Original Article

Patients with Newly Diagnosed Multiple Sclerosis Are Less Seropositive for *Helicobacter Pylori* Infection: A Case Control Study in Iran

Mohammad Javad Zahedi [1], Kaveh Shafiee [2], Mohammad Mehdi Hayatbakhsh Abbasi [1], Reza Malekpour Afshar [3], Sara Shafieipour [1,*], Maysam Rohani [4], Abdolallahe Pooshani [4], Fatemeh Karami Robati [4], Azam Dehgani [4]

[1] Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[2] Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[3] Pathology and Stem Cell Research Center, Kerman University of Medical Sciences, Kerman, Iran
[4] Clinical Research Development Unit, Afzalipour Hos¬pital, Kerman University of Medical Sciences, Kerman, Iran

ABSTRACT

Background:
Multiple sclerosis (MS) is a common chronic demyelinating disease of the central nervous system with various potential etiology, including infectious disease. The number of studies on the association between *Helicobacter pylori* (*H. pylori*) infection and MS is limited. So, in this study, we aimed to assess the relation between *H. pylori* infection and MS in Kerman city, the center of the largest province in Iran.

Materials and Methods:
In a case-control study, 71 patients with newly diagnosed MS and 145 sex- and age-matched controls were included. Blood samples for IgG anti-HP antibodies were collected from all individuals. SPSS software version 22 was used for data analysis. $p < 0.05$ was considered statistically significant.

Results:
71 patients with newly diagnosed MS consisted of 48 (67.6%) women and 23 (32.39%) men were included in our study. The mean age was 43 ± 10 years. The mean ages in the case and control groups were 43.83 ± 10.40 and 44.41±16.30 years, respectively ($p = 0.114$). The control group more commonly had used smoking ($p = 0.814$). Alcohol consumption was higher in the control group ($p = 0.965$). More than 40% of the patients in the case group and 55.17% in the control group had body mass index (BMI) > 25 ($p = 0.074$). *H. pylori* seropositivity was observed in 61.97% of the MS group compared with 76.55% of the non-MS group ($p = 0.021$).

Conclusion:
We concluded that patients with newly diagnosed MS had low *H. pylori* seropositivity, so *H. pylori* infection may have a protective effect against MS.

Keywords: *Helicobacter pylori*, Multiple sclerosis, Diagnosis, Serology

please cite this paper as:
Zahedi MJ, Shafiee K, Hayatbakhsh Abbasi MM, Malekpour Afshar R, Shafieipour S , Rohani M, Pooshani A, Karami Robati F, Dehgani A. Patients with Newly Diagnosed Multiple Sclerosis Are Less Seropositive for *Helicobacter Pylori* Infection: A Case Control Study in Iran. *Govaresh* 2021;26:113-117.

Corresponding author:
Sara Shafieipour, MD
Department of Gastroenterology, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
Telefax: + 98 34 33257470
E-mail: sarashafieipour@yahoo.com

Received: 12 Dec. 2020
Edited: 10 May 2021
Accepted: 11 May 2021

INTRODUCTION

Multiple sclerosis (MS) is one of the most prevalent chronic demyelinating diseases of the central nervous system with various etiology (1-3). It is mainly defined as a heterogeneous, complex, and multifactorial disease (4). Interaction between genetic susceptibility, infections such as Epstein-Barr virus and measles, and other environmental factors have been proposed for the pathogenesis of this disease (5).

Helicobacter pylori (*H. pylori*) is a gram-negative

bacterium, which has infected more than 50% of the general population, especially in developing countries (6,7). Historically the relation between *H. pylori* and peptic ulcer disease was discussed by Warren and Marshall in 1983 (8,9). Recently, some considerations about the association between *H. pylori* and various extra-intestinal disorders, including rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, migraine, Alzheimer's disease, epilepsy, and Parkinson's disease, has come to attention (10-14).

There is contradictory evidence about the protective effect of *H. pylori* infection in MS. Although the results of some studies show a high prevalence of *H. pylori* infection in patients with MS (15-18), some studies show chronic infection with *H.pylori* might play a protective role in MS (19,20). A meta-analysis of nine studies found a protective effect of *H. pylori* in patients with MS, especially in western countries (21). Infections with *H. pylori* in early life possibly modulate the immune system and decrease the risk of allergy and autoimmune disorders in adulthood (22). In addition, none of these studies have assessed *H. pylori* diagnostic tests in patients with newly diagnosed MS.

Despite the higher prevalence of *H. pylori* in Iran and the increasing incidence of MS in the Iranian population (23), the number of studies about the association between *H. pylori* infection and MS is limited. So, in this study, we aimed to assess the relation between *H. pylori* infection and MS in Kerman city, the center of the largest province in Iran.

