

Is Two-Point Discrimination Test a New Diagnostic Method for the Diagnosis of Fibromyalgia?

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ABSTRACT

Introduction: Fibromyalgia is a syndrome of obscure pathogenesis without objective diagnostic criteria and is frequently associated with diagnostic delays due to symptomatic heterogeneity. This study aimed at assessing the response to two-point discrimination test in extremities, neutrophil/lymphocyte ratio (NLR), Numeric Rating Scale (NRS) score, and Widespread Pain Index (WPI) score in patients with fibromyalgia.

Methods: The patient group consisted of 26 subjects diagnosed with fibromyalgia based on the 2016 revision to the American College of Rheumatology 2010 diagnostic criteria, while 25 healthy individuals comprised the control group. In both groups, basal amplitude and somatosensory temporal discrimination (STD) measurements at the dorsum of the hands and feet were performed in addition to NLR

measurements. Also, NRS and WPI were determined in fibromyalgia patients.

Results: STD was significantly prolonged in all extremities among fibromyalgia patients as compared to controls. WPI and NRS were also increased, paralleling the STD measurements in all extremities ($p < 0.05$). NLR was higher in the patient group than in controls, although the difference was insignificant.

Conclusion: STD values were high in fibromyalgia patients. So, STD appears to have a potential role as an auxiliary diagnostic tool in fibromyalgia. Still, further studies are needed to support this conclusion.

Keywords: Fibromyalgia, somatosensory temporal discrimination, perception of pain

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INTRODUCTION

Fibromyalgia is a musculoskeletal disorder characterized by chronic fatigue, widespread pain, sleep disorder, and cognitive dysfunction that affects 2-8% of the population with a female to male ratio of 2:1 (1). Due to its obscure pathophysiology, no objective diagnostic criteria have been defined and a complete cure is generally unlikely. Lately in most instances, the diagnosis is based on the 2016 revision of the American College of Rheumatology 2010 set of criteria (2). Pathogenesis is thought to involve genetic predisposition and environmental factors, together with the occurrence of symptoms due to increased reactivity to sensory stimuli secondary to a peripheral or central insult (3).

Somatosensory temporal discrimination (STD) threshold is defined as the shortest interval at which an individual recognizes paired stimuli as separate in time (4). A normal STD threshold reflects normal functioning of the peripheral and central pathways with the primary somatosensory cortex. Functional magnetic resonance studies of both temporal and spatial functions of the two-point discrimination showed cranial activation in both sensorial modalities at the inferior parietal lobule, middle and inferior frontal gyrus, anterior portion of the right insula, and right anterior cingulate gyrus. At the subcortical level, basal ganglia have been found to be activated, with contributions, particularly from both caudate heads, substantia nigra, and sub-thalamic nuclei. Additionally, significant cerebellar activity has been noted (5). The afferent-input gate mechanism plays a role in the temporal-spatial discrimination of the two stimuli and allows separate processing of the data. Any deficit effecting this mechanism

Highlights

- Fibromyalgia is a syndrome of obscure pathogenesis without objective diagnostic criteria.
- STD may be an objective method for diagnosing Fibromyalgia.
- STD is a practical, non-invasive measurement method.
- neutrophil/lymphocyte ratio is increased in fibromyalgia patients.
- In addition to STD, correlation of Numeric Rating Scale and Widespread Pain Index score were investigated.

may lead to STD threshold abnormality. Temporal discrimination of the stimuli is made possible by the involvement of several sensorial structures, in addition to neuronal structures including the cerebellum and basal ganglia that play a role in the timing function (6). In terms of the underlying mechanisms of STD, thalamus and cortical structures are thought to play a significant role, in addition to the demonstrated contributions of the posterior parietal cortex, primary somatosensory cortex, supplementary

motor area, and subcortical structures. Detection of abnormal STD in patients with subcortical pathologies also is supportive of the role of subcortical structures in this process (7). Cortical output from the basal ganglia is projected to the supplementary motor area via the lateral thalamus, and the effect of the basal ganglia on STD is thought to occur via this pathway (8). Since the changes in the perception and processing of pain are seen in fibromyalgia patients, we wanted to objectively evaluate the perception and processing of sensory stimulus through electrical stimulation with STD (3).

Neutrophil/lymphocyte ratio (NLR) is one of the inflammatory markers that has been utilized as a prognostic indicator of systemic inflammatory response. Recent studies have suggested an etiologic role of NLR for inflammatory processes in fibromyalgia syndrome (9).

