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The Relationship between Quiescent Inflammatory Bowel Disease and Peripheral Polyneuropathy

Züleyha Akkan Çetinkaya*, Yılmaz Çetinkaya†, Mehmet Gencer†, Mesut Sezikli‡, Hülya Tireli†, Oya Övünç Kurdaş‡, Kayıhan Uluç§, Önder Us§, and Tülin Tanrıdağ§

Department of Gastroenterology, Kocaeli Derince Research and Education Hospital, Kocaeli, Departments of †Neurology, ‡Gastroenterology, Haydarpaşa Numune Research and Education Hospital, Istanbul, and §Department of Neurology, Marmara University, Istanbul, Turkey

Background/Aims: Inflammatory bowel disease is a chronic, recurrent disorder that involves multiple organ systems. Polyneuropathy is the most common neurological manifestation. The aim of the present study was to investigate the relationship between polyneuropathy and inflammatory bowel disease. **Methods:** The study included 40 patients with inflammatory bowel disease (20 with ulcerative colitis and 20 with Crohn's disease) and 24 healthy controls. The patients had no clinical signs or symptoms of polyneuropathy. Nerve conduction studies were performed using an electroneuromyography apparatus. **Results:** Mean distal motor latencies, conduction velocities, and F wave minimum latencies of the right median nerve were significantly abnormal in the patient group, compared to the healthy controls ($p<0.05$). **Conclusions:** Some electrophysiological alterations were observed in chronic inflammatory bowel disease patients who showed no clinical signs. While investigating extra-intestinal manifestations in inflammatory bowel disease patients, nerve conduction studies must be performed to identify electrophysiological changes and subclinical peripheral polyneuropathy, which can subsequently develop. **(Gut Liver 2011;5:57-60)**

Key Words: Inflammatory bowel disease; Polyneuropathy; Electroneuromyography

INTRODUCTION

Inflammatory bowel disease (IBD) refers to a group of chronic, recurrent intestinal disorders, each with a complex pathogenesis; the 2 most common are Crohn's disease (CD) and ulcerative colitis (UC). The extra-intestinal manifestations of CD and UC are diverse. The exact incidence rate of neurological complications is unknown; reports vary from 0.2% to 35.7%, which could be due to selection bias or variations in disease definition.[1-4]

Peripheral polyneuropathy (PN) is one of the most frequently reported neurological complications. Several PN phenotypes have been described in IBD patients. Paresthesias and an increase in the threshold for temperature detection, which could be indicative of early PN, are common in patients with CD that have been treated with metronidazole (21-39%), but they are also seen in patients that have not received this medication (19%).[5] When the known risk factors for neuropathy are excluded, such as vitamin B12 deficiency and metronidazole exposure, the relationship between IBD and PN has been described only in case reports and small series. In the 2 largest retrospective series on the neurological complications of IBD the incidence of PN varied from 0.9% to 3.6%.[6-10]

The aim of the present study was to compare the electrophysiological findings in IBD patients that were in remission and asymptomatic for peripheral polyneuropathy with those in a control group, and to determine the existence of subclinical peripheral polyneuropathy.

MATERIALS AND METHODS

The study included 40 IBD patients 15-60 years of age (20 with UC and 20 with CD) that were follow-up at our hospital's Gastroenterology Department for 12 months and 24 healthy controls. The patients were evaluated according to Trulove-Witts and Crohn's Disease Activity Index (CDAI) score. CD patients with a CDAI score <150 and UC patients in remission were included in the study.

Serum levels of glucose, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, albumin, vitamin B12, and folate were measured, and hemogram, erythrocyte sedimentation rate, thyroid hormone levels, human immune deficiency virus, and hepatitis B and C tests were

Correspondence to: Züleyha Akkan Çetinkaya
Department of Gastroenterology, Kocaeli Derince Research and Education Hospital, Kocaeli, Turkey
Tel: +90-532-3734524, Fax: +90-262-233-54-90, E-mail: zakkan2000@yahoo.com
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performed in the patient and control groups. Alcohol and drug habituation were also noted.

Exclusionary criteria included diabetes mellitus, thyroid disease, renal disease, and vitamin B12 deficiency. Additionally, patients that used metronidazole and tumor necrosis factor (TNF)-α antagonists before the study began, or were receiving metronidazole and TNF alpha antagonists at the onset of the study were excluded.

The patients and controls were examined by the same neurologist, and detailed neurological examinations for probable symptoms of PN (muscle weakness, muscle atrophy, paresthesia, etc.) were performed. Motor and sensorial nerve conduction studies, and minimum F latency investigations were conducted on the right upper and lower limbs in the control and patient groups. These tests were performed in the neurophysiology laboratory of the Marmara University Faculty of Medicine using an electromyography apparatus (Medelec Synergy Electromyography Machine; Oxford Instruments, Oxford, UK). Nerve conduction studies were recorded with surface electrodes over the skin. Written informed consent was obtained from patients and controls. The study was approved by the Marmara University Ethics Committee.

