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Helicobacter Pylori Infection Might be a Potential Protective Factor against Classic Multiple Sclerosis in Guilan, Iran

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAJM managed the analyses of the study and wrote the manuscript. Author HH designed the study, performed the tests and statistical analysis and wrote the protocol. Authors H. Hatamian and AR managed the literature searches and sampling. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The current study was aimed to investigate any relation between *H. pylori* seropositivity to IgA and IgG with MS.

Study Design: Cross sectional study

Place and Duration of Study: The present study was performed in the Department of Microbiology, Guilan University of Medical Sciences between April 2012 and April 2013

Methodology: *H. pylori* infection was certified by ELISA in study group (n=46) and control group (n=46) using commercial assays (Anti *H. pylori* IgG and IgA,). Data were analyzed by using two statistical tests (Chi square and Spearman's rho correlation).

Results: Seropositivity rate of *H. pylori* IgG was 33.3% in study group but 67.4% in control group and seropositivity rate of *H. pylori* IgA was 11.9% in study group but 30.2% in control group. The frequency of IgG seropositivity was significantly more in control group than study group ($P_{\text{Chi-Square}} = 0.002$, Correlation Coefficient = -0.341 and $P_{\text{Spearman's rho correlation}} (\text{Sig. 2-tailed}) = 0.001$) and the frequency of IgA seropositivity was also significantly more in control group than study group ($P_{\text{Chi-Square}} = 0.039$ and Correlation Coefficient = -0.224, $P_{\text{Spearman's rho correlation}} (\text{Sig. 2-tailed}) = 0.039$).

Conclusion: *H. pylori* seropositivity to IgG and IgA showed significant inverse association with affection to MS. Findings of this study suggests that *H. pylori* infection is not a causative factor but might be a protective factor against development of classic MS.

Keywords: *H. pylori* infection; immunological effect; multiple Sclerosis.

1. INTRODUCTION

Multiple Sclerosis is an inflammatory demyelinating disease of the Central Nervous System (CNS). It seems that environmental and genetic factors are the predominant risk-determining elements and many other factors must be considered [1].

Most commonly *H. pylori* colonize the gastric mucosa in early childhood and can persist throughout life, if no antibiotic therapy is given. Its worldwide prevalence is variable, with highest prevalence in areas with overcrowding and poor sanitation. The outcome of *H. pylori* infection is dependent on host, environmental and bacterial factors [2,3].

This bacterium has been associated with many intestinal and extra intestinal diseases. A high *H. pylori* seroprevalance has been reported in different neurological disorders including cerebrovascular diseases, migraine, Alzheimer's disease, epilepsy, Parkinson's disease, multiple sclerosis [4].

Persistent *Helicobacter pylori* (*H. pylori*) infection is a chronic inflammatory stimulus to hosts with an inverse correlation to atopic disorders. *H. pylori* infection has been linked to multiple sclerosis (MS) and demyelinating peripheral neuropathies as it can trigger cellular and humoral immunity due to the sharing of similar epitopes present in the nervous tissue [5-6]. These antibodies cross-react with different components of central and peripheral nerves resulting in their damage [5,6]. Many other factors like platelet activation and aggregation; different vasoactive and inflammatory substances, stimulation of mononuclear cells to produce different tissue factor - like procoagulants, reactive oxygen species, and apoptotic processes may be important factors in the association of *H. pylori* infection with MS and peripheral neuropathies like Guillain–Barre syndrome [5,6].

In this cross sectional prospective study we attempted to determine the seroprevalence of anti- *H. pylori* antibodies (IgG and IgA) in sera of study group (patients with MS) comparing to control group to determine the role of *H. pylori* infection in pathogenesis of MS.

