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RESEARCH ARTICLE

Correlation of Dietary Intake and Helicobacter pylori Infection with Multiple Sclerosis, a Case-Control Study in Rafsanjan, Iran, 2017 – 18

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ABSTRACT

Background: Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system. Some environmental factors, such as *Helicobacter pylori* infection (HPI), are likely to be considered a protective factor in MS. Dietary intake may provide exposure to or have protective effects for MS. The present study aimed to determine the relationship between serum anti-H. pylori IgG antibody (HPIA) level and dietary intake in patients with MS referred to the MS Clinic in Rafsanjan city, Iran.

Methods: The present case-control study was conducted on 97 patients with MS and 95 controls. The two groups had no significant difference in age and gender ($p > 0.05$). HPIA was checked, and the food frequency questionnaire was completed in both groups to measure nutritional intake. All data were analyzed by the SPSS 20 software using independent t-test, Chi-Square, Mann – Whitney U test, and correlation.

Results: The median serum HPIA level was significantly lower in MS cases than in controls. Furthermore, the median consumption of glutamic acid, arginine, serine, aspartic acid, alanine, proline, and caffeine was significantly lower in MS cases than in controls. A significant positive correlation was found between the levels of linoleic acid, lactose, Ca, molybdenum, galactose, leucine, and valine, and the level of HPIA in controls.

Conclusion: Our study results demonstrated that some dietary nutrients had correlations with MS and HPI. Therefore, professionals from multiple disciplines must find which foods contain these dietary nutrients in future studies.

Keywords: Helicobacter pylori, Multiple Sclerosis, Dietary Intake, IgG Antibody

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune and demyelinating disease of the central nervous system.[1]

Although this disease's etiology and pathogenesis are not fully understood, the interaction of genetic and environmental factors appears to decrease the resistance to central nervous system antigens.[1,2]

Unfortunately, no definitive treatment for MS has been found, and existing treatments only control and prevent disease progression. Perhaps, a specific cause cannot be accurately attributed to MS, but some environmental factors appear to play a protective or exacerbating role in the MS risk process.

An environmental factor affecting this disease is a diet that is diverse in different regions and cultures. Epidemiology studies have suggested a possible correlation between diet and the prevalence of MS.[3] Also, empirical evidence has documented that diet may affect the immune response in MS.[4]

Nutrition may play a role in MS presentation and prevent the progression of MS in involved patients. Antioxidants, vitamin D, and vitamin B12 play a crucial role in this regard.[5] Furthermore, it is possible that a micronutrient deficiency and a high burden of heavy metals play a role in multiple sclerosis pathogenesis. Therefore, dietary treatment may be an effective approach to this disease.[6]

Dietary factors that reduce inhabitant central nervous system inflammation act against oxidative stress or protect mitochondria, which may prevent chronic demyelination and axonal/neuronal damage.[7]

Dietary factors influencing remyelination and repair could certainly be useful in MS. In a study, a proinflammatory diet was associated with an increased risk of MS.[8] Polyunsaturated fatty acids (PUFA) and alpha linoleic acid play a protective role against MS disease involvement.[9] Another study recommended a healthy diet for patients with MS.[10]

Furthermore, epidemiological studies have demonstrated that dietary habits are influential factors in the occurrence of *Helicobacter pylori infection* (HPI).[11] *Helicobacter pylori* (HP) is a gram-negative and microaerophilic bacterial pathogen with a global release. It causes gastritis through colonization in the human stomach but usually remains asymptomatic.[12]

The prevalence of HP is different throughout the world and depends mainly on regional living standards. In developing countries, 80% of the population may experience infection until the age of 20, whereas the prevalence ranges from 20% to 50% in industrialized countries.[13] In Iran, the prevalence rate of infection in people varies in different cities. For example, it is ~66% in Kashan, 86.8% in Tehran, and 31% in the south of Iran.[14] The results of studies investigating the association between HPI and MS differ, and in some cases, vary. Therefore, it seems that the infection plays a protective role and a role in the occurrence of MS.[15] This study aimed to investigate the correlation between serum anti-H. Pylori IgG antibody (HPIA), dietary intake, and MS as the three following aims. First, the correlation between HPIA and MS was compared to controls. Next, the correlation between dietary intake and MS was compared to controls. Last, the correlation between dietary intake and HPIA in MS cases and controls was compared.

METHODS

The statistical population of this case-control study consisted of patients with MS referred to the Unique Specific Diseases Clinic of MS in Ali-Ibn Abi Talib Hospital, the referral hospital of Rafsanjan city, Iran, from April 2017 to June 2018. This center manages all diagnostic, therapeutic, and supportive measures for patients with MS of the Rafsanjan population.