Statistical analysis was performed using the NCSS 2007 program. Descriptive statistical methods (mean±SD) were used to evaluate the data. One-way analysis of variance (ANOVA) was used for between-group comparisons, Tukey's multiple comparison test was used for comparisons between subgroups, the independent t test was used for comparisons between dual groups, and the κ^2 test was used for comparison of qualitative data. Results were evaluated with statistical significance set at $p<0.05$.

RESULTS

The study included 20 UC patients (10 male and 10 female), 20 CD patients (8 male and 12 female), and 24 controls (9 male and 15 female). There weren't any significant differences between the UC, CD, and control groups in terms of gender, age, or median height and weight ($p>0.05$) (Table 1).

Neurological examination findings in the control and patient

Table 1. Demographic Characteristics of the Patient and Control Groups

	CD	UC	Control	p-value
Age, yr	39.60±11.20	35.85±9.13	36.58±8.69	0.43
Height, cm	163.55±5.62	163.54±6.15	163±6.90	0.95
Weight, kg	60.28±7.67	59.50±7.54	60.71±7.48	0.86
Sex Male	8	10	5	0.05
Female	12	10	19	
Disease duration, mo	75.2±64.36	59.5±44.72	0	0.67

CD, Crohn's disease; UC, ulcerative colitis.

Table 2. Motor Nerve Conduction Study Results for the CD, UC, and Control Groups

		CD	UC	Control	F	p-value
Right median	Distal latency	3.57±0.31	3.43±0.43	3.11±0.29	10.48	0.0001
	Distal amplitude	9.37±2.07	10.3±2.26	10.71±2.32	2.04	0.138
	Conduction velocity	57.45±3.86	58.74±3.9	59.92±4.68	1.89	0.159
	F response	26.23±1.61	26.5±1.66	24.78±1.32	8.24	0.001
Right ulnar	Distal latency	2.63±0.46	2.84±0.45	2.58±0.3	2.46	0.094
	Distal amplitude	10.48±1.83	10.99±1.75	10.5±1.98	0.48	0.618
	Distal conduction velocity	57.68±4.25	57.86±3.11	61.18±4.77	5.08	0.009
	Proximal conduction velocity	56.71±4.74	60.67±4.04	62.43±4.72	8.98	0.0001
	F response	26.36±1.47	26.52±1.47	25.57±1.59	2.54	0.087
Right tibial	Distal latency	4.05±0.66	4.2±0.79	3.93±0.54	0.93	0.399
	Distal amplitude	7.32±1.52	7.97±2.77	9.02±2.41	3.08	0.053
	Conduction velocity	47.58±3.67	46.3±2.35	49.08±3.99	3.58	0.034
	F response	47.12±3.13	46.33±4.32	46.88±2.52	0.29	0.75
Right peroneal	Distal latency	4.15±0.74	4.37±0.66	3.89±0.64	2.81	0.068
	Distal amplitude	4.92±1.22	5.08±1.29	6±1.83	3.47	0.038
	Distal conduction velocity	48.79±4.82	48.08±2.91	50.13±3.97	1.53	0.225
	Proximal conduction velocity	50.89±4.45	50.84±3.97	52.43±4.99	0.90	0.411
	F response	46.41±3.3	45.85±3.55	45.99±2.97	0.16	0.851

CD, Crohn's disease; UC, ulcerative colitis.

groups were normal, and no symptoms of neuropathy were observed. Neither the patients nor controls had alcohol habituation. There were not any significant differences between the CD and control groups in mean distal motor latency of the median nerve (p=0.0001), mean F latency of the median nerve (p<0.007), mean motor conduction velocity of the ulnar nerve (p<0.009), or mean compound muscle action potential (CMAP) amplitude of the peroneal nerve (p<0.05) based on motor nerve conduction studies. There were significant differences between the UC and control groups in terms of mean distal motor latency of the median nerve (p<0.019), mean F latency of the median nerve (p<0.001), mean motor conduction velocity of the ulnar nerve (p<0.028), and mean motor conduction velocity of the tibial nerve (p<0.026) based on motor nerve conduction studies (Table 2).

The results of sensorial nerve conduction studies showed that there were significant differences between the CD and control groups in terms of mean sensory nerve action potential (SNAP) amplitude of the median nerve (p<0.007), mean sensorial conduction velocity of the median nerve (p<0.0001), mean sensorial conduction velocity of the ulnar nerve (p<0.0001), mean SNAP amplitude of the sural nerve (p=0.05), and mean sensorial conduction velocity of the sural nerve (p<0.041). There were significant differences between the UC group and control group in mean SNAP amplitude of the median nerve (p<0.038), mean sensorial conduction velocity of the median nerve (p<0.036), mean sensorial conduction velocity of the ulnar nerve (p<0.004), mean SNAP amplitude of the sural nerve (p<0.039), mean sensorial conduction velocity of the right sural nerve (p<0.03), and mean sensorial conduction velocity of the left sural nerve (p<0.017) (Table 3).

