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RESEARCH ARTICLE

Relationship Between Fatigue and *Helicobacter pylori* Infection in Patients with Multiple Sclerosis

Mustafa Cam[1], Alper Akcalı[2]

[1]Canakkale Onsekiz Mart University Faculty of Medicine, Department of Neurology, Canakkale, Turkey
[2]Canakkale Onsekiz Mart University Faculty of Medicine, Department of Microbiology, Canakkale, Turkey

Abstract

Objective: One of the common complaints in patients with multiple sclerosis (MS) is fatigue. Studies have reported that 75-87% of patients complain of fatigue. In our study, the possible relationship between fatigue severity and *Helicobacter pylori* (*H. pylori*) infection in patients with MS was investigated.

Materials and Methods: The fatigue severity scale was applied to patients who presented to the neurology clinic during the study to assess fatigue. The Beck Depression Inventory was used to evaluate depression, and the Epworth sleepiness scale was used to assess sleepiness. Serum quantitative Immunoglobulin G (IgG) levels for *H. pylori* were measured using the enzyme-linked immunoassay. IBM SPSS Statistics version 26.0 was used for analysis.

Results: The MS and control groups consisted of 105 and 79 people, respectively. *H. pylori* seropositivity was not significant in the intergroup analysis. In the MS group, *H. pylori* IgG level was significantly higher in patients with fatigue than in patients without fatigue. The Beck Depression Scale and Expanded Disability Status Scale scores were significantly higher in the MS group.

Conclusion: Individual, environmental, and developmental factors were thought to play a role in fatigue, which is common in patients with MS. Another factor could be depression. In our study, *H. pylori* IgG levels were significantly higher in patients with fatigue in the MS group. This result suggests that *H. pylori* may be a factor in the pathophysiology of fatigue.

Keywords: Fatigue, multiple sclerosis, *Helicobacter pylori*

Introduction

Multiple sclerosis (MS) is a degenerative, autoimmune disease of the central nervous system characterized by inflammation and demyelination (1). Genetic and environmental factors that cause immune defects are thought to lead to MS development (2). Lesions known as MS plaques are associated with inflammation and loss of axons, leading to signs involving the entire central nervous system (3). MS is a heterogeneous disease and causes clinical symptoms and signs depending on the involved regions, which can be related to motor, coordination, sensory, and visual pathways (4). Fatigue was reported to be an irritating symptom that affected 50-80% of patients with MS (5).

Fatigue is defined as a subjective emotional state that is thought to develop with different pathophysiological mechanisms in MS and causes difficulty in initiating or maintaining an effort that one wishes to voluntarily realize (6). Fatigue may be due to the disease itself, or it may be caused by secondary causes. Although its etiology is not exactly known, individual, environmental, and developmental factors were thought to play a role (7).

Helicobacter pylori (*H. pylori)* is a Gram-negative bacterium that exhibits broad-spectrum pathogenicity that is not limited to the gastrointestinal tract, although it is mainly found in the human stomach (8,9). Studies have shown that it is associated with some diseases outside the gastrointestinal system, such as migraine, coronary heart disease, cirrhosis, pancreatic cancer, and stroke (10). Thus, this study aimed to contribute to the etiology of fatigue by investigating the possible relationship between fatigue, which is a very common complaint in patients with MS, and *H. pylori* infection.

Address for Correspondence: Mustafa Cam, Canakkale Onsekiz Mart University Faculty of Medicine, Department of Neurology, Canakkale, Turkey
E-mail: mustafacam20@hotmail.com **ORCID-ID:** orcid.org/0000-0003-3116-203X
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Materials and Methods

This case-control study was conducted on patients who applied to our clinic between January 2019 and September 2020. The study included a patient group diagnosed with MS and clinically isolated syndrome according to the 2017 revised McDonald criteria (11). The control group included patients who stated that they were tired when presenting to the neurology outpatient clinic, but did not have MS or any other known chronic/acute disease diagnosis.