In this study, the role of STD as measured in four extremities in patients with fibromyalgia was explored in conjunction with NLR measurements. In addition to STD, correlation of Numeric Rating Scale (NRS) and WPI score were investigated.

METHODS

This study was conducted at the Balıkesir Health Practice and Training and Research Hospital, Faculty of Medicine, Department of Neurology with the inclusion of 26 fibromyalgia patients (21 female, 5 male) aged between 20–50 years and diagnosed with 2016 revision to American College of Rheumatology 2010 criteria (2) and 25 healthy volunteers (21 male, 4 female). The study protocol was approved by Clinical Research Ethics Committee (2019/33). All patients provided written informed consent prior to study procedures. Inclusion criteria were age between 20–50 years, absence of known systemic disorders or medical treatment, normal liver and kidney functions in the past 6 months, absence of vitamin B12 deficiency, hypothyroidism, and anemia, in addition to normal neurological examination. Psychiatric consultation was requested for all patients; Patients with psychiatric comorbidity were excluded from the study. STD measurements were performed by the same investigator in both patient and control group in all extremities, and NRS, NLR, WPI values were evaluated. STD estimations were performed in four different sites (dorsum of both hands and feet) in both controls and patients, using Ag-AgCl superficial electrodes with a diameter of 10 mm and with anode-cathode distance of approximately 1 cm. For tactile stimulation, a constant current stimulator (Medtronic, Keypoint) was used, and the current intensity required for minimal sensory threshold was determined with 0.2 ms stimuli. Again, to detect the minimal sensory threshold level, the current intensity was increased from 1 mA with 0.2 mA incremental steps.

When all 3 stimuli administered at the same current intensity could be sensed by the subject, this intensity level was recorded as the minimal sensory threshold. STD measurements were performed at the minimal sensory threshold and 1.5-fold higher. At the initiation of the test, the inter-stimuli interval was 4 ms, and the paired stimuli were administered with 10 sec intervals and 2 ms increments. For each stimulus, subjects were asked whether they sense a single or double stimulus. When the subject reported 3 consecutive paired stimuli after that step, this current intensity was recorded as the ascending sensorial temporal discrimination (aSTD) threshold. After that, starting from the first current intensity at which the subject reported paired sensation, the inter-stimulus interval was reduced 10 sec at each step using pairwise stimuli, and again subjects were inquired whether they felt single or paired stimuli. When the subject reported 3 consecutive single stimuli after that step, this was taken as the descending sensorial temporal discrimination (dSTD) threshold. The same procedures were also repeated at 1.5-fold higher intensity. The arithmetic means of aSTD, dSTD as well as the aSTD and dSTD recorded at 1.5-fold current intensity were calculated to obtain a single STD value.

For identification of the attention level, a single stimulus was given after each 3 paired stimuli, and subjects reporting paired stimuli after a single stimulus were excluded from the analysis.

Statistical Analysis

SPSS for Windows Release 22.0 was used for statistical analyses. The qualitative data were compared with chi-square test. Normal distribution of the data was examined with Kolmogorov-Smirnov test, and those with normal distribution were analyzed with Student's t test, and those without normal distribution were analyzed with Mann-Whitney-U test. Continuous measurements were compared with variance analysis or Friedman's test. Measured data were expressed with mean and standard deviation while counted data were expressed as percentages. The level of significance was set at a p level of <0.05.

RESULTS

Patient and control subjects did not differ significantly in terms of demographic data. The mean age in fibromyalgia patients (21 female, 5 male) was 42.7 ± 7.8 years vs. 39.2 ± 5.4 years among controls (21 female, 4 male). In STD tests, basal amplitude values were higher among fibromyalgia patients as compared to controls in all extremities ($p < 0.05$) (Table 1) (Figure 1). Similarly, STD duration was significantly longer among patients than among controls in all extremities ($p < 0.05$) (Table 2) (Figure 2). Despite higher NLR in the patient group, the difference was not statistically significant (1.94 ± 0.8 and 1.54 ± 0.6 , respectively). NRS and WPI among patients were 7.7 ± 0.9 and 8.6 ± 2.4 (Figure 3).

