.08	r:0.17	r:-0.08	**r:-0.40**	**r:-0.40**
	p:0.60	p:0.28	p:0.62	**p:0.01****	**p:0.01***
NHPT duration-right	r:0.24	r:-0.16	r:0.27	r:0.04	r:-0.16
	p:0.13	p:0.34	p:0.09	p:0.79	p:0.31
NHPT duration-left	r:0.09	r:0.003	r:0.13	r:0.06	r:-0.006
	p:0.59	p:0.99	p:0.40	p:0.72	p:0.97
Edinburgh score-right	-	**r:-0.40**	**r:0.77**	r:0.15	r:0.15
		p:0.01*	**p<0.001***	p:0.36	p:0.35
Edinburgh score-left	**r:-0.40**	-	**r:-0.83**	r:-0.006	r:0.03
	p:0.01*		**p<0.001***	p:0.97	p:0.84
Geschwind score	**r:0.77**	**r:-0.83**	-	r:0.10	r:-0.02
	p<0.001*	**p<0.001***		p:0.53	p:0.88
BDI score	r:0.15	r:-0.006	r:0.10	-	**r:0.64**
	p:0.36	p:0.97	p:0.53		**p<0.001***
BAI score	r:0.15	r:0.03	r:-0.02	**r:0.64**	-
	p:0.35	p:0.84	p:0.88	**p<0.001***	

*Statistical significance level for correlation p=0.01 (2-tailed); **Statistical significance level for correlation p=0.05 (2-tailed); NHPT: Nine-hole peg test; BAI: The Beck Anxiety Inventory; BDI: The Beck Depression Inventory.

TABLE 3a: Correlations between variables in the control group.

	Edinburgh score-right	Edinburgh score-left	Geschwind score	BDI score	BAI score
Handgrip strength-right	r:-0.04	r:-0.21	r:0.06	r:-0.22	r:-0.23
	p:0.80	p:0.18	p:0.73	p:0.88	p:0.16
Handgrip strength-left	r:-0.05	r:-0.03	r:-0.03	r:-0.11	r:-0.17
	p:0.75	p:0.84	p:0.84	p:0.50	p:0.28
Tip pinch strength-right	r:0.10	**r:-0.42***	r:0.26	r:-0.003	r:-0.09
	p:0.55	**p:0.006**	p:0.11	p:0.98	p:0.58
Tip pinch strength-left	r:0.06	r:-0.25	r:0.14	r:-0.11	r:-0.13
	p:0.69	p:0.12	p:0.40	p:0.51	p:0.43
NHPT duration-right	r:0.22	r:-0.15	r:0.24	r:-0.11	r:-0.01
	p:0.16	p:0.36	p:0.13	p:0.52	p:0.94
NHPT duration-left	r:0.19	r:-0.26	r:0.29	r:0.03	r:0.25
	p:0.24	p:0.10	p:0.07	p:0.84	p:0.11
Edinburgh score-right	-	**r:-0.65**	**r:0.89**	r:-0.13	r:-0.25
		p<0.001*	**p<0.001***	p:0.43	p:0.12
Edinburgh score-left	**r:-0.65**	-	**r:-0.89**	r:-0.19	r:0.05
	p<0.001*		**p<0.001***	p:0.24	p:0.75
Geschwind score	**r:0.89**	**r:-0.89**	-	r:0.04	r:-0.12
	p<0.001*	**p<0.001***		p:0.80	p:0.45
BDI score	r:-0.13	r:-0.19	r:0.04	-	**r:0.69**
	p:0.43	p:0.24	p:0.80		**p<0.001***
BAI score	r:-0.25	r:0.05	r:-0.12	**r:0.69**	-
	p:0.12	p:0.75	p:0.45	**p<0.001***	

*Statistical significance level for correlation p=0.01 (2-tailed); **Statistical significance level for correlation p=0.05 (2-tailed); NHPT: Nine-hole peg test; BAI: The Beck Anxiety Inventory; BDI: The Beck Depression Inventory.

burgh score with the SSS score and FIQR-symptoms (FIQR-S) score (for both correlations; r=-0.36 p=0.02). No statistically significant correlations were found between the right Edinburgh score with WPI, FSS, FIQR-function (FIQR-F), FIQR-overall impact (FIQR-OI), and FIQR-total (FIQR-T) scores, and fibromyalgia diagnosis time (p>0.05).