The Turkish version of the Fatigue Severity Scale (FSS) was used to determine the fatigue levels of the patients (12). Each question was scored between 1 (totally disagree) and 7 (totally agree), and patients with an FSS score of ≥4 were considered to have fatigue (13). The Beck Depression Inventory, whose Turkish validity and reliability were confirmed, was used to assess depression (14). Clinical disability status was evaluated using the Expanded Disability Status Scale (EDSS) (15). Epworth sleepiness scale (ESS) was used to assess sleepiness, with the following scoring guide: 0-5, normal; 6-10, increased daytime sleepiness; 11-12, moderate daytime sleepiness; 13-15, moderate sleepiness; and 16-24, severe sleepiness. The Turkish version of the ESS was used for evaluation (16). Patients' blood samples (5-10 mL) were obtained, and sera were separated with 3,350 g for 15 min by centrifugation. All samples were stored at -80 °C until enzyme immunoassays (EIAs) were performed. *H. pylori* Immunoglobulin G (IgG) levels were measured using Dia. Pro HP IgG ELISA kit (Diagnostic Bioprobes Srl, Milano, Italy). EIAs were performed according to the manufacturer's instructions. Assay washings were made using BioTek ELx50 microplate washer, and microplate readings were performed using BioTek EL800 (Biotek, Winooski, USA) devices. Samples with an IgG level ≥5 arbU/mL were accepted as seropositive for *H. pylori*.

The exclusion criteria were as follows: pregnancy; demyelinating diseases other than MS; recent use of amantadine, modafinil, and corticosteroids; and psychotic disorder.

The study was conducted following the approval of the Canakkale Onsekiz Mart University Clinical Research Ethics Committee (decision number: 2018-20, date: 11.14.2018). All patients were informed about the study and a written consent form was signed by all participants.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normal distribution was assessed using Kolmogorov-Smirnov test and Shapiro-Wilk-Francia test. The Mann-Whitney U test and Monte Carlo test were used to compare two independent groups. After controlling for sex, the partial correlation test was used to examine it with the EDSS score. Monte Carlo simulation technique, Pearson chi-square, and Fisher-Freeman-Holton tests were used to compare categorical variables. The ratios were compared with each other and expressed according to Benjamini-Hochberg corrected p-value results. In the tables, quantitative variables are presented as mean ± standard deviation. Categorical variables are indicated as n (%). Confidence analysis of the variables was at the level of 95%, and p-value of <0.05 was considered significant. All patients with MS who applied during the study period were enrolled in the study, so the sample size was not calculated.

Results

A total of 105 and 79 individuals were included in the patient and control groups, respectively. The female-to-male ratio was 77:28 (73.3%) in the MS group and 50:29 (63.3%) in the control group. The mean age values were 42.47±9.75 and 44.82±13.61 years for the MS and control groups, respectively. The groups did not differ significantly in terms of age and sex. *H. pylori* seropositivity was detected in 73 (69.5%) patients in the MS group and 61 (77.2%) patients in the control group (Table 1).

No significant difference was found between the groups in terms of *H. pylori* seropositivity. The Beck Depression and EDSS scores were higher in the MS group than in the control group. The ESS scores were not significant in the intergroup analysis (Table 1). When MS and control groups were divided into two groups according to the severity of fatigue, the mean age and EDSS scores in patients with MS and fatigue were significantly higher than in those in the group without fatigue (Table 2).

While a significant positive correlation was found between EDSS scores and mean age, a significant negative correlation was found with ESS score. No significant relationship was noted between EDSS scores and *H. pylori* IgG levels and Beck Depression Scale score (p=0.240, p=0.463) (Table 3).

Discussion

Fatigue significantly impairs the quality of life of patients with MS. It is believed to be distinctly different from fatigue seen in other chronic conditions described by healthy individuals, with its frequency, severity, and long-term persistence. Moreover, two-thirds of these patients stated fatigue as one of the three worst symptoms of their illness (17).

In our study, 69% of the patients in the MS group had fatigue. FSS scores were not significantly different in the analysis between the control and MS groups. The EDSS scores in patients with MS and fatigue were significantly higher than in those without fatigue. These findings suggest that the fatigue that develops in patients with MS is related to its unique characteristics and impairs the quality of life.

