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The importance of medial plantar nerve conduction study in detectıon of polyneuropathy in inflammatory bowel disease

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Abstract

Background & Objective: Peripheral neuropathy is the most frequent neurologic complication of inflammatory bowel disease (IBD). We aimed to evaluate the clinical utility of medial plantar nerve conduction study (NCS) in the detection of distal sensory polyneuropathy in IBD patients. *Methods:* The study was performed with 21 Crohn's disease (Group 1) patients, 24 Ulcerative Colitis (Group 2) patients without clinical peripheral neuropathy and 28 healthy participants (Group 3). Each patient group underwent electrophysiological conduction studies. The findings were analyzed statistically. *Results:* Abnormal medial plantar nerve conduction was present on both sides in 11 (24.4 %) patients with IBD; 5 (11.1 %) patients had low sural nerve amplitude, and 5 (11.1 %) had low superficial peroneal nerve amplitude bilaterally. There were significant differences between the IBD groups (Group 1 and 2) and Group 3 in the mean sensory nerve action potential amplitude of the right medial plantar nerve ($p<0.024$), and in the mean sensory nerve action potential amplitude of the left medial plantar nerve ($p<0.025$). The polyneuropathy pattern was mostly of the sensory axonal type in patients with IBD. *Conclusions:* These electrophysiologic findings indicate that peripheral neuropathy is more prevalent in IBD. In IBD patients the amplitudes of the medial plantar nerve were abnormal more than in the sural and superficial peroneal nerves.

Keywords: Polyneuropathy, medial plantar nerve, inflammatory bowel disease (IBD), peripheral neuropathy, medial plantar nerve conduction study, polyneuropathy detection, electrophysiology, subclinical neuropathy, Crohn's disease, ulcerative colitis, nerve action potential amplitude.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD), and both are clinically heterogeneous conditions with immune-mediated extraintestinal involvement.[1] The extraintestinal involvement of CD and UC are very diverse. Peripheral neuropathy is the most reported neurologic complication of IBD.[2-4] When the known risk factors for neuropathy are excluded, such as vitamin B12 deficiency and metronidazole exposure, the relationship between IBD and immune-mediated neuropathies has been described only in case reports and small series. Although the frequency of peripheral neuropathy varies in IBD, studies have reported that it is between 0% and 39%.[2-4]

Distal sensory polyneuropathy (DSP) is the most common subtype of peripheral neuropathy.[5] Routine electrophysiological tests are recommended for investigating extra-intestinal involvement in IBD.[6] In the early stage, patients show minimal signs or symptoms of neuropathy; therefore, clinical examination is less sensitive and specific than nerve conduction studies (NCSs), which serves as the sensitive test in detection of subclinical neuropathy. Subclinical neuropathy was used to describe subjects who had an abnormal nerve conduction study suggestive of a distal symmetrical polyneuropathy but who did not fulfill criteria for definite clinical neuropathy.[7] NCS provides a sensitive but nonspecific index on the onset of distal peripheral neuropathy (DPN) and is a valuable tool in detecting subclinical cases.[8,9] Subclinical neuropathy is best detected

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by the sensory NCS. In general, the motor NCS is able to detect subclinical neuropathy in 16% to 27% of diabetic subjects, whereas the sensory NCS is abnormal in 36% to 48% of diabetic patients.[10] As a part of the dying phenomen, sensory nerves in the lower extremities are usually first affected in the early stages of polyneuropathy.[11-13] The sural nerve action potential (NAP) has an important value electrophysiologic marker of DSP. However, routine nerve conduction study (NCS) of sural nerve has a limitation as the sural NAP is within the normal range in 38 to 67% of patients with suspected DSP. The medial plantar nerve of the feet may be affected in the early stages of polyneuropathy. Therefore, the medial plantar NAP may be a more sensitive marker in the early detection of DSP.[14]

In this study, we aimed to demonstrate the association between medial plantar nerve conduction studies and the electrophysiologic detection of peripheral neuropathy in patients with IBD who had no clinical findings and symptoms of peripheral neuropathy.

