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Helicobacter Pylori Infection and Fibromyalgia Syndrome: Is There any Association?

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ÖZET

Helicobacter pilori infeksiyonu ve fibromyalji sendromu: Bir ilişki var mı?

Amaç: Çalışmamızda Helikobakter pilori (HP) infeksiyonu ile Fibromyalji Sendromu (FMS) gelişimi arasında bir ilişki olup olmadığını değerlendirmek için HP ile enfekte ve enfekte olmayan hastalar arasında FMS varlığı açısından bir fark olup olmadığını araştırdık.

Gereç ve Yöntem: Gastroenteroloji Ünitesine başvuran ve başvuru şikayetlerinin incelenmesinin bir parçası olarak Gastroskopi yapılan hastalar prosedürün yapıldığı gün Romatoloji Uzmanı tarafından da değerlendirildiler. Hastalardan Amerikan Romatoloji Birliği 2010 modifiye FMS Tanı Kriterleri Yaygın Ağrı Endeksine (YAE) göre son yedi günde mevcut olan ağrılı veya hassas vucüt bölgelerini belirtmeleri istendi. YAE de üç ya da daha fazla bölgede şikayeti olan hastalar daha sonra aynı kriterlere göre FMS varlığı açısından değerlendirildiler. HP hızlı üreaz testi- HelicotecUT Plus ile test edildi ve biyopsi örnekleri mide antrumundan ve korpusundan 2'şer örnek olarak elde edildi. Test 24 saate uzayan bir sürede değerlendirildi.

Bulgular: 53 (%55.8) HP pozitif ve 42 (%44.2) HP negatif 95 vaka değerlendirildi. Hastaların ortalama yaşı 36.16±11.62 yıl idi. 51 hasta (%53.7) erkek ve 44 (%46.3) kadın idi. HP pozitif ve negatif vakalar arasında yaş açısından anlamlı bir fark saptanmadı (p=063). Erkeklerde HP pozitifliği (%68.6) kadınlara göre (%40.9) anlamlı olarak yüksekti (p=0.012). FMS 6 vakada teşhis edildi (%6.3). 2 HP pozitif (%3.8) ve 4 HP negatif (%9.5) vakalar arasında FMS varlığı açısından istatistiksel olarak anlamlı bir fark saptanmadı (p=0.4).

Sonuç: Çalışmamızda HP ile enfekte hasta grubunda, enfekte olmayan hasta grubuna göre FMS oranını daha yüksek saptanmadı. Bulgularımız HP enfeksiyonu ile FMS arasında bir bağlantı olup olmadığı konusunda herhangi bir ipucu vermemiştir.

Anahtar kelimeler: Helikobakter pilori, fibromyalji sendromu, patogenez

ABSTRACT

Helicobacter pylori infection and fibromyalgia syndrome: is there any association?

Objective: We searched the difference between Helicobacter pylori (HP) positive and negative patients for Fibromyalgia Syndrome (FMS) to explore any association between HP infection and FMS.

Material and Methods: Patients who presented to Gastroenterology and were done Gastroscopy as a part of their work-up were evaluated by the same Rheumatologist at the same day of Gastroscopy. Patients indicated painful or tender areas that present over the last week according to widespread pain index of 2010 modified FMS Diagnostic Criteria. If 3 or more areas were indicated, patients were further evaluated for FMS. HP was tested with rapid urease test- HelicotecUT Plus, and biopsy specimens were obtained from antrum and the body of stomach (2 from each sites). Test reading were done up to 24 hours.

Results: We studied 95 cases; 53 HP positive and 42 HP negative. Their mean age was 36.16±11.62 years. There were 51 (53.7%) males and 44 (46.3%) female patients. There was no statistically significant difference for the age between HP positive and negative patients (p=063). HP positivity in men (68.6%) was significantly higher than women (40.9%) (p=0.012). FMS was diagnosed in 6 cases (6.3%); 2 (3.8%) of HP positive patients and 4 (9.5%) of HP negative patients, and the difference was not statistically significant (p=0.4).

Conclusion: In a group of HP infected patients, we could not find higher rate of FMS compared to non infected patients. Our findings do not give any clue for any association between HP infection and FMS.

