Central and Peripheral Neurological Manifestations of Inflammatory Bowel Disease

İnflamatuvar Barsak Hastalığında Santral ve Periferik Nörolojik Belirtiler

Aslı Demirtaş, Münevver Gökyiğit, Canan Alkım*, Kemal Barkut, Ender Uysal**, Mehmet Sökmen*

Şişli Etfal Research and Training Hospital, Department of Neurology, Istanbul, Turkey
*Şişli Etfal Research and Training Hospital, Department of Gastroenterology, Istanbul, Turkey
**Şişli Etfal Research and Training Hospital, Department of Radiology, Istanbul, Turkey

Summary

Objective: The aim of this study is to evaluate the spectrum, frequency and coincidence of central and peripheral neurological involvement in a cohort of patients with inflammatory bowel disease (IBD).

Material and Method: Thirty consecutive patients, with a biopsy proven diagnosis of IBD (15 Crohn's disease, 15 ulcerative colitis) were enrolled and followed for a period of one year. Clinical neurological evaluations, electrodiagnostic examination and neuroimaging were performed in all patients. Neuroimaging findings were compared with an age- and sex-matched healthy control group.

Results: Among the 25 patients who completed the study, mild peripheral neuropathy was the most commonly encountered neurologic pathology. Twelve percent had distal symmetrical sensory and sensorimotor polyneuropathy, and 16% had mononeuropathy. Peripheral neuropathy predominantly affected females (p<0.05). Focal white matter lesions were demonstrated in 20.8% of the patients, which was not significantly different from the control group (p>0.05). Seizure disorder and steroid myopathy occurred once each during the study period. Concurrent central and peripheral nervous system pathologies were detected in three cases with longer disease duration. Two new neurological incidents were observed during the one year follow-up period and included cranial mononeuropathy and cerebral venous thrombosis in two patients.

Discussion: Our findings suggest higher vulnerability of the peripheral nerves among women throughout the course of inflammatory bowel disease. Focal white matter lesions appear unlikely to represent another neurological manifestation of IBD. Larger controlled prospective studies should be conducted in order to observe common etiological pathways and identify the nature of neurological involvement in IBD. (Turkish Journal of Neurology 2012; 18:145-150)

Key Words: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, neurological manifestations

Özet

Amaç: Bu çalışmanın amacı inflamatuvar barsak hastalığı (İBH) olan bir hasta kohortunda santral ve periferik nörolojik belirtilerinin dağılımı, frekansı ve birlikte görülenin değerlendirilmesidir.

Gereç ve Yöntem: Biyopsi ile doğrulanmış İBH tanısı olan 30 ardışık hasta (15 Crohn hastağı, 15 ülseratif kolit) çalışmayı dahil edilmiş ve bir yıl boyunca takipte olmuştur. Tüm hastaların klinik nörolojik değerlendirilmesi, elektrodiyagnostik muayene ve görüntüleme özellikleri incelenmiştir. Nörogörüntüleme bulguları yaş ve cinsiyet yönünden uyumlu sağlıklı gönüllülerden oluşan bir kontrol grubu ile karşılaştırılmıştır.

Bulgular: Çalışmayı tamamlayan 25 hasta en sık rastlanan nörolojik patoloji ilirli periferik neuropati olup distal simetrik duysal ve duysal-motor neuropati %12, mononüropati %16 oranında görülmüştür. Periferik neuropati kadınların erkeklerine göre anlamlı olarak daha sıkктır (p<0.05). Fokal akıllı lezyonların hastaların %20,8'inde gösterilmiş ve kontrol grubu ile aralarında anlamlı fark saptanamamıştır (p>0.05). Epileptik noyerter ve steroid kullanımlarına bağlı miyopati birer hasta teşpit edilmiştir. Hastalık süresi uzun olan üc hasta santral ve periferik sinir sistemini patolojileri birlikteliği saptanmıştır. Bir senelik takip sürecinde bir hasta kronik mononüropati ve başka bir hasta serebral versus tromboz olmak üzere ikisi yeni nörolojik olay gelişmiştir.


Anahtar Kelimeler: Inflamatuvar barsak hastalıkları, Crohn hastalığı, ülseratif kolit, nörolojik belirtiler

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Address for Correspondence /Yazışma Adresi: Münevver Gökyiğit MD Şişli Etfal Research and Training Hospital, Department of Neurology, Istanbul, Turkey
Phone: +90 212 373 50 00 E-mail: gokyigitmunever@gmail.com
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Introduction

Ulcerative colitis (UC) and Crohn’s disease (CD) are the two main forms of chronic idiopathic inflammatory bowel disease (IBD), which primarily affect the colon and terminal ileum, respectively. In addition to local intestinal complications, systemic or extra-intestinal complications occur frequently and may involve almost any organ system besides the bowel (1,2,3). Along with other extra-intestinal manifestations, a wide spectrum of neurological complications have been reported to occur as a consequence of immune-mediated neuropathy and cerebral demyelination, systemic/cerebral vasculitis or cerebrovascular disorders due to thromboembolism (4). The cause-and-effect relationship for these manifestations is rather complex and still largely unknown (5). Furthermore, it has not yet been evaluated whether the central and peripheral nervous system pathologies in IBD show any concurrence; these manifestations may be expected to coincide to some extent in individual patients if central and peripheral neurological complications share common etiological pathways.

