Large Fibre Neuropathy: Part of Fibromyalgia or Coexisting Entity?

Ist eine Neuropathie der großen Fasern ein Teil der Fibromyalgie oder existieren sie häufig nebeneinander?

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Key words

fibromyalgia syndrome, sleep, quality of life, depression, large fibre neuropathy

Schlüsselwörter

Großfaser-Neuropathie, Fibromyalgie-Syndrom, Schlaf, Lebensqualität, Depression

Published online 07.04.2020

Bibliography

Akt Rheumatol 2020; 45: 568–573

DOI 10.1055/a-1135-8471

ISSN 0341-051X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

Objectives The aim of this study was to investigate the incidence of large fibre neuropathy (LFN) in fibromyalgia (FM) patients with peripheral neuropathy symptoms and to examine the effect of LFN and FM on pain, quality of life, sleep quality, disability, and depressive symptoms.

Methods Between June 2018 and February 2019, a total of 104 patients (67 females, 37 males; mean age: 52.21 ± 9.53years; range, 31–74 years) with the diagnosis of FM were included in the study. The patients were divided into 2 groups, Group 1 including polyneuropathy (PNP) patients (n = 48) and Group 2 including non-PNP patients (n = 54). Group 1 was further divided into 2 subgroups: sensory PNP (n = 28) and sensorimotor PNP (n = 20). All patients were evaluated using the Visual Analog Scale (VAS), Fibromyalgia Impact Questionnaire (FIQ), Short Form-36 (SF-36), Pittsburgh Sleep Quality Index (PSQI), and Beck Depression Inventory (BDI).

Results There was no statistically significant difference in demographic characteristics between the groups ($p > 0.05$). There was a statistically significant difference in the VAS, SF-36, BDI, FIQ, and PSQI scores between Group 1 and Group 2 ($p < 0.05$). There was no statistically significant difference in the VAS, SF-36, BDI, FIQ, and PSQI scores between the sensory and sensorimotor PNP groups ($p > 0.05$).

Conclusions Our study results show that FM associated with LFN has an adverse effect on pain, quality of life, sleep quality, disability, and depressive symptoms compared with FM without LFN, indicating the importance of neuropathy management in FM patients.

ZUSAMMENFASSUNG

Zielsetzung Ziel dieser Studie ist es, die Inzidenz von Large Fibre Neuropathy (LFN) bei Fibromyalgie (FM) -Patienten mit peripheren Neuropathie-Beschwerden zu untersuchen und den Einfluss von LFN und FM auf Schmerzen, Lebensqualität, Schlafqualität, Behinderung, und depressive Symptome.

Methoden Zwischen Juni 2018 und Februar 2019 wurden insgesamt 104 Patienten (67 Frauen, 37 Männer; Durchschnittsalter: 52,21 ± 9,53 Jahre; Spanne 31–74 Jahre) mit der Diagnose FM in die Studie eingeschlossen. Die Patienten wurden in 2 Gruppen eingeteilt: Gruppe 1, einschließlich Patienten mit Polyneuropathie (PNP) (n = 48) und Gruppe 2, einschließlich Nicht-PNP-Patienten (n = 54). Gruppe 1 wurde auch weiter in 2 Untergruppen als sensorische PNP (n = 28) und sensomotorische PNP (n = 20) unterteilt. Alle Patienten wurden anhand der Visual Analog Scale (VAS), des Fibromyalgia Impact Questionnaire (FIQ), des Short Form-36 (SF-36), des Pittsburgh Sleep Quality Index (PSQI) und des Beck Depression Inventory (BDI) bewertet.

Ergebnisse Es gab keinen statistisch signifikanten Unterschied in den demografischen Merkmalen zwischen den Gruppen ($p > 0,05$). Es gab einen statistisch signifikanten Unterschied in den VAS-, SF-36-, BDI-, FIQ- und PSQI-Werten zwischen Gruppe 1 und Gruppe 2 ($p < 0,05$). Es gab keinen statistisch signifikanten Unterschied in den VAS-, SF-36-, BDI-, FIQ- und PSQI-Werten zwischen den sensorischen und sensomotorischen PNP-Gruppen ($p > 0,05$).

