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Central Transmission Time in Irritable Bowel Syndrome

İrritabl Bağırsak Sendromunda Merkezi İletim Zamanı

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ÖZ

Amaç: İrritabl bağırsak sendromunun (İBS) patofizyolojisi tam olarak anlaşılamamıştır. Bu nedenle, hastalık etkili bir tedaviden yoksundur. Somatosensoriyel uyarılmış potansiyel (SEP), somasensoriyel yoldaki bozuklukları tespit etmek için kullanılan elektro-nörofizyolojik bir ölçüm yöntemidir. Çalışmamızda İBS'de SEP ile somatosensoriyel bozukluk olup olmadığını araştırmayı amaçladık.
Gereç ve Yöntemler: Çalışmaya dahil edilme kriterlerine göre 13 İBS hastası ve 13 kontrol seçilmiş, deneyimli bir nörolog tarafından tibial ve sural somatosensoriyel uyarılmış potansiyeller ölçülmüştür. Sonuçlar, hastalar hakkında bilgi sahibi olmayan deneyimli başka bir nörolog tarafından yorumlandı.
Bulgular: Hasta grubunda 8 kişide (61.5%), kontrol grubunda 13 kişide (11%) SEP yanıtı ölçtük ve her iki grup arasında bu oranlar arasında istatistiksel olarak anlamlı fark vardı. Kontrol grubuna kıyasla IBS hastalarında Sural N27P32 ve Sural P32N50'nin tepe amplitüdlerinde istatistiksel olarak anlamlı bir artış gözlemledik. Gruplar arasında sural SEP latansı, tibial SEP latansı ve amplitüdleri açısından anlamlı fark yoktu.
Sonuç: İBS hasta grubunda sağlıklı kontrol grubuna göre somatosensoriyel yolda bozulma görüldü. Bu bozukluk somatik bileşenden ziyade sensoriyal kompenenti içeriyordu. Bu, İBS hastalarında sensorial bileşendeki bozulmayı SEP yöntemiyle ortaya koyan ilk çalışmadır.
Anahtar Kelimeler: İrritabl barsak sendromu, somatosensoriyel uyarılmış potansiyeller, merkezi iletim zamanı

ABSTRACT

Objective: Pathophysiology of irritable bowel syndrome (IBS) is not completely understood. Thus, the disease lacks an effective treatment. Somatosensory evoked potential (SEP) is an electro-neurophysiological measurement method used to detect disorders in the somasensory pathway. In our study, we aimed to investigate whether there is a somatosensory disorder with SEP in IBS.
Material and Methods: Thirteen IBS patients and 13 control case were selected according to inclusion criteria of the study and tibial and sural somatosensory evoked potentials were measured by an experienced neurologist. The results were interpreted by another experienced neurologist who was not informed about the cases.
Results: We measured SEP response in 8 cases (61.5%) in patient group and in 13 cases (11%) in control group and there was a statistically significant difference between these ratios of both groups. We observed a statistically significant increase in peak to peak amplitudes of Sural N27P32 and Sural P32N50 in IBS patients compared to control group. There was no significant difference between groups in terms of sural SEP latency, tibial SEP latency and amplitudes.
Conclusion: The somatosensory pathway was impaired in the IBS patient group compared to the healthy control group. This disorder included the sensory component rather than the somatic component.
Keywords: Irritable bowel syndrome, somatosensory evoked potentials, central transmission time

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disease which is considered to have no underlying organic cause and changes in defecation habits together with abdominal pain are the main symptoms. The diagnosis is established based on the symptoms according to the Roman criteria (Maning, Roman criteria) (1). Disease symptoms occur or increase in periods of intense emotional stress. The incidence of IBS in Western societies ranges from 3% to 20%. The diagnostic and treatment processes of IBS have a high economic cost and, given the frequency of incidence, constitute a significant burden on health expenditures of communities (2). The pathophysiology of the disease is not clear. As the main symptom is abdominal pain, it is suggested that there is a decrease in pain threshold and visceral hypersensitivity without an organic pathology that may cause pain sensation in these patients. There is also a theoretical model that accepts the pathological process in IBS as a dysregulation of the brain-intestinal axis, a two-way communication disorder between the enteric, autonomic and/or central nervous system (3).

There is no biological, anatomical, or physiological marker to indicate IBS (4). The somatosensory evoked potential (SEP) is an electro-neurophysiological study that reliably assesses somatosensory impairment.
However, there is no study investigating the sematosensory disorder in IBS through the literature review with the keywords 'irritable bowel syndrome' and 'sensorimotor evoked potentials' in June 2022, electro-neurophysiological evaluation with the SEP method.