Sample size

The sample size was calculated with 95 persons in each group according to the study conducted by Mohebi et al.,[16] and the formula:

$$n = \left\{ z_{1-\alpha}\sqrt{\left[2\bar{p}(1-\bar{p})\right]} + z_{1-\beta}\sqrt{\left[p_1(1-p_1)+p_2(1-p_2)\right]} \right\}^2 / (p_1-p_2)^2$$

The sample size was determined to examine the difference in the ratio of indicators in the case and control groups. The appropriate sample size in each group was at least 90 persons with a 95% confidence level and 80% power in cases where the minimum distance ratio in the above two groups was at least 20%. The final sample size was considered at least 95 people in each group, after considering the 5% of missing samples.

Sampling method

A total of 100 subjects were selected by convenience sampling from the statistical population. Inclusion criteria were 16 – 59 years of age and patients diagnosed with clinical examination and cerebrospinal fluid analysis based on McDonald's diagnostic criteria.[17] Moreover, patients with the expanded disability status scale over four were excluded (due to the likelihood of failure to collaborate). As the control group, 95 relatives of patients (64% first degree and 36% second degree), after the maximum attempt to homogenize the age and gender (individual matching), were entered into the study using the convenience sampling method. First, the study objectives were explained to the participants and then written informed consent was obtained. A trained medical student and a neurologist performed history taking and examinations for both groups. Five cc blood samples were drawn from individuals in both groups and sent to the laboratory of Ali-ibn Abi Taleb Hospital to evaluate HPI. The HPIA level was measured by the ELISA method. The diet was then checked with the food frequency questionnaire (FFQ). The FFQ is a suitable tool to group food items. This questionnaire includes 136 food items, such as bread and cereals, legumes, meat and meat products, milk and dairy, various types of vegetables, eggs, fruits (fresh, compote, and juice), oil varieties, oilseeds, butter, sugars, dairy products (milk, yogurt, cheese, among others), and salt. For each item, a unit is specified regarding the amount normally used. For example, glasses, cups, teaspoons, and other measures are listed. In a face-to-face interview, the questioner asked the participants about the frequency of intake (never or less than once a month, one to three times a month, once a week, two to four times a week, five to six times a week, once a day, two to three times a day, four to five times a day, more than six times a day).[18] Then, the FFQ information was entered using Nutritionist IV Database Manager 4.0 software (Tinuviel Software, Warrington, UK) to calculate the amount of micronutrient intake per person (micronutrients are reported as grams). The reliability correlation coefficients of this questionnaire in a study by Saloheimo et al., (2015) showed that values ranged from 0.37 to 0.7.[19]

Statistical analysis

Finally, the data were analyzed by SPSS version 20 software (IBM Corporation, Armonk, NY).

A comparison between baseline characteristics of cases and controls was analyzed by the independent t-test and Chi-Square. The frequency of HPIA seropositivity was compared between the cases and the controls with the Chi-Square (χ^2) test. The normality of all quantitative data was tested by the one-sample Kolmogorov – Smirnov test. Regarding the results of this test, the distribution of variables was non-normal ($p > 0.05$). Therefore, the nonparametric equivalent of the t-test was used (Mann – Whitney U test). Pearson correlation coefficients were calculated to assess associations between the serum HPIA level and micronutrient intake. A p value < 0.05 was considered statistically significant. Odds ratios and confidence intervals were calculated.

Ethical considerations: This thesis was accepted by the Ethical Committee of Rafsanjan University of Medical Sciences (code: IR.RUMS.REC.1395.96).

RESULTS

Patients and samples

This case-control study was conducted on 192 subjects who were divided into two groups: MS cases (n = 97) and controls (n = 95), nine of whom disagreed with taking a blood sample (five cases and four controls) and only completed the questionnaire. Blood samples were drawn from 183 people despite completing the questionnaire. Table 1 presents a summary of the two groups' baseline characteristics.

Serum anti- H. pylori IgG antibody

The Mann – Whitney U test results indicated that the median serum HPIA level was significantly lower in MS cases than in controls ($p = 0.005$) (Table 1). The prevalence of *H. pylori*-positive (HP +) subjects was significantly lower in the cases than in the controls ($p = 0.021$) (Table 2). MS cases had lower odds of having HPIA (OR = 0.423, 95% CI 0.20 – 0.88) compared to controls.

Diet assessment

Mann – Whitney U test results demonstrated that the median consumption of glutamic acid, arginine, serine, aspartic acid, alanine, proline ($p < 0.001$), and caffeine ($p = 0.015$) were significantly lower in cases than in controls (Table 3).

