Electrophysiological Identification of Central Sensitization in Patients with Chronic Prostatitis

Selda Korkmaz,[1]* Mert Ali Karadag,[2] Kemal Hamamcioglu,[3] Mustafa Sofikerim,[4] Murat Aksu[5]

Purpose: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a chronic pain condition and a common problem in urology clinics. Although many different etiologies and mechanisms exist, the exact cause of the disease has been unknown. Central sensitization (CS) is defined as an augmentation of responsiveness of central cortical neurons to input from peripheral nociceptive structures. Somatosensory evoked potentials (SEPs) is an electroneurophysiological method to assess cortical activity in somatosensory area of brain related to sensorial stimuli. We aimed to determine the presence of CS using the SEPs of dorsal penile nerve stimulation in patients with CP/CPPS.

Materials and Methods: Seventeen male patients diagnosed CP/CPPS and 17 male healthy controls were prospectively included in the study. For SEP study, electrical stimulus was applied with penile ring electrodes. Recording electrodes were placed as active to Cz' and reference electrode on Fz' according to the 10–20 International System. Latency of N50 was defined as the second negative (upward) deflection of the W-shaped averaged cortical waveform.

Results: N50 latencies were significantly shortened in the patient group compared to the healthy controls ($P < .001$).

Conclusion: These results support the presence of central sensitization because of exaggerated transmission of pain sensation to the somatosensory cortex. Therefore, normalization of transmission might be an important step in treatment of pain in patients with CP/CPPS. This study can be counted as an important guiding on pathogenesis and treatment of disease.

Keywords: chronic pain; physiopathology; evoked potentials; somatosensory; neuropsychological tests; prostatitis; physiopathology.

INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a chronic pain condition and a common problem in urology clinics. According to the current National Institutes of Health (NIH) definition, CP/CPPS is characterized by chronic pelvic pain symptoms that last for at least three of the prior six months, occur in the absence of a urinary tract infection or another identifiable cause such as malignancy, bacterial infection but in the presence of urinary symptoms or sexual dysfunction. The main complaint of CP is chronic pain that cannot be explained by any organic or morphological local change. CP/CPPS is associated with a wide spectrum of symptoms including irritative and obstructive voiding symptoms, pain in the pelvic region, and sexual dysfunction like pain during ejaculation, depression, and psychosocial maladjustment.[1] It has been estimated that between 2% and 14% of men worldwide may have symptoms of CP/CPPS.[2,3]

Although many proposed etiologies and mechanisms exist to explain the pathogenesis of CP/CPPS,[4-9] neither cause of disease has been exactly known nor effective treatments have been identified.[10,11]

Central sensitization (CS) is defined as an augmentation of responsiveness of central cortical neurons to input from unimodal and polymodal receptors. The main cause of CS is the long-term potentiation or sensitization of nociceptive neurons and decreased activity in the antinociceptive system. Here, the balance deteriorates to facilitate the formation of pain. Although CS is usually an important factor in the modulation of pain sensation, in some conditions it can be the cause of chronic pain. The main complaint of CP/CPPS is chronic pain that cannot be explained by any organic or morphological local change. Therefore, CS might be the etiological factor for the pain sensation in CP/CPPS. A previous study using thermal algometry as an indicator for the presence of CS in patients with CP/CPPS demonstrated that noxious heat stimuliincreased pain sensitivity.[12]

There are several methods, most of them electroneurophysiological, to determine presence of CS. Somatosensory evoked potentials (SEPs) is an electroneurophysiological method that assesses cortical activity

1 NIH/NINDS Human Motor Control Section, Bethesda, Maryland, USA.
2 Department of Urology, Kafkas University College of Medicine, Kars, Turkey.
3 Department of Neurology, Acibadem Kayseri Hospital, Kayseri, Turkey.
4 Department of Urology, Acibadem Kayseri Hospital, Acibadem University College of Medicine, Istanbul, Turkey.
5 Department of Neurology, Acibadem Kayseri Hospital, Acibadem University College of Medicine, Istanbul, Turkey.
*Correspondence: NIH/NINDS Human Motor Control Section, Bethesda, Maryland, USA.
Tel: +1 240 8010674. E-mail: korkmazs78@gmail.com.
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Table 1. Demographic and electroneurophysiological data of study groups.