Schlussfolgerungen Unsere Studienergebnisse zeigen, dass FM mit LFN die Schmerzen, die Lebensqualität, die Schlafqualität, die Behinderung und die depressiven Symptome negativ beeinflusst, gegenüber denjenigen ohne LFN, was auf die Bedeutung des Neuropathiemanagements bei FM-Patienten hinweist.

Introduction

Fibromyalgia (FM) is a common widespread rheumatic disease characterized by widespread pain, fatigue, sleep disturbances, and cognitive symptoms, as well as somatic symptoms [1, 2]. It is the second most common rheumatic disease after osteoarthritis and its prevalence increases with age and peaks in the fifth and sixth decade of life, mostly affecting women [3, 4]. The prevalence of FM has been reported as 2 % in the United States, 3.3 % in Canada, and 3.6 % in Turkey [5]. Its prevalence also increases, as socioeconomic and education level decrease [6].

Polyneuropathy (PNP) is a condition which affects the peripheral nervous systems of both upper and lower limbs. Its nature may be axonal or demyelinating. Reduced compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes are the major electrophysiological hallmarks of axonal loss, while increased sensory and motor nerve conduction velocity indicating distal motor latency and increased minimum F latency suggest demyelinating exposure in PNP [7, 8].

In recent years, there is growing evidence that peripheral neuropathy is an important component of FM [9–13]. This can also explain burning sensation, allodynia, stinging, numbness, and hypersensitivity to normal stimuli in FM patients.

In the present study, we aimed to investigate the incidence of large fiber neuropathy (LFN) in FM patients and to examine the effect of LFN and FM on pain, quality of life, sleep quality, disability, and depressive symptoms.

Patients and Methods

This prospective study was conducted at musculoskeletal outpatient clinic of University of Health Sciences, Umraniye Training and Research Hospital between June 2018 and February 2019. A total of a total of 104 patients presenting with generalized pain, burning sensation, stinging, numbness, and allodynia who were diagnosed with FM according to the 2010 American College of Rheumatology (ACR) diagnostic criteria [2] were included in the study. All patients included in the study had pain within the last three months without any other rheumatic disease. The patients were divided into two groups according to electromyographic (EMG) findings as Group 1 including polyneuropathy (PNP) patients (n = 48) and Group 2 including non-PNP patients as the control subjects (n = 54). Group 1 was also further divided into 2 subgroups as sensorial PNP (n = 28) and sensorimotor PNP (n = 20). Those with diabetes mellitus, vitamin B12 deficiency, malignancies, connective tissue disorders, and toxic, infectious, or hereditary diseases were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Electrophysiological studies

Electrophysiological studies of FM patients with and without PNP were performed by a single electrophysiologist. Standard motor and sensory nerve conduction studies (NCS) were performed. The methods described by Falck et al. [14] and Stalberg and Falck [15] were used. Electrophysiological studies were performed with bilateral sural NCS, right common peroneal, right tibial nerve, right median-ulnar motor and sensory NCS protocols using the Medelec Synergy on Nicolet AT2 EMG/EP system (Nicolet Biomedical, Madison, WI, USA). Surface bar recording and ring electrode recording were used. Median, ulnar, and sural sensory NCSs were performed using the antidromic method. Motor NCSs were performed analyzing the CMAP, distal latency, conduction velocity, mean F-response latency, and F-wave persistence. The median F-response latency was calculated based on series of 10 responses. Sensory NCSs were performed measuring the baseline-to-peak latency, baseline-to-peak nerve conduction velocity (NCV), and SNAP.

The latency of sensory nerve was related to the onset of the first negative deflection and to the negative peak. The sensory NCV was calculated based on the latency and the distance between the stimulating and recording electrode. The amplitude of the SNAP was measured from the baseline to the negative peak. Stimulation duration was 0.2 ms for motor stimuli and 0.1 ms sensory stimuli. All NCSs were performed with supramaximal stimulation. The band of frequencies was 20 Hz-2 kHz in the sensory and 5 Hz-10 kHz in the motor and F-wave studies. Skin temperature was kept at 31 °C to 34 °C in all patient groups.

