



## Irritable Bowel Syndrome In Multiple Sclerosis Patients and Its Relation To Attacks

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### Abstract

**Objective:** Knowledge about bidirectional microbiome-gut-brain interactions has gradually increased in multiple sclerosis (MS) and many other diseases. The aim of this study is to determine the prevalence of irritable bowel syndrome (IBS) in MS patients, to compare with a control group and to identify the relationship between MS attacks and gastrointestinal (GI) symptoms.

**Methods:** Patients with at least a two-year diagnosis of relapsing-remitting MS (RRMS) from our outpatient clinic were included in the study. The duration of disease, expanded disability status scale and time of MS attacks were recorded. ROME- IV criteria were used for diagnosis of IBS. Results were compared with the control group. IBS symptoms prior to, during and after an attack were recorded and their relationship to MS attacks was investigated.

**Results:** 93 RRMS patients and 101 controls were included in this study. The prevalence rate of IBS was found to be 16.1% (n=15) in MS patients and 8.9% (n=9) in the control group. No significant difference can be found in IBS prevalence rate between MS patients and controls (p=0.127). MS attacks had no significant effect on constipation, diarrhea, abdominal pain and distention.

**Conclusion:** This study showed that MS patients have a similar IBS prevalence to the control group. In addition, MS attacks have no significant effect on GI symptoms.

**Keywords:** Abdominal Pain, Constipation, Diarrhea, Irritable Bowel Syndrome, Multiple Sclerosis

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## Multipl Skleroz Hastalarında İrritabl Barsak Sendromu ve Ataklarla Olan İlişkisi

### Öz

**Amaç:** Multipl skleroz (MS) ve diğer hastalıklarda; mikrobiyom-barsak ve beyin iki yönlü etkileşimi konusundaki bilgi birikimi giderek artmaktadır. Bu çalışmanın amacı MS hastalarında irritabl barsak sendromu prevalansını belirlemek, kontrol grubu ile karşılaştırmak ve MS atakları ile gastrointestinal semptomlar arasındaki ilişkiyi belirlemektir.

**Yöntemler:** Kliniğimizde en az 2 yıldır yineleyici MS (RRMS) teşhisi ile izlenen hastalar çalışmaya dâhil edildi. Hastalık süresi, özürülük skalası (EDSS) ve MS atak zamanları kaydedildi. İrritabl barsak sendromu tanısında Roma-IV kriterleri kullanıldı. Sonuçlar kontrol grubu ile karşılaştırıldı. MS atakları öncesindeki, atak sırasındaki ve sonrasındaki gastrointestinal semptomlar kaydedilerek MS atakları ile ilişkisi araştırıldı.

**Bulgular:** 93 RRMS hastası ve 101 kontrol çalışmaya dâhil edildi. MS hastalarında irritabl barsak sendromu prevalansı %16,1 (n=15) bulunurken, kontrol grubunda %8,9 (n=9) bulundu. İrritabl barsak sendromu sıklığı açısından MS hastaları ve sağlıklı kontroller arasında istatistiksel olarak anlamlı farklılık izlenmedi (p=0,127). MS ataklarının ishal, kabızlık, şişkinlik ve karın ağrısı üzerine anlamlı etkisi bulunamadı.

**Sonuç:** Bu çalışma MS hastalarındaki irritabl barsak sendromu sıklığının sağlıklı kontroller ile benzer olduğunu göstermiştir. Ayrıca MS ataklarının gastrointestinal semptomlar üzerine anlamlı etkisi yoktur.

**Anahtar kelimeler:** İshal, kabızlık, karın ağrısı, irritabl barsak sendromu, multipl skleroz.

## INTRODUCTION

Comorbidity has become a subject of increasing interest in multiple sclerosis (MS) due to the emergence of evidence that comorbidity is linked with diagnostic delay, the progression of disability, health-related quality of life and the progression of lesion burden on magnetic resonance imaging (MRI)<sup>1-5</sup>. With that said, the reported prevalence of comorbidity in MS varies greatly, this depends on the number and type of conditions considered along with the characteristics of the study population<sup>6,7</sup>.

Neurologists in their examination of MS patients often focused on sensorial and motor symptoms. Over the last twenty years, gastrointestinal (GI) symptoms have been noticed and used in patient assessments. GI symptoms such as constipation, dysphasia and fecal incontinence are observed in the majority of MS patients. By means of these, connections between the intestine and the brain have been researched. Knowledge about bidirectional microbiome-gut-brain interactions has gradually increased in MS and many other diseases. It is indicated that a disordered brain may cause gastrointestinal symptoms by affecting motility, acid secretion and mucosal

immune response through sympathetic and parasympathetic branches of its autonomic nervous system<sup>8-10</sup>.

Studies on irritable bowel syndrome (IBS) in MS patients are limited and these studies were carried out alongside other comorbid conditions. The results of these studies recorded a changeable prevalence rate of IBS in MS patients<sup>11</sup>.

The first aim of this study is to validate the results of previous studies by investigating and comparing the prevalence rates of IBS in MS patients and controls. The second aim is to bring gastrointestinal symptoms of MS patients to light by investigating the relationship between GI symptoms and MS attacks.