DISCUSSION

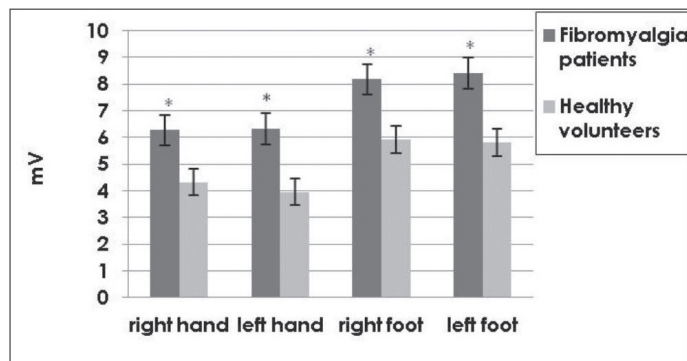
In this study we examined STD duration, NLR, WPI and NRS in patients with fibromyalgia. Our findings showed a prolongation of STD in this patient group that was associated with higher pain scores as well as with the severity of non-pain symptoms such as functional disability.

In a recent study, fibromyalgia patients were reported to have longer STD measurements in the dorsum of the hand as compared to control subjects (10). Considering the widespread involvement in fibromyalgia syndrome, we examined and compared STD in the upper and lower extremities. Our results showed significantly longer STD in all four extremities in comparison with controls. To our knowledge, this is the first study examining STD in all four extremities in patients with fibromyalgia. Also, STD allowed us to show the extensive involvement of the central sensory processing using an electrophysiological method. In conjunction with the extensive STD alterations, high mean NRS and WPI among patients were supporting the notion that STD is altered in parallel with the increase in the severity and intensity of pain. Reported STD measurements in healthy individuals exhibit certain differences in different parts of the body, with the reported mean values being 28.6 msec in the dorsum of the hand and 40 msec in the feet (4). In our study, the similar measured values found in the healthy controls. On the other hand, the values of fibromyalgia patients were statistically longer. While these significantly elevated STD values provide objective evidence for the widespread involvement in this condition, they also show correlation with the NRS pain scale used to evaluate the general pain intensity and widespread pain index included in fibromyalgia diagnostic criteria, suggesting that the central cognitive processing of the sensory stimuli without pain elicitation may also be disturbed. Furthermore, higher basal amplitude measurements in fibromyalgia patients than in controls may indicate a higher peripheral excitability of the nerve fibers.

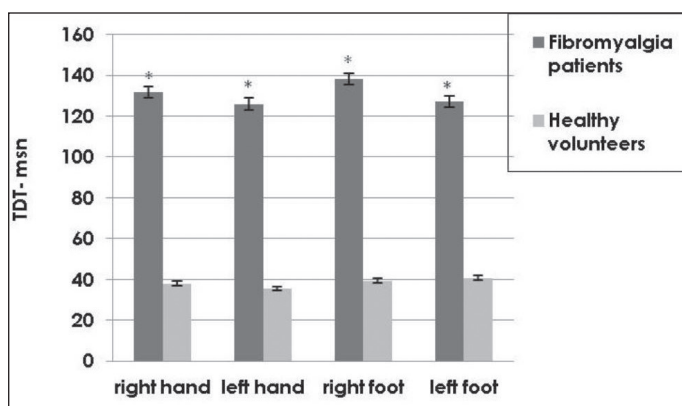
Chronic pain associated with fibromyalgia is thought to result from impaired neuroplasticity caused by continuous painful stimuli (11). Pain and sensory processes are differentially handled within the central

Table 1. Basal amplitude measurement values of somatosensory temporal discrimination in extremities (mV)

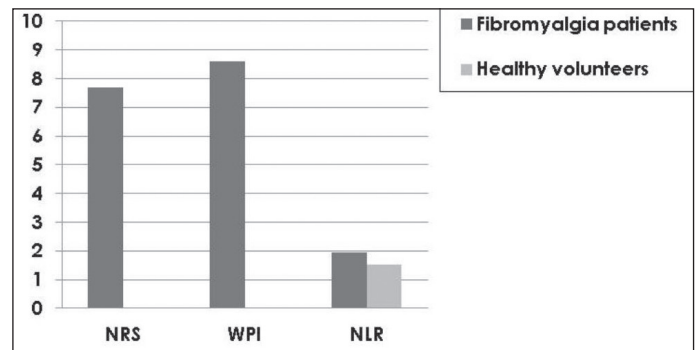
	Fibromyalgia patients	Healthy volunteers	p
Right hand	6.3±2.2	4.3±1.6	p≤0.05
Left hand	6.3±2.5	3.9±1.7	p≤0.05
Right foot	8.1±2.4	5.9±1.5	p≤0.05
Left foot	8.4±2.9	5.8±1.6	p≤0.05

