Enhanced sensory conduction in primary fibromyalgia: a case–control pilot study

Mohamed N. Thabit1*, Mostafa Abdelmomen1, Esam Aboelfadl2 and Saber Hadad3

Abstract

Background: This study aimed to test the changes in the conduction properties of peripheral nerves in patients with primary fibromyalgia (FM). Thirty patients with FM and sixteen healthy controls participated in this study. Visual analogue scale (VAS) for pain severity, pain duration, Widespread Pain Index (WPI), Symptom Severity (SS) scale, Hamilton depression rating scale, Taylor’s manifest anxiety scale, and Fibromyalgia Impact Questionnaire (FIQR) were used for measurement of psychiatric comorbidities and quality of life for each patient. Routine motor and sensory nerve conduction studies of both median, ulnar, common peroneal, posterior tibial, and sural nerves were measured for all study participants.

Results: We found statistically significant increase in Sensory Conduction Velocity (SCV), Sensory Nerve Action Potential (SNAP) amplitude, and decrease in Sensory Latency (SL) in patients with FM compared to controls. There were no significant changes in motor nerve conduction between patients and controls. Regression analysis showed a significant relation between WPI and both SCV and SL especially in nerves of upper limbs. However, no significant relation between SCV and SL and other presumed predictors including VAS for pain severity, pain duration, SS scale, FIQR, and psychiatric comorbidities. Patients with FM suffered more depression and anxiety than controls.

Conclusions: We found enhanced conductivity of the sensory rather than the motor nerves in patients with FM. To our knowledge, this is the first study to describe these sensory changes which may add further evidence of peripheral sensitization in patients with FM.

Keywords: Fibromyalgia, Chronic pain syndromes, Nerve conduction studies, Peripheral sensitization

Background

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain in ≥ 11 out of 18 tender points in addition to various other complaints including fatigue, emotional distress and disturbed sleep [1, 2]. FM represents the extreme end of a whole spectrum of chronic musculoskeletal pain and affects women more than men in a ratio of 9:1. The prevalence rate of FM in the general population is very high ranging from 7.3% to 12.9% across different countries.

Pain in FM occurs due to augmentation of nociceptive transmission and processing in the CNS, a phenomenon known as Central Sensitization (CS). Many studies support the hypothesis of CS as it was found that patients with FM have abnormal concentrations of CNS neuropeptides, biogenic amines, and functional alterations of the hypothalamus–pituitary–adrenal axis [3, 4]. Those changes are associated with a widespread lowering of the pain threshold leading to hypersensitivity to mechanical pain (alldynia) which is diffuse one, not limited to specific tender points [5, 6]. Pain itself induces two emotional components in reciprocal relationship: pain sensation itself, and the negative feeling of depression, anger and fear. The two components increase each other’s and both are CNS processed phenomena [7].
Older FM studies did not show consistent changes in the painful peripheral tissues [8]. However, many recent studies showed consistent changes in skin and muscles in patients with FM. Those changes included elevated levels of substance P, DNA fragmentation of muscle fibers, increased levels of interleukins-1 in cutaneous tissues, and perfusion abnormalities in muscles [9–13]. Those changes may provide a possible link between peripheral tissues and pain in patients with FM. There is evidence of Peripheral Sensitization (PS) in patients with FM including hypersensitivity of polymodal pain receptors, lowered thermal threshold, and increased responses to mechanical nociceptive stimuli, and decreased pain and number of tender points after topical application of capsaicin or injection of tender points [14–17]. Moreover, many studies reported a reduction of nociceptive thresholds in the neurons of the dorsal horn of the spinal cord which may be induced by the changes responsible about PS [18–20]. According to the previous facts, FM seems to be a pain condition due to CS of the CNS induced through PS or a stress induced changes in the hypothalamus—pituitary—adrenal axis that causes various changes responsible about the PS which itself induces the CS as several studies reported co-morbid depressive disorders in patients with FM [21–23].