According to EMG findings, neuropathy was defined as damage to the axons (axonal neuropathy) or the myelin (demyelinating neuropathy), or both (mixed). We used mean ± 2 standard deviations (SDs) as the limit for the controls in our laboratory with 95 % confidence interval (CI) and stated the deviation from normal mean for the individual subject as Z-score (i. e., deviations in SD from the normal of mean) [16].

Outcome measurements

Data including demographic and clinical characteristics of the patients were recorded. Sociodemographic characteristics of the patients were standardized between the groups. All outcome measurements were evaluated by a single researcher.

The Visual Analog Scale (VAS), which is a self-rated questionnaire, was used to evaluate pain severity. The scale ranges from 0 to10. 0 indicates no pain, while 10 indicates unbearable pain [17].

The Short Form-36, which is a multi-item scale and consists of eight subscales and 36 items, was used to evaluate the quality of life, and physical and mental health of the patients. The eight subscales are physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental

health [18]. The validity and reliability of the SF-36 in the Turkish population have been shown by Demiral et al. [19].

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which evaluates sleep quality and disturbances in the previous month. The overall score ranges from 0 to 21 and higher scores indicate worse sleep quality [20].

The Beck Depression Inventory (BDI), which is one of the most widely used tools to assess depressive symptoms, consists of 21 items. The overall scores range from 0 to 63. The sum of each item score of 0 to 9 denotes normal, 10 to 15 mild depression, 16 to 23 moderate depression, and 24 to 63 severe depression [21]. The validity and reliability of the BDI in the Turkish population have been shown by Ulusoy et al. [22].

The Fibromyalgia Impact Questionnaire (FIQ), which is a 10-item, self-rated instrument, is used to measure functional disability and to evaluate work performance, pain, fatigue, morning stiffness, anxiety, and depression [23]. The overall score ranges from 0 to 100 and higher scores indicate a greater impact of FM on functioning. The validity and reliability of the FIQ in the Turkish population have been shown by Sarmer et al. [24].

The Symptom Severity Scale (SSS) is a self-administered questionnaire with a score range from 0 to 12. It measures severity of fatigue, cognitive dysfunction, somatic symptoms, and unrefreshed sleep over the past week each on a scale from 0 to 3: 0 = no problem, 1 = mild, 2 = moderate, and 3 = severe [2].

The Widespread Pain Index (WPI) is used to measure the extent of bodily pain on a 0 to 19 scale by asking patients if they have had pain or tenderness in 19 different body regions (shoulder girdle, hip, jaw, upper arm, upper leg, lower arm, and lower leg on each side of the body, as well as upper back, lower back, chest, neck, and abdomen) over the past week, with each painful or tender region scoring 1 point [2].

Statistical analysis

Statistical analysis was performed using the SPSS version 20 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± SD, median (min-max), or number and frequency. The Student's t-test was used to compare the qualitative variables showing normal distribution between the groups, while the Mann-Whitney U test was used to compare non-normally distributed variables. The Fisher's exact test was used to examine significant differences in the sociodemographic characteristics between the groups. The Pearson correlation analysis was performed to analyze possible correlations between the variables. A *p* value of $p < 0.05$ was considered statistically significant.

Results

A total of 104 patients with FM were included in this study. Of the patients, 67 were females and 37 were males with a mean age of 52.21 ± 9.53 (range, 31 to 74) years. Of all patients, 48 (46.15 %) had PNP and 56 (53.85 %) had no PNP. According to EMG findings, 28 patients (58.33 %) had sensorial PNP and 20 patients (41.66 %) had sensorimotor PNP. There was no statistically significant difference in baseline sociodemographic characteristics between the groups ($p > 0.05$). Baseline sociodemographic and clinical characteristics of the patients are shown in ▶ **Table 1**.

▶ **Table 1** Demographic features of participants.