Key words: Helicobacter pylori, fibromyalgia syndrome, pathogenesis

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread musculoskeletal pain, muscular tenderness, fatigue, and psychological distress. Chronic widespread pain (CWP) is a common condition that is found in 10-11% of the population in some industrialized countries (1). For the classification of fibromyalgia syndrome, in addition to CWP, 1990 American College of Rheumatology (ACR) classification criteria requires finding of at least 11 of 18 possible tender points on examination of specifically determined sites in the body (2). With this criteria, FMS has the population prevalence of 0.5-4% (3). Pathogenesis of the syndrome remains elusive, although recently centrally altered pain perceptions have strongly been implicated (4,5).

Helicobacter pylori (HP) is a Gram-negative and microaerophilic bacterium (6). HP is one of the most prevalent infection in the World, but the incidence of HP infection in adults is particularly high in developing countries compared with developed countries (7-9). HP colonizes the stomach in childhood and persists throughout life, causing diseases mainly in adults, including chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer (10,11). This persistent infection elicits a chronic inflammatory and immune response (12). The interaction of the host with HP can have profound systemic effects (13). A growing body of evidence has implicated HP infection in extragastrointestinal diseases such as cardiovascular, liver and biliary diseases (14-16).

Seemingly, studies about the association between HP and FMS are in limited number. With this insight, we have decided to study the subject further. In our study, we have searched the prevalence of FMS, and if there is any difference for the presence of FMS between HP positive and negative patients.

MATERIAL AND METHODS

The study was conducted in a private hospital affiliated with University. We have received official approval from ethics committee of Kemerburgaz University Medical School for the study. Patients who were presented to Gastroenterology Unit and performed gastroscopy with HP test as a part of their diagnostic work-up were also referred to Rheumatology. At the same day of gastroscopy, patients were evaluated by the same rheumatologist. Patients with serious internal or psychiatric diseases, or taking medications that would interfere with FMS symptoms were excluded. Patients indicated painful or tender areas that present over the last week according to widespread pain index of 2010 modified FMS Diagnostic Criteria (17). If 3 or more areas were indicated, patients were further evaluated for the presence of FMS. Patients who were diagnosed FMS based on 2010 Diagnostic Criteria were also evaluated according to 1990 FMS Classification Criteria (2). Physical examinations and laboratory work-up (hemogram, sedimentation rate, C-reactive protein, creatinine, alanine aminotransferase, aspartate aminotransferase, electrolytes, calcium, phosphorus, urinalysis, rheumatoid factor, antinuclear antibody, thyroid stimulating hormone) were done to exclude conditions that would cause widespread pain. HP was tested with rapid urease test-HelicotecUT Plus (Strong Biotech Corporation; SBC 17F, No3, park St, Tapei 11503, Taiwan R.O.C.). Biopsy specimens were obtained 2 from antrum, 1 from anterior corpus and 1 from posterior corpus of stomach. Test readings were done after gastroscopy and if negative up to 24 hours. Lack of antibiotic use at least for the last 4 weeks and proton pump inhibitor use at least for the last 2 weeks before the procedure was confirmed.

SPSS (Statistical Package for Social Sciences) for Windows 15.0 was used for statistical analyzes. Quantitative data are expressed as means and standard deviations, and for the comparison of variables between groups, Student's t test was used. For the comparison of qualitative data, Pearson's chi-square test, Fisher's exact test and the Continuity Correction (Yates) test were used. p values <0.05 were considered as statistically significant.

RESULTS

We have studied 95 cases. The age of patients ranged between 18 and 65 years, and mean age was 36.16±11.62 years. Fifty one of cases (53.7%) were males and 44 (46.3%) of them were females (Table 1).

Body mass indexes of cases were between 15.32 and 48.91 kg/m^2, mean was 25.32±4.94 kg/m^2. Three of the cases (3.2%) did not know reading or writing; 19 (20%) were primary school graduates; 8 (8.4%) were secondary school graduates, and 37 (38.9%) were high school graduates. Twenty eight (29.5%) were University graduates. Family