## METHODS

The MS patients who participated in this study were recruited from the outpatient clinic of a university hospital. All participating patients were existing patients at our clinic and were already being followed by our clinic and our neurologists.

The Rome- IV criteria were used to diagnose IBS<sup>12</sup>. A questionnaire was prepared by deriving Turkish validated form of the adult functional GI disorders Questionnaire<sup>13</sup>. The questionnaire includes 5 subgroups one of which is aimed at IBS.

The IBS diagnostic criteria: Recurrent abdominal pain at least 1 day per week in the last 3 months (on average), associated with 2 or more of the following criteria: 1) related to defecation, 2) associated with a change in frequency of stool, 3) associated with a change in form of stool. Criteria are currently fulfilled 3 months with symptom onset at least 6 months prior to diagnosis.

Inclusion criteria: Patients above 17 years old and having a minimum of a 2-year RRMS diagnosis were included. The control group consisted of hospital employees over the age of 18 with no history of systemic illness and who do not currently take any medication.

Exclusion criteria: The presence of alarm symptoms (persistent constipation, persistent diarrhea, anemia, fever, weight loss, a family history of malignancy, high ESR), pregnancy, chronic medical disease, persistent drug usage, teriflunamide and dimethyl fumarate usage for MS patients.

The diagnostic criteria of McDonald were used for the diagnosis of MS<sup>14</sup>. Kurtzke's Expanded Disability State Score (EDSS) was used to assess the severity of the disease<sup>15</sup>. The patients' age, gender, duration of disease, EDSS score and Disease-Modifying Drugs usage were recorded. GI symptoms (constipation, abdominal distention, abdominal pain and diarrhea) experienced 1 week prior to, during and 8 weeks after MS attacks were also recorded. In case of an MS attack, patients were evaluated before any steroid use.

### **Statistical Analysis**

The sample size was calculated by OpenEpi version 3.01. Sample size was calculated

minimum as 98 patients in each group with 95% two-sided significance level and 80% power if the percentage of IBS prevalence were 19.3% with MS and 6% with a control group. The assumptions regarding the estimated between-group difference were based on epidemiological studies<sup>11</sup>.

Statistical analysis was performed using the PASW Statistics 18.0 software. Frequency distributions and percentages were calculated. T-test, chi-square test and Cochran's test were performed. Results were considered to be statistically significant at the level of  $p < 0.05$

During the study, 110 MS patients and 110 healthy controls were assessed for eligibility. 17 persons declined to participate. The participation rate was 92.3%. 9 participants were excluded because of pregnancy, medication overuse and malignancy. Patients and healthy controls were matched for age and sex. 93 RRMS patients and 101 controls were included in this study. This study was approved by the local ethics committee. The approval number is 2016/514/93/2.

### **RESULTS**

93 RRMS patients and 101 controls were included in this study. All patients and healthy controls were from the Turkish population. The mean age of MS patients was  $36.84 \pm 10.6$  years, 65 patients were female and 28 patients were male. The female/male ratio was 2.3. The mean age of controls was  $36.84 \pm 9.0$  years, 77 were female and 24 of them male. The female/male ratio was 3.2. There was no statistically significant difference between the mean age of the MS patients and healthy controls ( $p = 0.998$ ). Similarly, there were no significant differences between the female/male ratio of the two groups ( $p = 0.319$ ). The demographical and clinical characteristics of the two groups are shown in Table 1. Disease-modifying treatments of MS patients are shown in Table 2.

**Table I:** The demographical and clinical characteristics of the two groups.

|                    | MS Patients(n=93) | Controls(n=101) | p values           |
|--------------------|-------------------|-----------------|--------------------|
| Mean Age           | 36.84±10.6        | 36.84±9.0       | 0.998 <sup>1</sup> |
| Female/male ratio  | 2.3               | 3.2             | 0.319 <sup>2</sup> |
| IBS prevalence (%) | 16.1%             | 8.9%            | 0.127 <sup>3</sup> |

p1: student t test, p2: chi-square test, p3: chi-square test

**Table II:** Disease Modifying Treatments of MS patients

|                    | Interferon-β1a | Interferon-β1b | Glatiramer Acetate | Natalizumab | Fingolimod | None |
|--------------------|----------------|----------------|--------------------|-------------|------------|------|
| Number of Patients | 21             | 19             | 17                 | 19          | 16         | 1    |

The prevalence rate of IBS in MS patients was found to be 16.1% (n=15) and 8.9% (n=9) in the control group. There was no statistically significant difference in the IBS prevalence rate between MS patients and controls (p=0.127).

### Factors related to IBS in MS patients

In MS patients, the mean duration of the disease was found to be 6.1±4.7 years. There was no statistically significant difference between the duration of MS in those with IBS and those without (p=0.567). The mean EDSS of the patients was 3.1±1.4. The difference in EDSS in MS patients with IBS and those without was not statistically significant (p=0.894).

### Evaluation of GI symptoms

Constipation was observed in 29 patients one week before attacks whilst observed in 26

patients during attacks. It was observed in 27 patients 8 weeks after attacks. There was no statistically significant difference (p = 0.717).