There were no statistically significant correlations between the Geschwind score and the left Edinburgh score, with WPI, SSS, FSS, FIQR-F, FIQR-OI, FIQR-S, FIQR-T scores, and fibromyalgia diagnosis time (p>0.05).

It was observed that there was a low-moderate negative correlation between right handgrip strength with WPI (r=-0.33 p=0.04). The left handgrip strength was negatively correlated moderately with the fibromyalgia diagnosis time (r=-0.40 p=0.01), low-moderately with FIQR-OI (r=-0.32 p=0.05), FIQR-S (r=-0.36 p=0.02) and FIQR-T (r=-0.33 p=0.04).

There was a positive, low-moderate, significant correlation between the right NHPT duration with the fibromyalgia diagnosis time (r=0.35 p=0.02). The left NHPT duration was positively correlated excellently with the fibromyalgia diagnosis time (r=0.95 p=0.01), moderately with WPI (r=0.50 p=0.001) and FSS scores (r=0.42 p=0.006), low-moderately with FIQR-OI (r=0.35 p=0.03).

No statistically significant correlations were found between tip pinch strengths with WPI, SSS, FSS, FIQR-F, FIQR-OI, FIQR-S, and FIQR-T scores and fibromyalgia diagnosis time (p>0.05).

Correlations in terms of outcome parameters related to fibromyalgia are presented in Table 4.

EVALUATION OF RISK FACTORS

It was observed that ambidexterity was a statistically significant risk factor for fibromyalgia [OR%95CI: 6.02 (1.48-25.25), p=0.01]. Age, female gender, pres-

TABLE 4: Correlations in terms of outcome parameters related to fibromyalgia.

	WPI	SSS score	FSS score	FIQR-F score	FIQR-OI score	FIQR-S score	FIQR-T score	Diagnosis time
Geschwind score	r:-0.14	r:-0.28	r:-0.09	r:0.01	r:0.005	r:-0.21	r:-0.09	r:0.25
	p:0.93	p:0.08	p:0.6	p:0.95	p:0.97	p:0.20	p:0.59	p:0.11
BAIscore	**r:0.60**	**r:0.64**	**r:0.74**	**r:0.58**	**r:0.48**	**r:0.68**	**r:0.67**	r:-0.04
	p<0.001*	**p<0.001***	**p<0.001***	**p<0.001***	**p:0.002***	**p<0.001***	**p<0.001***	p:0.81
BDI score	**r:0.51**	**r:0.53**	**r:0.62**	**r:0.38**	**r:0.52**	**r:0.68**	**r:0.64**	r:-0.04
	p:0.001*	**p<0.001***	**p<0.001***	**p:0.01****	**p:0.001***	**p<0.001***	**p<0.001***	p:0.82
Edinburgh score-right	r:0.15	**r:-0.36**	r:-0.23	r:-0.12	r:-0.15	**r:-0.36**	r:-0.26	r:0.15
	p:0.35	**p:0.02****	p:0.15	p:0.45	p:0.36	**p:0.02****	p:0.10	p:0.36
Edinburgh score-left	r:-0.09	r:0.22	r:-0.02	r:-0.02	r:-0.10	r:-0.05	r:-0.04	r:-0.30
	p:0.57	p:0.17	p:0.91	p:0.88	p:0.53	p:0.75	p:0.82	p:0.06
Handgrip strength-right	**r:-0.33**	r:-0.17	r:-0.31	r:-0.30	r:-0.17	r:-0.20	r:-0.20	r:-0.29
	p:0.04**	p:0.30	p:0.05	p:0.06	p:0.29	p:0.22	p:0.21	p:0.07
Handgrip strength-left	r:-0.29	r:-0.15	r:-0.30	r:-0.22	**r:-0.32**	**r:-0.36**	**r:-0.33**	**r:-0.40**
	p:0.07	p:0.38	p:0.06	p:0.16	**p:0.05****	**p:0.02****	**p:0.04****	**p:0.01***
Tip pinch strength-right	r:0.01	r:-0.05	r:-0.01	r:0.07	r:0.03	r:-0.17	r:-0.05	r:0.07
	p:0.94	p:0.74	p:0.93	p:0.69	p:0.87	p:0.30	p:0.76	p:0.66
Tip pinch strength-left	r:-0.14	r:-0.12	r:-0.17	r:-0.11	r:-0.15	r:-0.28	r:-0.22	r:-0.15
	p:0.37	p:0.47	p:0.31	p:0.48	p:0.34	p:0.08	p:0.17	p:0.35
NHPT duration-right	r:0.29	r:0.06	r:0.24	r:0.09	r:0.20	r:-0.17	r:0.04	**r:0.35**
	p:0.07	p:0.72	p:0.13	p:0.56	p:0.23	p:0.92	p:0.81	**p:0.02****
NHPT duration-left	**r:0.50**	r:0.11	**r:0.42**	r:0.26	**r:0.35**	r:0.07	r:0.18	**r:0.95**
	p:0.001*	p:0.49	**p:0.006***	p:0.11	**p:0.03****	p:0.66	p:0.26	**p:0.01****