This study aimed to investigate whether there is a somatosensory disorder with SEP in the IBS patient group.

MATERIAL AND METHODS

The study was approved by the Academic Board of the Department of Internal Diseases and the Local Ethics Committee of the Faculty of Medicine (Ethics committee decision no: 2013/613). The study was conducted in accordance with the Declaration of Helsinki.
A total of 13 patients diagnosed as IBS (Irritable Bowel Syndrome) according to the Rome III criteria who admitted to Erciyes University Medical Faculty Gastroenterology outpatient clinic between August 2013 and August 2014 and 13 healthy controls were included in the study.

Inclusion criteria

Patients with the following characteristics were included in the study;
1) aged between 18 to 50 years,
2) diagnosed with IBS according to the Rome III criteria for the patient group,
3) free of any known chronic disease for the control group,
4) agreed to participate in the study and signed the informed consent form,
5) free of diseases that can lead to neuropathy such as diabetes mellitus and chronic renal failure,
6) with normal electro-neurographical findings.

Exclusion criteria

Patients with the following characteristics were excluded;
1) Those with a central or peripheral nervous system tumor,
2) History of cerebrovascular or demyelinating intracranial event, or having neuropathy,
3) Presence of potential causes of abdominal pain such as organic lesions of the gallbladder or gastrointestinal tract,
4) Pregnant or lactating women,
5) Those who received anti-spasmodic or antidepressant medications that may affect nerve conduction within the last week,
6) Fever, gastrointestinal bleeding, weight loss, anemia, abdominal mass or
other symptoms not explained by functional bowel disorder.

Somatosensory evoked potential (SEP)

This is an electro-neurophysiological method that measures and evaluates amplitudes of nerve conduction velocities, nerve latencies and amplitudes of latency differences between nerves. SEP is induced by stimulation of afferent peripheral nerve fibers by physiological or electrical methods. SEP stimulates the large fibers of the peripheral nerves. These stimuli are transmitted to the nerve axons of sensorial, proprioceptive and motor neurons by the cutaneous and subcutaneous nerve fibers [5,6]. Stimulation of afferent peripheral nerve fibers occurs by receiving a series of potentials recorded on the sensorial system that extends to the cortex through the posterior cord, medial lemniscus, and thick myelinated fibers. The stimulus is an electrical stimulus that is strong enough to create a slight finger movement. The result comes out by the comparison of latency, latency difference, cortical amplitude, and inter-partial values. The abnormal findings in the SEP examination are the absence of the expected potential to emerge at the level and distal of the lesion, or prolongation of the latency values. Besides, SEP is a method that contributes to the data provided by electro-myelography (EMG) in some diseases involving the proximal segments of the peripheral nerves such as Guillain Barre Syndrome (GBS), thoracic outlet syndrome (TOS), cervical spondy-

lotic myelopathy (CSM), and subacute combined degeneration (7). In a study of patients with spastic paraplegia which can affect SEP response, the authors reported that motor and sensory SEP response receivability was reduced and measured latencies were prolonged (7).

The SEP can be used in the case of coma. Considering the lack of response in some of the SEP waves in coma, interpretations regarding the prognosis of comatose patients can be made accurately with a positive predictive value of 99% (8). Another potential area of use is in recognition of the spinal ischemia during scoliosis surgery. In this way, its use has been shown to result in a reduction of paraplegia after surgery by 50-60% (9). In SEP studies in fibromyalgia patients, it was shown that the threshold of stimulation was lower, while SEP latencies and SEP amplitudes were higher in these patients compared to the control group (10).

One of the uses of SEP is to detect peripheral neuropathy. For this purpose, the nerve conduction velocity can be measured during the delivery of the stimulus from the extremities to the central nervous system, and considering the reduction in nerve conduction velocities, it is possible to understand which extremities are involved by neuropathy and whether the patient has mononeuropathy or polyneuropathy. Some of the neuropathies detected by SEP are hereditary neuropathies (Charcot-Marie-Tooth's disease, Friedreich's ataxia), diabetic neuropathies, inflammatory polyneuropathies, chronic acquired demyelinating neuropathies, infectious neuropathies (especially HIV neuropathy), and toxic neuropathies (5,6,11).