Diarrhea was seen in 10 patients one week prior to attacks. It was recorded in 10 patients during attacks. It was seen in 5 patients 8 weeks following attacks. There was no statistically significant difference (p= 0.082).

Abdominal pain was observed in 16 patients 1 week prior to attacks and in 14 patients during attacks. 10 patients experienced these symptoms 8 weeks following attacks. There was no statistically significant difference (p= 0.193).

Abdominal distention was experienced in 25 patients 1 week prior to attacks and 25 patients experienced this during attacks. 22 patients experienced abdominal distention 8 weeks following attacks. There was no statistically significant difference (p=0.651).

The relationship between gastrointestinal symptoms and MS attacks is illustrated in Table 3.

**Table III:** The relationship between gastrointestinal symptoms and MS attacks

|                       | Prior to Attacks | During Attacks | After Attacks | p value* |
|-----------------------|------------------|----------------|---------------|----------|
| Constipation n, (%)   | 29, (31.2%)      | 26, (27.9%)    | 27, (29.0%)   | 0.717    |
| Diarrhea n, (%)       | 10, (10.8%)      | 10, (10.8%)    | 5, (5.4%)     | 0.082    |
| Abdominal Pain n, (%) | 16, (17.2%)      | 14, (15.1%)    | 10, (10.8%)   | 0.193    |
| Distention n, (%)     | 25, (26.9%)      | 25, (26.9%)    | 22, (23.7%)   | 0.651    |

\* Cochran test was used.

## DISCUSSION

Our study shows no difference in the IBS prevalence rate between MS patients and the control group. However, even though the prevalence rate of IBS in MS patients is not statistically significant, its frequency is higher in MS patients. Disease duration and severity have

no link to IBS in MS patients. Results indicate no correlation between GI symptoms such as constipation, diarrhea and abdominal distention and MS attacks. Although the results do not support any statistical link between GI symptoms and MS attacks, symptoms are shown to decrease following an attack.

There are two IBS prevalence studies carried out on the Turkish adult population. One of them was conducted as a face-to-face study in Sivas city center (Middle Anatolia) in 2003. In this study, the IBS prevalence rate was recorded as 19.1%<sup>16</sup>. The second study was a self-reported study carried out in 2004 in an urban area in Elazığ city close to Sivas. Their study recorded that the prevalence rate of IBS was 6.3%<sup>17</sup>. Both studies used the Rome-II diagnostic criteria. The use of Rome-II diagnostic criteria which covers a longer duration of abdominal pain may be one of the reasons for the difference in prevalence rates. Our control group prevalence rate of 8.1% was very similar to the prevalence rate in the Elazığ study.

The other prevalence studies on IBS in MS patients are mainly based in Western countries. None of these studies excluded other comorbidities such as hypertension, diabetes mellitus and regular medicine use. A population-based study showed that all GI symptoms were more frequent in diabetic patients than the control groups<sup>18</sup>. In addition, it has been reported that antihypertensive drugs may have an effect on intestinal motility along with kidney<sup>19,20</sup>.

Marrie et al. found that IBS is common in the MS population and occurs more than accepted when compared to the general population<sup>11</sup>. T lymphocytes might be responsible for this phenomenon and the pathogenesis with the defects of Fas protein<sup>21</sup>. Some studies on gastrointestinal symptoms in MS patients recorded a 9.4% to 19.3% rate after an MS diagnosis<sup>22-24</sup>. A population-based study

reported a prevalence of 12.2% whilst another recorded a 1.09% prevalence rate at MS symptoms onset increasing to 1.6% at MS diagnosis<sup>25,26</sup>. A self-reported study in MS patients recorded at least one co-morbidities in 66% of all participants. Most commonly recorded comorbidities were %37 hypercholesterolemia, %30 hypertension, %16 arthritis, %13 IBS, %13 lung disease<sup>24</sup>. A study indicated a 5.9% IBS prevalence rate in all MS types while using medical records. The same study showed a 9.4% IBS prevalence when using the questionnaire<sup>22</sup>.

It is very difficult to compare our results with other studies because none of these studies excluded other comorbidities which can have an effect on gastrointestinal symptoms. In addition, the diagnostic criteria and methods of their studies are different.

### **Limitations of the study**

This was a retrospective study that adopted a self-reported methodology. MS patients who had cognitive dysfunction may have had recall problems. Also, the selection of healthy controls may create a bias. Another limitation is that psychiatric evaluation of patients and data about physical activities that could affect IBS are not available. Additionally, the effects of different disease-modifying therapies on IBS symptoms have not been investigated.

### **Strengths of the study**

A major strength is that this study was carried out by a neurologist using Rome-IV diagnostic criteria. Another additional strength is that all other comorbidities were excluded.

### **CONCLUSION**

This study recorded that the prevalence rate of IBS in MS patients does not differ much from the control group. There is no relationship between MS attacks and IBS symptoms in patients. Further prospective studies investigating gastrointestinal symptoms and consisting of

more participants may shed more light on this issue.

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**Declaration of Conflicting Interests:** The authors declare that they have no conflict of interest.

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