**Figure 1.** Basal amplitude values in all extremities (p≤0.05).**Table 2.** Basal measurement values of somatosensory temporal discrimination in all extremities (msec)

STD (msec)	Fibromyalgia patients	Healthy volunteers	p
Right hand	131.8±56.6	38.1±14.9	p≤0.05
Left hand	125.9±46	35.5±14	p≤0.05
Right foot	138.2±54.9	39.3±13.3	p≤0.05
Left foot	127±41	40.8±14.9	p≤0.05

**Figure 2.** STD duration in all extremities (p≤0.05) (TDT, temporal discrimination time).

nervous system. While lower levels of noxious stimuli may induce pain in these patients as compared to controls, the increase in the perception of pain due to repetitive noxious stimuli (i.e. temporal summation of pain) is supportive of a defect in the endogenous analgesic system. Again, a decrease in the control of the inhibitory pathway for widespread noxious stimuli (pain is reduced with a second acute painful stimuli) is observed, together with a decline in the inhibition of different sensory stimuli following repetitive non-pain stimulation.

**Figure 3.** NRS (Numerical Rating Scale), WPI (Widespread Pain Index), and NLR (neutrophil/lymphocyte ratio) in fibromyalgia patients. Although NLR was higher as compared to controls, the difference was not significant (1.94±0.8; 1.54±0.6, respectively).

An increase in the activation of pain-sensitive areas in fibromyalgia patients have been shown, and these include the somatosensory cortex, insula, and anterior cingulate cortex (12, 13). Again, in a functional MRI study, increased activity of the insula, anterior cingulate cortex, and anterior pre-frontal cortex, and peri-aqueduct gray matter have been shown in fibromyalgia patients, suggesting that this increased function during the resting state is due to the dysfunction of the endogenous pain modulator system, probably leading to reduced pain inhibition (14). While prolonged STD may represent an electrophysiological sign of the altered intra-cortical inhibition, the increase in pain and decline in functions may also be associated with the clinical signs. Similarly, Lim and colleagues reported an association between increased generalized pain and intra-cortical inhibition deficit in S1 in fibromyalgia patients (15).

Recent studies also suggested that inflammatory mechanisms may also play a role in the pathogenesis of fibromyalgia. Patients with fibromyalgia have been shown to have abnormal levels of many cytokines, which mediate the inflammation (16). Also, a similar role has been reported for the pro-inflammatory mediators IL-6, IL-8, and TNF-α in the pathogenesis of fibromyalgia (17). It has been suggested that NLR may be a prognostic marker for determining the systemic inflammatory response (18). Semra and colleagues detected significantly higher NLR among fibromyalgia patients as compared to controls (9). Although NLR was higher in fibromyalgia patients without statistical significance in our study compared to control.

Fibromyalgia is a disorder of unknown etiology with increasing prevalence. Genetic factors, environmental triggers, inflammatory processes, and neuromodulation are thought to play a role both in the initiation and course of the disease.

STD is a practical, non-invasive measurement method. In fibromyalgia patients, the duration of STD showed a parallel increase with increased widespread pain, reduced functionality, severity of other symptoms, as well as with the NLR. Currently, there is a lack of objective criteria for establishing a diagnosis of fibromyalgia, and although STD appears to be a feasible measurement tool in this group of patients, further studies are warranted to evaluate the role of STD alterations in the diagnosis of fibromyalgia as well as in its follow-up. Additionally, higher NLR was detected among the controls in our study. Although an association with inflammation has been reported for NLR in fibromyalgia, this requires further clarification.

Since STD measurements require cooperation and attention of the study participants, it should be used in individuals without cognitive impairment. Due to the methodology utilized in our study, the association

between NLR and clinical measures such as pain, disease activity, and quality of life could not be evaluated. Furthermore, these parameters were not used for monitoring disease activity. Larger studies are required to test the generalizability of our results.

Ethical Committee Approval: The study protocol was approved by Balikesir University Clinical Research Ethics Committee (2019/33).

Informed Consent: Patients provided written informed consent prior to study procedures.

Peer-review: Externally peer-reviewed

Author Contributions: Concept– OFT, NT; Design– OFT, NT; Supervision– OFT, NT; Resources– OFT, NT; Materials– NT; Data Collection and/or Processing– NT; Analysis and/or Interpretation– NT; Literature Search– OFT, NT ; Writing Manuscript– OFT, NT; Critical Review– OFT, NT.

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