Variables	Patients	Controls	*P* Value
Age, years	38.0 ± 8.5	34.6 ± 8.0	.2
Height, cm	170.5 ± 2,7	170.8 ± 3,2	.7
Weight, kg	77.6 ± 4.2	77.6 ± 4.2	.8
Sensory threshold, mA	12.0 ± 3.8	12.8 ± 2.5	.5
N50 latency	44.7±3.9	59.1±5.8	<.0001

Data are presented as mean ± SD.

in the somatosensory area of brain related to sensorial stimuli.[13-15] SEP recording of dorsal penile nerve stimulation is not a commonly used clinical test, however it is analogous to other SEP studies in that it is a neurophysiological test to show the excitability of the sensorial cortex via a pathway from the dorsal penile nerve to brain. Therefore, we studied the SEPs of dorsal penile nerve stimulation in CP/CPPS and compared them with healthy control subjects to determine if CS increases in patients with CP/CPPS. This increase in CS could explain the cause of pain for at least some patients with CP/CPPS, thus this affirmation of this hypothesis could lead to alterations in the therapy modalities of CP/CPPS patients who experience increased CS.

MATERIALS AND METHODS

Study Subjects

Seventeen male patients with CP/CPPS and 17 healthy male controls were prospectively included in the study between September 2012 and January 2014, after obtaining local ethics review committee approval and written informed consent forms. This study was performed in accordance with the Helsinki Declaration of the World Medical Association. The study group was constructed from patients diagnosed by the urology outpatient clinic of Acibadem Kayseri Hospital. Control group members were selected from subjects applying by the announcement. A total of 83 patients with pelvic pain from the outpatient clinic applied for participation in the study. Exclusion criteria for all subjects were presence of ongoing urinary tract infection or uropathogen documented within the past year, chronic bacterial prostatitis after lower urinary tract localization studies, history of urinary tract malignancy, radiation therapy, postoperative pain, any known neurological abnormalities including spinal cord injury, previous cerebrovascular disease, neuropathy, and presence of medical treatment history with diagnosis of CP/CPPS.

All patients completed a National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) [16] and Likert scale pain index, and underwent detailed neurological/urologic examinations and laboratory tests that included urine analysis, semen and urine cultures, and expressed prostatic secretion (EPS) after prostate massage. Blood tests included a liver function test, kidney function test, thyroid function test, complete blood count, and vitamin B12 levels were normal in all.

The patient group: 17 patients clinically diagnosed with CP/CPPS. Inclusion criteria included pelvic pain symptoms (i.e., perineum, rectum, testicles, penis, or lower back pain), presence or absence of pain during urination or ejaculation for three or more months and a desire for treatment, severe NIH-CPSI and Likert pain scale index scores (i.e., 20-29 and 7-10, respectively), negative urine, semen, and EPS cultures, 26 to 52 years old, height in the range of 166 to 175 cm, weight in the range of 70 to 84 kg.

The control group: 17 healthy volunteers men, no history of pelvic pain and any pain treatment, between the ages of 23 and 48, ranged in height from 165 to 177 cm, ranged in weight from 69 to 86 kg.

Blood tests including liver function test, kidney function test, thyroid function test, complete blood count, vitamin B12 levels were performed in all study subjects to exclude subjects with any systemic disorder that might cause neuropathy.

Procedure

Tests were performed in the Neurophysiology Laboratory in afternoon hours between three and five. All subjects are asked to forego sexual activities for 24 hours prior to test. Before SEP, a nerve conduction study was performed on all study subjects to exclude peripheral neuropathy. The room temperature was set to 23-centigrade degrees. For the SEP study, stimuli were applied with penile ring electrodes. The cathode was placed 1 cm proximal to the anode. Recording electrodes were placed as active to Cz' (i.e., 2 cm posterior to Cz) and reference electrode on Fz' (i.e., midway positions between Fz and Fpz) according to the 10–20 International System (**Figure 1**).

Before the SEP recordings, the sensory threshold was determined in each subject. This was defined as the lowest stimulus intensity required to evoke sensory perception. In this procedure, the electrical stimulus is applied to all study subjects via stimulus electrodes,

Table 2. N50 latencies of patients and controls.

