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Evaluation of the neuropathic component of pain in patients with fibromyalgia with painDETECT and DN4

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Abstract

Fibromyalgia (FMS) is generally associated with neuropathic pain (NP) because of the neuropathic symptoms frequently observed in patients with FMS. The aim of the study is to evaluate the neuropathic component of FMS with the painDETECT (PD-Q) and Douler Neuropathic 4 (DN4) scales. Female patients diagnosed as FMS according to the American College of Rheumatology's 2010 FMS criteria and female healthy volunteers are included in the study. After demographic evaluation, the patients and volunteers were asked to fill out Visual Analog Score (VAS), PD-Q, and DN4 scale forms. The Fibromyalgia Impairment Questionnaire (FIQ) evaluated life quality and function. There were 66 patients in the FMS group with a mean age of 46.16± 10.66 and 61 patients in the control group with a mean age of 44.93± 12.72. It was determined that there was a significant difference between the VAS, PD-Q, and DN4 values of FMS and control groups (tVAS = 5,025 $p < 0.05$, t PD-Q = 5,025 $p < 0.05$, tDN4 = 7,885 $p < 0.05$). The mean pain score (VAS) and NP level (DN4 and PD-Q) of FMS patients were significantly higher than healthy individuals. In addition, it was determined that VAS ($p = 0.001$) and PD-Q ($p = 0.046$) values were found to be significant predictors of the FIQ values. FMS patients may have pain with a neuropathic component, and it seems useful to evaluate neuropathic characteristics with PD-Q and DN4. If the components of pain are researched carefully, more improvement may be achieved in pain and functional capacity.

Keywords: chronic fatigue, fibromyalgia, fibromyalgia syndrome, neuropathic pain

1. Introduction

Fibromyalgia Syndrome (FMS) is considered a syndrome of symptoms unrelated to pain, such as widespread body pain, fatigue, sleep disturbances, and cognitive dysfunction. For this reason, it can also be classified as a kind of somatization disorder. It is more common in women, usually between the ages of 30-55, and overwhelmingly has a female-to-male ratio of 7:1 or 9:1. It is seen in 2-5% of the general population (1). FMS is accepted as the second most common rheumatic disease after osteoarthritis (2).

The most common complaint in FMS is widespread pain. Studies have shown that FMS pain, unlike other rheumatic diseases, is not only of nociceptive origin (3). Chronic pain seen in FMS is heterogeneous and may also include components and typical symptoms of neuropathic pain (NP), such as tingling, numbness, burning, and cutaneous hyperalgesia. Therefore, it is accepted that FMS and NP are associated, but the underlying mechanisms have not been clearly clarified yet (4, 5).

Self-reported questionnaires are helpful for identifying NP. The most commonly used questionnaires are the Self-Report Leeds Assessment of Neuropathic Symptoms (S-LANSS), PainDETECT Questionnaire (PD-Q), and Douler Neuropathic 4 (DN4) (6). Some studies detected that FMS exhibits an NP component by using LANSS or PD-Q. Some studies also investigated the correlation between PD-Q or S-LANSS with functional impact, tender point count, and clinical pain features of FMS (7-9).

The aim of this study is to investigate the neuropathic component of pain in FMS patients with PD-Q and DN4 and evaluate its impact on FMS or well-being. A secondary aim of the study is to evaluate the relationship between the neuropathic component of pain and demographic data.

2. Materials and methods

Female patients aged 20-65 years who were newly diagnosed with primary FMS according to the American College of Rheumatology (ACR) 2010 diagnostic criteria in physical therapy and rehabilitation outpatient clinics and age-sex-matched healthy volunteers were included in the study.

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Patients with a previous diagnosis of endocrine diseases such as diabetes mellitus, polyneuropathy, neuropathy, nerve damage, radiculopathy, plexopathy, rheumatic diseases such as inflammatory arthritis and connective tissue disease, severe cardiac-lung disease, serious psychiatric disease, malignancy, a history of medical neuropathy or FMS treatment, and pregnant patients were excluded from the study.