METHODS

Subjects

This study was conducted in the Neurology and Gastroenterology departments. Informed consent was obtained from all patients prior to conducting the study. Ethical approval was obtained from the Ethics Committee of Umraniye Training and Research Hospital (Date: 20.09.2013, Number: 12980).

This study was performed with 21 patients with Crohn's disease (Group 1), 24 patients with ulcerative colitis (Group 2) and 23 healthy control groups (Group 3). Participants in the study were between 18-60 years of age and patients with clinically polyneuropathy were excluded from the study. The patients and controls were examined by the same neurologist and the ones, and detailed neurological examinations for probable symptoms of PN (muscle weakness, muscle atrophy, paresthesia, etc.) were performed. Extremity muscle and sensory examinations of all participants were normal, and deep tendon reflexes were evaluated as normoactive in the upper and lower extremities. Patients who did not have sensory, motor and reflex disorders on clinical examination were included in the study. In addition, Group 1 was evaluated according to Crohn's Disease Activity Index (CDAI). Group 2 was evaluated using the Truelove Witts and "Clinical Activity Index" of ulcerative colitis criterion. Accordingly, patients in remission were included in the study.

Inclusion criteria

- Diagnosis of inflammatory bowel disease (IBD): Participants must have a confirmed diagnosis of IBD, as defined by established clinical, endoscopic, and histological criteria.
- Age: Participants aged 18-65 years old.
- Clinical remission: Participants must be in clinical remission at the time of enrollment, as evidenced by a Crohn's Disease Activity Index (CDAI) score of less than 150 or a Simple Clinical Colitis Activity Index (SCCAI) score of less than 5, as appropriate.
- Informed consent: Participants must be able to understand the study procedures and provide informed consent.

Exclusion criteria

- Other neuropathies: Participants with a history of other known causes of peripheral neuropathy such as diabetes mellitus, alcohol abuse, vitamin B12 deficiency, or chemotherapy-induced neuropathy.
- Other neurological disorders: Participants with a history of other neurological disorders such as multiple sclerosis, Parkinson's disease, or stroke.
- Concomitant serious illness: Participants with any other serious medical conditions that, in the opinion of the investigator, might interfere with the participant's ability to comply with study procedures.
- Use of neurotoxic medications: Participants currently on medications known to cause peripheral neuropathy, or have taken such medications in the last six months.
- Previous surgery: Participants who have undergone surgery within the previous three months or have planned surgery within the next three months.

Electrophysiologic investigations

The nerve conduction study was conducted using a Medelec Synergy Nicolet AT2 EMG/EP system (Nicolet Biomedical, Madison, WI, USA).

Neurologic examinations and electrophysiologic evaluations of the patient and control groups were conducted by the same electrophysiology specialist. The method suggested by Falck *et al*. (1994) and Stalberg and Falck (1993) was used

for routine motor and sensory nerve conduction studies (NCS).[15,16] Unilateral motor nerve studies were performed in the ulnar, median, peroneal and tibial nerves. Unilateral sensory studies were performed in the median and ulnar nerves. Medial plantar, superficial peroneal, and sural sensory NAPs were recorded bilaterally. Standardantidromic methods were used in the sural, superficial peroneal, median, ulnar nerves sensory NCS. An average (typically 10 runs) was used to improve signal-to-noise ratio for all sensory nerve recordings. Surface bar recording and bipolar surface recording electrodes (Nicolet EDX) were used in the NCS. In case of suspected carpal tunnel syndrome, median motor and sensory NCSs were performed bilaterally. Compound muscle action potential (CMAP) amplitude, distal latency, nerve conduction velocity (NCV), mean F-response latency, and F-wave persistence calculated for motor NCSs. Median F-response latency was calculated using 20 obtained stimulations. Baseline-peak latency, baseline-peak NCV, and sensory nerve action potential(SNAP) amplitude were measured in the sensory nerve recordings. The latency of sensory nerve was measured to the onset of the first negative deflection and to the negative peak. The sensory NCV was calculated using the onset and peak latencies. Amplitude of the sensory NAP was measured from the baseline to the negative peak. Stimulation duration was 0.2 ms for motor stimuli and 0.1 ms for sensory stimuli. In order to obtain the NAP, the stimulus intensity was supramaximal. Filter settings were 20 Hz-2kHz for sensory NCS, 5Hz-10kHz for motor and F-wave NCSs. Skin temperature was maintained at between 31°C and 34°C in all subjects.