No.	Patients	Controls
1	40.64	NE
2	50.72	62.10
3	49.12	49.12
4	42.88	62.10
5	43.64	NE
6	NE	58.70
7	39.84	55.20
8	47.50	69.20
9	50.40	61.10
10	43.20	66.17
11	41.60	60.96
12	47.84	48.60
13	48.80	57.60
14	43.30	55.60
15	44.64	58.40
16	42.50	56.16
17	38.40	65.28

Abbreviation: NE, not evocable.

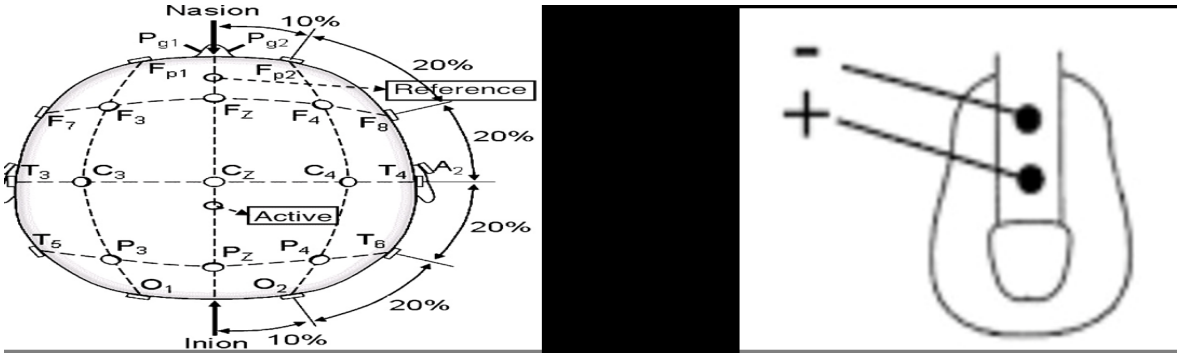

Figure 1. Illustration of recording and stimulating electrodes localization.

beginning at 1mA (milliampere) intensity and 0.1 ms (millisecond) duration. Stimulus intensity is gradually increased in 1 mA increments until the subject feels the stimulus sensation. This stimulus level was described as the subject's sensory threshold and was used for the identification of stimulus severity. For the SEP study, Stimulus intensity was determined as two times the sensory threshold and we applied that ranges in all subjects. Cutaneous stimulus parameters were set at 0.1 ms duration, frequency 4.1 Hz. Bandpass filter was set to 2 to 5000 Hz and sweep time to 100 ms. An average of 300 stimuli were recorded, and the test was three times repeated to ensure repeatability.

Latency of N50 was defined as the second negative (upward) deflection of the W-shaped average cortical waveform. If the response could not be reproduced at least twice or if the cortical response could not be clearly identified, the N50 was classified as not evocable. N50 latencies of both patients and controls have been given in **Table 1**.

Statistical Analysis

This study was designed to detect up a 40% difference in SEPs of dorsal penile nerve stimulation between control (healthy) and study (patients with CP/CPPS) groups with 90% power, assuming a significant difference level of 0.05 and a two-sided statistical test. Relying on the results of a pilot study performed in our department and Lee et al.[17], we calculated the sufficient sample size for our study. The Statistical Package for Social Sciences (SPSS) version 16.0 was used for statistical analyses. All variables including age, weight, height, latency of N50, and sensory threshold were compared between patients and healthy control groups using two independent student's *t* tests that were based on distribu-tion characteristics. The Shapiro-Wilk test was used to determine distribution characteristics. The impact of potential confounding variables such as age, height, and weight was assessed by analyses of covariance.

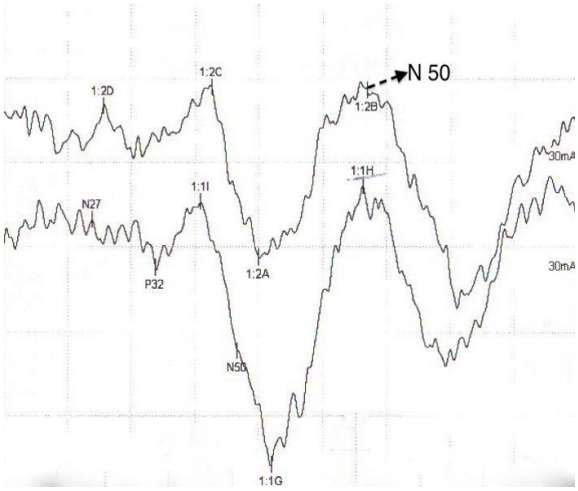

Figure 2. Sample of N50 latency of control number 10.

