Original article

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GENERALIZED PAIN HYPERSENSITIVITY IN FIBROMYALGIA PATIENTS

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Chronic widespread pain is one of the leading symptoms of fibromyalgia. Signs of generalized hyperalgesia can often be observed in these patients. However, it is not clear if the pain hypersensitivity is present for different painful stimuli. Therefore, the aim of this study was to determine if there were differences in pressure pain threshold - PPT, heat pain threshold - HPT and cold pressure threshold - CPT between fibromyalgia patients and healthy subjects. The present cross-sectional study included 45 subjects (average age 54.60 ± 7.96 years, 88.9% females), of whom 23 (51.1%) were diagnosed with fibromyalgia, while 22 (48%) were the healthy control group in whom PPT, HPT and CPT were measured on the forearm and on the paraspinal musculature of the lumbosacral region of the spinal column. Fibromyalgia patients had a significantly lower PPT compared to the group of healthy subjects: 26.13N/cm2 vs. 53.54N/cm2, (Z=-4.439, p<0.001); HPT 39.70 °C vs. 44.85°C, (Z=-3.871, p<0.001); CPT 20.51°C vs. 12.51°C, (Z=-2.612, p=0.009). In the area of the paraspinal musculature, PPT was 37.01 N/cm2 vs. 75.77 N/cm2, (Z=-4.178, p<0.001); HPT - 38.18°C vs. 44.13°C (Z=-3.758, p<0.001); CPT - 21.52°C vs. 11.16°C (Z=-2.737, p=0.006). Fibromyalgia patients demonstrated generalized hyperalgesia for all tested modalities (pressure, heat and cold). *Acta Medica Medianae 2023;62(2): 15-22.*

Key words: *pain threshold, fibromyalgia, hyperalgesia*

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Introduction

Fibromyalgia (FM) represents a chronic painful condition characterized by chronic widespread pain, sleep problems, chronic fatigue, headache, depression, functionality and cognitive impairments (1–3). FM affects around 5% of population, most of which are women usually around 30−35 years old (4). The diagnosis of fibromyalgia is made exclusively by history data based on the criteria of the American College of Rheumatology (ACR) from 2016 (5). We still do not understand the mechanisms of pain origin in FM completely. However, it is assumed that the altered process of pain signal processing is probably the main cause of pain in FM. It most often occurs in genetically predisposed individuals, and the triggers of fibromyalgia can be diverse (4, 6, 7). Dysfunction of endogenous modulation system in the CNS plays an important role in generalized pain sensitivity seen in patients with FM. This increased responsiveness of nociceptive neurons in CNS is defined by the IASP as central sensitization (CS) (8). CS is characterized by allodynia (pain to touch and other stimuli that normally do not cause pain) and hyperalgesia (excessive response to minimally painful stimuli). Although mechanisms that lead to CS are not fully understood, increased activity of neurons of the posterior horns of the spinal cord and activation of N-methyl-D-aspartate (NMDA) receptors, central afferent pain enhancement and reduction of central descending inhibition (facilitation) play an important role (4). Various methods of examining central sensitization have been developed (9–11), of which quantitative sensory testing (QST) stands out (12). QST is a method that provides insight into pain thresholds and differentiation of local versus generalized and peripheral versus central neural mechanisms (13, 14). QST results depend on the age, gender (15–20) and body composition (21, 22). The prevailing opinion is that repeated exposure to painful stimuli can increase the pain threshold. On the contrary, it has been shown in numerous studies that chronic pain can lead to the

opposite effect and decrease the pain threshold (23–25). Signs of generalized hyperalgesia can often be observed in fibromyalgia patients. However, it is not clear if pain hypersensitivity is present for different painful stimuli (26–28). Therefore, the aim of this study was to determine if there were differences in pressure pain threshold - PPT, heat pain threshold - HPT and cold pressure threshold - CPT between fibromyalgia patients and healthy subjects.

Material and methods

The research was designed as a cross sectional study. It was conducted at the Medical Rehabilitation Clinic of the University Clinical Centre of Vojvodina, after obtaining the consent of the Ethics Committee of the University Clinical Centre of Vojvodina. Participation in the study was completely voluntary and all participants signed informed consent.

