

WJGP 5th Anniversary Special Issues (1): *Helicobacter pylori****Helicobacter pylori* and neurological diseases: Married by the laws of inflammation**

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Abstract

The purpose of this paper is to review current information about the role of inflammation caused by *Helicobacter pylori* (*H. pylori*) infection in neurological diseases such as Parkinson's disease, Alzheimer's disease, Guillain-Barré syndrome, multiple sclerosis, and other inflammatory diseases including ischemic stroke. Infection with *H. pylori* usually persists throughout life, resulting in a chronic inflammatory response with local secretion of numerous inflammatory mediators including chemokines [interleukin (IL)-8, macrophage chemotactic protein (MCP)-1, growth-regulated oncogene (GRO)- α] and cytokines [IL-1 β , tumor necrosis factor (TNF)- α , IL-6, IL-12, interferon (IFN)- γ], which can pass into the circulation and have a systemic effect. The persistence of detectable systemic and local concentrations of inflammatory mediators is likely to alter the outcome of neurological diseases. These pro-inflammatory factors can induce brain inflammation and the death of neurons and could eventually be associated to Parkinson's disease and also may be involved in the development of Alzheimer's disease. However,

most neurological diseases are the result of a combination of multiple factors, but the systemic inflammatory response is a common component and determinant in the onset, evolution, and outcome of diseases. However, more studies are needed to allow understanding of the effects and mechanisms by which the inflammatory response generated by *H. pylori* infection affects neurological diseases.

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Key words: Gastrointestinal diseases; *Helicobacter pylori*; Immune disease; Mediators of inflammation; Neurodegenerative diseases**Core tip:** Neurological diseases such as Parkinson, Alzheimer, Guillain-Barré syndrome, multiple sclerosis, and ischemic stroke are the result of a combination of multiple factors, but the chronic and systemic inflammatory response to *Helicobacter pylori* could be a common component and determinant in the onset, evolution, and outcome of these diseases.Álvarez-Arellano L, Maldonado-Bernal C. *Helicobacter pylori* and neurological diseases: Married by the laws of inflammation. *World J Gastrointest Pathophysiol* 2014; 5(4): 400-404 Available from: URL: <http://www.wjgnet.com/2150-5330/full/v5/i4/400.htm> DOI: <http://dx.doi.org/10.4291/wjgp.v5.i4.400>**INTRODUCTION**

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that chronically infects more than 50% of the human population^[1]. It is well known that infection with the bacterium increases the risk of gastric diseases including peptic ulcers and gastric cancer^[2,3]. *H. pylori* is able to infect and live persistently in the human stomach and elicits