Various neurophysiological measures can be used to assess functional changes in the peripheral nervous system and the state of activity of the motor and sensory axons including both sensory and motor Nerve Conduction Studies (NCS). NCS are easily measured, safe, widely available and non-invasive tool to assess changes in the peripheral nervous system. To the best of our knowledge, all the previous studies that used NCS in patient with FM were aiming to discover pathological changes in the peripheral nervous system in those patients. None of those studies aimed to find changes between healthy individuals and patients with FM who have normal routine NCS and do not suffer peripheral nervous system disorders that can explain the occurrence of pain. Moreover, those studies were very little regarding the huge researches in this field of chronic pain syndromes [24, 25].

The aim of our study is to find any changes in sensory and/or motor NCS in patients with primary FM with normal NCS compared to healthy controls. These changes may add more evidence of an undergoing PS in the peripheral nervous system in those patients. The findings of this study may point to the importance of further studying the changes of the peripheral nervous system in those patients. These changes might be not less important than changes in the CNS in those patients.

**Methods**

**Subjects**

Thirty patients suffering from FM (26 females and 4 males; mean age ± SD = 33.1 ± 8.4), and 16 healthy controls (13 females and 3 males; mean age ± SD = 29.1 ± 9.7) participated in this study. Patients with FM were diagnosed according the 2010 ACR Fibromyalgia Diagnostic Criteria (Modified 2011). These criteria included the following: widespread musculoskeletal pain for more than 3 months distributed both above and below waist with moderate or high intensity tenderness at 11 or more out of 18 specific tender points on digital presses. Participants fulfilled the criteria of 7 or more scores on Widespread Pain Index (WPI) and a score of 5 or more on the Symptoms Severity scale (SS) or a score of 3–6 on WPI and a score of 9 or more at the SS scale without evidence of other disorder that would explain the pain [2, 26, 27]. Patients were recruited from Neurology, Psychiatry, and Rheumatology clinics in our university hospital. Patients who are suspected or proved to suffer any autoimmune or other rheumatological disorder were excluded from the study. In addition, patients who suffer any disease that affects the results and interpretation of the NCS were excluded from the study including patients who suffer polyneuropathy or entrapment neuropathies and those who have any abnormal findings in the recorded NCS parameters. Healthy volunteers who participated in the control group of the study were recruited from the staffs and workers in our hospital. All the study participants gave an informed consent for participation in the study and the study protocol was approved by the local ethical committee of university.

**Demographic data**

Demographic measures were taken from all study participants including age, sex, marital status, weight, height, and Body Mass Index (BMI).

**Pain related parameters and psychiatric comorbidity measurements**

In addition to the previous demographic data, visual Analogue Scale (VAS) for pain severity, pain duration in months, in addition to the WPI and SS scores were measured in patients with FM only. Arabic validated version of the Hamilton Depression Rating Scale (HAM-D) was used to measure depression in both patients and healthy controls [28]. Scores from 0 to 7 were considered as normal, 8 to 13 was considered as mild depression, 14–18 were considered as moderate depression, 19–22 were considered as severe depression, and finally scores of 23 or more were considered as very severe depression. Arabic version of the Taylor’s Manifest Anxiety Scale (TMAS) was used for measurement of anxiety in both
patients and controls [29]. This scale has a score range from 0 to 50, scores from 0 to 16 indicate no anxiety, scores from 17 to 20 indicate mild anxiety, scores from 21 to 26 indicate moderate anxiety, scores from 27 to 29 indicate severe anxiety, and finally scores from 30 to 50 indicate very severe anxiety.

Measurement of the quality of life in patients with FM

For measurement of the quality of life, the Arabic validated version of the Revised Fibromyalgia Impact Questionnaire (FIQR) was used [30]. This questionnaire is used specifically for patients with FM in clinical researches worldwide. The total score of this questionnaire ranges from 0 to 100, scores from 0 to 42 signifies mild, scores from 43 to 59 signifies moderate, from 60 to 74 signifies severe, and finally scores from 75 to 100 signifies extreme impact on the quality of life of the patients.