Among many other important dietary intakes, vitamin D, vitamin B12, vitamin A, folate, PUFA, saturated fatty acids, omega-3, salt, polyphenols, including

Table 1. Characteristics of case and control groups.

	Case (n = 92)	Control (n = 91)	*p* Value
Age in years (mean ± SD)	36.88 ± 9.55	38.55 ± 10.83	0.056[a]
Gender (male/female)	16/81	16/79	0.94[b]
Level of Serum anti-Helicobacter pylori IgG antibody U/ml Median (Interquartile Range)	43.37 (114.63)	80.78 (179.35)	0.005[c]
Duration of illness in years(mean ± SD)	5.90 ± 4.90	–	–
Type of multiple sclerosis n (%)			
Clinically Isolated Syndrome (CIS)	4 (4.1)	–	–
Relapsing-remitting MS (RRMS)	53 (54.6)	–	–
Secondary progressive MS (SPMS)	39 (40.2)	–	–
Primary progressive MS (PPMS)	1 (1)	–	–
Treatment n (%)			
Glatiramer acetate	18 (18.3)	–	–
Interferon beta-1a IM	50 (51)	–	–
Fingolimod	5 (5.1)	–	–
Interferon beta-1a SC	10 (10.2)	–	–
Interferon beta-1b SC	15 (15.4)	–	–

[a]Independent Sample t-Test
[b]Chi-Square
[c]Mann-Whitney U test

Table 2. Frequency of positive Helicobacter pylori IgG antibody in the two study groups.

	Hp + n (%)	Hp− n (%)	95% Confidence Interval		Odds Ratio	*p* Value	Pearson Chi-Square
			Lower	Upper			
Case	66 (71.7)	26 (28.3)	0.20	0.88	0.423	0.021	0.532
Control	78 (85.7)	13 (14.3)					
Total	144 (78.7%)	39 (21.3%)					

Table 3. Amino acid and caffeine intake in case and control groups.

		Median	Interquartile range	*p* value (Mann – Whitney U)
Glutamic acid (g)	Case	69.891	107494	< 0.001
	control	2351.118	149584	
Arginine (g)	Case	11.616	16773.5	< 0.001
	control	23.174	245500	
Serine (g)	Case	12.834	20488.5	< 0.001
	control	24.552	30161	
Aspartic acid (g)	Case	25.172	28341.5	< 0.001
	control	41.504	34417	
Alanine (g)	Case	11.238	14015	< 0.001
	control	20.066	17712	
Proline (g)	Case	21.375	38539	< 0.001
	control	43.228	56492	
Caffeine (g)	Case	25.574	52253	< 0.001
	control	32.986	58604	

Table 4. Correlation between serum anti-Helicobacter pylori IgG antibody level and micronutrient intake in case and control groups.

Group	Variable		Linoleic acid	Lactose	Calcium	Molybdenum	Galactose	Leucine	Valine
Case (n = 92)	anti-Helico bacter pylori	Pearson correlation	0.030	0.136	0.117	0.117	0.80	0.019	0.155
		Sig. (2-tailed)	0.774	0.198	0.268	0.266	0.446	0.856	0.140
control (n = 91)	anti-Helico bacter pylori	Pearson Correlation	0.230	0.215	0.213	0.239	0.209	0.229	0.225
		Sig. (2-tailed)	0.028	0040	0.043	0.022	0.047	0.029	0.032

flavonoids and nonflavonoids, carotenoids, selenium, and zinc, were not significantly different between the two groups ($p > 0.05$).

Table 4 presents a summary of the correlation analysis results in cases and controls.

These results show no significant correlation in the cases. However, a positive weak correlation existed between levels of linoleic acid ($p = 0.028$), lactose ($p = 0.040$), Ca ($p = 0.043$), molybdenum ($p = 0.022$), galactose ($p = 0.047$), leucine ($p = 0.029$), valine ($p = 0.032$), and the level of HPIA in controls (Table 4).

DISCUSSION

In this study, a significant correlation was found between the mean HPIA level and MS risk reduction. Therefore, it may be reasonable to conclude that the presence of HPIA plays a protective role against MS. However, this issue is expressed with caution in a nonexperimental study. The results of a study by Malli et al., (2015) are consistent with our results. They reported that HPI caused resistance to MS since HPI can regulate the immune system and ultimately protect individuals against autoimmune diseases, such as MS, in the future.[15]

Mohebi et al., (2013) concluded that HPI played a protective role against MS.[16] Salim et al., obtained similar results.[20] Although Allameh et al., (2016) indicated that previous infection with HP played a protective role against MS, this correlation was not significant.[21] Following HPI, the proinflammatory factors of TH1 and TH17 in the body, causing it to cope with the infection. However, HP confronts these defenses through induction of TH2 and regulatory T cells by producing IL10 anti-inflammatory factor. The suppression of TH1 and TH17 regulates inflammation in the brain and spinal cord in MS. Therefore, HPI plays a protective role against MS.[22]

Pedrini et al., (2015) and Yao et al., (2016) also stated that HPI was a protective factor against MS.[23,24] Deretzi et al., (2016) reported that the prevalence of HPI was significantly higher in patients with MS than in controls. HP+ patients also had higher inflammatory factor serum concentrations,[25] which are inconsistent with the present study results.