*Statistical significance level for correlation p=0.01 (2-tailed); **Statistical significance level for correlation p=0.05 (2-tailed); WPI:Widespread pain index; SSS: Symptom severity scale; FSS: Fibromyalgia severity scale; FIQR-F: The revised fibromyalgia impact questionnaire-function; FIQR-OI: The revised fibromyalgia impact questionnaire-overall impact; FIQR-S: The revised fibromyalgia impact questionnaire-symptoms; FIQR-T: The revised fibromyalgia impact questionnaire-total; BAI: The Beck anxiety inventory; BDI: The Beck depression inventory; NHPT: Nine hole peg test.

TABLE 5: The results regarding the evaluation of risk factors.

	OR (%95CI)	p value
For fibromyalgia;		
Age	1.04 (0.99-1.09)	0.15
Female gender	1.16 (0.35-3.88)	0.81
Presence of anxiety	1.51 (0.50-4.57)	0.46
Presence of depression	2.0 (0.68-5.88)	0.21
Ambidexterity	6.02 (1.48-25.25)	**0.01***
For anxiety;		
Age	1.02 (0.97-1.07)	0.48
Female gender	4.05 (1.19-13.85)	**0.03***
Presence of depression	5.85 (1.66-20.58)	**0.006***
Presence of fibromyalgia	1.47 (0.49-4.44)	0.49
Ambidexterity	1.61 (0.38-6.74)	0.51

*Statistical significance level p=0.05; OR:odds ratio; CI: confidence interval.

ence of anxiety, and depression were not statistically significant risk factors for fibromyalgia (p>0.05).

Female gender [OR%95CI: 4.05 (1.19-13.85), p=0.03] and presence of depression [OR%95CI: 5.85 (1.66-20.58), p=0.006] were statistically significant risk factors for anxiety. Age, presence of fibromyalgia, and ambidexterity were not statistically significant risk factors for anxiety (p>0.05).

The results regarding the evaluation of risk factors are presented in Table 5.