Another factor that causes fatigue can be depression. Depression can manifest itself in fatigue, and symptoms can be confused with fatigue. This makes it difficult to distinguish depressive symptoms from MS-related fatigue (18). Depression

Table 1. Clinical characteristics of the study group

	Total (n=184)	Control group (n=79)	Patient group (n=105)	p-value
Age median (Q1/Q3)	44.5 (36/51)	46 (40/51)	43 (33/51)	0.134[u]
Sex, n (%)				0.151[p]
Female	127 (69.0)	50 (63.3)	77 (73.3)	
Male	57 (31.0)	29 (36.7)	28 (26.7)	
***Helicobacter pylori*,** median (Q1/Q3)	41.65 (13.6/72.2)	53.5 (11.8/84.9)	37.4 (17.1/62)	0.427[u]
***Helicobacter pylori* presence**, n (%)				0.315[p]
Positive	50 (27.2)	18 (22.8)	32 (30.5)	
Negative	134 (72.8)	61 (77.2)	73 (69.5)	
Fatigue, n (%)				0.095[p]
Non-fatigue	73 (39.7)	37 (46.8)	36 (34.3)	
Fatigue	111 (60.3)	42 (53.2)	69 (65.7)	
Beck, n (%)				**0.036[ff]**
Minimal depression	61 (33.2)	21 (26.6)	40 (38.1)	ns
Mild depression	86 (46.7)	46 (58.2)	40 (38.1)	**0,007**
Moderate depression	36 (19.6)	12 (15.2)	24 (22.9)	ns
Severe depression	1 (0.5)	0 (0.0)	1 (1.0)	ns
Epworth, n (%)				0.318[p]
Rare	135 (73.4)	61 (77.2)	74 (70.5)	
Often	49 (26.6)	18 (22.8)	31 (29.5)	
EDSS, median (Q1/Q3)	0 (0/2)	0 (0/0)	1 (0.5/4.5)	**<0.001[u]**

[u]Mann-Whitney U test (Monte Carlo), [p]Pearson chi-square test (Monte Carlo), [ff]Fisher-Freeman-Halton test (Monte Carlo); post hoc test: Benjamini-Hochberg correction, Q1: 25th percentile; Q3, 75th percentile, ns: Not significant, EDSS: Expanded Disability Status Scale

is seen in up to 50% of patients with MS (19). In this study, Beck Depression and EDSS scores were significantly higher in the MS group than in the control group.

H. pylori is found in >50% of humans in the gastric mucosa (20). Studies have shown that it is associated with neurodegenerative diseases (21). Some studies have investigated the serology of MS and *H. Pylori;* however, conflicting and limited data have been published regarding the correlation between *H. Pylori* seropositivity and MS (22-24). *H. pylori* is quite high in the population and can become chronic. In addition to chronic diseases, *H. pylori* is also known to affect the development of anemia, peptic ulcer, and cancer (25). Various hypotheses such as bacterial translocation and gut microbiota dysbiosis have been put forward to explain the possible mechanism of fatigue (26,27). The relationship between fatigue and immuno-inflammatory pathways has begun to attract more attention from clinicians. Fatigue is a common complaint in other chronic diseases and gastrointestinal diseases besides MS. Thus, *H. pylori* may need to be investigated as a cause of fatigue, especially in patients with chronic diseases, who were selected in our study (28).

To our knowledge, no other study has shown the relationship between *H. pylori* seropositivity and fatigue symptoms in patients with MS. In our study, we found *H. pylori* seropositivity in 73 (69.5%) patients in the MS group and 61 (77.2%) patients in the control group. No significant relationship was found between the two groups.

To our best knowledge, no study has included the relationship between *H. pylori* seropositivity and fatigue symptoms in patients with MS. According to our results, *H. pylori* was seropositive in 73 (69.5%) patients in the MS group and 61 (77.2%) patients in the control group, and no significant relationship was found between the two groups. In our study, we investigated the relationship between the presence of fatigue and *H. pylori* levels in patients with MS.

The *H. pylori* IgG levels in patients with fatigue were significantly higher than in those without fatigue. Thus, patients with MS and fatigue should be screened for *H. pylori* and treated if necessary. However, considering the limitations of our study, we believe that multicenter studies with more patient groups will be needed.

