



## Evaluation of Inflammatory Cytokine and Anti *Helicobacter Pylori* Antibodies in the Pathogenesis of Parkinson's Disease

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### ABSTRACT

#### BACKGROUND:

Parkinson's disease is a neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the substantia nigra. Previous studies have shown that *Helicobacter pylori* (*H. pylori*) infection is associated with treatment and clinical response to Parkinson's disease. In the present study, we aimed to investigate the effect of *H. pylori* infection in the pathogenesis of Parkinson's disease.

#### METHODS:

75 patients who suffered from Parkinson's disease and *H. pylori* infection and 91 healthy controls were recruited. All the subjects were evaluated for serum IgM, IgG, and IgA antibodies as well as TNF- $\alpha$ , IL-6, and IL-4 cytokines by Enzyme-Linked ImmunoSorbent Assay (ELISA) methods.

#### RESULTS:

The participants included 102 men and 64 women with a mean age of  $66 \pm 10.2$  and  $52.6 \pm 10.7$  years in the patients and control groups, respectively. The level of IgG, TNF- $\alpha$ , IL-6 in the patients with Parkinson's infected with *H. pylori* was significantly more than that in the control group. In contrast, IgA was significantly lower in patients with Parkinson's disease compared with the control group.

#### CONCLUSION:

Probably, persistent infection with *H. pylori* could be effective in the pathogenesis of Parkinson's disease by dominating the systemic inflammatory profile. It is suggested that pro-inflammatory cytokines followed by *H. pylori* infection through the promotion of immune response or neurotoxicity might have a role in the pathogenesis of Parkinson's disease.

#### KEYWORDS:

Parkinson's disease; *Helicobacter pylori*; Pro-inflammatory cytokines; Anti *H. pylori* antibodies.

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## INTRODUCTION

Neurodegenerative disorders are a common problem and their incidence increase with age. In Parkinson's disease, neural cell damage occurs due to a variety of reasons such as oxidative, metabolic, and ionic stress; infections; and aging.<sup>1</sup> The progressive degeneration of the neurons leads to cognitive and motor dysfunction and other symptoms of Parkinson's disease.<sup>2</sup> These mentioned changes are also seen in physiological processes in frontotemporal dementia, amyotrophic lateral sclerosis, Alzheimer's disease, and the parkinsonian plus cases.<sup>3</sup> Physiological changes are mediated by neuroendocrine and hypothalamic pathways, reward pathways, motor systems, and the autonomic nervous system.<sup>3</sup>

The main feature of Parkinson's disease (PD), as a neurodegenerative disorder, is degeneration of dopaminergic neurons in the substantia nigra, which leads to a wide range of motor features such as tremor, imbalance in motion, muscle stiffness, bradykinesia,<sup>4</sup> and non-motor and neuropsychiatric impairment like gastrointestinal dysfunctions including constipation, autonomic dysfunction, hyposmia, sleep disorders, and depression, which may be present before motor symptoms.<sup>1-3</sup>

The etiology of this disease is unknown, but genetic and environmental factors such as toxins and infectious agents may be involved.<sup>8</sup> The progressive multi-system neuronal degeneration and the essential role of the gastrointestinal (GI) system in the development of this disease are presented as a hypothesis.<sup>4-8</sup>

The enteric nervous system is known as "the second brain" since the digestive tract contains a very complex neural network and a multitude of neurotransmitters that act very similar to the function of the brain. In addition, viruses and bacteria in the digestive tract help to regulate the emotional state.<sup>14</sup> Therefore, any changes in the digestive tract may be correlated to the onset of pathological conditions.