Pain thresholds for pressure, heat and cold between healthy subjects and patients with previously diagnosed FM were compared, using locally applied pressure, heat and cold on both the forearm and the lower back.

The sample consisted of a total of 45 respondents (average age 54.60 ± 7.96 years). The sample consisted of two groups, a control group of healthy subjects (n=22, average age 51.8 ± 5.20, females 81.8%) and an experimental group of FM patients (n=23, average age 57.3 ± 9.23, females 95.7%).

The criteria for inclusion (in the experimental group) in the research were: age over 18 years, diagnosed with FM based on the ACR 2016 criteria (5).

The criteria for inclusion (in the control group) in the research were: age over 18 years, absence of any chronic pain condition or current acute pain.

Exclusion criteria were: age under 18 years and incomplete data, presence of cancer, rheumatic inflammatory disorders, diabetes mellitus, multiple sclerosis, polyneuropathy, Parkinson's disease, and patients who were using neuroleptics, strong opioids, or benzodiazepines on a regular basis.

All involved subjects were tested according to the protocol for pain thresholds examination previously developed by Knezevic et al. and Kovacevic et al. (19, 29).

In the present study, data on pressure pain thresholds (PPT), heat pain thresholds (HPT) and cold pain thresholds (CPT) were examined. A digital algometer (Wagner Instruments, FDX-50), with a rubber tip with a diameter of 1 cm, was used to test PPT. With this algometer, PPT was examined in 2 places: 1) on the paravertebral musculature of the lumbar segment (2−3 cm lateral from the processus spinosus of the L3 vertebra), 2) on the opposite forearm (proximal part of the body of the extensor carpi radialis longus). We gradually increased the pressure with the algometer at a speed of about 5 N/s, and the subject said "stop" as soon as the feeling of pressure turns into a feeling of burning, stinging, stabbing or pain, and the value in N/cm2 was recorded. At each place, 3 measurements were taken, with an interval of 10 s, and their mean value was taken as the final value. The left/right side was tested randomly.

HPT and CPT were examined using a device (Pathway Pain and Sensory Evaluation System, Medoc Ltd, Ramat Yishai, Israel) using an ATS (Advanced Thermal Stimulation) thermode measuring 30x30mm. HPT and CPT were examined at 2 sites: 1) on the paravertebral musculature of the lumbar segment (2−3 cm lateral to the spinous process of the L1 vertebra) and 2) on the proximal volar side of the opposite forearm (C8 dermatome). The left/right side was tested randomly. During HPT/CPT testing, the initial temperature of 32°C increased/decreased at a rate of 0.7°C/s. The subject pressed the stop button as soon as the hot/cold sensation changed to burning, stinging, stabbing or pain. At that moment, the temperature decreased/increased to the initial temperature, at a rate of 7°C/s. Four stimuli for hot and then four stimuli for cold were performed with an intermediate interval of 10 s, and the final value of HPT and CPT were taken as the mean values of the last three measurements.

Pain thresholds (first PPT, then HPT and CPT) on the forearm were first tested while the subject was lying on his back. Then the subject turned on his stomach and first the PPT, then the HPT and the CPT on the lumbar segment were examined at previously defined places.

Data analysis

SPSS 20.0 software package was used for data entry and processing. For the purposes of analysis and description of the structure of the sample according to relevant variables, frequency and percentage displays were used to show the representation of a certain category or response. Descriptive statistics methods were used to determine measures of central tendency (arithmetic mean), measures of variability (standard deviation) and extreme values (minimum and maximum) of observed numerical characteristics. The limited sample size and the broken normality of the distribution of certain parameters allowed the use of non-parametric methods. Within the comparative statistics method, the Mann-Whitney U-test was used for differences between two independent samples. In the applied tests, the limit values of the probability of risk are at the significance level of 95% ($p<0.05$).

Results

There was no difference in age, gender and BMI between healthy controls and FM patients (for more details see Table 1).

Pain threshold for pressure, heat and cold in the forearm area was significantly lower in subjects with FM compared to the control group. Given that the samples were small, non-parametric statistics (Mann-Whitney Test) were used for comparison between groups. PPT, HPT and CPT in the lower back region were significantly lower in subjects with FM compared to controls (Table 2).