Consecutive Sampling method was used for sampling. The sample size was calculated with the G power program at a medium effect level, 0.05 significance level, and 0.95 confidence interval. The minimum sample size calculated with this method was 107. Data were obtained from 140 patients, but 13 of them were excluded because they did not meet inclusion criteria.

The patients were evaluated by the same physiatrist. The diagnosis of FMS was confirmed according to ACR 2010 criteria. Demographic information, including age, height, weight, marital status, occupation, comorbidity, smoking, medication, and FMS history in the family, was obtained. Body mass index (BMI) was calculated using the formula BMI=weight (kg)/height (cm2). The duration and severity of widespread pain (evaluated with the Visual Analogue Scale - VAS) were noted. The scale is 10 cm long, and the left extreme point defines no pain, and the right extreme point defines the most pain. The patients determined the severity of the pain they felt with a point on this scale. The distance between the point determined by the patient and the left extreme point was measured in cm, and the numerical value found was accepted as the patient's pain intensity. Values 0-4 indicate low pain, 5-7 indicate medium pain, and > 7 means severe pain (10).

The PD-Q and DN4 scales were used to evaluate the neuropathic component of the widespread pain. They were also asked to fill out the Fibromyalgia Impact Questionnaire (FIQ) scale to evaluate quality of life and well-being.

PD-Q was first developed to detect NP in patients with low back pain. It is a self-assessment questionnaire consisting of nine questions in total. Seven questions are about sensory perception, and two questions are about the spread of pain and temporal characteristics. The total score ranges from 0 to 38. While a total score higher than 19 indicates NP, scores between 13 and 18 indicate probable NP and scores lower than 12 indicate the absence of NP. The Turkish validity and reliability study of the scale was performed by Alkan et al. in 2013 (11).

DN4 is a scale filled out by physicians. It consists of 10 questions, answered yes or no. Seven questions are about neuropathic components of the pain, and three questions are asking about allodynia and hypoesthesia, confirmed by examination. The patients take one point for each ‘’yes’’ answer. The total score ranges from 0 to 10. Scores more than four indicate NP. Turkish validity and reliability study of the scale was performed by Celik et al. in 2016 (12).

FIQ is a scale consisting of 10 questions in total. In the first question, physical functional capacity is assessed; in the second and third questions, the level of illness and ability to go to work are determined; and between the fourth and tenth questions, difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression are evaluated. A maximum of 100 points can be obtained in total. A score of 50-70 is considered moderately affected, and scores above 70 are considered severely affected. The Turkish validity and reliability of the scale were performed by Sarmer et al. in 2000 (13).

2.1. Statistical analysis:

Data were analyzed with the SPSS program (IBM Corp., Chicago, Illinois, USA, 25.00), and all results were interpreted at a significance level of 0.05 and a confidence interval of 95%. Normally distributed values were defined as mean ± SD, non-normal distributed values were defined as median (min-max), and categorical variables were defined as frequency and percentage. Independent group t-test technique was used to determine whether there was a significant difference between the VAS, DN4, and PD-Q values of patients with FMS and healthy individuals.

The independent t-test was used to determine whether the VAS, PD-Q, DN-4, and FIQ values of the patients with FMS showed significant differences according to medication (yes or no), smoking (yes or no), and FMS history in the family (yes or no). The difference for age (grouped as 15-25 years, 26-35 years, 36-45 years, 46-55 years, and >56), BMI (grouped as 0-18 low, 18.5- 24.9 normal, 25-29.9 overweight, and >30 morbidly obese), occupation (five groups including housewife, civil servant, health worker, student, freelance and private sector), and comorbidity (yes or no) was determined with Peranova technique (nonparametric variance analysis), as the values were not normally distributed.