MATERIALS AND METHODS

Patients with newly diagnosed MS were enrolled in a case-control study from May to April 2018. Group matching was used in this study. To do this, the case group should be assigned to subcategories based on its characteristics, and then the appropriate control group should be determined. The MS diagnosis was according to the new McDonald criteria (24). All patients had been visited, and diagnoses were confirmed by neurologists at Shafa Hospital, Kerman University of Medical Sciences. Body mass indexes (BMI), smoking, and alcohol consumption that are the possible risk factors for MS; in addition to the demographic data from all patients with MS and control group were collected from their medical records and entered into a checklist.

The solid-phase enzyme-linked immunosorbent assay (ELISA) (Anti *H. Pylori* IgG kits, Teriniti, American) was used to indicate infection with *H. pylori*. Values of more than 40 U/mL were considered as positive for *H. pylori* chronic infection.

The protocol of our study was approved by the Ethics Committee of Kerman University of Medical Sciences. All the participants signed a consent form, and their information was kept secret.

Statistical analysis

Frequency and percentage were used for categorized qualitative variables, in addition to mean and standard deviation for quantitative variables. Pearson's Chi square test and also Fisher's exact test were used to compare sex and age difference between the two groups. SPSS software version 22 was used for data analysis. $p < 0.05$ was considered statisti¬cally significant.

RESULTS

From May to April 2018, 71 patients with MS consisting of 48 (67.6%) women and 23 (32.39%) men were included in our study. The mean age was 43 ± 10 years. The mean ages in the case and control groups were 43.83 ± 10.40 and 44.41 ± 16.30 years, respectively (p =0.114). The control group consisted of 145 participants without MS, and both groups had no statistically significant differences according to sex distribution and the mean of age. The control group more commonly had used smoking (p = 0.814). Alcohol consumption was higher in the control group (p = 0.965). More than 40% of the patients in the case group and 55.17% in the control group had BMI > 25 (p = 0.074), but this difference was not statistically significant.

H. pylori seropositivity was observed in 61.97% of the MS group compared with 76.55% of the control group (figure 1), which was statistically significant (table 1).

DISCUSSION

MS is a more prevalent, multi-factorial chronic neuro-demyelinating disease with an increasing incidence, especially in juveniles. It is an inflammatory disorder caused by self-reactive T helper type 1 (Th1) lymphocytes, while Th2 cells may confer protection (25).

Table 1: The difference between the case and control groups in age, sex, and anti-*H. pylori* IgG seropositivity

Variables	Case (N = 71)	Control (N = 145)	*p* value*
Sex (female)	48 (67.60)	95 (65.5)	0.814
Smoking	20 (28.16)	47 (32.41)	0.526
Alcohol	6 (8.45)	12 (8.27)	0.965
BMI > 25	30 (42.25)	80 (55.17)	0.074
IgG seropositivity (N)	44 (61.97)	111 (76.55)	0.021

Data were shown frequency (percent) *: based on Chi-square test

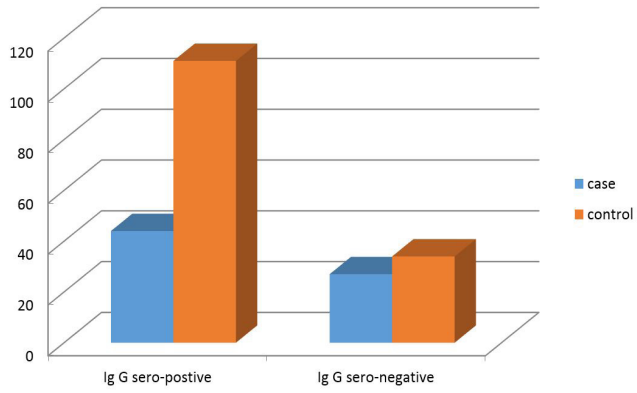

Fig.1: Shows the difference between the case and control groups in anti-*H. pylori* IgG seropositivity

Although the direct etiology of this disorder has remained uncertain, autoimmunity and inflammation are the most acceptable hypotheses. Chronic infections such as *H. pylori* may play a different role in the pathology of this disorder (1,2,5,19-21,26,27). In this survey, we studied the relation between *H. pylori* infection and MS.

Our study showed that the prevalence of *H. pylori* seropositivity might be significantly less in patients with MS compared with the control. Our finding was compatible with the majority of previous studies. Wender and colleagues in their study in Poland showed *H. pylori* seropositivity in 18.9% of the patients with MS, which is markedly lower than the proportion of positive anti-*H. pylori* IgG antibodies in the general population of this country (28). Li and co-workers in the other study in the Japanese population reported a significantly lower *H. pylori* seropositivity in patients with MS (22.6%) compared with healthy subjects (42.4%) (29). In a recent large controlled study, Fabis Pedrini and others found *H. pylori* seropositivity was lower in Western Australian women (19). Likewise, other studies in the other parts of Iran, such as Tehran and Gilan, had similar results (20,30).