Nerve conduction velocity measurements were performed to determine whether there was a neuropathy before SEP study. Two patients were excluded because of neuropathy.
According to the international 10-20 system, the recording electrodes (active and reference) were placed in the region of Cz' (2 cm posterior of the Cz) and Fpz' (the midpoint of the distance between Fpz and Fz). For stimulation, active and reference electrodes were placed as: i. for medial tibial SEP, at medial of the medial malleolus, and medial to the midline of Achilles tendon, ii. for Sural SEP, the reference electrode was placed just 3 cm below the active one on the lateral malleolus, respectively. In all of the participants, the stimulation was given at the same (right) lower extremity. The ground electrodes were placed on the calf area. EEG recordings were filtered at a frequency of 2-2500 Hz, and impedance was kept below 5 kΩ. The stimulus threshold was determined before the SEP study as the first level when the patient feels the stimulus. The stimulus magnitude given during SEP study was 2-3 times more than the threshold. A total of 300 stimuli were given and responses were obtained by averaging. We accepted 'SEP response could not be obtained' if there was no response from the SEP study, which occurred in the excluded patients.

Latency and amplitudes of the N27, P32 and N50 components were determined from the sural and tibial SEP responses. The results were evaluated by another neurologist experienced in this field, who was blind to the study groups.

Statistical Analysis: The normal distribution of the data was assessed by histogram and q-q graphs and Shapiro-Wilk test. Homogeneity of variance was examined by Levene's test. The chi-square test for qualitative variables, the independent two-sample t-test and the Mann-Whitney U test were used for quantitative variables in the inter-group comparisons. Data were analyzed with R 3.1.1 (www. r-project. org). A p value of <0.05 was considered as statistically significant.

RESULTS

A total of 26 participants were included in our study, 13 of whom met the inclusion criteria and 13 healthy controls. The gender distributions of the patient and control groups were similar (n=10, 76.9% 10 women, and n=3, 23.1% men). The mean age of patients and the control group was 31.84±6.26 years vs. 27.84±4.59 years, respectively and there was no statistically significant difference between groups in terms of age (p=0.076).

Lack of neuropathy was revealed with nerve conduction study in the study group. There was no statistically significant difference between the patient and the control groups in terms of the stimulus threshold that determines the magnitude of the stimulus given during the SEP study (p=0.75). The mean age and stimulus thresholds of the patient and control groups are shown in Table 1.

Sural SEP response could not be obtained in 5 patients, while tibial SEP response could not be obtained in 4 patients in the study group and 3 subjects in the control group.

All of the control subjects responded to stimuli given during SEP study. Whereas, SuralP32 and SuralN50 responses could not be obtained in 5 (38.5%) patients in the patient group. There was a statistically significant difference between the two groups in terms of response rate. Com-

parisons of Sural and Tibial SEP response are shown in Table 2 and Table 3, respectively.

The median latencies of SuralN27 in the patient and control groups were 32 (24-38) msec and 25 (23-33) msec, respectively, and the difference between groups was not statistically significant (p=0.396). The median latencies of SuralP32 were 39.76 (36.08-40.80) msec and 36.40 (31.84-40.96) msec in the patient and control groups, respectively, and the difference between the groups was not statistically significant (p=0.192). The median latencies of SuralN50 in the patient and control groups were 50.64 (44.32-54.64) msec and 46.40 (42.08-49.12) msec, respectively, and the difference between the groups was not statistically significant (p=0.247). The median SuralN27P32 amplitudes were 2.40 (2.11-2.82) μV and 1.36 (0.84-1.84) μV in the patient and control groups respectively, and the SuralN27P32 amplitude of the patient group was significantly higher than that of the controls (p = 0.025). The median SuralP32N50 amplitudes were 2.75 (2.08-3.70) μV and 1.60 (0.85-1.69) μV in the patient and control groups respectively, and the SuralP32N50 amplitude of the patient group was significantly higher than that of the control group (p=0.003).

Median latencies of TibialN27 in the patient and control groups were 29.92 (24.96-35.04) msec and 29.44 (24.96-38.40) msn respectively, and there was no statistically significant difference between the groups (p=0.967). Median TibialP32 latencies in the patient and control groups were 40.32 (36.16-44.24) msec and 39.76 (32.00-48.00) msec, respectively, and there was no statistically significant difference between the groups (p=0.935).
Median TibialN50 latencies were 53.12 (42.08-58.56) msec and 50.56 (41.76-56.96) msec in the patient and control groups, respectively, and there was no statistically significant difference between the groups (p=0.624).
Median TibialN27P32 amplitudes were 1.68 (1.42-2.41) μV and 2.06 (1.61-2.38) μV in the patient and control groups, respectively, and there was no statistically significant difference between the groups (p=0.683).
Median tibialP32N50 amplitudes were 2.00 (1.82-2.23) μV and 1. 98 (1.47-2.76) μV in the patient and control groups, respectively, and there was no statistically significant difference between the groups (p=0.744).
The latencies and amplitudes of the patient and control groups in sural and tibial SEP responses are shown in Table 3.