2. MATERIALS AND METHODS

This study is a analytical cross sectional one which was conducted with all clinical samples from MS patients who were under supervision of MS society of Guilan province, Northern Iran and also, healthy blood donors (they were matched with patients based on age and gender) who voluntarily submitted for Pars medical laboratory of Rasht, Iran for 8 months from April, 2012 to Dec, 2012. MS patients were diagnosed with magnetic resonance imaging (MRI) and Evoked Potential (EP) and also McDonald criteria were recruited. Serum samples were collected by standard methods. All Specimens were stored at -70°C until the experiment was performed. Some demographical and other required data were collected by filling a questionnaire including: age, Gender, duration of the disease, number of crisis, duration of interferon intake, score of EDSS, result of MRI, result of Evoked Potential test and type of antiviral therapy(if prescribed).

A group of 46 subjects with classic multiple sclerosis (CMS) along with 46 healthy controls were examined with the serological test for the presence of antibodies against *Helicobacter pylori* surface antigen. Patients who were residents of the area (more than 6 months) with age range of 10-50 years had classic MS (not opticospinal MS) confirmed by MRI and Evoked Potential test. All patients were under supervision of MS society of Guilan.

Serological test was performed using commercial ELISA Tests (Anti *H. Pylori* IgG and Anti *H. Pylori* IgA kits, Euroimmune, Germany). Titers>100 Ru/ml were considered as high titer, Titers from 51 to 100Ru/ml were considered medium titer and titers lower than 50Ru/ml were considered low titer.

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 16 was used for statistical analysis. Chi square and Spearman's rho correlation tests were applied to analyze all variables. All P-values were two-tailed and significant at P<0.05.

The study conformed to the Helsinki declaration and was reviewed and approved by the local research committee, it was approved by ethics committee, and written informed consent was obtained from all subjects and control group. We did not encounter important limitations in this study but taking samples that took a long time.

3. RESULTS AND DISCUSSION

Average age of patients (n=46) was 32 years with min-max 28-38(average 32.8%). Most patients were women (71.4%). Most individuals in study group had Expanded Disability Status Scale (EDSS) between 2.5 and 3.5(45.2%) and 28.6% of them had EDSS score lower than 2.5. Evoked potential test and MRI were positive in all study group.

About 33.3% of Patients had seropositivity to *H. pylori* IgG (16.8% with high titer, 9.6% with medium and 6.9% with low titers). Seropositivity rate to *H. pylori* IgG in control group was more than that in patients (67.4% versus 33.3%) (Fig. 1) and this difference was significant (Chi-Square=9.889 and P_{Chi-Square} =0.002, correlation coefficient=-0.341 and P_{Spearman's rho correlation} (Sig. 2-tailed) = 0.001) and odd. Ratio= 0.297(Table 1). Frequency of high titer seropositivity to IgG in control group was also more than that in patients (46.5% versus

16.8%) (Fig. 1) and this difference was also significant (Chi-Square=9.668 and $P_{\text{Chi-Square}}=0.004$, correlation coefficient=-0.323 and $P_{\text{Spearman's rho correlation}}(\text{Sig. 2-tailed}) = 0.002$ and odd. Ratio= 0.255. Seropositivity with medium and lower titer to *H. pylori* IgG in control group was also more frequent than that in patients (11.5% versus 9.6% and 9.4% versus 6.9% consequently).