The retrospective reports regarding the frequency of neurological manifestations show marked variations between 0.2% and 35.7% (3,6,7,8). Currently, prospective data regarding the neurological involvement in IBD is very limited and points to remarkably higher numbers of peripheral neuropathy compared to prior retrospective studies (9). Therefore, the actual frequency of the neurological manifestations still remains to be elucidated.

In the present study, we performed a detailed assessment of cerebral structure together with an electrodiagnostic study in an attempt to evaluate the spectrum, frequency and the coincidence of the central and peripheral neurological manifestations in a cohort of patients with IBD.

Materials and Methods

Patients

Thirty consecutive patients (15 Crohn’s disease, 15 ulcerative colitis) between the ages 18 and 65 and with a biopsy proven diagnosis of IBD were enrolled in this study. The patients with a history of diabetes, hypertension, hypothyroidism, vitamin B12/folic acid deficiency and/or metronidazole exposure were excluded to eliminate other possible etiological factors. The study was approved by the local ethics committee. All the patients signed a consent form to take part in the study after the study protocol was fully explained.

Neurological evaluations

Clinical neurological evaluations were performed by two neurologists. Personal history, duration of disease, medications and neurological symptoms were collected in an interview using a standard questionnaire. Patient demographics and medications are summarized in Table 1; additional drugs were azathioprine (n=5) and cyclosporine (n=1). Sensory and autonomic symptoms (e.g. orthostatic hypotension), symptoms related to systemic vasculitis (e.g. Behcet’s disease) were a particular point of focus. Motor abnormalities were established by manual testing of major muscle groups with the 6-level scheme proposed by the Medical Research Council (10) and functional motor assessments (e.g. ability to arise from a squatting position without using the arms). Detailed sensory examination included testing of vibration (extinction time with a standard 128 Hz tuning fork; tarsal, tibial and carpal sides bilaterally), proprioception, light touch, pain and temperature. The battery of laboratory tests for each patient included complete blood count, biochemistry, blood coagulation parameters, folic acid, vitamin B12, thyroid and parathyroid hormones and urine Ca levels. Routine follow-up evaluations were performed three times (months 0, 6, 12); patients were also requested to inform our clinic in case of a new-onset neurological complaint.

Electrodiagnostic study

The electrodiagnostic examination included standardized assessments of nerve conduction measurements and needle electromyography (using Medelec Sapphire 4ME electromyograph [Medelec Ltd, Surrey, UK]) for all patients. In all cases, motor conduction measurements included studies of median and ulnar nerves in the upper limb, and tibial and peroneal nerves in the lower limb. Distal latency, velocity of conduction and the combined muscle action potential amplitudes were measured. Sensory responses were recorded orthodromically from the upper extremities and antidromically from the lower extremities; median and ulnar nerves were studied for the upper limb while sural nerve was examined for the lower limb. The latency and amplitudes of sensory action potentials were estimated. Limb temperatures were continuously monitored during the examination. The needle electromyography studies included

<table>
<thead>
<tr>
<th>Table 1. Patient demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD (n=15)</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Female: Male</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
</tr>
<tr>
<td>Daily mesalazine (g)</td>
</tr>
<tr>
<td>Daily prednisolone equivalent (mg)</td>
</tr>
</tbody>
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Abbreviations: CD: Crohn’s disease, UC: ulcerative colitis, IBD: inflammatory bowel disease.
bilateral abductor pollicis brevis and abductor digiti minimi muscles for the upper extremities, and bilateral tibialis anterior and abductor hallucis muscles for the lower extremities. An extensive and complete evaluation was performed in patients with initial findings. All nerve conduction studies were evaluated according to the standard criteria (11,12,13).

**Neuroimaging**

Brain magnetic resonance imaging (MRI) were performed by 1.5-T Picker-Eclipse MRI equipment (Cleveland, Ohio). Axial spin-echo T1 weighted images with a magnetization transfer pulse (TR/TE, 560/15; number of excitations, 1; 5-mm-thick slices with 0.5-mm gap; 256x192 matrix; 24-cm field of view), axial, coronal and sagittal T2-weighted fast spin-echo (TR/TE, 4,800/102; number of excitations, 2; 5-mm-thick slices with 0.5-mm gap; 256x192 matrix; 24-cm field of view) and inversion recovery sequences with water suppression (FLAIR) (TR/TE, 8,800/102; number of excitations, 2; 5-mm-thick slices with 0.5-mm gap; 256x192 matrix; 24-cm field of view) were obtained to achieve a complete MRI examination for clinical purposes. The results were compared with an age and sex-matched control group comprising healthy individuals.