Table 1. The mean age and stimulus threshold of the patient and control groups

Variable	Control (n=13)	Patient (n=13)	p	Male Patient (n=3)	Male Control (n=3)	p	Female Patient (n=10)	Female Control (n=10)	p
Age (year)	27,84±4,59	31.84±6,26	0,076	33,33±8,38	31,66±2. 88	0,71	31,40±5,38	26,70±4,47	0,74
Evoke Threshold (milliamperes)	9,76±1,87	9. 51±2,19	0,512	11,00±2,00	9,33±1,52	0,31	9,07±2,14	9,90±2,02	0,38

Data are expressed as mean±standard deviation.

Table 2. Comparison of the study groups regarding Sural SEP responsiveness

		Sural SEP			p
		response (+)	response (-)	Total	
Group	Patient n (%)	8 (%61,5)	5 (%38,5)	13 (%100)	0,039
	Control n (%)	13 (%100)	0 (%0,0)	13 (%100)	
	Total n (%)	21 (%80,7)	5 (19,3)	26 (%100)	
		Tibial SEP			p
		response (+)	response (-)	Total	
Group	Patient n (%)	9 (%69,2)	4 (%30,8)	13 (%100)	1,00
	Control n (%)	10 (%76,9)	3 (%23,1)	13 (%100)	
	Total n (%)	19 (%73,1)	7 (%26,9)	26 (%100)	

Sural and Tibial SEP response availability between groups was compared. Eight patients received Sural SEP responses in the patient group, while the entire control group received Sural SEP responses. The tibial SEP response was received in all patients in both groups.

Table 3. Latency and amplitudes of sural and tibial SEP responses in the patient and control groups

Variable	Patient (n=13)	Control (n=13)	p
SuralN27 latency (millisecond)	32 (24-38)	25(23-33)	0,396
SuralP32 latency (millisecond)	39,76 (36,08-40,80)	36,40 (31,84-40,96)	0,192
SuralN50 latency (millisecond)	50,64 (44,32-54,64)	46,40 (42,08-49,12)	0,247
TibialN27 latency (millisecond)	29,92 (24,96-35,04)	29,44 (24,96-38,40)	0,967
TibialP32 latency (millisecond)	40,32 (36,16-44,24)	39,76 (32,00-48,00)	0,935
TibialN50 latency (millisecond)	53,12 (42,08-58,56)	50,56 (41,76-56,96)	0,624
SuralN27P32 Amplitude (microvolt)	2,40 (2,11-2,82)	1,36 (0,84-1,84)	**0,025**
SuralP32N50 Amplitude (microvolt)	2,75 (2,08-3,70)	1,60 (0,85-1,69)	**0,003**
TibialN27P32 Amplitude (microvolt)	1,68 (1,42-2,41)	2,06 (1,61-2,38)	0,683
TibialP32N50 Amplitude (microvolt)	2,00 (1,82-2,23)	1. 98 (1,47-2,76)	0,744

Data were expressed as median (25th-75th percentiles). The median SuralP32N50 amplitudes were 2.75 (2.08-3.70) μV and 1.60 (0.85-1.69) μV in the patient and control groups respectively, and the SuralP32N50 amplitude of the patient group was significantly higher than that of the control group (p=0.003).

DISCUSSION

To the best of our knowledge, this is the first study to show sensory impairment in IBS patients by SEP measurements in the literature. In our study when we compared the IBS patients and healthy controls in terms of Sural and Tibial SEP responsiveness; SuralP32 and SuralN50 SEP responses were obtained in 8 (61.5%) patients in the patient group, while 13 (100%) in the control group. The difference between the groups was statistically significant. We thought that this difference might arise from the deterioration of central pain perception in the patient group, and from neuropathies which could not be excluded by EMG in the patient group, as well. In our study, the SEP response rate was lower in the other parameters in the patient group compared to healthy controls, but the differences between the groups were not statistically significant. The lack of a statistically significant difference was thought to be related with relatively low sample volume in the patient and control groups.

In our study, there was no statistically significant difference between IBS patients and healthy controls regarding latency durations of SuralN27, SuralP32, SuralN50, TibialN27, TibialP32, and TibialN50 measurements. TibialN27P32 and TibialP32N50 amplitudes were similar in both groups. However, the difference in Sural amplitudes of study groups was remarkable in our study. SuralN27P32 and SuralP32N50 amplitudes were significantly higher in IBS patients compared to the control group.