DISCUSSION

In this study, we aimed to evaluate the relationship between handedness, which is an indicator of brain lateralization, and fibromyalgia disease severity and functional outcomes related to fibromyalgia in fibromyalgia patients; we observed that right-handedness, which we evaluated with the higher values of the right Edinburgh score and the Geschwind score, was lower in fibromyalgia patients compared to the control group. In addition, the number of non-right-handed participants in the fibromyalgia group was significantly higher than in the control group. This difference was due to the significantly higher number of ambidextrous participants in the fibromyalgia group (there was no significant difference between the groups in terms of the number of left-handed participants). In addition, we observed that being ambidextrous was a significant risk factor for the presence of fibromyalgia. The only significant correlations between laterality scores and fibromyalgia-related disease duration, disease severity, and disease-related functionality were negative, low-moderate statistically significant correlations between the right Edinburgh score with SSS score and FIQR-S score. This finding suggests that right-hand laterality severity may be associated with symptom severity in fibromyalgia. In functional evaluations of the hand, we observed that the strongest relationships were between left NHPT duration with fibromyalgia diagnosis time, left NHPT duration with WPI and FSS scores, and left-hand grip strength with fibromyalgia diagnosis time. These findings suggest that impairment in left-hand functions may be associated with fibromyalgia diagnosis time, widespread pain, and symptom severity. Considering all the findings together, we concluded that right-handedness and right-hand laterality scores were found to be significantly lower in fibromyalgia patients compared to controls, but that right-handedness may be associated with longer disease duration and greater disease severity.

Studies in neuroimaging have reported that some structural changes in white matter connections (interhemispheric and intrahemispheric) and neuroanatomical structures may have important roles in lateralized motor behaviors.[1,6] Regarding relationships between structural and functional brain asymmetries and handedness, the most significant relationships have been reported with the asymmetries of the frontoparietal association pathways (especially the superior branch of the superior longitudinal fasciculus), which is important in visuomotor and visuospatial processes, and with variations of the corpus callosum which is important in the bimanual coordination, and main connection pathway between the hemispheres.[1]

The course of fibromyalgia with central pain and cognitive and emotional disorders supports that central nervous system changes are an important point in the formation of the disease.[10,25] As a matter of fact, there are studies reporting that some changes are observed in brain structure and functions in fibromyalgia.[10,25,26] The most striking changes related to brain morphology in fibromyalgia were the functional and morphological changes in the gray and white matter in the orbitofrontal cortex, which plays a role in the

cognitive modulation of pain, and in the rostral anterior cingulate cortex, which plays a role in the descending inhibitory pain pathways, and in the anterior insula.[10] It has been shown that changes in brain activity are also observed in fibromyalgia.[10] In particular, increased activation can be seen in the brain areas that play a role in pain catastrophizing, which is the cognitive dimension of pain (posterior cingulate cortex), pain expectation (cerebellum, medial frontal cortex), emotional dimension of pain (amygdala, claustrum), attention to pain (dorsolateral prefrontal cortex and dorsal anterior cingulate cortex), and decreased activation can be seen in the rostral anterior cingulate cortex, which is involved in the inhibition of descending pain.[10,25,27-29] Dysfunctions of the diffuse noxious inhibitory control pathway, which is responsible for nociceptive activity in the brain and spinal cord interaction in fibromyalgia, have also been found to be important in the emergence of pain and other clinical features.[25] On the other hand, the ability of pharmacological (pregabalin) and various non-pharmacological treatments (cognitive behavioral therapy, exercise, transcranial direct current stimulation, virtual reality therapy) to reduce pain by changing brain activities in various regions (by decreasing activity in various brain regions (esp. insula) associated with pain formation and increasing activity in brain regions associated with descending pain pathways responsible for pain inhibition) supports the role of changes in brain activities in the pathogenesis of fibromyalgia.[10,26]

The role of changes in brain morphology and activation in fibromyalgia is still unclear.[10] As far as we know, there is no study evaluating structural or functional hemispheric asymmetries in fibromyalgia. However, the presence of structural and functional brain changes reported to be seen in fibromyalgia makes us think that hemispheric asymmetry changes and, thus, handedness changes may be possible in fibromyalgia.