Testing changes in routine nerve conduction studies

Both motor and sensory NCS were done for both patients and controls participating in the study. Motor NCS for the major motor nerves including median, ulnar, common peroneal, and posterior tibial nerves were recorded bilaterally for all the study participants with the usual standards [31, 32]. The Distal Motor Latency (DML) in ms, Motor Conduction Velocity (MCV) in m/s, and the Compound Muscle Action Potential (CMAP) amplitude in mV were recorded for each nerve. Antidromic sensory NSC were conducted for median, ulnar, and sural nerves bilaterally with the recording of the Sensory Latency (SL) in ms, Sensory Conduction Velocity (SCV) in m/s, and Sensory Nerve Action Potential (SNAP) amplitude in μV measured from baseline to peak for each nerve. Fixed distances between the stimulating and the recording surface electrodes were used for sensory NCS, namely; 13 cm, 11 cm, and 14 cm for median, ulnar, and sural nerves, respectively. Filter settings were 5 Hz–10 kHz for motor studies and 20 Hz–2 kHz for sensory studies. Skin temperature was kept between 31 and 34 °C in all subjects. The onset latency for the SNAP (onset of the initial negative deflection) was used to calculate the SCV. All electrophysiological studies were recorded using apparatus (Neuropack MEB-2300; Nihon-Kohden, Tokyo, Japan).

Statistical analysis

Demographic data, psychiatric measures, measures of the quality of life in patients with FM were presented as mean±SD, and percentage for categorical data. Electrophysiological data were presented as mean±SEM. Testing the normality of the numerical data was done using the Kolmogorov–Smirnov test to assess whether it is normally distributed or not. The statistical package SPSS for Windows (Version 16) was used for statistical analysis. Independent sample T test and ANOVA were used to determine the significant differences between groups for the numerical data. Chi-squared test and Mann–Whitney U tests were used for categorical data and non-normally distributed numerical data. A P value of < 0.05 was considered statistically significant.

Results

There were no statistically significant differences between patients with FM and healthy controls regarding age, sex, marital status, and BMI. However, there was statistically significant differences between both groups regarding psychiatric comorbitides. Patients with FM suffers more depression and anxiety compared to healthy controls in HAM-D and TMAS scales (t = 8.4, P < 0.0001; and t = 10.2, P < 0.0001, respectively). The demographic data, for both patients and controls are presented in Table 1. Data of the psychiatric comorbidity and quality of life are presented in Table 2.

| Table 1 | Demographic data for both patients with FM and controls |
|---------|--------------------------------------------------------|
| Number | Patients with FM | Healthy controls |
| Age (years) | 33.1 ± 8.4 | 29.1 ± 9.7 |
| Sex | 4 males (13.3%); 26 females (86.7%) | 3 males (18.75%); 13 females (81.25%) |
| Marital status | 25 married (83.3%); 5 single (16.7%) | 12 married (75%); 4 single (25%) |
| BMI | 27.4 ± 3.2 | 24.6 ± 3.7 |
| Pain duration (months) | 24.4 ± 18.1 | – |
| VAS for pain | 6.6 ± 2.2 | – |
| WPI | 12 ± 2.5 | – |
| SS scale | 8.4 ± 1.4 | – |
| Medications | 16 (53.3%) were using SNRI; 14 (46.7%) were using NSAID |

FM: Fibromyalgia; BMI: Body Mass Index; VAS: Visual Analogue Scale; WPI: Widespread Pain Index; SS: Symptoms Severity; SNRI: Serotonin Norepinephrine Reuptake Inhibitors; NSAID: Nonsteroidal Anti-inflammatory Drugs.
Table 2  Data of psychiatric comorbidities and quality of life for both patients with FM and controls

| Variable | Patients with FM | Healthy controls | P value |
|----------|-----------------|-----------------|---------|
| HAM-D    | 16.2 ± 5.6      | 5.4 ± 1.4       | .000*   |
| TMAS     | 21.3 ± 5        | 9.6 ± 1.7       | .000*   |
| FIQR     | 68.2 ± 10.7     | –               | –       |