Medial plantar nerve recordings

Medial plantar NAP was recorded bilaterally with the same surface bar recording electrodes. Standard sensory nerve conduction setup was used. To test medial plantar NAP, the recording electrode was placed on the tibial nerve above and posterior to the medial malleolus. The distance between the recording electrode and stimulating electrode was 140 mm. For the medial plantar nerve, the stimulator was placed on the medial sole region.[15-17]

Reference data and limits of normal

We use mean ± 2 standard deviations (SD) as the limit for the controls in our laboratory, i.e. approx. corresponding to the 95% confidence limit, and state the deviation from normal mean for individual subjects as Z-scores, i.e. deviations in SD from the normal of mean.[18,19] Subclinical DPN was defined by many researchers as the finding of changes in NCS in at least two independent neurophysiological nerve parameters.[8,9]

Statistical analysis

Statistical analysis was performed using the SPSS Version 20 program (IBM Corporation; Armonk, NY, USA). Descriptive statistical analyzes (mean, median and standard deviation) were performed. The relevance of the variables to normal distribution was analyzed through analytical methods (Shapiro-Wilk tests). Pearson's Chi-Square test was used to compare qualitative variables. For the normal distribution of quantitative variables, the Independent Sample t test was used to compare the two groups and the One-way analysis of variance (ANOVA) was used to compare three groups. Additionally, for the abnormal distribution of quantitative variables, the Mann-Whitney U test was used to compare the two groups and the Kruskal-Wallis test was used to compare three groups. The statistical significance level was set at $p<0.05$. The upper limit of normal (ULN) (for distal latency parameter) and lower limit of normal (LLN) (for amplitude and NCV parameters) of NCS data were calculated, based on calculation of the mean ± 2 standard deviations (SD): values within this range were considered normal, and based on calculation of the mean ± 2 SD of logarithmic transformed data: values not within this range were considered abnormal.

RESULTS

Forty-five patients with IBD (21 in Group 1, 24 in Group 2) who had no sensory sign and symptom of peripheral neuropathy, and 28 healthy age- and sex-matched controls were included in the study. On neurological examination, none of participants had exteroceptive and proprioceptive sensory impairments. Deep tendon reflexies were normal in the upper and lower extremities in all participants. There was no significant difference between the groups in terms of age, sex, and BMI (body mass index) ($p>0.05$) (Table 1). Disease duration was 7.48 ± 5.46 years in Group 1 and 5.79 ± 4.75 years in Group 2. In all patients in Group 1 and Group 2, mesalazine and azathioprine were used together. The patients were found to be in clinical remission in disease activity scores. In Group 1, the mean of Crohn's Disease Activity Index (CDAI) was 95.14 ± 20.36. In Group 2, the

Table 1: Demographic characteristics of participants

		Group 1 (CD) (n:21)	Group 2 (UC) (n:24)	Group 3 (Control) (n:28)	p-values
Sex (F/M)		10/11	9/15	14/14	[a] 0.64
Age (year)	*Mean ± Std. Dev.*	40.04 ± 10.2	39.12 ± 11.7	44.14 ± 8.71	[b] 0.17
BMI (kg/m²)	*Mean ± Std. Dev.*	25.53 ± 3.71	25.09 ± 3.85	27.44 ± 3.68	[c] 0.32
Disease Time (year)	*Mean ± Std. Dev.*	7.48 ± 5.46	5.79 ± 4.75		[d]0.26
Clinical Activity Index	*Mean ± Std. Dev.*	95.14 ± 20.36	4.58 ± 1.64		

[a] Pearson Chi-Square, [b] Oneway Anova, [c]Kruskal Wallis Test, [d]Mann Whitney U test, p<0.05
CD: Crohn's Disease, UC: Ulcerative Colitis, BMI: Body Mass Index

mean of "Clinical Activity Index" of Ulcerative Colitis was calculated as 4.58 ± 1.64 (Table 1) and Group 2 was evaluated as mild level according to Truelove Witts disease activity.