For the first time in 1960, it was shown that there was a relationship between *Helicobacter pylori* (*H. pylori*) infection and Parkinson's disease. In patients with Parkinson's disease, the gastric ulcer was common, but it was initially considered as an independent part of the disease; therefore, GI problems were the symptoms that patients experienced, and gastritis is seen as hypokinesia

in patients with Parkinson's disease.<sup>9-12</sup> Several studies have shown that infections caused by excessive growth and involvement of cytomegalovirus, Epstein Barr virus, herpes simplex virus type-1, and *H. pylori* in the small intestine have a role in the etiology of Parkinson's disease.<sup>8,13</sup>

*H. pylori* is a bacterium found on the luminal surface of the gastric epithelium, which can cause chronic inflammation of the underlying mucosa.<sup>8</sup> Helicobacter infection is very common in Asian countries.<sup>14,15</sup> People are usually infected in childhood, and they may not have clinical symptoms; in these cases, GI and extra GI disorders are seen.<sup>22</sup> Several studies have shown that in patients with Parkinson's disease, HP infection occurs and elimination of the infection causes a significant improvement in motor symptoms.<sup>22</sup>

In many studies, it has been shown that by elimination of HP in Parkinson's disease, motor symptoms, especially fluctuations improved, causing an effective improvement in the clinical response to levodopa.<sup>16-18</sup> Only in two studies, it was shown that there was a correlation between Helicobacter infection and Parkinson's severity.<sup>26</sup>

Although, neurodegenerative changes after *H. pylori* infection in patients with Parkinson's disease are not known. However, *H. pylori* infection can cause inflammation through the intestinal tract and brain and increase the risk of developing Parkinson's disease.<sup>27</sup>

On the other hand, evidence suggests that *H. pylori* infection is associated with inflammation of the gut or excessive secretion of gastric acid, which reduces the solubility of levodopa that worsens motor symptoms in patients suffering from Parkinson's disease.<sup>28</sup>

In the present study, we investigated the correlation between Helicobacter infection and the pathogenesis of Parkinson's disease. Also, we checked some cytokines related to *H. pylori* infection and evaluated the possible pathologic role of these cytokines in patients with Parkinson's disease.

## MATERIALS AND METHODS

### Patients and control group

A total of 166 individuals, including 75 patients with Parkinson's disease and *H. pylori* infection who were visited and diagnosed by an expert neurologist in the neurology clinic affiliated to Shiraz University of Medical Sciences

and 91 healthy subjects without *H. pylori* infection who were referred for routine medical checkups participated in this study. *H. pylori* infection of the studied subjects was evaluated by stool Ag test, rapid urease test (RUT), and dyspepsia symptoms. Patients enrolled in the study were referred for stool antigen tests and rapid urease test in the setting of clinical symptoms of dyspepsia. Exclusion criteria were; the patients with *Parkinson-plus* syndromes (PPS), Parkinson's disease dementia, gastric cancer, acute or chronic renal failure, autoimmune diseases, and those who received anticholinergic, anti-inflammatory agents, antimicrobial drugs, or proton-pump inhibitors at least 4 weeks prior to sampling. A blood sample was taken after written informed consent was obtained from the participants. Individuals were categorized into two groups. Group I: subjects with Parkinson's disease and *H. pylori* infection (n=75); Group II: participants without Parkinson's disease and *H. pylori* infection (n=91). Patients with malignancy and autoimmune diseases and those who used anti-inflammatory drugs were excluded from the study. The protocol of this study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Ethics code: 92-01-13-6261). Clinical data, such as reflux, constipation, flatulence, cerebrovascular accident (CVA), dementia, heartburn, and smoking status, were collected from the patients' files.

### Sample Collection

Five ml of peripheral blood was taken from all subjects (75 patients and 91 healthy control), collected in tubes containing Ethylene-Diamine-Tetra- Acetic acid (EDTA) anticoagulant, followed by centrifugation at 189 g, 4°C for 15 minutes, and stored frozen at -70°C.

### Anti-*H.pylori* Antibodies Assay

Serum samples were isolated for the enzyme-linked immune sorbent assay (ELISA) test. The serum levels of anti- *H. pylori* IgM, IgA, and IgG antibodies were measured using a commercially available *H. pylori* IgA/ IgG/IgM ELISA kit (IBL, Hamburg, Germany). The assay determined the serum titer of anti- *H. pylori* antibodies on the basis of a sandwich ELISA method. Anti- *H. pylori* antibodies were reported as U/mL, according to the manufacturer's instructions.