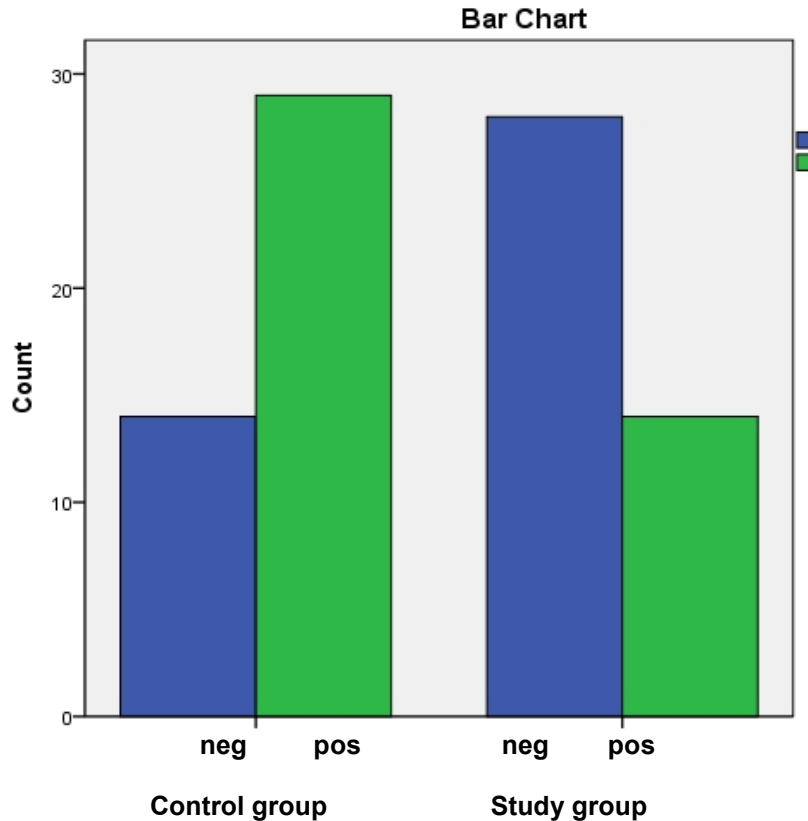


Fig. 1. seropositivity rate to H.pylori IgG in Study group and control group

About 11.9% of Study group had seropositivity to H.pylori IgA (2.3% with medium and 9.6% with lower titers). Seropositivity rate to H.pylori IgA in control group was more than that in Study group (30.2% versus 11.9%) (Fig. 2) and this difference was significant (Chi-Square=4.276 and $P_{\text{Chi-Square}}=0.039$, correlation coefficient=-0.224 and $P_{\text{Spearman's rho correlation}}(\text{Sig. 2-tailed}) = 0.039$, and odd. Ratio= 0.311 (Table 1). Seropositivity with medium titer in control group was also more frequent than that in patients (9.3% versus 2.3%) and this difference was significant (Chi-Square=4.166 and $P_{\text{Chi-Square}}=0.037$, correlation coefficient=-0.311 and $P_{\text{Spearman's rho correlation}}(\text{Sig. 2-tailed})= 0.022$, and odd Ratio= 0.237. Studied parameters did not show significant association with seropositivity to *H. pylori* IgG and *H. pylori* IgA (Table 2).

H. pylori have extensive interactions with the immune system. Their role as a causative agent of autoimmune diseases in genetically susceptible host has been studied and it has been associated with a variety of autoimmune disorders [4].

H. pylori have acquired several unique attributes helping them escape clearance through the normal immune mechanisms [4]. This prolonged coexistence of *H. pylori* in human raises the possibility of a rather symbiotic relationship in which its persistence may at least in part be beneficial to humans [4].

There are some recent data suggestive of a protective effect of *H. pylori* against autoimmune and allergic diseases. A recent meta-analysis suggested a protective role of *H. pylori* in inflammatory bowel disease [7]. An inverse relationship between *H. pylori* infection and allergic conditions is also reported. Rate of asthma was found to be lower in children who were *H. pylori* positive when compared with those who were *H. pylori* negative [8]. In a Japanese cohort an inverse association of *H. pylori* seropositivity and MS was reported [9]. Based on a recent review of literature, it is concluded that in most autoimmune diseases the role of *H. pylori* remains inconclusive [10].

It seems that some viral and bacterial infections can precipitate, worsen or protect patients from MS [11,12]. It is a new hypothesis that some environmental factors might be suspected to have protective effects for MS. Some chronic infections such as *Helicobacter pylori* can modulate the immune system to prevent its hyperactivity causing allergies and autoimmune disorders. Results of three studies in Japan like the present study demonstrated that *H. pylori* infection had protective effects on MS [13-15]. Prevalence of *H. pylori* infection in developing countries is more than in developed ones, and it may reach 80% in some countries [16,17] but incidence rate of MS is lower. There are some descriptions that explain why allergic and autoimmune diseases are more prevalent in wealthy countries.