In order to determine the direction and severity of the relationship between the FIQ value and VAS, PD-Q, and DN4 values, Correlation with Pearson's coefficient was used as the values were in a normal distribution. Then, the predictive power of VAS, PD-Q, and DN4 values on FIQ values was determined by using multiple regression analysis. The R program was used for the analysis, and the codes used are shown in Table 1. Imperium, npvm, and Dunn tests were studied, and Peranova analysis was performed. The R code was used to perform these analyses. The codes were given in Table 1 to maintain data transparency.

Table 1. Codes used in R program

```
>library(lmPerm)
>library(npvm)
>library(dunn.test)
>summary(aovp(data$independentvariable~data$group, seqs=T))
>nonpartest(independentvariable~grup, data=X, permreps=1000, tests=c(1,1,1,1), releffects=T, plots=T)
>ssnonpartest(independentvariable~grup, data=data, test=c(1,0,0,0), alpha=.05, factors.and.variables = T)
>t.test()
```

3. Results

A total of 127 female patients were analyzed. There was no statistically significant difference between the demographic data of the patients in the FMS group (n=66) and the control group (n=61) (p> 0.05). The mean ages of the FMS and control groups were 46.16±10.66 and 44.93±12.72. In both groups, most of the patients were married and housewives. The mean disease duration in the FMS group was 5.26±4.64 months.

In the FMS group, the mean value of VAS was 6.73 (indicates medium pain), PD-Q was 15.24 (probable NP), and DN4 was 4.7 (indicates NP). This issue shows that the pain level was medium, and the neuropathic component of the pain was higher in FMS patients. In addition, it was determined that there was a significant difference between the VAS, PD-Q, and DN4 values of FMS and control groups (tVAS = 5,025 p < 0.05, tPD-Q = 5,025 p < 0.05, tDN4 = 7,885 p < 0.05) which means the mean pain score (VAS) and NP level (DN4 and PD-Q) of FMS patients were significantly higher than those of healthy individuals. A comparison of the VAS, PD-Q, and DN4 values of the FMS and control groups is shown in Table 2.

Table 2. Comparison of DN4, VAS, and PD-Q values of FMS and control groups

		N	x	ss	t	df	p
DN4#	FMS group	66	4.71	2.461	7.885	125	0.001*
	Control group	61	1.67	1.805			
VAS#	FMS group	66	6.73	1.819	6.682	125	0.001*
	Control group	61	3.79	3.034			
PainDETECT#	FMS group	66	15.24	7.555	5.025	126	0.001*
	Control group	61	8.59	7.343			

#Independent group t-test *p<0.05 statistically significiant
VAS: Visuel Analog Scale, PD-Q: painDETECT questionnaire, DN-4: Douler Neuropathic 4

It was determined that VAS, PD-Q, DN-4, and FIQ values in FMS patients did not differ according to demographic data (p > 0.05). Only the DN-4 level differs according to comorbidity (p=0.024) (Table 3).

There was no significant difference between the mean VAS (t (64) = -0.771; p = 0.82), PD-Q (t (64) = 0.169; p = 0.82), DN4 (t (64) = -0.218; p = 0.82), and FIQ values (t (64) = -0.042; p = 0.82) of FMS patients according to marital status (p> 0.005). Also, there was no significant difference between the mean VAS (t (64) = -0.012; p = 0.99), PD-Q (t(64) = 1.117; p = 0.26), DN4 (t (64) = 0.436; p = 0.66), and FIQ values (t(64) = 0.943; p = 0.34) of FMS patients according to smoking status (p > 0.05). It may be stated that marital status and smoking are not determining factors in terms of the severity and neuropathic component of the pain.