### Cytokines Assay

The serum levels of tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, and IL-4 were measured by ELISA kits specific for these cytokines (bioscience, Campus Vienna Biocenter, Vienna, Austria) on the basis of the sandwich ELISA method. The concentrations of TNF- $\alpha$ , IL-6, and IL-4 were reported as pg/mL, according to the manufacturer's instructions.

### Statistical Analysis

Chi-square test was used to calculate the qualitative variables. The Mann-Whitney U-test was used to evaluate the cytokines and antibodies level between the patients with Parkinson's disease and the control group. Statistical analysis was performed using SPSS software (version 18, SPSS Inc, Chicago, IL, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Study participants

A total of 166 individuals, including 75 patients with Parkinson's disease and *H. pylori* infection and 91 healthy subjects without *H. pylori* infection as the control group participated in our study. The subject's demographic and clinical characteristics are summarized in table 1. In our study, we showed that clinical manifestations, such as reflux, constipation, CVA, dementia, and DM, were significantly more prevalent in patients with Parkinson's disease and *H. pylori* infection compared with the healthy subjects. There was a significant difference in the mean age of the patients with Parkinson's disease and *H. Pylori* infection and the control group, but there was a significant difference in sex only in patients with Parkinson's disease (table 1).

### Anti-*H. Pylori* Antibodies Levels in Patients with Parkinson's Disease and *H. Pylori* Infection and Control Group

In comparison with Parkinson's disease and control groups, the level of IgG increased significantly in patients with Parkinson's disease and *H. pylori* infection ( $P \leq 0.0001$ ). In contrast, anti-*H.pylori* IgA antibody was significantly lower in patients with Parkinson's disease compared with the healthy subjects ( $P \leq 0.001$ ). Meanwhile, IgM levels decreased in the patients with Parkinson's disease

**Table 1:** The symptoms, and medical history related to the patients with Parkinson's disease and *H. Pylori* infection, and the control group

Clinical data		Parkinson's Disease No (%)	Healthy Control No (%)	P value
Age		65.96±10.479	52.60±10.25	0.001
Sex	Male	53 (70.7%)	49 (53.8%)	0.03
	Female	22 (29.3%)	42 (46.2%)	
Reflux	Yes	15 (20%)	39 (43.8%)	0.001
	No	60 (80%)	50 (56.2%)	
Constipation	Yes	35 (46.7%)	4 (4.5%)	<0.001
	No	40 (53.3%)	85 (95.5%)	
Flatulence	Yes	10 (13.3%)	12 (13.5%)	0.98
	No	65 (86.7%)	77 (86.5%)	
CVA	Yes	6 (9.5%)	0 (0.0%)	0.003
	No	57 (90.5%)	89 (100%)	
Dementia	Yes	17 (27.0%)	0 (0.0%)	<0.001
	No	46 (73.0%)	89 (100%)	
Heartburn	Yes	12 (19.0%)	29 (32.6%)	0.06
	No	51 (81.0%)	60 (67.4%)	
DM	Yes	3(4.7%)	27(30.3%)	<0.001
	No	60(95.3%)	62(69.7%)	
Smoking	Yes	16 (25.4%)	41 (46 %)	0.01
	No	47(74.6%)	48 (54%)	
Diet	Vegetarian	2 (3.2%)	0 (0.0%)	0.2
	Nonspecific diet	60 (96.8%)	41 (100%)	

CVA: Cerebrovascular Accident, DM: Diabetes mellitus

compared with the control group, but the difference was not significant ( $P=0.06$ , figure 1).

### Serum Cytokine levels in Patients with Parkinson's Disease and *H. Pylori* infection and the Control Group

We observed a significant increase in IL-6 and TNF- $\alpha$  levels in the patients with Parkinson's disease group compared with the control group ( $P\leq 0.001$ ,  $P\leq 0.001$ , respectively). Similarly, we found higher levels of IL-4 in patients with Parkinson's disease compared with the healthy group, but it was not statistically significant ( $P=0.07$ , figures 2).