**Data analysis**

Statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Two-tailed nonparametric statistics (Fisher’s Exact Test) was employed to compare gender and group related effects. Statistical significance was set at p<0.05.

**Results**

Of the thirty patients included, five were lost to follow-up and a total of 25 patients (13 CD, 12 UC; mean age: 33.2±13.1; duration of disease: 6.8±6.3) completed the study (Table 2).

Patient histories included a deep venous thrombosis in a 20-year-old female, who had no other known predisposing factors (e.g. surgery, catheter or immobilization) but an acute attack of CD. One case with a history of seizure disorder is explained in detail below. Four patients were being treated for mood disorders; three suffered from major depression, one had depression and accompanying generalized anxiety disorder. In all cases, depression occurred during the course of IBD. Headache was present in four patients; one patient had classical migraine while the rest had tension type headaches. One patient had a history of meningitis 12 years prior to the onset of IBD. None of the other patients had a significant medical history. No autonomic complaints were reported. Family history included cerebrovascular disorders in first-degree relatives of two patients.

Neurological examination findings are summarized in Table 2. In regards to the laboratory examination, anemia was detected in six patients. Coagulation abnormalities were present in a total of seven and fibrinogen was the most frequently affected parameter. Calcium metabolism was affected in seven cases; PTH levels were elevated in four patients while urine Ca levels were below normal in five. None of the patients were shown to have a folic acid or vitamin B12 deficiency.

### Table 2. Clinical, electrodiagnostic and neuroimaging features of the patients with IBD

<table>
<thead>
<tr>
<th></th>
<th>CD (n=13)</th>
<th>UC (n=12)</th>
<th>IBD (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NE (n=25)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>5</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Abnormal vibration</td>
<td>5</td>
<td>2</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Abnormal vibration and diminished DTR</td>
<td>1</td>
<td>2</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Proximal weakness in extremities</td>
<td>1</td>
<td>-</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Ankle dorsiflexion impairment, steppage gait</td>
<td>1</td>
<td>-</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>-</td>
<td>1</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Uni/bilateral equivocal plantar response</td>
<td>1</td>
<td>2</td>
<td>3 (12%)</td>
</tr>
<tr>
<td><strong>EDX (n=25)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8</td>
<td>7</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>1</td>
<td>1</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Sensory motor polyneuropathy</td>
<td>1</td>
<td>-</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Mononeuropathy</td>
<td>1</td>
<td>3</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Neurogenic changes of motor unit potential</td>
<td>1</td>
<td>1</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Myopathy (steroid-induced)</td>
<td>1</td>
<td>-</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>MRI (n=24)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>11</td>
<td>8</td>
<td>19 (79.2%)</td>
</tr>
<tr>
<td>Focal white matter lesions</td>
<td>1</td>
<td>4</td>
<td>5 (20.8%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CD: Crohn’s disease, UC: ulcerative colitis, IBD: inflammatory bowel disease, NE: neurological examination, EDX: electrodiagnostic examination, MRI: cranial magnetic resonance imaging.
Three patients (12%) had large-fiber neuropathy, 2 with sensory and one with sensorimotor polyneuropathy, whereas 4 patients (16%) had mononeuropathies including bilateral peroneal nerve entrapment (n=1), carpal tunnel syndrome (n=1), and median nerve mononeuropathy (n=2). None of the electrodiagnostic examinations demonstrated demyelinating features. Steroid myopathy was detected in one patient, who was on long-term systemic steroid therapy. Nerve conduction studies were normal in five patients that had positive sensory symptoms or reduced vibration sense clinically. When compared, females were found to be significantly more affected than males (p<0.05).

Focal white matter lesions (FWML) were detected in a total of 5 patients (20.8%) and 3 healthy controls (12%) however there was no statistically significant difference (p>0.05). Typical focal white matter lesions of a patient are illustrated in Figure 1.

Concurrent central and peripheral neurological pathologies were detected in three patients, who had relatively longer durations of disease (mean: 10 years). The first case suffered from three episodes of generalized tonic-clonic seizures on the same day, during an acute exacerbation of CD. Her subsequent EEG and MRI were found to be normal; she was not on any antiepileptic medication and had no further seizures. Her neurological and electrodiagnostic examinations revealed concurrent bilateral peroneal nerve entrapment. The other two cases had FWML with median nerve mononeuropathies and they both had UC.