Table 3. The mean values of VAS, PD-Q, DN4, and FIQ according to age, occupation, BMI, comorbidity, and medication

		ANOVA type test statistic	df1	df2	Permutation Test p-value	P<0.005
DN4#	Age	2.031	4	18.79	0,294	
	Occupation	0.150	3	18.90	0.876	
	BMI	2.389	3	30.31	0.132	
	Comorbidity	4.443	4	10.538	0.024*	
	Medication	0.596	3	23.38	0.567	
PainDETECT#	Age	0.581	4	18,79	0,619	
	Occupation	0.171	3	18.90	0.877	
	BMI	1.264	3	30.31	0.302	
	Comorbidity	0.634	4	10.53	0.649	
	Medication	1.744	3	23.38	0.186	
VAS#	Age	1.542	4	18,79	0.375	
	Occupation	0.243	3	18.90	0.865	
	BMI	0.498	3	30.31	0.686	
	Comorbidity	2.533	4	10.53	0.240	
	Medication	0.968	3	23.38	0.424	
FIQ#	Age	0.522	4	18,79	0.720	
	Occupation	0.050	3	18.90	0.985	
	BMI	0.421	3	30.31	0.739	
	Comorbidity	2.218	4	10.53	0.136	
	Medication	0.413	3	23.38	0.698	

#Peranova technique *p<0.05 statistically significiant VAS: Visuel Analog Scale PD-Q: painDETECT Questionnaire DN-4: Douler Neuropathic 4 FIQ: Fibromyalgia Impact Questionnaire

When Table 4 is examined, it is seen that mean DN4 and PD-Q values (tDN4 = 3.025 p =0.004, t PD-Q = 2.966 p = 0.004) were significantly higher in FMS patients who have a FMS history in families ($p < 0.05$), but there was no significant difference in VAS and FIQ values ($p > 0.05$).

Table 4. Comparison of VAS, PD-Q, DN-4, and FIQ median values in FMS patients according to family history

	Family History	N	x	ss	t	df	p
DN4#	Yes	33	5.58	2.092	3.025	64	0.004*
	No	33	3.85	2.526			
VAS#	Yes	33	6.82	2.007	0.403	64	0.688
	No	33	6.64	1.636			
PainDETECT#	Yes	33	17.85	6.671	2.966	64	0.004*
	No	33	12.64	7.578			
FIQ#	Yes	33	56.47	13.327	1.882	64	0.073
	No	33	50.05	15.243			

#Independent group t-test *p<0.05 statistically significiant VAS: Visuel Analog Scale PD-Q: painDETECT Questionnaire DN-4: Douler Neuropathic 4 FIQ: Fibromyalgia Impact Questionnaire

FIQ values were accepted as dependent variables. Scores of VAS, PD-Q, and DN4 were revealed as independent predictor factors of FIQ values. So, multiple regression analysis was performed. These three independent variables were found to explain approximately 45% ($R2 = 0.442$) of the FIQ values. It was determined that VAS, PD-Q, and DN4 were significant predictions of the FIQ values ($p = 0.001$). It was observed that the relationship between VAS and DN4 values is low, but relationships between the other factors were moderately significant. The relationship between VAS, PD-Q, DN4, and FIQ in the FMS group is shown in Table 5.

Table 5. The relationship between VAS, PD-Q, DN4 and FIQ variables

		DN4	FIQ	VAS
FIQ#	r	0.339		
	p	0.005		
VAS#	r	0.147	0.582	
	p	0.238	0.001	
PD-Q#	r	0.637	0.544	0.455
	p	0.001	0.001	0.001

#Pearson's Correlation test VAS: Visuel Analog Scale PD-Q: painDETECT Questionnaire Dn-4: Douler Neuropathic 4 FIQ: Fibromyalgia Impact Questionnaire

It was determined that the DN4 value was not a significant predictor of FIQ ($p = 0.461$), while VAS ($p = 0.001$) and PD-Q ($p = 0.046$) values were found to be significant predictors. VAS explains more variance in FIQ values than PD-Q; therefore, it may be revealed to be more predictive. The predictive power of the independent variables is shown in Table 6.