In all participants, we obtained median, ulnar, tibial, peroneal motor nerve CMAPs and median, ulnar, sural, superficial peroneal, medial plantar sensory nerve SNAPs, ulnar, median, tibial F-waves. In the control group, all of them demonstrated normal latency, amplitude, NCS values compared to Oh's findings.[20-22] These results of the NCSs in the control and patient groups are listed Table 2, 3. For the medial plantar, sural, superficial peroneal nerves, mean amplitude was 17.30 μV, 20.86 μV, 19.35 μV, respectively. As Shapiro-Wilk normality test showed that NAP amplitudes of the medial plantar, sural, superficial peroneal nerves were not normally distributed, lower limits of normal values for these nerves were calculated as mean -2 SD of logarithmic transformed data. The lower limits of normal (inversed logarithmic value) of the medial plantar, sural, superficial peroneal amplitudes were 3.57 μV, 6.37 μV, and 4.79 μV, respectively. The lower and upper limits of normal (inversed logarithmic value) of the medial plantar, sural, and superficial peroneal amplitude, onset latency, and NCV values are shown in Table 4.

Table 2: Sensory nerve conduction study results for the Crohn's disease, ulcerative colitis, and control groups

		Group 1 (CD)	Group 2 (UC)	Group 3 (Control)	p-values
Medial Plantar (right)	*Distal latency (ms)*	2.20 ± 0.44	2.11 ± 0.36	2.07 ± 0.37	0.08
	Distal amplitüde (μV)	13.52 ± 4.49	12.84 ± 3.89	17.29 ± 6.73	*[a]0.02**
	Conduction Velocity (m/s)	50.36 ± 5.02	50.03 ± 4.38	53.56 ± 6.98	0.78
Medial Plantar (left)	*Distal latency (ms)*	2.21 ± 0.40	2.16 ± 0.56	2.13 ± 0.35	0.13
	Distal amplitüde (μV)	14.38 ± 6.12	13.13 ± 4.37	17.31 ± 6.08	*[a]0.03**
	Conduction Velocity (m/s)	51.18 ± 5.78	49.60 ± 4.51	52.87 ± 6.98	0.16
Sural (right)	*Distal latency (ms)*	1.99 ± 0.25	1.84 ± 0.30	2.01 ± 0.33	0.16
	Distal amplitüde (μV)	20.50 ± 6.97	18.91 ± 7.44	20.54 ± 6.49	0.44
	Conduction Velocity (m/s)	53.65 ± 6.04	53.28 ± 5.99	54.13 ± 6.24	0.90
Sural (left)	*Distal latency (ms)*	1.89 ± 0.24	1.86 ± 0.19	1.96 ± 0.15	0.22
	Distal amplitüde (μV)	20.46 ± 7.09	18.48 ± 6.16	21.17 ± 6.73	0.24
	Conduction Velocity (m/s)	53.28 ± 6.77	53.11 ± 6.41	54.08 ± 6.23	0.91
Superficial peroneal (right)	*Distal latency (ms)*	2.13 ± 0.21	2.22 ± 0.30	2.26 ± 0.31	0.24
	Distal amplitüde (μV)	17.97 ± 5.44	16.53 ± 4.19	18.98 ± 7.08	0.43
	Conduction Velocity (m/s)	51.35 ± 4.95	49.14 ± 4.85	52.24 ± 6.04	0.15
Superficial peroneal (left)	*Distal latency (ms)*	2.23 ± 0.45	2. 30 ± 0.33	2.28 ± 0.19	0.17
	Distal amplitüde (μV)	17.80 ± 5.76	16.57 ± 4.70	19.71 ± 6.39	0.21
	Conduction Velocity (m/s)	50.94 ± 4.85	49.75 ± 4.27	52.20 ± 6.39	0.51