The hygiene hypothesis explains the potential protective role of chronic *H. pylori* infection in MS and other allergic and autoimmune diseases. For appropriate development of the immune system, infections in early life seem to be necessary. Th1 response that is promoted in bacterial infections can change the balance between cellular Th1 and Th2. Th2 is involved in autoimmune diseases. Also, increased production of interleukin 10 in infectious disease can down-regulate activated eosinophils and modulate immune responses (22,31,32).

Nevertheless ,The lower *H. pylori* infection in MS has not been shown in some studies. In a recent study in Greece, histologically active *H. pylori* infection was found in 86.4% of patients with MS vs. 50% of the control healthy participants ($p = 0.002$) (33). Sanadgol and colleagues also showed that *H. pylori* infection in patients with MS was not different from healthy blood donors in Zahedan (34). The methods of these study, sample size, subtypes of MS may contribute on the results of studies (19, 33).

We think that the strength of our study compared with previous ones is selecting newly diagnosed patients with MS, which reduces confounding factors such as MS immunomodulatory therapy. Such therapy may change the serologic response to *H. pylori* infection as, during the time, about 50% of patients with MS become weaker and incapable. Besides, immunomodulatory therapies debilitate their immune system, so they will be prone to infectious diseases such as *H. pylori* infection. Up to now, no studies have considered this problem (35,36).

Due to the variety of studies that was discussed above, we suggest a systematic review for better determination of the role of *H. pylori* in MS. In conclusion, our study showed that *H. pylori* seropositivity might be protective against MS.

ACKNOWLEDGMENT

We would like to thank the staff and participants of this study for their kind contributions.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

REFERENCES

1. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: New insights. *Curr Opin Neuro*l 2006;19:248-54.
2. Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J* 2017; 19:1-10.
3. Talaei F. Pathophysiological concepts in multiple sclerosis and the therapeutic effects of hydrogen sulfide. *Basic Clin Neurosci* 2016; 7:121-36.
4. Heidari MM, Khatami M, Tahamtan Y. Molecular analysis of rs2070744 and rs1799983 polymorphisms of NOS3 gene in iranian patients with multiple sclerosis. *Basic Clin Neurosci* 2017;8:279-84.
5. Banwell B, Bar-Or A, Arnold DL, Sadovnick D, Narayanan S, McGowan M, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. *Lancet Neurol* 2011;10:436-45.
6. Porras C, Nodora J, Sexton R, Ferreccio C, Jimenez S, Dominguez RL, et al. Epidemiology of *Helicobacter pylori* infection in six Latin American countries (SWOG Trial S0701). *Cancer Causes Control* 2013;24:209-15.
7. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 2014; 19:1-5.
8. Mirzaei SM, Zahedi MJ, Shafiei Pour S. Prevalence of *Helicobacter Pylori*-negative, non-steroidal anti-inflammatory drug related peptic ulcer disease in patients referred to Afzalipour hospital. *Middle East J Dig Dis* 2015;7:241-4.
9. Kusters JG, Van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev* 2006;19:449-90.
10. Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. *Helicobacter pylori* and autoimmune disease: cause or bystander. *World J Gastroenterol* 2014;20:613-29.
11. Kountouras JMDP, Tsolaki M, Boziki M, Gavalas E, Zavos C, Stergiopoulos C, et al. Association between *Helicobacter pylori* infection and mild cognitive impairment. *Eur J Neurol* 2007; 14:976-82.
12. Han ML, Chen JH, Tsai MK, Liou JM, Chiou JM, Chiu MJ, et al. Association between *Helicobacter pylori* infection and cognitive impairment in the elderly. *J Formos Med Assoc* 2018;117:994-1002.
13. Kountouras JMDP, Tsolaki M, Gavalas E, Boziki M, Zavos C, Karatzoglou P, et al. Relationship between *Helicobacter pylori* infection and Alzheimer disease. *Neurology* 2006; 66:938-40.
14. Beydoun MA, Beydoun HA, Elbejjani M, Dore GA, Zonderman AB. *Helicobacter pylori* seropositivity and its association with incident all-cause and Alzheimer's disease dementia in large national surveys. *Alzheimers Dement* 2018;14:1148-58.
15. Ranjbar R, Karampoor S, Jalilian FA. The protective effect of *Helicobacter Pylori* infection on the susceptibility of multiple sclerosis. *J Neuroimmunol* 2019; 337:577069.
16. Gavalas E, Kountouras J, Deretzi G, Boziki M, Grigoriadis N, Zavos C, et al. *Helicobacter pylori* and multiple sclerosis. *J Neuroimmunol* 2007; 188:187–9.
17. Gerges SE, Alosh TK, Khalil SH, El Din MM. Relevance of *Helicobacter pylori* infection in Egyptian multiple sclerosis patients. *Egypt J Neurol Psychiatr Neurosurg* 2018;54:41.
18. Kountouras J, Papaefthymiou A, Gavalas E, Polyzos SA, Boziki M, Kyriakou P, et al. *Helicobacter pylori* infection as a potential risk factor for multiple sclerosis. *Med Hypotheses* 2020; 143:110135.
19. Pedrini MJ, Seewann A, Bennett KA, Wood AJ, James I, Burton J, et al. *Helicobacter pylori* infection as a protective factor against multiple sclerosis risk in females. *J Neurol Neurosurg Psychiatry* 2015;86:603-7.
20. Mohebi N, Mamarabadi M, Moghaddasi M. Relation of *Helicobacter Pylori* infection and multiple sclerosis in Iranian patients. *Neurol Int* 2013;5:31-3.
21. Yao G, Wang P, Luo XD, Yu TM, Harris RA, Zhang XM. Meta-analysis of association between *Helicobacter pylori* infection and multiple sclerosis. *Neurosci Lett* 2016; 620:1-7.
22. Albataineh EM, Alnawaiseh NA, Al-Zayadneh E, Alamer R, Kaplan N, Abu-lobbad MA. The Relationship between *Helicobacter pylori* (*H. pylori*) and Atopy and Allergic Diseases. *Jordan J Biolog* Sci 2018;11:123-8.
23. Nouraie M, Latifi-Navid S, Rezvan H, Radmard AR, Maghsudlu M, Zaer-Rezaii H, et al. Childhood hygienic practice and family education status determine the prevalence of *Helicobacter pylori* infection in Iran. *Helicobacter* 2009;14:40-6.
24. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162-73.