Table 6. The predictive power of the independent variables

	B	Beta	t	p
(Constant)	18.656		3.268	0.002 *
VAS#	3.511	0.438	4.024	0.000 *
PD-Q#	0.550	0.285	2.040	0.046 *
DN4#	0.553	0.093	0.742	0.461

#Multiple regression analysis *p<0.05 statistically significiant VAS: Visuel Analog Scale PD-Q: painDETECT Questionnaire Dn-4: Douler Neuropathic 4

4. Discussion

Our study showed that the VAS, PD-Q, and DN-4 values of the FMS group were found to be significantly higher when compared to the healthy control group. In other words, pain in FMS patients contained more neuropathic components than in healthy people. Another result obtained was that VAS and PD-Q were significantly predicted and had an effect on FIQ value in the FMS group. Only family history was related to NP among demographic characteristics, which were considered as the secondary aim of the study.

Many studies have been designed to understand the pathogenesis of FMS, but they have not been cleared yet. However, it has been suggested that the pathogenesis may be related to multiple mechanisms, such as neuroendocrine disorders, environmental and genetic factors, psychological factors, muscle dysfunction, sleep disorders, immune system changes, autonomic nervous system dysfunction, and central or peripheral nervous system disorders (1).

Recently, the effects of central and peripheral nervous system disorders in patients with FMS have been widely researched because of the unexplained symptoms such as fatigue, sleep disorders, and brain fog that FMS patients suffer from (4). Symptoms like fatigue, sleep disorders, and brain fog have been suggested that there might be a disorder in the in processing of pain in the brain. This led to FMS being classified as central sensitization syndromes (14-16). On the other hand, FMS patients often suffer from tingling, numbness, burning, and hyperalgesia, which are the typical symptoms of NP. It is well known that the peripheral nervous system and the neuroendocrine system are effective in the pathogenesis of NP (17). It was detected that serotonin, norepinephrine, and dopamine levels decrease in cerebrospinal fluid, but glutamate and substance P levels increase in patients with FMS. Also, opioid receptors decrease in the central nervous system but increase in peripheral regions. This issue causes low pain threshold and hyperalgesia (1, 14).

This issue brought up a question: ‘’Is FMS pain a kind of NP? ‘’or ‘’Does the pain in FMS have a neuropathic character? (3). Koroschetz et al. (18) compared patients with FMS and diabetic polyneuropathy (PNP), and it was shown that patients described similar symptoms such as burning, pricking, and allodynia. It has been found that the burning symptom is more common in patients with diabetic PNP, and pain attacks, numbness, and hyperalgesia due to heat and pressure are more common in patients with FMS. Pain seen in diabetic polyneuropathy is the prototype of the NP. This study showed that FMS patients had neuropathic symptoms at least as much as diabetic polyneuropathy patients. In another study where patients with chronic low back pain and FMS were compared, it was revealed that there is a neuropathic pain component in both disease groups, although the rate varies according to the scale used for determining neuropathic pain (19). In the study designed by Kösehasanoğulları et al. (20), FMS patients and

patients diagnosed with subacromial impingement syndrome were included, and patients with impingement syndrome were revealed as the control group with nociceptive pain. When they compared the two groups' pain characteristics, they found that scores of NP screening tools were significantly higher in patients with FMS. Our study also detected that pain in FMS patients contained more neuropathic components than the healthy people.

Recently, various scales such as LANSS, PD-Q, and DN4 have been frequently used for NP assessment. However, these scales have not been validated in patients describing diffuse body pain. In Gauffin's study performed with 158 FMS patients, Gauffin et al. argued that these scales should not be used alone in patients complaining of widespread body pain; they should be combined with clinical examination (9). Despite this, Koroschetz et al. (18) used PD-Q in patients with FMS and suggested that FMS also has a neuropathic component. Freynhagen et al. (21) reviewed five different studies in which PD-Q was used in FM patients in their review, and they suggested that PD-Q can be used not only in NP evaluation but also in the evaluation of pain in conditions such as chronic low back pain, FMS, cervical radiculopathy, total knee replacement, osteoarthritis, rheumatoid arthritis, and postthoracotomy pain. DiCarlo et al. (22) indicated that PD-Q and DN-4 screening tools have a good concordance in determining NP symptoms in patients with FMS. They also assessed that DN-4 was more powerful than PD-Q. In light of this information, FMS patients were evaluated with the PD-Q and DN4 scales, and these scores were found to be significantly higher in FMS patients than in healthy people.