RESULTS

All results were reported as mean ± SD. Mean age, height, and weight of patient and healthy control groups were (38.0 ± 8.5) versus (34.6 ± 8.0), (170.5 ± 2.7) versus (170.8 ± 3.2), (77.3 ± 3.7) versus (77.6 ± 4.2), respectively. Sensory thresholds of patient and healthy control groups ranged from 6 to 20 mA (12.0 ± 3.8), 8 to 17 mA (12.8 ± 2.5), respectively. There were no significant differences between the two groups in terms of age, height, weight, and sensory threshold ($P > .05$). In one CP/CPPS patient and two healthy subjects, SEP responses could not be achieved. Cortical latencies of N50 after dorsal penile nerve stimulation in the patient and healthy control groups were 44.7 ± 3.9 vs. 59.1 ± 5.8 respectively. N50 latencies were significantly shorter in the patient group compared to the healthy controls ($P < .0001$). None of the covariates including age, weight, and height indicated a significant impact on the latency of N50. All statistical results are presented in **Table 1**. All demographic characteristics and N50 latencies of patients and control subjects are given in **Table 2**. Also, the SEP of control number 10 has been shown on **Figure 2** to exemplify what N50 component of SEP is.

DISCUSSION

Peripheral pain sensation is carried to the somatosensory cortex by different fibers. Whereas noxious stimulus is carried by thin myelinated Aδ and unmyelinated C fibers, non-noxious stimulus is carried by thick myelinated Aβ fibers. Fibers that transmit pain reach the somatosensory cortex via the spinal cord and thalamus. During normal pain transmission, whereas Aβ fibers have an inhibitory effect on pain transmission at the level of the spinal cord, Aδ and C fibers have a stimulatory effect. In the presence of central sensitization, both Aβ and Aδ and C fibers affect stimulation at the same level. Therefore, the total effect of transmission throughout those fibers, transmission of pain sensation is increased into the somatosensorial cortex.

CP/CPPS is a clinical condition characterized by the presence of peripheral pain sensation even in the absence of a stimulus. Therefore, we believe that central sensitization plays an important role in the pathogenesis of this disease. Abnormal SEP responses are not surprising in the presence of central sensitization. In this study, in terms of N50 latency there was a significant difference between patients with CP/CPPS and healthy controls. In a previous study conducted in patients with CP/CPPS, Aδ and C fibers were assessed by thermal sensory analysis (TSA) and Aβ fibers were assessed by SEPs and bulbocavernous reflex (BCR).[17] In this study, neither SEP nor BCR showed any significant difference when compared with study subject's normal laboratory values, yet the results of visual analog scale applied post-TSA were found to be higher for pain sensation. In this study, it was thought that the Aδ and C fibers were responsible for the pain experienced by CP/CPPS patients. On the other hand, another study found no difference in TSA between CP/CPPS patients and healthy controls, however SEP was not used to evaluate pain.[18] In our study, we hypothesized that the central sensitization that occurs in chronic pain conditions such as CP/CPPS will be shown by SEPs, as there may be a functional alteration in somatosensory pathway even if the pathway is structurally normal (i.e., similar to other conditions that also have central sensitization.

While our previous study attempted to determine which type of fiber damage was responsible for pain in patients with CP/CPPS by SEPs response, the aim of present study was to determine activity of pain related to the cortical area. The aims of these two studies were different although the same electroneurophysiological method was used. On the other hand the results of our study and the previous study contradict each other. Although SEP study is frequently conducted in urological disorders such as erectile dysfunction, this is only the second study assessing SEP responses in CP/CPPS patients. A change in somatosensorial transmission may be the principal mechanism responsible for the pain experienced by this patient group. All sensory stimuli including pain sensation are transmitted to same area in the cerebral cortex by somatosensorial nerve fibers. We suggest that hypersensitized nerve fibers that transmit the pain sensation cause an alteration in cortical responses.

CONCLUSIONS

We concluded that latencies of SEP responses are significantly shorter in patients with CP/CPPS than in healthy controls. These results support the hypothesis of presence of central sensitization due to exaggerated transmission of pain sensation to the somatosensory cortex. Therefore, normalization of transmission might be an important step in the treatment of pain in patients with CP/CPPS.

CONFLICT OF INTEREST

None declared.

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