*[a]Oneway Anova, [b]Kruskal Wallis Test, p<0.05**
CD: Crohn's cisease, UC: Ulcerative colitis

Table 3: Motor nerve conduction study results for the Crohn's disease, ulcerative colitis, and control groups

		Group 1 (CD)	Group 2 (UC)	Group 3 (Control)	LLN / ULN	p-values
Right Median	*Distal latency (ms)*	2.80 ± 0.47	2.98 ± 0.52	2.65 ± 0.37	*3.39*	0.06
	Distal amplitüde (μV)	8.39 ± 2.53	8.51 ± 2.44	9.79 ± 1.96	*5.84*	0.08
	Conduction Velocity (m/s)	59.29 ± 5.87	53.69 ± 3.57	56.30 ± 4.33	47.64	0.002*
	F Response	25.29 ± 1.88	27.32 ± 2.26	23.54 ± 1.53	*26.60*	*<0.001**
Right Ulnar	*Distal latency (ms)*	2.63 ± 0.44	2.71 ± 0.56	2.50 ± 0.35	*3.20*	0.14
	Distal amplitüde (μV)	10.39 ± 1.98	10.58 ± 2.04	11.35 ± 1.91	*7.53*	0.27
	Conduction Velocity (m/s)	60.63 ± 6.47	56.14 ± 4.52	59.38 ± 4.80	49.78	0.02*
	F Response	25.98 ± 2.10	27.88 ± 2.48	24.13 ± 1.87	*27.87*	*<0.001**
Right Tibial	*Distal latency (ms)*	4.43 ± 0.65	4.51 ± 0.70	4.37 ± 0.33	*5.03*	0.08
	Distal amplitüde (μV)	7.40 ± 2.75	7.92 ± 2.69	9.87 ± 3.28	*3.31*	0.42
	Conduction Velocity (m/s)	49.57 ± 6.42	50.27 ± 6.54	52.44 ± 6.50	*39.44*	0.37
	F Response	49.17 ± 5.50	50.57 ± 4.32	43.46 ± 4.28	*51.21*	*<0.001**
Right Peroneal	*Distal latency (ms)*	4.23 ± 0.54	4.31 ± 0.34	4.18 ± 0.45	*5.08*	0.22
	Distal amplitüde (μV)	5.20 ± 2.36	4.45 ± 1.79	5.31 ± 2.10	*1.11*	0.37
	Conduction Velocity (m/s)	47.43 ± 6.52	45.98 ± 4.85	51.46 ± 5.15	41.16	0.001*

*p<0.05**
CD: Crohn's Disease, UC: Ulcerative Colitis, LLN: Lower Limits of Normal for amplitude and velocity parameters, ULN: Upper Limits of No1rmal for latency parameters

The results of sensory, motor nerves conduction studies and F-wave latency parameter showed that there were significant differences between the IBD (Group 1, Group 2) and control groups (Table 2, 3).

Abnormal nerve conduction was found to be present in patients with IBD. Five patients had abnormality for NAP amplitude of the sural and five patients had abnormal result for the superficial peroneal nerve amplitude bilaterally. On the other hand, medial plantar NAP amplitude was abnormal on both sides in 11 (24.4%) patients. In addition, five patients had carpal tunnel syndrome.

For sural and superficial NAP amplitudes, no significant difference was found between patients and healthy subjects (right p=0.44, left p=0.24 and right p=0.43, left p=0.21). However, in the patient group NAP amplitude of the medial plantar nerve was significantly lower than the control group (right p=0.024, left p=0.025) (Table 2, Figure 1). There were not any significant differences in medial plantar NAP amplitude between the CD and UC groups.