Table 1. Demographic characteristics of participants

	Healthy controls (n=22)	Fibromyalgia patients (n=23)	Total (n=45)	$t/Z/x^2$	p
Age (mean ± SD) (years)	51.8 ± 5.20	57.3 ± 9.23	56.6 ± 7.96	Z=-1.910	p= 0.056
Gender (female, %)	18 (81.8%)	22 (95.7%)	40 (88.9%)	X^2= 2.179	p=0.187
BMI[1] (mean ± SD) (kg)	24.37 ± 3.03	26.02 ± 3.50	25.21 ± 3.35	t= -1.638	p= 0.100

[1]*BMI = Body Mass Index (kg/m2)*

Table 2. Differences in pain thresholds

	Fibromyalgia patients	Healthy controls	Z	p
Forearm				
PPT (mean ± SD) ($N/cm^{2)}$	26.13 ± 11.26	53.54 ± 26.13	Z= - 4.439	P<0.001
HPT (mean ± SD) (°C)	39.70 ± 4.14	44.85 ± 2.77	Z= - 3.871	P<0.001
CPT (mean ± SD) (°C)	20.51 ± 8.33	12.51 ± 10.20	Z= -2.612	P=0.009
Lower back				
PPT (mean ± SD) ($N/cm^{2)}$	37.01 ± 22.79	75.77 ± 34.84	Z= -4.178	P<0.001
HPT (mean ± SD) (°C)	38.18 ± 4.49	44.13 ± 3.96	Z= -3.758	P<0.001
CPT (mean ± SD) (°C)	21.52 ± 10.40	11.17 ± 11.16	Z= - 2.737	P=0.006

Discussion

Sensitivity to pain is an individual characteristic of each person and is conditioned by various factors, from ethnic, psychophysical, psychological, genetic, demographic and social factors (30–35).

The results of this research show that the pain threshold for pressure in the area of both the forearm and the low back was significantly lower in subjects with FM compared to the control group. Pressure pain threshold represents minimum pressure quantity applied to particular body site able to produce sensation of pain (36). Transduction of mechanical noxious stimuli includes mechanical stimulation of unmyelinated C-MH fibers (37) and myelinated A-HTM fibers (38). Majority of the studies found decrease of PPT in fibromyalgia patients (26, 39–43).

Similar to the PPT we found that the pain threshold for heat and cold in the forearm and low

back area was significantly lower in subjects with FM compared to the control group. Majority of studies showed similar result to our study (43–48), while certain authors did not find differences in heat and cold pain thresholds between FM patients and healthy controls (27, 28). A possible reason for the discrepancy in the results of the studies is that in the study by Klauenberg et al., respondents were allowed to continue taking pharmacological therapy (in addition to coanalgesics and other medications, more than a third of the respondents were on NSAIDs and/or opioids), while the use of NSAIDs, narcoleptics, opioids and benzodiazepines in our study was a criterion for exclusion from the research. Nerve fibers implicated in heat and cold transmission are A-delta mechano-heat fibers and C-polymodal fibers (49). Transduction of heat sensation involves nociceptive afferent fibers which leads to release of glutamate and peptides in the dorsal horn of spinal cord (50). These substances play role in excitation of second order sensory neurons and projection neurons in spinothalamic tract (STT) (51, 52).