Increased visceral sensitivity in the pathophysiology of IBS has recently been acting attention (12). Many studies have highlighted the increased intestinal sensitivity in patients with IBS. Rectal hypersensitivity has been described as a marker of IBS, and many studies have focused on colorectal hypersensitivity. However, some studies have shown increased sensitivity in other gastrointestinal sites such as the esophagus, stomach, and small intestine (13).

In a study conducted in patients with IBS-D, the patients who were treated with cleansed moxibustion from "Kurtboğan" (tiger grass) were evaluated by a 100 ml rectal balloon test, which showed a decrease in pain score and an increase in the threshold of defecation impulse and pain sensation (14). In previous studies, patients were evaluated using brain magnetic resonance imaging (MRI) after distension with a rectal balloon, and IBS patients were shown to have different visceral sensory areas than healthy controls (15).

In the study by Törnblom et al., the authors examined whether the sensitivity in IBS patients was different from the control group with starvation and satiety by rectal barostat method. The stimulation thresholds at fasting and satiety in the IBS group were found to be 34.2±13.2 mmHg and 31.5±13.2 mmHg, respectively, and 53.1±11.3 mmHg and 51.5 ± 12.8 mmHg in the control group; and they observed that the stimulation threshold was lower in

the IBS group than the controls in both fasting and satiety state (16). In our study, stimulation thresholds measured by SEP were measured as 9.51±2.19 and 9.76±1.87 milliamperes in the patient and control groups, respectively; though the mean stimulation threshold was lower in the patient group compared to the control group, this difference was not statistically significant.

In many previous studies, hypersensitivity has been examined with different methods in IBS patients. In the study conducted by Ludidi et al., they measured barostat with the help of rectal balloon and compared the mean visual pain scores of IBS patients and healthy controls. In this study, similar to previous studies, an increase in excitability and pain sensitivity was shown in IBS patients compared to healthy individuals (17). In another study by Ludidi et al., the parameters which affect hypersensitivity were explored, and hypersensitivity was shown to be more frequent in the female sex, younger age and selective serotonin reuptake inhibitor drug users in IBS patients (18). In our study, patients under antidepressants and other drugs that affect nerve conduction were excluded from the study.

Fang Cui et al. observed that hypersensitivity was higher in rats which had a lower synthesis of epidermal growth factor (EGFR) and serotonin transporter (SERT). In addition, in this study, they observed that increased SERT level due to increased EGFR synthesis in cell culture generated from rat intestine, which resulted in an increase in serotonin reuptake and they have suggested that hypersensitivity might decrease by this mechanism (19).

Some of the previous studies have shown that there may be some different disorders related to the nervous system other than visceral hypersensitivity in patients with IBS. In a study conducted with 62 IBS patients and 20 healthy controls, Liu et al. showed that there was not only visceral hypersensitivity in the nervous system of IBS patients, but also somatic hypersensitivity and autonomic cardiovascular dysfunction along with visceral hypersensitivity (20).

In the literature, the SEP responsiveness has been examined in many diseases before, but not in IBS patients. Lorenz et al. compared 10 women with fibromyalgia and 10 healthy women. In this study, the mean stimulus threshold was significantly lower in fibromyalgia patients compared to the control group (7.65 mA vs. 10.72 mA, respectively). In the same study, there was a statistically significant difference between N1-N2 'peak to peak' amplitudes, whereas no significant difference was found between latencies (21).

Our study had some limitations. The first of these was the small number of patients. This was due to the lack of willingness to practice SEP and the fact that a practicing neurologist and a SEP laboratory were not always available for SEP. The second was that SEP shots were performed in a single session and perhaps there were no follow-up SEP measurements to distinguish periodic differences.

CONCLUSION

Compared with healthy controls, there is a deterioration of the somatosensory pathway in the IBS patient group, and this can only be demonstrated by sensory SEP recordings (sural SEP). A northworthy result of this study is that the rate of SEP responsiveness in sural SEP recordings were lower, and sural amplitudes were higher in the patient group compared to the control group. Because these differences were in sural SEP measurements rather than tibial ones, the impairment in the somatosensory pathway in the patient group was shown to be more prominent in the sensory component than in the somatic component.

Conflict of Interest: No conflict of interest was declared by the authors.
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Ethics Committee Approval: The study was carried out after taking consents of the patients and obtaining approval from the Local Ethics Committee of the Faculty of Medicine (Ethics committee date and decision no: 2013/613).
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