Groups		Control	PNP
Sex (M/F); n		36/20	31/17
Age (year)	Mean ± SD	50.7 ± 8.84	54.0 ± 10.08
	Median (Range)	50 (31–71)	51 (36–74)

(n:104) (n: number of samples, M: male, F: female, SD: standard deviation)

There was a statistically significant difference in the VAS, SF-36, BDI, FIQ, and PSQI scores between Group 1 and Group 2 ($p < 0.05$). However, there was no statistically significant difference in the VAS, SF-36, BDI, FIQ, and PSQI scores between the sensorial and sensorimotor PNP groups ($p > 0.05$). The VAS, SF-36, BDI, FIQ, and PSQI scores are presented in ▶ **Table 2** and **3**.

The correlation analysis revealed a moderate, negative, and statistically significant relationship between the changes in the VAS scores and changes in the SF-36 mental health ($r = -0.434$), SF-36 bodily pain ($r = -0.501$) scores in the PNP group. In addition, there was a weak, negative, and statistically significant relationship between the changes in the VAS scores and the changes in the SF-36 general health ($r = -0.287$) scores in the PNP group. There was also a weak, positive, and statistically significant relationship between the changes in the VAS and the changes in the PSQI ($r = 0.342$) scores in the PNP group. There was a moderate, positive, and statistically significant relationship between the changes in the VAS and the changes in the BDI ($r = 0.413$) scores in the PNP group. There was a weak, negative, and statistically significant relationship between the changes in the FIQ scores and the changes in the SF-36 mental health ($r = -0.355$) scores in the PNP group. There was a moderate, negative, and statistically significant relationship between the changes in the FIQ scores and the changes in the SF-36 bodily pain ($r = -0.401$) and SF-36 general health ($r = 415$) scores in the PNP group. There was also a weak, positive, and statistically significant relationship between the changes in the FIQ and the changes in the PSQI ($r = 0.331$) and BDI ($r = 379$) scores in the PNP group. In addition, there was a weak, positive, and statistically significant relationship between the changes in the SSS and the changes in the PSQI ($r = 0.352$) and SF-36 vitality ($r = 0.263$) scores in the PNP group. In addition, there was a weak, negative, and statistically significant relationship between the changes in the SSS and the changes in the SF-36-GH ($r = -0.307$) scores in the PNP group. There was also a weak, positive, and statistically significant relationship between the changes in the WPI and the changes in the SF-36 vitality ($r = -0.347$) scores in the PNP group. There was a weak, negative, and statistically significant relationship between the changes in the WPI and the changes in the SF-36 bodily pain ($r = -0.247$) scores in the PNP group. The results of the correlation analysis of all scales in the PNP group are summarized in ▶ **Table 4**.

▶ **Table 2** Comparison of VAS, SF-36, PSQI, BDI, NDI, FACIT, FIQ, SSS and WPI values between PNP and control groups

	PNP n:48	Control n:54	p-values
	Mean ± SD (Median)	Mean ± SD (Median)	
VAS[a]	8.29 ± 1.11 (8.0)	4.16 ± 1.76 (4.0)	*<0.001*
Sf36-PF[b]	35.31 ± 7.54 (30.0)	59.46 ± 15.54 (60.0)	*<0.001*
Sf36-DPR[b]	35.42 ± 12.46 (25.0)	66.07 ± 18.73 (75.0)	*<0.001*
Sf36-DER[b]	38.19 ± 19.43 (33.3)	75.00 ± 22.25 (66.7)	*<0.001*
Sf36-VT[b]	31.98 ± 6.50 (30.0)	55.54 ± 15.34 (62.5)	*<0.001*
Sf36-MH[b]	31.42 ± 6.09 (32.0)	55.54 ± 16.50 (53.0)	*<0.001*
Sf36-SF[b]	31.98 ± 9.14 (25.0)	56.21 ± 16.05 (62.5)	*<0.001*
Sf36-BP[b]	30.89 ± 6.41 (32.5)	56.61 ± 18.92 (57.5)	*<0.001*
Sf36-GH[b]	29.48 ± 5.18 (30.0)	51.25 ± 14.69 (50.0)	*<0.001*
PSQI[b]	15.40 ± 1.99 (16.0)	9.23 ± 3.57 (8.0)	*<0.001*
BDI[b]	13.15 ± 3.71 (12.5)	6.77 ± 2.96 (6.0)	*<0.001*
FIQ[b]	65.30 ± 6.18 (65.8)	38.70 ± 10.88 (36.7)	*<0.001*
SSS[b]	9.83 ± 1.19 (10.0)	7.95 ± 0.90 (8.0)	*<0.001*
WPI[b]	6.88 ± 1.10 (7.0)	6.00 ± 0.93 (6.0)	*<0.001*

