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Original Article

Internal Medicine Section

The Association between Helicobacter Pylori Infection and Parkinson's Disease: A Case-Control Study

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ABSTRACT

Introduction: Conflicting results have been reported about the association between *Helicobacter pylori* infection and Parkinson's disease.

Aim: To evaluate the relation between *H. pylori* infection and Parkinson's disease in patients living in northern Iran.

Materials and Methods: In this case-control study, 99 consecutive patients with Parkinson's disease visiting a Neurology Clinic were included. Also, 297 controls were chosen from the participants of the Amirkola Health and Ageing Project, who were matched to the patients with Parkinson's disease for sex, age and educational level. *H. pylori* infection was assessed by IgG Enzyme-Linked Immunosorbent Assay. The severity of Parkinson's disease was assessed by using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Scale (HYS).

Results: A rate of 66.7% (n=33) of the patients with Parkinson's disease were positive for *H. pylori* infection, while it was 79.5% (n=236) in the controls {Odds Ratio (OR)=0.52, 95% Confidence Interval (CI)=0.31-0.86, p=0.01}. Scores of UPDRS and HYS were less in *H. pylori*-positive Parkinson's disease patients than in those who were not infected, however, the differences were not significant.

Conclusion: The results of this study suggest that *H. pylori* infection may protect people from Parkinson's disease. More definitive studies are necessary to confirm this finding.

Keywords: Aging, Bacteria, Neurologic manifestations

INTRODUCTION

Parkinson's disease is known as a progressive neurodegenerative disorder associated with the loss of dopaminergic neurons in the pars compacta of the substantia nigra. This disease includes a range of motor disorders (bradykinesia, rigidity, tremor at rest) as well as non-motor disorders (autonomic dysfunction, pain, depression, dementia, digestive system problems, sleep disorders) [1-3]. In the 21st century, Parkinson's disease is regarded as the second most prevalent central nervous system disease after Alzheimer's disease and one of the most common causes of disability in older age-to the extent that age is one of its major risk factors [4,5]. The standardised prevalence of Parkinson's disease based on age distribution is estimated as 1601 out of 100,000 individuals in Europe, North America, and Australia, compared with 646 out of 100,000 individuals in Asia [4]. It could be considered a disease of developed countries.

Parkinson's disease consists of several complicated pathological features with unidentified aetiology [6,7]. According to the previous studies, a myriad of genetic, environmental, and immunologic factors may be responsible for the destruction of dopaminergic neurons [8]. Environmental factors such as exposure to toxins and infectious agents like *Helicobacter pylori* are found to be probably involved with this disease [9]. *H. pylori* are gram-negative bacterium that causes chronic infection in about half of the human population, but it is a disease of developing counties like Iran. The chronic infection is usually acquired during childhood and it remains in the body until it is cured [10,11].

Over the past years, some reports showed high rates of *H. pylori* infection among patients with Parkinson's disease, and stated that *H. pylori* may be a risk factor for Parkinson's disease and its related motor dysfunction outcomes [12-14]. Despite these surveys, some other studies had contrary findings [15-17]. Considering that the available studies on this topic are not enough and the conflict has not been resolved yet, it needs to be explored more through new surveys, potentially helping to resolve the contradictions. Therefore, this study aimed to investigate the relationship between *H. pylori* and Parkinson's disease and motor dysfunction of the patients with Parkinson's disease, in an area of the world with a high prevalence of *H. pylori* [10].

MATERIALS AND METHODS

Study population

In this case-control study, the consecutive patients with Parkinson's disease were recruited from the Neurology Clinic of Rohani Teaching Hospital in Babol, Northern Iran, during routine outpatient visits between March 2017 and September 2017. The Parkinson's disease was diagnosed by a neurologist based on the usual clinical signs, including tremor, hypokinesia, rigidity and loss of postural reflexes [18]. The exclusion criteria were those patients with neuroleptic-induced Parkinson's syndrome and those who had received medications to treat *H. pylori* infection. The Research Ethical Committee of Babol University of Medical Sciences and Health Services approved the study (code: MUBABOL.REC.1395.256). All individuals gave written informed consent.

The subjects in the control group were selected from individuals recruited to the Amirkola Health and Ageing Project (AHAP); its methodological details have been described previously [19]. Briefly, it is a comprehensive population-based cohort study conducted on the elderly aged 60 and above in Amirkola, located near Babol city, northern Iran. Those subjects who did not have a history of Parkinson's disease and had never received medications for Parkinson's disease and/or *H. pylori* infection were included. We tried to randomly select three controls from AHAP who were individually matched for sex, age (with 5-year ranges) and educational level (illiterate/literate) to each patient with Parkinson's disease. Each patient had three controls.