DISCUSSION

Neurologic involvement in IBD is an important health issue that affects the morbidity of the disease. In the literature, there is evidence of both central nervous system and peripheral nervous system involvement in IBD. Peripheral polyneuropathy is one of the most frequently reported neurological complication in patients with IBD. The literature includes only a very limited number of studies that thoroughly document the clinical and electrodiagnostic characteristics of patients with IBD, and there are no detailed electrodiagnostic studies involving medial plantar NCS. This study has the focus of the usefulness of medial plantar NCS in detection of distal polyneuropathy. We have studied in IBD patients who had no sign or symptom of peripheral neuropathy and compared them with healthy controls.

Polyneuropathy is a disease that bilaterally affects the upper and lower extremity peripheral nervous systems. This exposure in peripheral nerves may be of an axonal and/or a demyelinating nature. Reduced in CMAP and SNAP amplitudes,

Table 4: Medial plantar, sural, superficial peroneal nerves action potential values in healthy subjects

	Medial Plantar		Sural		Sup-peroneal	
	Mean ± SD	LLN / ULN	Mean ± SD	LLN / ULN	Mean ± SD	LLN / ULN
Distal latency (ms)	2.09 ± 0.33	2.75	1.99 ± 0.23	2.45	2.27 ± 0.21	2.69
Distal amplitüde (µV)	17.30 ± 6.32	3.57	20.86 ± 6.56	6.37	19.35 ± 6.70	4.79
Conduction Velocity (m/s)	53.22 ± 6.92	39.38	54.10 ± 6.17	41.76	52.22 ± 6.16	38.96

LLN: Lower Limits of Normal for amplitude and velocity parameters, ULN: Upper Limits of Normal for latency parameters

normal conduction velocity in motor and sensory nerves, and normal minimum F latency indicate axonal polyneuropathy. Delayed sensory and motor nerve conduction velocity, prolonged distal motor latency, and minimum F latency in NCSs suggest demyelinating polyneuropathy.[23,24] In our study, when compared with the control group, abnormal electrophysiologic findings were detected in patients with IBD who had no sensory sign or symptom of polyneuropathy and showed normal neurological examination. Electrophysiologic findings supporting demyelinating and axonal polyneuropathy in patients with IBD were present.

By using medial plantar NCS, we found low SNAP amplitude on both sides in 24.4% of patients with IBD. We found abnormal medial plantar NCS in 11.1% of patients with CD and in 13.3% of patients with UC that their sural, superficial NAPs were normal. The literature includes no studies that compare the medial plantar, sural, and superficial sensory nerve conduction and their responses, or that document such electrophysiologic findings for detection of subclinical sensory polyneuropathy in patients with IBD. Also, Turgut et al. found abnormalities in the nerve conduction of the dorsal sural in diabetic children who had no sensory sign or symptom of peripheral neuropathy.[22] Thus, these studies clearly showed that although electrophysiological studies were indicative of neuropathy, physical examination did not show any significant findings.

Previous studies have provided information on the diagnostic utility and yield of the medial plantar NAP than sural nerve in the diagnosis of DSN.[5,14,24] Nodera *et al*. found abnormalities in the nerve conduction of the medial plantar in 69%