VAS, visual analog scale; SF-36 PF, short form-36 physical functioning; SF-36 DPR, short form-36 diffuculty physical role; SF-36 PF, short form-36 diffuculty emotional role; SF-36 VT, short form-36 vitality; SF-36 MH, short form-36 mental health; SF-36 SF, short form-36 social functioning; SF-36 BP, short form-36 bodily pain; SF-36 GH, short form-36 general health; PSQI, Pittsburgh Sleep Quality Index; BDI, The Beck Depression Inventory; SSS,Symptom Severity Scale; WPI, Widespread Pain Index. [a] Independent Sample T Test; [b] Mann Whitney Test; * $p < 0.05$

▶ **Table 3** Comparison of VAS, SF-36, PSQI, BDI, NDI, FACIT, FIQ, SSS and WPI values between Sensorial PNP and Sensorimotor PNP groups

	Sensorial PNP n:28	Sensorimotor PNP n:20	p-values
	Mean ± SD (Median)	Mean ± SD (Median)	
VAS[a]	8.46 ± 1.00	8.05 ± 1.23	**0.231**
Sf36-PF[b]	34.64 ± 7.44	36.25 ± 7.76	**0.461**
Sf36-DPR[b]	34.82 ± 12.43	36.25 ± 12.76	**0.695**
Sf36-DER[b]	36.90 ± 7.44	39.99 ± 17.44	**0.789**
Sf36-VT[b]	32.86 ± 7.13	30.75 ± 5.45	**0.313**
Sf36-MH[b]	30.79 ± 5.51	32.30 ± 6.88	**0.226**
Sf36-SF[b]	32.68 ± 9.05	31.00 ± 9.40	**0.602**
Sf36-BP[b]	30.54 ± 6.10	31.38 ± 6.95	**0.843**
Sf36-GH[b]	28.93 ± 4.16	30.25 ± 6.38	**0.355**
PSQI[b]	15.43 ± 1.73	15.35 ± 2.35	**0.933**
BDI[b]	13.64 ± 3.32	12.45 ± 4.17	**0.234**
FIQ[b]	65.41 ± 6.35	65.16 ± 6.09	**0.738**
SSS[b]	9.89 ± 1.17	9.75 ± 1.25	**0.621**
WPI[b]	6.79 ± 1.10	7.00 ± 1.12	**0.498**

VAS, visual analog scale; SF-36 PF, short form-36 physical functioning; SF-36 DPR, short form-36 diffuculty physical role; SF-36 PF, short form-36 diffuculty emotional role; SF-36 VT, short form-36 vitality; SF-36 MH, short form-36 mental health; SF-36 SF, short form-36 social functioning; SF-36 BP, short form-36 bodily pain; SF-36 GH, short form-36 general health; PSQI, Pittsburgh Sleep Quality Index; BDI, The Beck Depression Inventory; FIQ, Fibromiyalgia Impact Questionnarie; SSS, Symptom Severity Scale;WPI, Widespread Pain Index. [a] Independent Sample T Test; [b] Mann Whitney Test; * $p < 0.05$

Discussion

In this study, we evaluated the effect of LFN and FM on pain, quality of life, sleep quality, disability, and depressive symptoms. Our study results showed that FM presenting with LFN had an adverse effect on pain, quality of life, sleep quality, and depressive symptoms than those without LFN.