Clinical Evaluation

In order to determine the severity of Parkinson's disease, the scoring systems of the Unified Parkinson's Disease Rating Scale (UPDRS) [20] and the modified Hoehn and Yahr Scale (HYS) [21] were used. UPDRS has four parts regarding the following topics: **1)** Mentation, behaviour and mood (4 questions); **2)** Activities of daily living (13 questions); **3)** Motor examination (14 questions); **4)** Complications of therapy (11 questions). HYS consists of eight stages regarding motor severity of Parkinson's disease, from 0 (without signs of disease) to 5 (wheelchair bound or bedridden unless aided). In both scales, higher scores reveal worsening disability. Motor severity was evaluated when the patients were in their on-medication state. All clinical examinations were performed by one neurologist. Data regarding Parkinson's disease duration and demographic information, including age, sex, occupation (employed/unemployed/retired/homemaker), educational level (illiterate/literate), parent's educational level (illiterate/literate), marital status (married/unmarried), number of siblings, residency (urban/rural), smoker (yes/no), were collected from the Parkinson's disease patients.

Blood Sampling and *H. pylori* Serology Test

Blood sample from each patient after the clinical evaluation of Parkinson's disease was collected. The samples were centrifuged, and the serum sent to the immunology laboratory of the Babol University of Medical Sciences. The sera were stored at -20°C until analysed for *H. pylori* antibody. IgG Enzyme-Linked Immunosorbent Assay (ELISA) to test the samples for *H. pylori* seropositivity was used. For both the patients with Parkinson's disease and controls, the EUROIMMUN kit (Luebeck, Germany) was used, and *H. pylori* positivity was defined when the IgG antibody was >20 RU/mL according to manufacturer's instructions. Sensitivity and specificity of ELISA was more than 95%.

STATISTICAL ANALYSIS

SPSS version 19.0 software for data analysis was used. To compare baseline characteristics between case and control groups, chi-square and independent t-test analyses were used for categorical and continuous variables, respectively. The association between *H. pylori* infection and Parkinson's disease was assessed by univariable logistic regression analysis by estimating ORs and 95% CIs. To evaluate the relation between *H. pylori* infection and severity of Parkinson's disease, the mean scores of UPDRS and HYS were compared between *H. pylori*-positive and negative cases using independent t-test analysis. The p-value less than 0.05 were considered as statistically significant.

RESULTS

Characteristics of the Subjects

[Table/Fig-1] represents the baseline characteristics of 99 patients with Parkinson's disease and the 297 healthy controls. As shown, there was no significant difference between the groups.

Variables	Subjects		p-value
	Parkinson's disease (n=99)	Controls (n=297)	
Gender n (%)			
Male	58 (58.6)	174 (58.6)	1.000
Female	41 (41.4)	123 (41.4)	
Age (years), Mean±SD	70.49±9.10	70.36±7.99	0.894
Education n (%)			
Illiterate	56 (56.6)	168 (56.6)	1.000
Literate	43 (43.4)	129 (43.4)	

[Table/Fig-1]: Baseline characteristics of the Parkinson's disease cases and the matched controls.

Association between *H. pylori* Infection and Parkinson's Disease

In total, 76.3% (n=302) were positive for *H. pylori* infection. This rate was significantly less in the patients with Parkinson's disease (33/99, 66.7%) than in controls (236/297, 79.5%) (OR=0.52, 95% CI=0.31-0.86, p=0.01).

Association between *H. pylori* Infection and Severity of Parkinson's Disease

Comparisons were conducted into the clinical characteristics between *H. pylori* infected and non-infected patients with Parkinson's disease [Table/Fig-2]. No significant differences were observed between the two groups for any of the variables.

Variables	*Helicobacter pylori* ELISA		p-value
	Seropositive (n=66)	Seronegative (n=33)	
Gender n (%)			
Male	36 (54.4)	22 (66.7)	0.248
Female	30 (45.5)	11 (33.3)	
Age (years), Mean±SD	69.68±7.55	72.12±11.58	0.277
Occupation n (%)			
Employed	14 (21.2)	4 (12.1)	0.118
Unemployed	15 (22.7)	15 (45.5)	
Retired	10 (15.2)	5 (15.2)	
Homemaker	27 (40.9)	9 (27.3)	
Education n (%)			
Illiterate	37 (56.1)	19 (57.6)	0.886
Literate	29 (43.9)	14 (42.4)	
Father education n (%)			
Illiterate	63 (95.5)	28 (84.8)	0.068
Literate	3 (4.5)	5 (15.2)	
Mother education n (%)			
Illiterate	63 (95.5)	31 (93.9)	0.746
Literate	3 (4.5)	2 (6.1)	
Marriage n (%)			
Yes	52 (78.8)	24 (72.7)	0.501
No	14 (21.2)	9 (27.3)	
Number of siblings n (%)			
≤1	4 (6.1)	1 (3)	0.471
2-3	10 (15.1)	8 (24.2)	
≥4	52 (78.8)	24 (72.8)	
Residence n (%)			
Urban	22 (33.3)	11 (33.3)	1.000
Rural	44 (66.7)	22 (66.7)	
Smoking n (%)			
Yes	1 (1.5)	1 (3)	0.613
No	65 (98.5)	32 (97)	
Parkinson's disease duration (years), Mean±SD	5.83±4.49	6.85±5.54	0.330

[Table/Fig-2]: Comparison of baseline characteristics between *Helicobacter pylori*-positive and negative subjects in patients with Parkinson's disease.