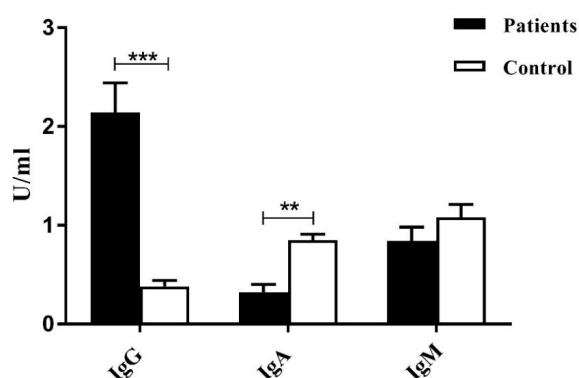
## DISCUSSION

Parkinson's disease is 1.5 times more common in men than women, and this male/female ratio increases with age.<sup>29</sup> In the present study, a significant difference was

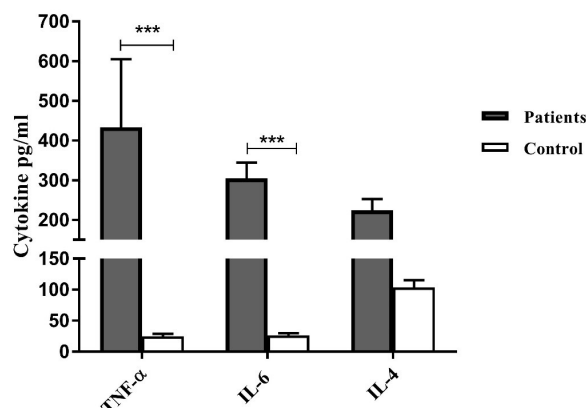
observed between the sexes in patients with Parkinson's disease.

In our study, we showed that two pro-inflammatory cytokines, TNF- $\alpha$ , was higher than those in patients with Parkinson's disease compared with the control group. In a study by Kouchaki and colleagues, it was indicated that the serum levels of TNF- $\alpha$  increased in patients with Parkinson's disease.<sup>30</sup> It has been reported that *H. pylori* infection induces microglia-mediated inflammation and neurotoxicity.<sup>31</sup> Moreover, Candelario-Jalil and others also showed that TNF- $\alpha$  was involved in blood-brain barrier (BBB) injury and increased the permeability of BBB through matrix metalloproteinase (MMP) up-regulation.<sup>32</sup>

In line with previous studies, we showed that the plasma levels of IL-6 were higher in patients with Parkinson's disease compared with the control group. In a study, Mogi



**Fig 1:** The serum levels of IgG, IgA, and IgM in patients with Parkinson's disease and *H. pylori* infection and control groups. The comparison of the serum concentrations of IgG, IgA, and IgM (U/mL) in patients with Parkinson's disease and *H. pylori* infection and control groups. (\*  $P \leq .05$ , \*\*  $P \leq .01$ , \*\*\*  $P \leq .001$ ).



**Fig 2:** The serum levels of TNF- $\alpha$ , IL-6, and IL-4 in patients with Parkinson's disease and *H. pylori* infection and control groups. The comparison of the serum concentrations of TNF- $\alpha$ , IL-6, and IL-4 (pg/mL) in patients with Parkinson's disease and *H. pylori* infection and control groups. (\*  $P \leq .05$ , \*\*  $P \leq .01$ , \*\*\*  $P \leq .001$ ).

and colleagues showed that IL-6 and IL-2 levels in the ventricular cerebrospinal fluid (VCSF) of patients with Parkinson's disease were higher than the control patients without parkinson's disease.<sup>33</sup> Moreover, Scalzo and co-workers indicated that concentrations of IL-6 were higher in the serum of patients with Parkinson's disease and were associated with physical and cognitive performance.<sup>34</sup> In another study, significantly higher levels of IL-6 and TNF- $\alpha$  were seen in the gastritis groups compared with the uninfected groups.<sup>35</sup>

Our results showed an increase in the IL-4 levels in patients with gastritis in comparison with the uninfected patients. Consistent with the present findings, Shamsdin and colleagues found that the serum levels of IL-4 increased in the group with chronic active gastritis.<sup>36</sup> Since IL-4 promotes Th2 cells differentiation and IgG production subsequently, high levels of IL-4 in patients with Parkinson's disease may be correlated with the higher production of IgG.