25. Etesam Z, Nemati M, Ebrahimizadeh MA, Ebrahimi HA, Hajghani H, Khalili T, et al. Different expressions of specific transcription factors of Th1 (T-bet) and Th2 cells (GATA-3) by peripheral blood mononuclear cells from patients with multiple sclerosis. *Basic Clin Neurosci* 2018;9:458-69.

26. Ascherio A. Environmental factors in multiple sclerosis. *Expert Rev Neurother* 2013;13: 3-9.

27. Ascherio A, Munger K. Epidemiology of multiple sclerosis: from risk factors to prevention. *Semin Neurol* 2008;28:17-28.

28. Wender M. Prevalence of *Helicobacter pylori* infection among patients with multiple sclerosis. *Neurol Neurochir Pol* 2003; 37:45-8.

29. Li W, Minohara M, Su JJ, Matsuoka T, Osoegawa M, Ishizu T, et al. *Helicobacter pylori* infection is a potential protective Factor against conventional multiple sclerosis in the Japanese population. *J Neuroimmunol* 2007; 184:227–31.

30. Ahmadi Jalali Moghadam M, Honarmand H, Hatamian H, Roudbary A. *Helicobacter Pylori* Infection Might be a Potential Protective Factor against Classic Multiple Sclerosis in Guilan, Iran. *Ann Res Rev Biology* 2014;4:4502-10.

31. Oderda G, Vivenza D, Rapa A, Boldorini R, Bonsignori I, Bona G. Increased interleukin-10 in *Helicobacter pylori* infection could be involved in the mechanism protecting from allergy. *J Pediatr Gastroenterol Nutr* 2007;45:301-5.

32. Schülke S. Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. *Front Immunol* 2018;9:455.

33. Gavalas E, Kountouras J, Boziki M, Zavos C, Polyzos SA, Vlachaki E, et al. Relationship between *Helicobacter pylori* infection and multiple sclerosis. *Ann Gastroenterol* 2015; 28:353-6.

34. Sanadgol N, Shahraki E, Estakhr J. Relationship between *Helicobacter pylori* (*H. pylori*) Infection and Multiple Sclerosis (MS) in Southeast of Iran. *Curr Res J Biolog Sci* 2012;4:422-6.

35. Aitila P, Mutyaba M, Okeny S, Ndawula Kasule M, Kasule R, Ssedyabane F, et al. Prevalence and Risk Factors of *Helicobacter pylori* Infection among Children Aged 1 to 15 Years at Holy Innocents Children's Hospital, Mbarara, South Western Uganda. *J Trop Med* 2019;2019:9303072.

36. Langer-Gould A, Popat RA, Huang SM, Cobb K, Fontoura P, Gould MK, et al. Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. *Arch Neurol* 2006;63:1686-91.