Table 1: Demographic features of patients

n=95	Min-Max	Mean±SD
Age (years)	18-65	36.16±11.62
BMI (kg/m^2)	15.32-48.91	25.32±4.94
	n	**%**
Gender		
Male	51	53.7
Female	44	46.3
Education		
None	3	3.2
Primary	19	20.0
Secondary	8	8.4
High School	37	38.9
University	28	29.5
Marital status		
Married	72	75.8
Single	23	24.2
Family origin		
Marmara	11	11.6
Agean	1	1.1
Mediterranean	5	5.3
Black Sea	31	32.6
Eastern Anatolia	23	24.2
Southeastern Anatolia	8	8.4
Central Anatolia	11	11.6
Balkans	5	5.3

n=number, BMI=Body mass Index, SD=Standard deviation

origins of patients were: 11 (11.6%) from Marmara Region; 1 (1.1%) from Aegean Region; 5 (5.3%) from Mediterranean region; 31 (32.6%) Black Sea Region; 23 (24.2%) from Eastern Anatolia; 8 (8.4%) from Southeastern Anatolia; 11 (11.6%) from Central Anatolia; 5 (5.3%) originated from Balcans.

Fifty three (55.8%) of patients were HP positive, and 42 (44.2%) were HP negative. There was no statistically significant difference for the age between HP positive and negative patients (p=0.637). The mean age of HP positive patients was 35.64±10.70, and was 36.81±12.86 for HP negatives (Table 2). HP positivity in men (68.6%) was significantly higher than women (40.9%) (p=0.012). According to the state of education, there was no statistically significant difference between HP positive and negative cases (p=0.352). While there was no statistically significant difference (p=0.116) for the presence of HP infection among patients according to family origin, in patients from the Southeast Anatolia, HP prevalence was noticeably higher.

In 53 cases (55.8%), pain was seen at least in one area of WPI. FMS was diagnosed in 6 cases (6.3%); 2 (3.8%) of HP positive patients and 4 (%9.5) of HP negative patients, and the difference was not statistically significant (p=0.4) (Table 3).

Table 2: Demographic features of patients according to Helicobacter Pylori status

	Helicobacter Pylori		
	Positive Mean±SD	**Negative Mean±SD**	**P**
Age (year)	35.64±10.70	36.81±12.86	
BMI (kg/m^2)	25.35±4.25	25.27±5.80	[1]0.943
	n (%)	**n (%)**	
Gender			
Male	35 (68.6)	16 (31.4)	[2]0.012*
Female	18 (40.9)	26 (59.1)	
Marital status			
Married	40 (55.6)	32 (44.4)	[2]1.000
Single	13 (56.5)	10 (43.5)	
Education			
None + Primary	12 (54.5)	10 (45.5)	[3]0.352
Secondary	5 (62.5)	3 (37.5)	
High School	17 (45.9)	20 (54.1)	
University	19 (67.9)	9 (32.1)	
Family Origin			
Marmara	4 (36.4)	7 (63.6)	[3]0.116
Agean	1 (100)	0 (0)	
Mediterranean	2 (40)	3 (60)	
Black Sea	20 (64.5)	11 (35.5)	
Eastern Anatolia	14 (60.9)	9 (39.1)	
Southeastern Anatolia	7 (87.5)	1 (12.5)	
Central Anatolia	3 (27.3)	8 (72.7)	
Balkans	2 (40)	3 (60)	

[1]Student t test, [2]Continuity Correction (Yates) test, [3]Pearson Ki-Kare test, *p<0.05, n=number, BMI=Body mass Index, SD=Standard deviation

Table 3: Chronic pain at least at one area of WPI and Fibromyalgia Syndrome according to Helicobacter Pylori status

	Helicobacter Pylori		
	Positive n (%)	Negative n (%)	P
Chronic Pain			
Absent	26 (61.9)	16 (38.1)	[1]0.390
Present	27 (50.9)	26 (49.1)	
Fibromyalgia			
Absent	51 (96.2)	38 (90.5)	[2]0.400
Present	2 (3.8)	4 (9.5)	

[1]Continuity Correction (Yates) test, [2]Fisher's Exact test, n= number, WPI: Widespread pain index.