There were not any significant differences in any of the parameters between the CD and UC groups based on motor and sensorial conduction studies (p>0.05).

DISCUSSION

The literature contains case reports and small series that report PN in IBD patients; however, its clinical and electrodiagnostic features are not well characterized. Polyneuropathy is a disease that primarily involves the distal parts of the upper and lower limbs, bilaterally. Demyelination and/or axonal degeneration in peripheral nerves can be seen. Delayed motor and sensorial conduction velocity, prolonged distal motor latency, and minimum F latency in nerve conduction studies indicate demyelinating polyneuropathy. Reduced CMAP and SNAP amplitude, normal conduction velocity in motor and sensory nerves, and normal minimum F latency suggest axonal polyneuropathy.[6,7] The F-wave is a late reflex used to test conduction status in proximal segments of peripheral nerves.

In the present study, abnormal electrophysiological findings were observed in the IBD patients who had no symptoms of PN and showed normal neurological examination results as compared with the controls. Electrophysiological findings obtained in the present study indicated the existence of axonal and demyelinating polyneuropathy in the IBD patients, in comparison with the controls. It is known that PN is an adverse effect of sulfasalazine and metronidazole treatment; however, neuropathy in association with mesalamine therapy is rare.[11] None of the patients in the present study were using sulfasalazine or metronidazole; however, they were using mesalamine or azathioprine. Serum vitamin B12 levels were normal in our UC and CD patients. Systemic diseases and/or the use of some agents that play a role in the etiology of PN were exclusionary criteria in the present study.

In the 2 largest retrospective series published to date the incidence of PN varied from 1.9% to 3.6%.[11,12] Lossos *et al*.[11] reported neuropathy in 1.9% of UC patients and only myelopathy, myopathy, and myasthenia gravis in CD patients (0% incidence

Table 3. Sensory Nerve Conduction Study Results for the CD, UC, and Control Groups

		CD	UC	Control	F	p-value
Right median	Latency	2.41±0.4	2.37±0.28	2.24±0.27	1.71	0.19
	Amplitude	47.45±12.37	42.08±13.4	54.86±14.09	5.09	0.009
	Conduction velocity	53.18±5.14	56.64±4.31	59.9±4.47	11.49	0.0001
Right ulnar	Latency	2.18±0.44	2.16±0.29	2.01±0.2	1.92	0.155
	Amplitude	39.13±12.61	34.61±11	42.12±12.67	2.09	0.132
	Conduction velocity	55.16±3.38	56.26±3.93	60.45±4.76	10.33	0.0001
Right sural	Latency	1.94±0.25	2±0.31	2.09±0.34	1.33	0.271
	Amplitude	21.12±7.31	23.9±8.48	27.79±7.75	4.02	0.023
	Conduction velocity	49.74±4.1	48.44±3.81	53.18±5.45	6.39	0.003
Left sural	Latency	1.93±0.29	2.1±0.3	2.07±0.31	1.76	0.181
	Amplitude	22.31±6.2	26.2±9.89	26.63±6.84	1.97	0.149
	Conduction velocity	51.27±4.78	48.35±4.32	52.46±5.21	4.12	0.021

CD, Crohn's disease; UC, ulcerative colitis.

of neuropathy), whereas Elsehety *et al*.[12] reported neuropathy in up to 3.6% of CD patients. In another study 13.4% of the IBD patients had otherwise unexplained large-fiber or small-fiber PN (7.3% with large-fiber SM PN) after excluding other known etiological or contributory factors for PN.[13]

Pathophysiologically, disorders of the peripheral and central nervous systems in association with IBD can be ascribed to at least 6 different mechanisms, which may be present in isolation or in combination: 1) malabsorption and nutrition, particularly vitamin deficiencies; 2) toxic metabolic agents; 3) infections as a complication of immunosuppression; 4) side-effects of medication or therapy; 5) thromboembolism; 6) immunological abnormalities. In addition to these -at least theoretically- clearly defined and distinct etiologies, neurologic signs, and symptoms may also be due to the neuronal influence of enteric disease on the nervous system (and vice versa).[10,14,15]

In conclusion, some electrophysiological alterations were observed in chronic IBD patients, even though there were no clinical signs. While investigating extra-intestinal manifestations in IBD patients, nerve conduction studies should be performed in order to identify electrophysiological changes and subclinical peripheral polyneuropathy which can subsequently develop.

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