There are increasing evidences that *H. Pylori* can play a protective role in the development of multiple sclerosis, systemic lupus erythematosus and inflammatory bowel disease. Ram M et al. tested various links between anti- *H. pylori* antibodies and a wide profile of autoimmune diseases and auto antibodies. In their study a total of 1290 patients diagnosed with 14 different autoimmune diseases from two geographical areas (Europe and Latin America) and two groups of healthy matching controls (n=385) were screened for the presence of *H. pylori* IgG antibodies. They reported that *H. pylori* does not play a causative role in the autoimmune diseases and the negative associations could possibly support the notion that in susceptible individuals, infections may protect them from the development of autoimmune diseases [4].

Table 1. Statistical association of serpositivity to *H. pylori*-IgG and *H. pylori* IgA with occurrence of MS

Test results	Seropositivity rate		Statistical analysis				
	Patients	Control	P1	FET	CC	P2	OR
<i>H. pylory</i> IgG	33.3%	67.4%	0.002	0.002	-0.341	0.001	0.297
<i>H. pylori</i> IgA	11.9%	30.2%	0.039	0.032	-0.224	0.039	0.311

P1: pearson chi square Asymp. Sig. (2-sided)

cc: Spearman's rho correlation coefficient

P2: Spearman's rho correlation test Sig. (2-sided)

FET: Fisher's Exact Test Exact Sig. (2-sided)

OR: odd. Ratio

We found that frequency of IgG seropositivity and high titer of *H. pylori* IgG was significantly more in controls than that it was in patients, indicating that people who were more immune to *H. pylori* were less vulnerable to be affected with MS. We also found that frequency of IgA

seropositivity and high titer of *H. pylori* IgA was significantly more in controls than that it was in patients, indicating that people who had chronic or persistent *H. pylori* infection were more protected against MS. Our findings are in consistent with other similar studies which are described as follow.

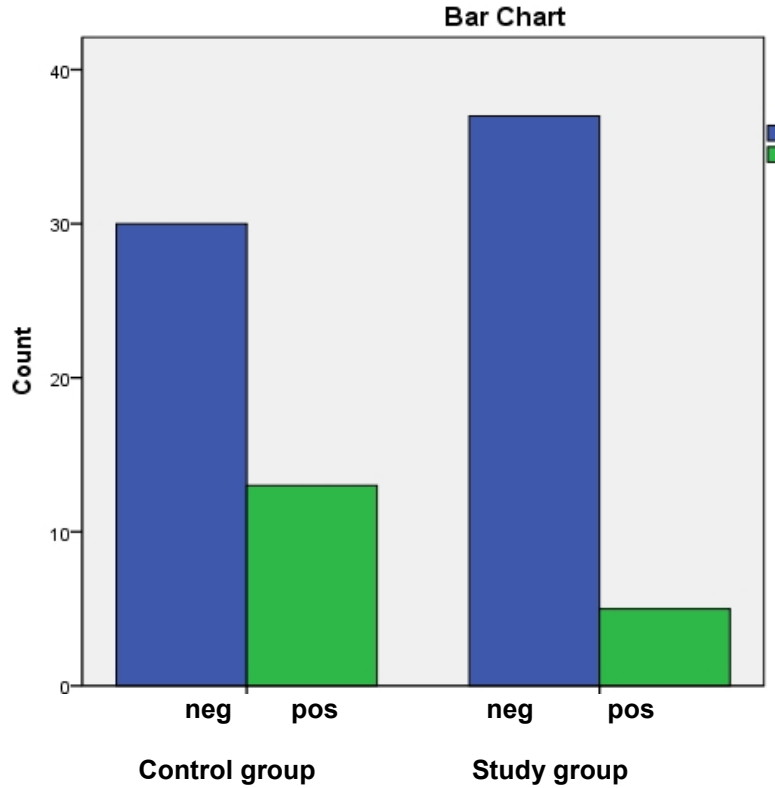


Fig. 2. Seropositivity rate to H.pylori IgA in Study group and control group

Table 2. Statistical association of studied parameter with seropositivity to *H. pylori*-IgG and *H. pylori* IgA