Recently, more and more attention has been paid to the process of neuroinflammation in FM. Neuroinflammation is thought to be responsible for many painful conditions possibly affecting process of CS (53). It implies the process of glial activation and activation of astrocytes with the release of an abundance of proinflammatory factors (54). As part of FM, there are changes in the serum and cerebrospinal fluid concentration of certain neurotransmitters, and it is assumed that they lead to increased sensitivity to pain because these transmitters are associated with the processes of pain transmission and modulation. It is known that the level of substance P is elevated in patients suffering from FM (55). It was also concluded that other biochemical changes occurred in FM, primarily reduced concentrations of serotonin, dopamine and noradrenaline metabolites (antinociceptive neurotransmitters) and high concentrations of substance P and nerve growth factor (pronociceptive, excitatory neurotransmitters) (56). The assumption that the dysfunction of the inhibitory descending system is to a certain extent responsible for the widespread pain in FM corresponds to the reduced concentration of the neurotransmitters serotonin and noradrenaline that occurs in this disease because these transmitters are responsible for the normal modulation of pain (descending pathways of the brain to the neurons of the posterior horns of the spinal cord) (57). In addition to the pain syndrome, changes in serotonergic transmission can explain the occurrence of other symptoms in FM, such as sleep and mood disorders (58). CS may explain the state of central hyperexcitability of the nociceptive system and the consequent reduced pain threshold in patients with FM (47). By shifting the modulation towards facilitation, the sensory "inflow" increases, resulting in sensitization, which is clinically manifested by a diffuse painful condition in the absence of peripheral disease (59). This supports the results we obtained. Other studies suggest reduced habituation to pain (60) and CS as mechanisms (61). In their study, Giesecke et al. (62) found hyperalgesia in FM patients and chronic back pain patients compared to healthy controls when experimental pain was applied to a neutral site, i.e., a location where FM patients had no pain. In addition to the neurotransmitter and neurosensory explanations, we can also explain the occurrence of greater sensitivity to pain in FM by the existence of pronounced persistent sympathetic (catecholamine) hyperactivity with a paradoxical hypoactive response to stress. The state of impaired autonomic regulation affects the manifestation of physical and psychological symptoms of FM. The mentioned mechanisms can, to a lesser or greater extent, increase the sensitivity to pain in an individual. All above mentioned mechanisms indicate the presence of non-selective CS in patients with FM. This CS leads to hyperalgesia to all modalities which we have proved in the present study.

Conclusion

Pain thresholds for pressure, heat and cold are significantly lower in subjects with FM, both in the forearm and lower back regions indicating the presence of generalized pain hypersensitivity to different modalities in patients with FM.

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GENERALIZOVANA PREOSETLJIVOST NA BOL KOD OBOLELIH OD FIBROMIJALGIJE

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Hronični široko rasprostranjeni bol je jedan od glavnih karakteristika fibromijalgije. Kod ovih pacijenata često se uočavaju znaci generalizovane hiperalgezije. Međutim, nije jasno da li je prisutna povećana osetljivost na bol za različite bolne stimuluse. Stoga, cilj ove studije bio je da se ustanovi da li postoje razlike u pragu bola za pritisak (engl. pressure pain threshold – PPT), pragu bola za toplo (engl. Heat pain threshold – HPT) i pragu bola za hladno (engl. Cold pain threshold – CPT) između pacijenata sa fibromijalgijom i zdravih ispitanika. Ova studija preseka uključila je 45 ispitanika (prosečne starosti 54.60 ± 7.96 godina, 88,9% žena), od kojih 23 (51.1%) boluje od fibromijalgije, dok su 22 (48%) bili kontrolna grupa zdravih ispitanika kod kojih PPT, HPT i CPT mereni na podlaktici i na paraspinalnoj muskulaturi lumbosakralne regije kičmenog stuba. Pacijenti oboleli od fibromijalgije imaju značajno niži prag bola na pritisak u poređenju sa grupom zdravih ispitanika: 26.13N/cm2 naspram 53.54N/cm2, (Z=-4.439, p<0.001); HPT 39.70°C naspram 44.85 °C, (Z=-3.871, p<0.001); CPT 20.51°C naspram 12.51°C, (Z=-2.612, p=0.009). U regiji paraspinalne musculature PPT je bio 37.01 N/cm2 naspram 75.77 N/cm2, (Z=-4.178, p<0.001); HPT - 38.18°C naspram 44.13°C (Z=-3.758, p<0.001); CPT - 21.52°C naspram 11.16°C (Z=-2.737, p=0.006). Kod pacijenata obolelih od fibromijalgije prisutna je generalizovana hiperalgezija za sve testirane modalitete (pritisak, toplotu i hladnoću). *Acta Medica Medianae 2023;62(2):15-22.*

Ključne reči: *prag bola; fibromijalgija; hiperalgezija*