In the literature, it has been reported that changes in structural and functional hemispheric asymmetries are observed in some neurodevelopmental disorders such as dyslexia, autism spectrum disorder, attention deficit and hyperactivity disorder, and psychiatric diseases such as schizophrenia, major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, stuttering, substance abuse, and Parkinson's disease, which is a neurological disease. It has been reported that changes in the form of a decrease in hemispheric asymmetries are observed in the aforementioned diseases.[2–4,30–32] Handedness, which is a behavioral predictor of cerebral lateralization, can also show an atypical lateralization pattern in these diseases.[3,4,30,32,33] Similar to our study, it has been suggested that non-right-handed handedness (mixed or left-handedness) is associated with some diseases. For example, it has been reported that mixed and left-handedness have a high prevalence in schizophrenia patients.[34] The prevalence of non-right-handedness was also found to be high in autism spectrum disorder and dyslexia.[35,36] A relationship with mixed handedness has also been shown in posttraumatic stress disorder, and it has been reported that the prevalence is approximately 2-fold in mixed-handed people.[37] It remains unclear why many diseases with different symptoms are associated with a decrease rather than an increase in typical hemispheric asymmetries.[2,3] In most of these diseases, the view is that the changes are related to the emergence of cognitive symptoms seen in the diseases rather than being directly responsible for the emergence of the diseases themselves.[2,3] In this context, the presence of frequently accompanying cognitive symptoms makes us think that similar hemispheric asymmetries may play a role in the pathogenesis of fibromyalgia.[38]

It is also still unclear how the chain of events that initiated the lateralization started and how it developed.[1,3,7] It has been reported in the literature that there are relationships between lateralization and handedness and genetic factors (around 40 genetic loci that also play a role in brain development and neurogenesis), epigenetic factors (DNA methylation, histone modification, microRNA posttranscriptional modification, etc.), environmental factors and social characteristics (ethnic origin, cultural structure, socioeconomic status, cultural pressures that force the right hand to use the right hand in daily life activities such as writing, eating, etc.), personal factors (duration of breastfeeding, year of birth, season of birth, birth weight, being a part of multiple births, engaging in professional sports activities, educational status,

gender, and sexual orientation), stress and sex hormone changes (high testosterone level and menstrual cycle changes).[3,5–7,39] It is thought that these factors create asymmetries in neural connections with their effects at different points of ontogenesis.[7]

The reason why diseases with quite different symptoms and etiologies share common characteristics related to changes in hemispheric asymmetries is also still unknown in laterality studies.[3] In these diseases, genetic and non-genetic factors were examined in terms of overlap.[3] It has been shown that some potential genetic determinants overlap in hemispheric asymmetries, handedness, and different psychiatric and neurodevelopmental diseases.[3,39] However, there was no evidence of any genetic loci that completely overlapped among all diseases and hemispheric asymmetries.[3] The fact that hemispheric asymmetries cannot be attributed to genetic effects has brought forward the evaluation of another mechanism common in the development of diseases with hemispheric asymmetries, and stress has been the most prominent mechanism.[2,3,7] The fact that stress is a powerful factor in the ontogenesis of many neurodevelopmental and psychiatric diseases makes it a strong possible cause of phenotypic similarities, such as decreased hemispheric asymmetries seen in these diseases.[3,7]

Stress increases both structural and functional hemispheric asymmetry changes as well as the risk of psychiatric and neurodevelopmental diseases by affecting brain development, creating chronic elevations in the HPA axis, and causing epigenetic changes in genes in the pathways involved in the HPA axis.[3] It has been reported that stress in adulthood also causes hypoactivity in the hippocampus and medial prefrontal cortex, hyperactivity in the amygdala, an increase in right hemispheric activity, and a decrease in the inhibitory activity of the corpus callosum.[3] In addition, stress creates different effects on the right and left hemispheres, and the regulatory effect of both hemispheres on the HPA axis is also different.[3]

The role of stress in fibromyalgia is a subject that has been emphasized a lot in the literature.[40] It is known that one of the most important causes of sleep, mood, and cognitive function changes accompanying the disease is the changes in the stress response.[38] Abnormalities leading to hyperactive stress response in the HPA axis, which plays a central role in the stress response in fibromyalgia, have been known for a long time.[25,40,41] Dysfunctions can be seen in many components of the HPA axis.[25] In general, the abnormalities reported in studies are basal ACTH secretion in response to stress, elevation in cortisol levels, and disruption in the circadian rhythm of release.[25,40,41] Serum cortisol levels, as a representative of stress, were also found to be important in the severity of neuropsychological problems in fibromyalgia patients.[42] These findings suggest that the reason for the hand laterality change observed in fibromyalgia patients in our study may be due to stress associated with fibromyalgia.