Despite these results, this study has some limitations. First, it was conducted in a single center. Second, since *Helicobacter* culture was not performed, it may be difficult to establish a relationship with active infection. Third, the sample size was not

Table 2. Comparison of the MS group and control group according to fatigue severity

	Total		p-value	Control group		p-value	Patient group		p-value
	Non-fatigue	Fatigue		Non-fatigue	Fatigue		Non-fatigue	Fatigue	
Age, median (Q1/Q3)	43 (32/48)	46 (38/53)	0.004[u]	48 (39/50)	45 (40/51)	0.870[u]	36.5 (26/44)	48 (37/54)	<0.001[u]
EDSS, median (Q1/Q3)	0 (0/0.5)	1 (0/4)	<0.001[u]	0 (0/0)	0 (0/0)	1	0.5 (0/1)	2.5 (1/5)	<0.001[u]
Helicobacter pylori, median (Q1/Q3)	27.6 (11.9/63.9)	53.1(16.74/72.9)	0.239[u]	57.4 (12.8/88.7)	53.1 (9.2/79)	-	18.8(9.2/26.3)	53.25 (18.75/71.2)	<0.001[u]
Helicobacter pylori serology, n (%)			0.092[p]			0.283[p]			<0.001[p]
Negative	25 (34.2)	25 (22.5)		6 (16.2)	12 (28.6)		19 (52.8)	13 (18.8)	
Positive	48 (65.8)	86 (77.5)		31 (83.8)	30 (71.4)		17 (47.2)	56 (81.2)	
Beck, n (%)			<0.001[ff]			0.004[p]			<0.001[ff]
Minimal depression	40 (54.8)	21 (18.9)	<0.001	16 (43.2)	5 (11.9)	0.002	24 (66.7)	16 (23.2)	<0.001
Mild depression	25 (34.2)	61 (55.0)	0,006	18 (48.6)	28 (66.7)	ns	7 (19.4)	33 (47.8)	0,004
Moderate depression	8 (11.0)	28 (25.2)	0,017	3 (8.1)	9 (21.4)	ns	5 (13.9)	19 (27.5)	ns
Severe depression	0 (0.0)	1 (0.9)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (1.4)	ns
Epworth, n (%)			0.088[p]			0.106[p]			0.507[p]
Rare	59 (80.8)	76 (68.5)		32 (86.5)	29 (69.0)		27 (75.0)	47 (68.1)	
Often	14 (19.2)	35 (31.5)		5 (13.5)	13 (31.0)		9 (25.0)	22 (31.9)	

[u]Mann-Whitney U test (Monte Carlo), [p]Pearson chi-square test (Monte Carlo), [ff]Fisher-Freeman-Halton test (Monte Carlo); post hoc test: Benjamini-Hochberg correction; Q1, 25th percentile; Q3, 75th percentile, ns: Not significant, MS: Multiple sclerosis

Table 3. EDSS corelations in the patient group

Patient group	EDSS	
	R	p-value
Age	0.571	<0.001
Helicobacter pylori presence	0.140	0.240
Beck Depression Scale	0.088	0.463
Epworth sleepiness scale	-0.273	0.020

Partial correlation test; sex effect was controlled; r: Corelation coefficient, EDSS: Expanded Disability Status Scale

calculated because all patients in the study were those who presented within the dates specified in the ethics committee approval. Fourth, in a study conducted against myelin antigens, especially against heat shock proteins (Hsp), in patients with MS, a positive significant correlation was found between high levels of Hsp60 antibodies and patients' age, disease duration, and EDSS (29). However, in our study, no significant difference was found between the MS group and the control group in terms of *H. pylori*, and cerebrospinal fluid (CSF) examination was not considered. Further studies involving Hsp60 level measurement in CSF would be more beneficial for investigations between fatigue and *H. pylori*.

Conclusion

In our study, no significant difference was found between patients and controls in terms of *H. pylori* seropositivity. In the patient group, the *H. pylori* IgG levels in patients with MS and fatigue were significantly higher than in those without fatigue. This result suggests that *H. pylori* may be a factor in patients with MS and fatigue. Therefore, the investigation and treatment of patients with MS and fatigue for *H. pylori* may be considered. We think that our study may lead to other studies that can be evaluated in terms of fatigue complaints after *H. pylori* treatment.

Ethics

Ethics Committee Approval: The study was conducted following the approval of the Canakkale Onsekiz Mart University

Clinical Research Ethics Committee (decision number: 2018-20, date: 11.14.2018).

Informed Consent: All patients were informed about the study and a written consent form was signed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.C., Concept: M.C., A.A., Design: M.C., A.A., Data Collection or Processing: M.C., A.A., Analysis or Interpretation: M.C., A.A., Literature Search: M.C., A.A., Writing: M.C., A.A.

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