DISCUSSION

It is very well known that the prevalence of HP infection varies widely by geographic area, age, gender, race, ethnicity, and socioeconomic factors. Seemingly, rates decrease with improvements in hygiene, and there is a decreasing trend in the prevalence in many parts of the world. Inadequate sanitation, low social class, and crowded or high-density living conditions seem to be related to a higher prevalence of HP infection (18). In our study, we found HP positivity rate as 55.8% in our patient population with a mean age 36.16±11.62 years by rapid urease test. There was no statistically significant difference for the mean age between HP positive and negative patients, but HP positivity in men was significantly higher than women. Education status did not show any influence for the HP positivity in our patients. While there was not any statistically significant difference for the presence of HP infection among patients according to family origin, patients from the Southeast Anatolia had higher HP prevalence (87.5%). In 1993, the EUROGAST study group described prevalence of HP as tested by the presence of anti-HP IgG antibodies using an enzyme linked immunoassay (ELISA) in asymptomatic subjects in 17 geographically defined populations. In all populations combined, the prevalence was higher in the older age group (62.4 % for 55-64 years) than in the younger age group (34.9% for 25-34 years). There was no difference for the infection of HP between men and women (19). In a study by Uyanıkoğlu et al. in an Eastern Anatolian city Erzurum, HP status of their patients which tested histologically by antrum biopsy were evaluated retrospectively (20). Seventy-one percent of their patients had HP infection. There was no significant difference between men and women, and between age groups. In another study in Sakarya Turkey, Yücel et al. studied HP prevalence among randomly selected University students by using monoclonal HP stool antigen test. The mean age of students was 21.14±2.06 and 63% of cases were HP positive (21). We think that diversity of our patient's birthplace and family origin is an important factor for the lower rate of HP infection in our patients compared to Turkish studies above.

In our study, we have diagnosed FMS in 6.3% patients according to 2010 ACR diagnostic criteria (5.2% according to 1990 FMS classification criteria). All of our patients with FMS were females and their ages changed between 19 and 64. We could not find any significant difference for the prevalence of FMS between HP positive and negative patients. The studies on the association of FMS and HP infection are limited, and we have reached only 3 studies so far (22-24). Two of these studies used serological test to determine HP infection contrary to ours. The tests used in the diagnosis of HP infection divided in two groups; invasive and non-invasive tests. Non-invasive tests include urea breath test, stool antigen test, serological tests. Invasive test needs endoscopy and include rapid urease test, histology, culture, polymerase chain reaction (18,25,26). All of these tests have advantages and disadvantages, and the choice of test depends on availability, cost, to aim a diagnosis or to confirm eradication. Serological tests to detect antibodies formed against HP are used commonly. Their applications are easy, less expensive, and ELISA is the most commonly used method. The sensitivity of serological tests 85-9%, the specificity is 79-83% (18). IgG and IgA antibodies do not discriminate current or old infections, and they cannot be used to show eradication of HP infection. In the study by Akkaya et al. in Denizli Turkey, they have found seropositivity of HP IgG antibody studied by ELISA in FMS patients (67.7%) significantly higher than in control group (43.9%) (22). All

FMS patients and controls were female, and the mean age of their patients 36.21±7.42 years. In another study done in Egypt, the prevalence of HP IgG antibody was significantly higher in 100 female patients with FMS than 100 healthy matched controls (23). Patients with HP infection had significantly higher pain, fatigue, global severity of disease, anxiety, fibromyalgia impact questionnaire and more tender points. In another study by Malt et al., in Norway, they did not find any difference between FMS patients and controls for the presence of HP infection, and HP status was associated with psychological distress (24).

We had the opportunity to use rapid urease test to detect HP infection in our patients, since it was done as a part of routine gastroenterological diagnostic work-up. It is a rapid and cheap test with high sensitivity and specificity for HP infection, but its post treatment sensitivity reduced (18,25,26). During test procedure, a gastric biopsy tissue placed into a medium containing urea and an indicator such as phenol red. The urease produced by HP hydrolyzes urea to ammonia which raises the PH of the medium, and changes the color to pink. This color change to pink indicates the presence of bacteria in the tissue, which can be scanned in a period of 3-24 hours. It shows active invasion of stomach by HP. We value the studies above detected higher rates of HP infection in FMS. But, since serological testing do not discriminate current and old infection of HP, this finding is hard to interpretate and not helpful to understand clear mechanisms of contribution HP to FMS. In our study, we detected real-time status of HP in our patients and could not find any increased rate of FMS among HP infected patients compared to HP not infected. HP status in a variety of autoimmune diseases found mixed results, and although there is evidence of HP infection in the development of immun thrombocytopenic purpura, for the majority of autoimmune diseases, the role HP remains controversial (27).

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