Small fiber neuropathy occurs when damage to the peripheral nerves which affects the small myelinated (Aδ) fibers or unmyelinated C fibers. The specific fiber types are involved in both small somatic and autonomic fibers. In the peripheral nerves, deep senses such as vibration, position sense, and afferent part of the tendon reflex arc are carried with large myelinated fibers, whereas pain and heat sense are carried by unmyelinated and small myelinated fibers. Large fiber function is evaluated by NCS and EMG. Therefore, it is difficult to obtain objective data in neuropathies where small nerve fibers are selectively captured. Quantitative sensory testing, bedside tests for the autonomic nervous system, and electrophysiological examinations, and nerve and skin biopsies can be used to demonstrate SFN. In this type of neuropathy, clinical, neurological, nerve conduction and EMG studies are usually normal [25, 26]. Small nerve fiber neuropathies can occur without large nerve fiber involvement, although there are some reports showing both types of neuropathy simultaneously developed or progressed to include large nerve fibers [27].

Previous studies have well documented that nearly half of FM patients have small fiber neuropathy (SFN) due to reduced intraepidermal fiber density [10, 11, 28]. In most cases, SFN causes sensory symptoms such as pain, burning, and paresthesia and occur in a length-dependent (stocking-glove distribution) pattern. Pa-

▶ **Table 4** Correlation analysis of SF-36, PSQI and BDI scores with VAS, FIQ, SSS and WPI scores in PNP groups.

		VAS	FIQ	SSS	WPI
Sf36-PF	r^2	−0.215	−0.229	−0.018	−0.213
	p	0.143	0.117	0.905	0.147
Sf36-DPR	r^2	−0.224	−0.181	−0.311	−0.213
	p	0.125	0.217	**0.032**	0.146
Sf36-DER	r^2	−0.232	−0.195	−0.148	0.095
	p	0.113	0.185	0.315	0.521
Sf36-VT	r^2	−0.067	−0.188	0.263	0.347
	p	0.651	0.202	**0.071**	**0.016**
Sf36-MH	r^2	−0.434	−0.355	−0.043	0.014
	p	**0.002**	**0.013**	0.772	0.923
Sf36-SF	r^2	−0.137	−0.188	0.070	−0.175
	p	0.354	0.201	0.636	0.233
Sf36-BP	r^2	−0.501	−0.401	−0.134	−0.247
	p	**0.000**	**0.005**	0.366	**0.090**
Sf36-GH	r^2	−0.287	−0.415	−0.307	−0.179
	p	**0.048**	**0.003**	**0.034**	0.223
PSQI	r^2	0.342	0.331	0.352	0.120
	p	**0.017**	**0.021**	**0.014**	0.416
BDI	r^2	0.413	0.379	0.213	−0.079
	p	**0.003**	**0.008**	0.146	0.595

VAS, visual analog scale; SF-36 PF, short form-36 physical functioning; SF-36 DPR, short form-36 diffuculty physical role; SF-36 PF, short form-36 diffuculty emotional role; SF-36 VT, short form-36 vitality; SF-36 MH, short form-36 mental health; SF-36 SF, short form-36 social functioning; SF-36 BP, short form-36 bodily pain; SF-36 GH, short form-36 general health; PSQI, Pittsburgh Sleep Quality Index; BDI, The Beck Depression Inventory; SSS,Symptom Severity Scale; WPI, Widespread Pain Index. Pearson correlation analysis * $p<0.05$

resthesia may manifest as burning, stinging, tingling, or hyperesthesia. In addition, allodynia which is the perception of non-painful stimuli as being painful or hyperalgesia which is the perception of painful stimuli as being more painful than expected may be seen in these patients. This can also explain the reason for lesser symptoms in FM patients without neuropathy than those with neuropathy. Symptoms usually begin at night, leading to reduced sleep quality. Of note, FM, itself, has been already associated with sleep disturbances. In addition, SFN may lead to abnormal sweating (reduced or increased) due to autonomic dysfunction, skin discoloration, dry mouth, dry eye, gastrointestinal disorders, constipation, and headache [28–31]. These symptoms can be also attributed to somatic problems in FM patients.