In our study, while the anxiety score was found to be significantly higher in the fibromyalgia group compared to the control group, there was no significant difference between the groups in terms of depression scores. Although the number of patients with depression and anxiety was higher in the fibromyalgia group compared to the control group, the difference was not significant. We did not observe a significant relationship between hand laterality scores and anxiety and depression scores in the patient and control groups. While there were significant negative correlations between anxiety and depression scores and handgrip and tip pinch strengths in the control group, we observed that there were no significant relationships between these scores and hand dexterity which we evaluated through the NHPT duration. In the fibromyalgia group, there were no significant relationships between anxiety and depression scores and handgrip and tip pinch strengths, and hand dexterities. Although there is no study on clinical laterality in anxiety disorders, which is one of the psychiatric disorders frequently accompanying fibromyalgia, there are limited studies on structural asymmetries in the literature.[2] It has been reported that there may be changes in functional hemispheric asymmetries, especially in areas related to basic processes such as self-perception and emotional processes and attention in major depressive disorder, which is another psychiatric problem that frequently accompanies fibromyalgia.[2,3] Studies related to structural-functional asymmetries in depression are lim-

ited.[2] In a new meta-analysis conducted by Packheiser et al. to examine the relationship between handedness and depression, it was reported that there was no significant relationship between right, left, or mixed-handedness and depression.[4] The fact that we did not find significant relationships between laterality scores and anxiety and depression scores in our study led us to think that the changing handedness in the fibromyalgia patient group was not associated with possible accompanying anxiety and depression states. On the other hand, we observed that anxiety and depression states might be associated with disease severity and disease-related functionality parameters in fibromyalgia.

The superior aspect of our study is that it is the first study to evaluate handedness and, thus, brain lateralization in fibromyalgia and its relationship with the characteristics of the disease. In this respect, we think that this study may provide a different perspective on the approach to fibromyalgia, a disease whose etiology still remains unknown. In terms of clinical practice, we think that laterality assessment to be made with this perspective may help to provide earlier detection, closer follow-up, and earlier treatment of patients with a high risk of developing fibromyalgia in patients presenting with widespread chronic pain. However, there are also some limitations of the study. The first of these is the relatively small sample size in order to make clearer evaluations. Due to the small number of participants in the left-handed and ambidextrous subgroups in our study, we preferred not to make comparisons between laterality groups in terms of hand performance. Although the factors thought to cause handedness are not known precisely, the fact that environmental, personal, and familial factors reported in the literature to affect handedness could not be questioned in more detail is another limitation of our study. Finally, since they are easily applicable methods, the hand preference and hand performance evaluations we preferred in our study, which indirectly give an idea about brain lateralization, can be counted among the limitations of the study. We think that future studies with larger patient groups, in which factors that may affect handedness are questioned in more detail and neuroimaging techniques used to evaluate structural and functional brain lateralization, can expand and improve the perspective opened by our study on the subject.

CONCLUSION

An increase in non-right-hand handedness can be observed in fibromyalgia patients. In particular, it is thought that ambidexterity may be a factor associated with the presence of fibromyalgia. No significant correlations were found between handedness and disease duration, disease severity, and disease-related functionality in fibromyalgia. The aforementioned characteristics of the disease seem to be associated with deterioration in hand performance (especially left hand) rather than laterality changes. As a result, it was concluded that right-handedness and right-hand laterality severity were found to be less in fibromyalgia patients, but right-handedness may be associated with more disease severity.

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