Parameters	<i>H. pylori</i> -IgG				Comment	<i>H. Pylori</i> -IgA				Comment
	P1	LLA	CC	P2		P1	LLA	CC	P2	
Duration of the disease	0.897	0.982	0.022	0.897	NS	0.984	0.409	0.182	0.273	NS
number of relapses	0.221	0.608	0.061	0.716	NS	0.961	0.434	0.178	0.285	NS
EDSS scores	0.876	0.429	0.129	0.435	NS	0.782	1.000	-	1.000	NS
Age of Study group	0.189	0.178	0.227	0.182	NS	0.022	0.032	0.362	0.030	NS
Gender of Study group	0.426	0.432	-	0.440	NS	0.579	0.584	0.089	0.591	NS

P1: Pearson chi square Asymp. Sig. (2-sided)
 cc: Spearman's rho correlation coefficient
 P2: Spearman's rho correlation test Sig. (2-sided)
 LLA: Linear-by-Linear Association Asymp Sig. (2-sided)
 NS: not significant

In the study of Wender, a group of 90 subjects with multiple sclerosis were examined with the serological Helicotest for the presence of antibodies against *H. pylori* in Poland. Positive results were found in 17 patients (18.9%), which was markedly lower than this infection incidence rate in the population of Poland. The results showed a lack of connection between the *Helicobacter pylori* infection and multiple sclerosis [18].

Li, et al. studied the prevalence of *H. pylori* infection in different MS subtypes including classic MS and opticospinal MS in the Japanese population and demonstrated that there is a difference in *H. pylori* seropositivity between Japanese patients with opticospinal MS and those with classic MS. *H. pylori* infection was significantly lower in patients with classic MS than in healthy controls or patients with opticospinal MS. This study suggested that the differences in childhood environment might cause some effects on the development of each MS subtype later in life and *H. pylori* might be a protective factor against Classic MS [9]. So there is consistency between results of that study and the present study.

Long Y, et al. showed that *H. pylori* infection was present in most Chinese patients with neuromyelitis optica and might be a risk factor for the neuromyelitis optica spectrum but not for MS [19]. It is another study whose results are compatible with our study.

Ramroodi N, et al. suggested that *H. pylori* infection is not a causative factor for MS in southeast Iran, but maybe help to established of MS progression [20]. Mohebi et al. observed a Significant difference in seropositivity between these two groups ($P < 0.001$) but no significant difference was seen in seropositivity between conventional and opticospinal MS ($P = 0.522$) [21]. Like our study they found no significant difference in seropositivity among ages ($P = 0.075$) and between genders ($P = 0.204$). A significant difference was seen in EDSS value between seropositive and seronegative patients ($P = 0.017$). They concluded that patients with *H. pylori* infection had lower incidence of multiple sclerosis and MS patients with *H. pylori* infection showed lower neurologic complications, which could demonstrate that *H. pylori* infection might have a protective influence on MS pathogenesis. That study was performed in the same country as we did but in two different region and it was the most current study which showed compatible results.

4. CONCLUSION

H. pylori seropositivity to IgG and IgA showed a significant inverse association with prevalence of MS. Findings of this study suggest that *H. pylori* infection is not a causative factor but might be a protective factor against classic MS. We suggest further studies for the association of *H. pylori* with MS and for more extensive understanding of *H. pylori* neurotropism and its association with the disease process and also more similar studies with higher sample sizes are recommended.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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