In a study, Caro et al. [32] divided the patients into three groups as FM (n = 29), FM + rheumatoid arthritis (RA) (n = 26), and non-FM/non-RA (n = 40). More than 90 % of the patients in the FM group had sensorimotor PNP, mainly sensorial and/or axonal PNP. Although similar results were obtained in the FM + RA group, only 7 % of the controls had sensorimotor PNP. In our study, we also observed sensorial or sensorimotor PNP in 48 (46.15 %) of the FM patients. In another study, complaints of numbness, burning, tingling, morning stiffness, insomnia, fatigue, and weakness were significantly more common in the FM group, compared to the controls [33]. Also, the mean scores of the BDS, FIQ, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and painDETECT were significantly higher in the FM patients. There was also a statistically significant correlation between the FIQ values and LANSS and the BDS and painDETECT scores in the FM group. Similarly, in our study, we found statistically higher BDI, FIQ, VAS, SSS, and WPI scores in the patients with LFN. In addition, we found a significant correlation between the FIQ scores and BDI, PSQI, and SF-36 subscale scores. However, the lack of an electrophysiological study in the aforementioned study precludes an accurate comparison of those with peripheral neuropathy to those without. In our study, we confirmed that not every patient with FM presenting with numbness, burning sensation, and tingling was diagnosed with peripheral neuropathy as evidenced by electrophysiological studies.

Although EMG and NCSs often produce normal results in SFN patients, it is unlikely to definitely rule out SFN based on electrophysiological studies, even in cases without peripheral neuropathy. Similarly, FM patients with and without peripheral neuropathy might have SFN, as well. This can explain the reason for the lack of LFN in all FM patients with neuropathy based on EMG findings.

Although previous studies have demonstrated that nearly half of the patients have SFN, there is a limited number of studies evaluating FM symptoms in SFN patients in the literature. In our study, the VAS, BDI, PSQI, and FIQ scores were statistically significantly higher, while the SF-36 subscale scores were statistically significantly lower in the FM patients with LFN than those without LFN. This finding indicates an adverse effect of FM presenting with LFN on pain, quality of life, sleep quality, disability, and depressive symptoms. Despite this statistically significant difference between the FM patients with and without LFN, we found no significant difference in sensorial and sensorimotor symptoms among FM patients. This can be attributed to the fact that sensorial involvement is much more important for FM symptoms. In addition, muscle strength, muscle balance, and physical function can be measured to evaluate motor involvement more accurately.

According to the correlation analysis, we found significant correlations between the SF-36, BDI, and PSQI and VAS, FIQ, SSS, and WPI scores. This finding indicates the evident relation of the sleep quality and depressive symptoms with pain, FM severity, and disability. Based on these results, we suggest that treatment of peripheral neuropathic pain and alleviate FM symptoms and improve daily living activities of patients.

Nonetheless, there are some limitations to this study. Further prospective studies in large series using electrophysiological studies are needed to evaluate the incidence of LFN in FM patients and its effect on FM symptoms. In addition, a head-to-head comparison study investigating the symptom severity and incidence in FM patients with SFN and LFN would be helpful to gain a better understanding of this topic. Additionally, the incidence of peripheral neuropathy among FM patients may shed light into the etiology of FM which has been long discussed. Therefore, further studies investigating the pathogenesis of FM are warranted. In our study, alt-

hough small fiber involvement is not known in the FM patient group, we believe that showing large fiber involvement would contribute to the pathogenesis. In further studies, both types of neuropathy involvement should be sought to gain a better understanding of the pathogenesis.

Conclusion

In conclusion, both LFN and SFN may present with generalized pain, burning sensation, numbness, and abnormal pain perception and FM presenting with LFN has an adverse effect on pain, quality of life, sleep quality, disability, and depressive symptoms than those without LFN, indicating the importance of neuropathy management in FM patients. In these cases, an effective treatment plan may improve sleep quality, quality of life, and depressive symptoms.

Competing interest

The authors declare that they have no conflict of interest.

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