HAM-D Hamilton Depression Rating Scale, TMAS Taylor’s Manifest Anxiety Scale, FIQR Revised Fibromyalgia Impact Questionnaire. *Significant

Table 3  Data of sensory conduction parameters for both patients with FM and controls

| Variable | Mean ± SEM | T value | P value |
|----------|------------|---------|---------|
| Median SL | 2.31 ± 0.04 | – 2.578 | .012* |
| Median SNAP Amp | 67.36 ± 2.61 | 3.839 | .000* |
| Median Sensory CV | 62.02 ± 0.82 | 2.534 | .013* |
| Ulnar SL | 1.87 ± 0.03 | – 2.999 | .004* |
| Ulnar SNAP Amp | 65.35 ± 2.40 | 3.417 | .000* |
| Ulnar Sensory CV | 57.61 ± 0.90 | 3.992 | .000* |
| Sural SL | 2.68 ± 0.05 | – 1.496 | .139 |
| Sural SNAP Amp | 20.78 ± 0.97 | 2.859 | .005* |
| Sural Sensory CV | 49.16 ± 1.03 | 2.260 | .028* |

Table 4  Adjusted P value for significant sensory NCS variables using Benjamini and Hochberg procedure

| Variable                  | Non-adjusted P value | Adjusted P value |
|---------------------------|-----------------------|------------------|
| Ulnar Sensory CV          | 0.00015               | 0.001575         |
| Median SNAP Amp           | 0.00025               | 0.000334         |
| Ulnar SNAP Amp            | 0.001                 | 0.007            |
| Ulnar SL                  | 0.004                 | 0.021            |
| Sural SNAP Amp            | 0.005                 | 0.021            |
| Median SL                 | 0.012                 | 0.042            |
| Median Sensory CV         | 0.013                 | 0.039            |
| Sural Sensory CV          | 0.028                 | 0.0735           |
| Sural SL                  | 0.139                 | 0.32433333       |

Table 5  Regression analysis of various dependent sensory conduction variables and WPI

| Odds ratio | T value | P value |
|------------|---------|---------|
| Median SL  | – 283   | – 2.353 | .023* |
| Median SNAP Amp | 1.67 | 1.015 | .315 |
| Median Sensory CV | 4.15 | 3.207 | .002* |
| Ulnar SL    | – 386   | – 2.422 | .019* |
| Ulnar SNAP Amp | 2.39 | 1.490 | .142 |
| Ulnar Sensory CV | 3.62 | 2.454 | .018* |
| Sural SL    | – 279   | – 1.771 | .082 |
| Sural SNAP Amp | 0.49 | 0.286 | .776 |
| Sural Sensory CV | 2.37 | 1.545 | .129 |

Neurophysiological data showed insignificant differences in all variables regarding motor NCS including the DML, the MCV and the amplitude of CMAP. However, sensory NCS showed significant increase in SCV and SNAP amplitudes and decrease in SL (Table 3). Since we did a large number of comparisons for both sensory and motor NCS variables, there might be a possibility of a false discovery rate. To avoid this, we further used the Benjamini and Hochberg procedure [33] to calculate an adjusted P value for the statistically significant sensory parameters and we found it still significant (Table 4). Moreover, linear regression analysis did not reveal significant stable relations between sensory NSC variables and the other presumed predictors including VAS, Pain duration, BMI, HAM-D, TMAS, and FIQR (Table 5). However, regression analysis between the statistically significant variables of sensory NCS and WPI revealed significant stable relation between the variables measuring the speed of conduction of the fastest conducting sensory fibers (SL and CV) in the upper limbs rather than the lower limbs. Interestingly, this significant relation was not present between WPI and SNAP amplitudes in sensory nerves (Table 5). Moreover, the significant changes in the variables of sensory NCS between patients with FM and healthy controls was not dependent on the side of measurement. Factorial ANOVA taking Subject and Side as between subject factors and all sensory parameters (SL, CV, and SNAP amplitudes) as within subject factors revealed an insignificant effect of Subject X Side interaction for all parameters meaning that those significant changes seem to be diffuse ones not restricted to specific anatomical area. Moreover, factorial ANOVA taking Subject and Medication as between subject factors and all sensory parameters (SL, CV, and SNAP amplitudes) as within subject factors revealed an insignificant effect of Subject X Medication interaction for all...
parameters meaning that those significant changes were not affected by the type of mediation the patient use.