Two new neurological incidents occurred during the one year follow-up period. One male with UC had cerebral sinus thrombosis while the disease was in remission (Figure 2). Comprehensive screening regarding the etiology revealed negative tests for vasculitis, and showed Factor-V-Leiden mutation. Another patient with UC developed mononeuropathy of CN VII, in the absence of infectious etiology or Melkerson-Rosenthal syndrome.

**Discussion**

This study aimed to evaluate the extent of central and peripheral neurological involvement related to IBD, and to search for clinical observational evidence whether manifestations in the central and peripheral nervous system show a degree of coincidence. Our findings suggest higher vulnerability of the peripheral nerves among women throughout the course of this inflammatory disease while we found no evidence indicating an excess of focal white matter lesions (FWML) in favor of IBD.

We detected three cases with concomitant central and peripheral nervous system manifestations and this finding needs to be further investigated. Seizure disorders in IBD are considered to occur secondary to structural or metabolic reasons (4). It seems likely that coincidental involvement of peripheral nerves may also be related to metabolic alterations; the nerves may be affected at the entrapment sites due to mechanical effects or diabetes-like inflammation (14). On the other hand, concurrence of cranial mononeuropathies and FWML was documented in a case with UC, and was suspected to occur due to immunologic mechanisms (15). The association of mononeuropathy and FWML in our cases may be incidental or related to common risk factors, such as longer duration of the disease, drugs or metabolic alterations, as well as immune mechanisms.

Peripheral neuropathy is among the most frequently reported neurological pathologies in IBD and its frequency varies between 0.9-3.6% based on retrospective data (6,7,16,17,18,19). A recent prospective study, which particularly focused on peripheral neuropathy in a cohort of 82 patients with IBD, reported considerably higher frequency of peripheral neuropathy in IBD (9). Despite the smaller sample size, the frequencies detected in our study appears comparable with this prospective study: unexplained axonal polyneuropathy (13.4% small and large-fiber vs. 12% large-fiber), demyelinating neuropathy (1.2% vs. 0%), mononeuropathies (13.5% vs. 16%). The current study also indicated that peripheral neuropathy was generally mild with predominantly sensory symptoms and significantly more common.
in females. The latter finding is supported by a recent retrospective study, which searched for the neurological manifestations of IBD and reported a slight overall female predominance (20). In regards to further follow-up, repeated investigations are required for patients who had a normal electrodagnostic examination albeit their symptoms and/or signs suggestive of peripheral neuropathy.

The investigation of the presence of FWML in IBD patients has so far yielded contradictory results. Although Geissler et al. reported a significant increase in FWML (21), a subsequent study by Hart et al. did not confirm their findings (22). While there are case reports which relate FWML with IBD, there is currently no sufficient prospective evidence for a conclusion (23). The present study showed results similar to those of Hart et. al. and suggested a normal frequency of FWML in IBD. FWML may be due to atherosclerosis, thrombosis, vasculitis or demyelination (22,23,24,25); the exact pathogenesis and clinical significance still remain controversial. The use of novel neuroimaging techniques, such as diffusion tensor imaging, may provide more insight on the microstructure and anatomy of affected white matter (26,27).

Screening tests revealed a Factor V Leiden mutation in the patient with cerebral venous thrombosis. The presence of Factor V Leiden mutation was reported to increase the relative risk of venous thrombosis in patients with IBD (28). Thrombembolic complications occur in 1.3% to 6.4% of adult patients with IBD and less frequently include cerebral vessels (29). The underlying mechanism for thrombosis is usually related to the clinical activity of the disease, which leads to a hypercoagulable state due to alterations in coagulation factors, fibrinolysis, platelet number and activity, cellular procoagulant mediators, blood rheology and vascular endothelial integrity (30,31). While these complications are more frequent during the active stage of the disease, events reported during remission point to a persistent procoagulant status (32).

In conclusion, our results indicate a higher susceptibility of female patients to peripheral neuropathy in the course of IBD and provide support that peripheral neuropathy in IBD may be more frequent than recognized. On the contrary, the findings from this study do not suggest that FWML may represent another neurological manifestation of IBD. A degree of coincidence between central and peripheral involvement in IBD seems possible and needs to be further studied. The strengths of this observational study are its prospective nature and the investigation of both central and peripheral nerve disorders and their concurrence in IBD for the first time. The major limitation of this study lies in its small sample size. Although previously reported, we did not detect any cases with multiple sclerosis or myelopathy in this study (6,33,34). This may be related to our small sample size or exclusion of patients with B12 and folate deficiency. Regarding our methodology, evaluation of small-fiber (sensory and autonomic) neuropathy (35) and sensorineural hearing loss (36) could have provided additional valuable information. Despite these caveats, however, we believe these findings are worthy of further study. Further randomized controlled prospective trials with larger cohorts of patients are warranted to illuminate the nature of neurological involvement in IBD.

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References