Esmael and colleagues also showed that patients with Parkinson's disease revealed higher serum IgG Abs against *H.pylori* compared with the control group, and patients with Parkinson's disease showed significantly higher scores of the unified Parkinson's disease rating scale (UPDRS) and the quality of life (PD-Q39) in comparison with patients without Parkinson's disease.<sup>37</sup>

Moreover, *H. pylori*-specific IgM shows no significant correlation between the patients with Parkinson's disease and healthy controls. The possible explanation is that Parkinson's disease is more prevalent among old age people, so it is reasonable to assume that IgM levels might be decreased by ageing in our studied subjects. In accordance with the current study, Dobbs and co-workers revealed that *H. pylori* IgM levels decreased by 0.9% per year.<sup>38</sup> Our results also indicated that *H. pylori* specific IgA, unlike IgG, was lower in patients with Parkinson's disease compared with healthy individuals. Dobbs and colleagues showed an increase in IgA with age by 0.5% per year. IgA1 and IgA2 in a quadratic relationship with age, respectively, increase after turning point of 57 years and decrease after turning point of 62 years. They assumed that IgA2 production by the bone marrow suppressed the IgA2 production by the gut-associated lymphoid tissue B cells until the development of mucosal tolerance. Moreover, they showed that IgG could not be affected by age, serological status, or their interaction.<sup>38</sup>

It seems that a decrease in IgM and mucosal IgA2 facilitates the persistence of *H. pylori* infection in the GI tract. In these conditions, excessive accumulation of colonic  $\alpha$ -synuclein, in turn, may underline the neo-antigens formation and unfolded protein response, prime auto-reactive T cells, and B cells to production of cross-



reactive IgG in normal healthy individuals. Transfer of  $\alpha$ -synuclein from the gut to CNS through the vagus nerve could direct auto-reactive responses to the brain.<sup>19-21</sup>

In support of this theory, Vojdani and colleagues show that specific monoclonal antibody made against A $\beta$ <sub>42</sub> binds not only to the A $\beta$ , tau, and  $\alpha$ -synuclein, but also to the bacteria, bacterial toxins, and viruses that have not previously been described as being involved in neurodegenerative diseases.<sup>42</sup>

Previous studies have shown that *H. pylori* may stimulate brain microglia and cause nerve damage by stimulating the vagus nerve or by producing a humoral immune response that produces pro-inflammatory cytokines and activation of leukocytes that cross the blood-brain barrier.<sup>22,23</sup>

Our results demonstrated increased pro-inflammatory cytokines such as IL-6 during the immune-pathologic responses. Also, we found that an increased level of IL-4 caused a high level of IgG in *H. pylori* infection. On the other hand, excessive secretion of antibodies and persistence of anti-*H. pylori* antibodies in patients with Parkinson's disease may increase the likelihood of Parkinson's disease due to the interaction with neuronal antigens induced by *H. pylori* molecular mimicry.

## CONCLUSION

*H. pylori* infection was shown to considerably impair the mucosal antibodies secretion. It is likely that a persistent infection with *H. pylori* could be effective in the pathogenesis of Parkinson's disease by dominating the systemic inflammatory profile. It is suggested that pro-inflammatory cytokines followed by *H. pylori* infection through promotion of immune response or neurotoxicity might have a role in the pathogenesis of Parkinson's disease.

## LIMITATIONS

Some confounding factors such as decreased GI motility in Parkinson's disease may be misinterpreted with *H. pylori* clinical symptoms. It is recommended that future studies enroll more cases.

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## ETHICAL APPROVAL

There is nothing to be declared.

## CONFLICT OF INTEREST

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

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