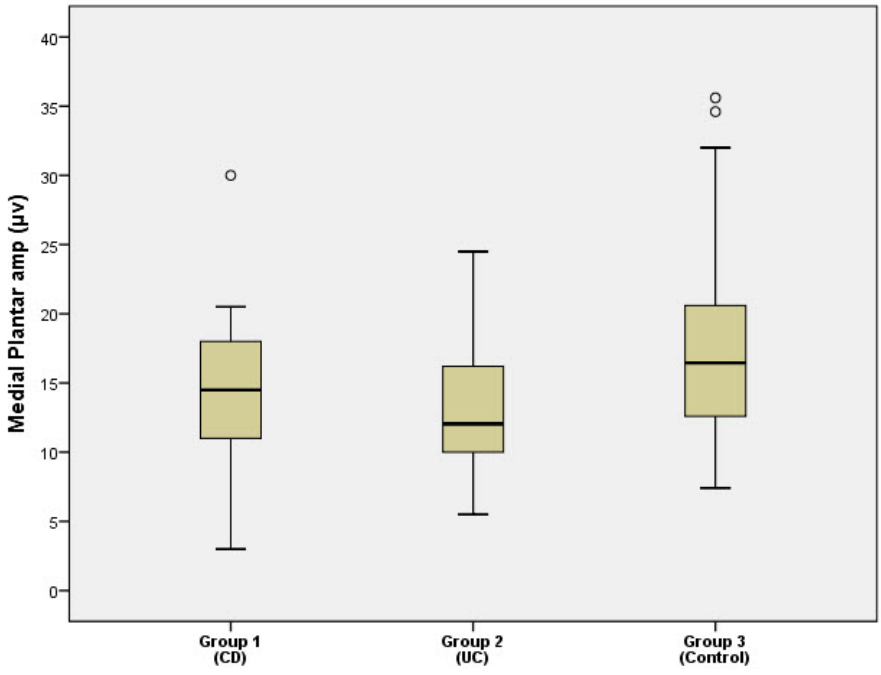

Figure 1. Medial plantar nerve amplitude results of both sides (right and left) of groups. Inflammatory bowel diseases were significantly lower than the control group. (p <0.05) (CD: Chron's disease, UC: Ulcerative colitis)

of DSN cases.[12] By using medial plantar NCS and skin biopsy in the evaluation of suspected DSN, Herrmann *et al*. found the medial plantar NAP was reduced or absent in 31.8% subjects that in 20.4% of patients with small fiber neuropathy and in 42.9% of patients with sensory neuropathy with large-miyelinated fiber involvement.[5] In another study, assessing the medial plantar NCS, Løseth *et al*. showed the reliability of the medial plantar response in patients under 70 years with diabetes mellitus. They found abnormal medial plantar NCS in 59% of patients.[25] In Uluç *et al*'s study, medial plantar NAP amplitude was abnormal in 60% and dorsal sural NAP was abnormal in 40% in diabetic patients.[26] We found abnormalities in the nerve conduction of the medial plantar NCS in 24.4% of IBD patients with no clinical symptoms and signs of neuropathy. Thus, all these studies showed the reliability and higher diagnostic sensitivity of the medial plantar NCS over routine NCS. In this study, we suggest that neurophysiological examination of the medial plantar nerve should be included in the complete work up in patients with IBD to search of DSN.

Unilateral abnormality of the medial plantar nerve does not necessarily indicate the presence of DSN. These local neuropathic conditions can be due to damage or entrapment of medial plantar nerve. Our patients with neuropathy consist of IBD, the medial plantar nerve was abnormal bilaterally and it can indicate DSN.

Non-immunologic mechanisms play a greater role than immunologic mechanisms in the neuropathy pathophysiology of chronic IBD. Neuropathy development may be related to different action mechanisms, the main ones being malabsorption, nutrition, and especially vitamin deficiencies, toxic metabolic agents, drug adverse effects, immunosuppressant treatment complications, infections, thromboembolism and immunologic action mechanisms.[6,27,28] Low levels of vitamin B12 and folic acid are the most reported findings.[29] In our patients, however, vitamin B12 and folic acid levels were normal. It has also been shown that sulfasalazine and TNF-α antagonist treatment could be related to polyneuropathy development[30-32], or that peripheral neuropathy could develop as a result of extended metronidazole use.[33] The patients included in our study had no sulfasalazine and TNF-α antagonist treatments, and none had recently started or been on an extended course of metronidazole.

In conclusion, we think that medial plantar nerve conduction study is important and more sensitive in detecting polyneuropathy in the early stages in patients with IBD. The limitation of this study is our relatively small number of patients. Also, medial plantar NAP amplitude is limited when clinical signs of large-fiber sensory dysfunction are lacking.

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DISCLOSURE

Ethic: The study was approved by the Ethics Committee of the University of Health Sciences, Umraniye Training and Research Hospital (Approval date: 21.07.2016, Approval number: 11060). Informed consent was obtained from the patients.

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Conflict of interest: None

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