Pakpoor et al., (2018) demonstrated no difference between patients and controls in consuming fats, proteins, carbohydrates, sugars, fruits, and

vegetables.[26] Ghazavi et al., (2019) stated that meat intake was higher in patients than in controls.[27]

Our study results revealed that the mean consumption of glutamic acid, arginine, serine, aspartic acid, alanine, proline, and caffeine was significantly higher in healthy subjects than in patients. However, it did not find a significant difference in macronutrients between patients and controls, as in the study conducted by Pakpoor.[26]

In a study by Massa et al., (2013), caffeine intake was not correlated with the risk of MS, being inconsistent with our study results.[28] However, Hedstrom et al., (2016) reported that caffeine intake reduced the risk of MS, which is consistent with our study results.[29]

Cortese et al., (2019) revealed no association between certain minerals (potassium, magnesium, calcium, phosphorus, iron, zinc, copper, and manganese) and MS risk,[30] which is consistent with our study results.

Bromely et al., (2018) stated that a decrease in carbohydrate intake and an increase in cholesterol, folate, iron, and magnesium intake could improve the performance of patients with MS. However, they found no correlation between the use of these macronutrients and micronutrients and MS in the present study.[31]

The above studies suggest that it is reasonable to correlate MS with diet. Hadgkiss et al., (2015) stated that the intake of fruits and vegetables reduced disease activity and disability.[10] In this regard, Toro et al., (2019) showed a significant difference in the consumption of sugary drinks and fast food between MS and healthy subjects. They also found no significant difference in the consumption of dairy products, gluten, meat, coffee, seafood, fruits, vegetables, eggs, and grains between MS and healthy subjects.[32]

Mashinchi et al., (2012) stated that the consumption of olive oil, nuts, fish, and vegetables, all containing omega-3, improved the symptoms of patients with MS.[33] It has been indicated that vitamin D deficiency increases the odds ratio of MS. Also, increased cadmium in the soil in residential areas (which can increase the amount of this substance in water or plants) may be associated with an increase in the prevalence of MS.[34] Research study findings demonstrated that the serum iron level in patients with MS was lower than that in healthy subjects. The serum copper and zinc levels were lower in patients with MS than in healthy subjects.[35] Some researchers have suggested that higher consumption of fruit and vegetables may correlate with the reduction of MS risk.[36]

In the study conducted by Shu et al., (2019) and Mard et al., (2014), HPI was shown to be related to high-salt diets more than high grain-vegetable diets.[37,38] Nevertheless, other studies did not demonstrate such a relationship.[39] Our study applied a unique research strategic approach to dietary intake and H-pylori relation in patients with MS, which could be used in further studies to compare and find a cause-and-effect relationship.

Our study had some limitations. One of our limitations is that it was impossible to say which routine diet is better based on our results because it requires further analyses.

Another limitation was the use of seropositivity to indicate HPI, which may not show active HPI produced as contracted in some studies. However, chronic infection of H-pylori might have a unique effect on the person's immunity by lowering the incidence of MS in the future. Therefore, checking seropositivity is useful, as some studies suggested. Another limitation was the use of dietary intake information, with a questionnaire completed only once.

The authors offer a cohort study from childhood to adolescence and a full report on annual dietary intake during these years for a better understanding of the nutritional backgrounds of people suffering from MS in the previous years.

CONCLUSIONS

The current study aimed to investigate the correlation between HPIA level, micronutrient dietary intake, and MS. This study's results demonstrated that the presence of IgG antibodies was found more with the absence of MS disease. Furthermore, it revealed the deficiency of dietary intake, including multiple amino acids and caffeine, in the MS cases compared to the controls. However, in controls, the levels of some dietary intake were positively correlated with the level of HPIA. These findings revealed a complicated relationship between dietary intake, HPIA, and MS, which require additional analyses and studies for use as prescriptions for patients. Therefore, it is

recommended that another analytical study about foods, including these dietary intakes, be conducted.

The authors suggest a cohort study of food intake and the incidence of MS. Furthermore, it is proposed that HPI be followed up over the years to obtain more complete results.

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