[Table/Fig-3] shows the results of comparisons between *H. pylori*-positive and negative patients in the severity of Parkinson's disease. The mean scores of total and different parts of UPDRS were higher in *H. pylori*-negative cases vs. *H. pylori*-positive ones, but the observed differences were not significant. A similar trend was observed in the scores of HYS as well, that is, higher stages had a lower infection rate, but the observed differences were also not significant.

Variables	*Helicobacter pylori* ELISA		p-value
	Seropositive (n=66)	Seronegative (n=33)	
UPDRS*, Mean±SD			
Mentation, Behaviour and Mood	2.72±2.65	3.18±3.10	0.475
Activities of Daily Living	12.00±7.75	14.54±10.46	0.222
Motor Examination	31.14±14.37	33.73±20.98	0.526
Complications of Therapy	1.42±1.98	1.58±3.02	0.766
Total UPDRS	47.28±20.45	53.03±29.99	0.327
HYS**, Mean±SD	2.55±0.81	2.80±1.09	0.201

[Table/Fig-3]: Relationship between severity of Parkinson's disease and *Helicobacter pylori* infection in Parkinson's disease cases.
* Unified Parkinson's disease Rating Scale
** Hoehn and Yahr Scale

DISCUSSION

According to present study results, *H. pylori* infection was inversely associated with Parkinson's disease and this association was statistically significant. As per authors' review of the literature, this is the only study reporting that continuing infection with *H. pylori* appears to protect against Parkinson's disease. Contrary to present findings, a recent meta-analysis by Shen X et al., on data from eight studies, reported that *H. pylori* infection may increase risk of Parkinson's disease [22]. Concerning the symptoms of motor dysfunction, we found a negative relationship between *H. pylori* infection and severity of Parkinson's disease in both UPDRS and HYS, although the results were not significant. These data are also in disagreement with some previously published results. Tan AH et al., showed that Parkinson's disease patients who were positive for *H. pylori* infection, had worse Parkinson's disease severity (UPDRS part III and total UPDRS) in comparison with those *H. pylori*-negative cases [23]. No difference was found between the two groups in terms of HYS in their study. In contrast, Rahne KE et al., found that patients simultaneously suffering from Parkinson's disease and *H. pylori* infection had less motor fluctuations, dyskinesias and sleep disturbance as compared with Parkinson's disease patients who were not infected by *H. pylori* [24]. The authors suggested that this may be due to higher Levodopa dosage used in the *H. pylori*-positive patients with Parkinson's disease. In other words, considering that higher exposure of Levodopa in the brain can increase the risk of motor complications, and also given that *H. pylori* infection can probably decrease absorption of Levodopa, the less motor complications can be explained in the *H. pylori*-positive patients with Parkinson's disease [24,25].

Several hypotheses have been formulated and tested about the relationship between Parkinson's disease and *H. pylori*. For instance, it is argued that through its neurotoxic effects, *H. pylori* can cause the degeneration of dopaminergic neurons [26]. In addition, it has been reported that in patients where the infection is not eradicated or controlled by the immune system, Parkinson's disease will progress [27]. Evidence shows that *H. pylori* can disrupt the intestinal absorption of some drugs. Levodopa (a precursor of dopamine) is an example of this type of drug, but it is one of the most useful medications to treat the motor symptoms of Parkinson's disease. Patients with Parkinson's disease receiving treatment show fluctuations in their symptoms, which are said to be relatively dependent on variation in the absorption of the drug in these patients [28]. Infection caused by *H. pylori* may affect the bioavailability of Levodopa through destruction of the mucous membrane in duodenum, the first area to absorb Levodopa [29,30]. The bioavailability of Levodopa improves and motor fluctuations decrease in patients with Parkinson's disease when their *H. pylori* is eradicated [13,30,31].

LIMITATION

The conflict between current results and others can be examined from two aspects. If we want to accept the previous studies reporting the positive association between *H. pylori* infection and Parkinson's disease, then the present study, may be related to any mistake in procedure or study limitations. One of the limitations can be related to the diagnostic test used for confirmation of *H. pylori* infection, that is, serology was used instead of other tests, like urea breath test and/or stool antigen test, which have more accuracy compared with serology. Another limitation may be related to the two different centres in which the study was carried out. Of course, the latter may not be very important, because Amirkola is close to and subset of Babol city anyway. But if we want to rely on the present results as novel achievements, one justification is that there is probably an unknown mechanism by which *H. pylori* can protect persons from Parkinson's disease. Another reason may be due to the fact that the present survey was conducted in a developing country and many of our patients might have developed atrophic gastritis; many had been infected in childhood, then lost *H. pylori*, and in turn became *H. pylori* antibody negative.

A strong point of the present study was that a substantial number of cases and controls were enrolled. Also, the two groups were matched by three factors, including sex, age and educational level, which could increase reliability of present outcomes.

CONCLUSION

This study indicated that *H. pylori* infection may play a protective role against Parkinson's disease. However, more studies are needed to be designed to evaluate the relation between *H. pylori* infection and Parkinson's disease.

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