**Discussion**

We found that the SCV and SNAP amplitude were significantly higher, and SL was significantly lower in patients with FM compared to healthy controls. Moreover, among all the predictor variables, only the WPI revealed a stable significant relationship with the SCV and SL. The more the WPI associated with more increase in the SCV, and decrease in SL. To our knowledge, this is the first study to show those findings. There were no significant changes regarding motor NCS between both groups.

Compared to the previous studies, we found only 2 studies that have tested NCS in patients with FM. Caro et al. included 55 patients with FM. Those patients were divided into two groups; group with FM alone (primary FM) and another one with FM and rheumatoid arthritis (secondary FM). They found that about 90% of cases in the FM only group were found to suffer sensorimotor polyneuropathy in various types. Moreover, they found that some of the patients in the second group (FM with rheumatoid arthritis) suffered polyneuropathy without statistically significant differences. There was many differences between this study and our study; first of all, in patient selection we excluded any patient with abnormal findings in NCS (primary FM without evidence of any peripheral nerve disease), the second that they did not statistically test the differences in the variables of the motor and sensory NCS. The study of Caro and his colleagues was just a descriptive one that found a significant proportion of patients suffering FM where having comorbid polyneuropathy without statisticaly significant differences. There was many differences between this study and our study; first of all, in patient selection we excluded any patient with abnormal findings in NCS (primary FM without evidence of any peripheral nerve disease), the second that they did not statistically test the differences in the variables of the motor and sensory NCS. The study of Caro and his colleagues was just a descriptive one that found a significant proportion of patients suffering FM where having comorbid polyneuropathy without statisticaly significant differences. Accordingly the aim of our study was completely different from the above mentioned one [25].

Ersoz et al. also tested the differences of the various parameters of both sensory and motor NCS between patients with FM and healthy controls. Our results were in agreement with his results regarding the parameters of motor NCS, there were insignificant differences between both groups in both studies. However, in Ersoz et al. There were no significant differences between both groups regarding the sensory NCS parameters. Again, taking a look at the group of patients with FM, we found that this group was not pure primary FM; some of the patients suffered focal neuropathies, others suffered entrapment neuropathies including carpal tunnel syndrome [24]. This may be in part an important cause of differences between our study and their study, especially if we taken the fact that changes in sensory NCS occur much earlier than motor NCS in entrapment and focal neuropathies.

We found that patients with FM significantly suffer more depression and anxiety compared to health controls. Many studies were in agreement with our study [21–23]. Many psychological risk factors were described in patients with FM including negative life events, psychological stress, increased focus on bodily symptoms, and passive pain coping mechanisms [34–36].

Taking a look on the pathogenesis of FM, there were amble evidences support the hypothesis of CS [37, 38]. As regards PS, a potential source of nociceptive inputs that initiate the CS in the spinal cord is the muscles. Several abnormalities have been described in the muscles of patients with FM including muscle ischemia and microtrauma [13, 39]. Muscle ischemia induces release of proinflammatory substances that sensitize muscle nociceptors which also indirectly induces CS through increase in the firing rate of the axons, namely, A-δ and C afferents to dorsal horn neurons, that transmit pain signals to the dorsal horn of the spinal cord leading to the first step of CS [40, 41]. After initiation of CS, low threshold A-β afferents, which normally do not transmit pain signals, are recruited to transmit spontaneous and movement-induced pain. Ultimately, the hypersensitive A-β fibers further stimulate postsynaptic neurons to transmit pain (vicious circle), where these A-β fibers previously had no role in pain transmission, all leading to CS [1].