Amris et al. detected that the PDQ score was found to correlate with tender point count and pressure-pain thresholds (23). Akaltun et al. (24) analyzed FMS patients with FIQ, Hamilton Depression Rating Scale, Pitsburg Sleep Quality Index, DN4, and LANNS. They determined a positive correlation between DN4, PD-Q, and FIQ. In our study, it was found that VAS, PD-Q, and DN-4 values correlated with FIQ values and predicted 45% of FIQ values.

Martinez-Lavin et al. (25) defined fibromyalgia as stress-induced NP in females that estradiol causes hyperalgesia by changing the expression of sodium channels. In fact, all patients in our study were female matched this view. Momi et al. (26) found that being female, age, BMI, and smoking were risk factors for NP in people with chronic widespread pain. Ubeda-D'Ocasar et al. (27) evaluated 126 FMS patients with LANNS, PD-Q, Central Sensitization Inventory, and pressure pain hyperalgesia. They determined that LANNS values were positively correlated with BMI, pain intensity, and CSI. While PD-Q values were negatively correlated with age, they found a positive correlation with pain intensity, CSI, anxiety, and depression. Kocyiğit et al. (28) detected that obese female FMS patients had higher levels of VAS, and also BMI was significantly and positively correlated with clinical manifestations of FMS. Our results were different from the literature. According to the results of our study, age, BMI, occupation, smoking, comorbidity, and medication were not found to be risk factors for pain, NP, or related to NP. Only FMS history in the family was found to be related to the neuropathic characteristics of the pain.

In recent studies, more objective methods such as quantitative sensory testing, nerve fiber density in skin biopsy and corneal biopsy, microneurography, and nociceptive evoked potentials have been used in addition to scales for evaluation of NP (29). A decrease in nerve fiber density in skin and corneal biopsy in FMS patients has been shown in several studies. It has been suggested that 49% of FMS patients have small-fiber neuropathy (1, 30-33). It has been thought that this issue may play a role in the neuropathic character of pain seen in patients with FMS. This assessment is the most important limitation of our study. We could not use an objective diagnosis method for NP in addition to NP scales. While talking about the shortcomings of the study, It can be added that "another shortcoming of the study is that patients who had pain and were not diagnosed with fibromyalgia were not included in the study. It is expected that VAS pain scores and neuropathic pain scores will be higher compared to healthy volunteers. Also, the small sample size and the fact that it consisted of only female patients are other limitations of the study. The strengths of our study include a control group, as well as correlation analysis and regression analysis.

Widespread pain in patients with FMS has a neuropathic component. The PD-Q and DN4 scales are easily applicable and useful scales for determining the NP in these patients. Furthermore, NP determined by PD-Q had an impact on FMS. Since the pathogenesis and treatment of the disease have not been clarified yet, defining the pain components and management of the treatment according to these components might be very helpful. The presence of a neuropathic component should be kept in mind and evaluated in all FMS patients before arranging treatment.

Ethical Statement

The study was approved by Katip Celebi University Ethical Committee on 22.12.2022 (IRB: 0626). The investigation was carried out according to the Declaration of Helsinki. A consent form was taken from all volunteers.

Conflict of interest

Authors declare that there is no conflict of interest for this article.

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Authors' contributions

Concept: U.S.D., O.K., Design: U.S.D., O.K., Data Collection or Processing: U.S.D., O.K., Analysis or Interpretation: U.S.D., O.K, A.A., A.T., Literature Search: U.S.D., O.K., Writing: U.S.D., A.A., A.T.

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