Recent studies provide ample evidences for the PS phenomena and peripheral nerves pathology in the pathogenesis of FM. Some studies described small nerve fibers pathology patients with FM including; insufficiencies in the number of small nerve fibers and small nerve fibers' neuropathy through skin biopsy and other immunological investigations whether the patients suffers clear concomitant autoimmune diseases like rheumatoid arthritis or Chron's disease or not. This form of small nerve fibers polyneuropathy develop with contribution of neuroinflammatory mediators [42–46].

The question that comes to our minds; what induces the muscle biochemical changes that starts the PS?. Several studies have shown abnormal stress-response system in patients with FM including increased responses to corticotropin releasing hormone from hypothalamus [47]. Stress activates the paraventricular nuclei of the hypothalamus leading to increased release of corticotropin releasing hormone which stimulates the locus coeruleus in the brainstem. The activation of locus coeruleus induces epinephrine release from the adrenal medulla which eventually cause muscle ischemia leading to increased muscle bradykinin [48]. Moreover, in an animal study, chronic stress increased levels of bradykinin in muscles which may be explained in part thorough the above mentioned mechanism (49). The above mentioned changes in the peripheral nociceptors and its related
nerve fibers (phenomenon of PS) might provide an explanation of our results. However, we could not simply explain this relatively enhanced sensory NCS results with the phenomena of PS using this method alone. Even if PS causes hyperexcitability of the peripheral sensory nerves, this cannot be only demonstrated by routine nerve conduction study, peripheral nerve excitability studies are required.

Conclusions
In conclusion, we found a significant increase in the SCV, SNAP amplitude, and significant decrease in SL of the examined sensory nerves in patients with FM compared to healthy controls. Some of these changes were significantly correlated with the WPI which is related to the number of the tender points in patients with FM. Those changes were absent in motor NCS which are not responsible about pain transmission. Finally, to the best of our knowledge, our study was the first pilot one to show probable ongoing difference in sensory NCS in patients with FM.

Limitations of the study
Our study tested limited number of patients and healthy controls using simple, and widely available neurophysiological examination (routine NCS) because the number of study participants especially healthy controls is relatively small.

Recommendations
Further studies using more sophisticated techniques as peripheral nerve excitability studies and other measures of intrinsic inhibition is needed for more clarification of this issue. In addition, further studies with inclusion of a larger number of patients with FM and healthy controls are needed to further clarify the relation between FM and changes in sensory NCS.

Prior presentation
No prior presentations have been done for this work.

Abbreviations
BMI: Body Mass Index; CNS: Central Nervous System; CS: Central Sensitization; CMAP: Compound Muscle Action Potential; DML: Distal Motor Latency; FM: Fibromyalgia; MCV: Motor Conduction Velocity; NCS: Nerve Conduction Studies; PS: Peripheral Sensitization; HAM-D: Hamilton Depression Rating Scale; WPI: Widespread Pain Index.

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Authors' contributions
MT and MA studied, analyzed and interpreted the nerve conduction techniques and related data of the patients and controls. MT and EA worked in initial selection and diagnosis of patients with FM. SH worked in psychiatric co-morbidities in patients with fibromyalgia. All authors participated in writing the manuscript and all authors read and approved the final manuscript.

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Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All study participants signed an informed written consent and the study protocol was approved by the local ethics committee (No 2019–58) of Sohag University Hospital.

Consent for publication
This manuscript does not contain any individual person's data in any form, including individual details, images or videos.

Competing interests
None of the authors has any financial conflict of interest relating to this manuscript.

Author details
1Department of Neurology, Sohag Faculty of Medicine, Sohag University, Madinat Nasser, Sohag 82524, Egypt. 2Department of Rheumatology, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt. 3Department of Psychiatry, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt.

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