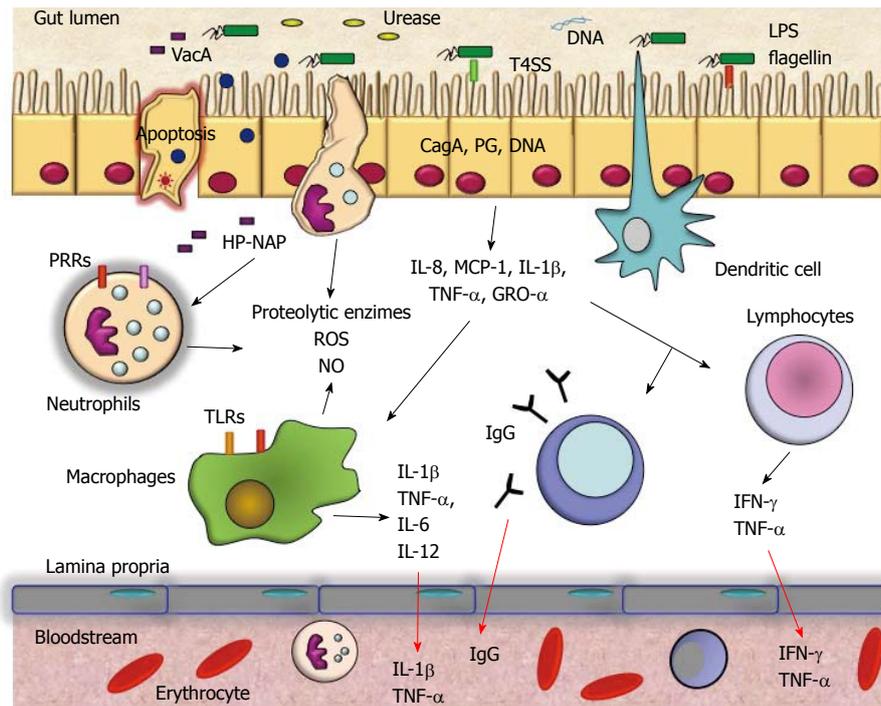


Figure 1 The inflammatory response in *Helicobacter pylori* infection. Immune cells are recruited to the lamina propria of the gastric epithelium by chemokines and cytokines (IL-8, MCP-1, GRO- α , IL-1 β , TNF- α) produced by epithelial cells or directly by bacterial products including *H. pylori* neutrophil-activating protein, VacA, and urease. At the site of infection, the immune cells are activated and exert their effector functions, including the production of cytokines (IL-1 β , TNF- α , IL-6, IL-12, IFN- γ , chemokines (IL-8, MCP-1), proteolytic enzymes, oxide nitric (NO) and reactive oxygen species (ROS). PG: Peptidoglycan; T4SS: Type IV secretion system; IL: Interleukin; TNF: Tumor necrosis factor; MCP: Macrophage chemotactic protein; GRO: Growth-regulated oncogene.

severe acute and chronic inflammatory responses, which may be of variable magnitude depending on the host's genetic makeup and lifestyle^[4]. Differing inflammatory responses among hosts may help to explain the different outcomes of infection with *H. pylori*^[5]. *H. pylori* induces infiltration to the gastric mucosa of neutrophils, macrophages, dendritic cells, T and B cells, and stimulates secretion of interleukin (IL)-8, tumor necrosis factor (TNF)- α , IL-6, IL-1 β , IL-12, IL-10, and interferon (IFN)- γ ^[5]. This persistent response causes significant changes in the physiology of the stomach by direct damage to the cells or by regulating cell proliferation and apoptosis (Figure 1). Neutrophils and macrophages release reactive oxygen and nitrogen species, which may induce irreversible changes in the gene expression of cells of the gastric mucosa. The levels of these chemical species decrease when *H. pylori* infection is eradicated^[6]. The secretion of inflammatory mediators is likely to have serious biological implications at the local and systemic level. For example, IL-8 is a chemoattractant of neutrophils and mediates responses to bacterial infection and to autoimmune disease^[7]. IL-6 activates target genes involved in cellular differentiation, survival, apoptosis, and proliferation^[8]. IL-6 may perpetuate inflammation by inducing antiapoptotic signals mediated by signal transducer and activator of transcription 3. IL-1 β signaling is absolutely necessary for the efficient control of *H. pylori* infection. IL-1R(-/-) mice failed to develop protective immunity against *Helicobacter*-associated gastritis and gastric preneoplasia as a result of

their inability to generate *Helicobacter*-specific T helper (Th)1 and Th17 responses^[9].

IL-10 is an anti-inflammatory cytokine that inhibits the production of proinflammatory cytokines by inhibition of Th1 lymphocytes and stimulation of B cells and Th2 lymphocytes, and consequently it downregulates the inflammatory response^[10]. This cytokine is very important for the maintenance of a balanced response in gastric inflammation. In contrast, IFN- γ mediates responses to bacterial infection and autoimmune disease. It is upregulated in the gastric mucosa by chronic *Helicobacter* infection^[11]. This cytokine is important in the production of gastric acid and its levels are correlated with the damage found in gastritis.

H. pylori infection has been associated with the development and progression of neurological diseases, principally by inducing systemic inflammation, molecular mimicry, and interference with the absorption of drugs. In this review, we summarize the most important research on this issue.

PARKINSON'S DISEASE

Parkinson's disease is the second most common neurodegenerative disease worldwide. It is characterized by the accumulation of cytoplasmic proteins, including α -synuclein, which leads to the progressive loss of dopaminergic neurons. The loss of dopaminergic neurons causes the resting tremors, rigidity and bradykinesia that are characteristic symptoms of the disease^[12]. *H. pylori* infection may

increase the risk of Parkinson's disease^[13]. The administration of L-3,4-dihydroxyphenylalanine (L-dopa), a precursor of dopamine, is used as a treatment for Parkinson's disease. *H. pylori* infection may affect the bioavailability of L-dopa by disrupting the duodenal mucosa, which is the site of primary absorption of L-dopa^[14,15]. Recent studies suggested that *H. pylori* eradication in patients with Parkinson's disease might improve the bioavailability of L-dopa and reduce motor fluctuations^[15-18].

Parkinsonism is a neurological syndrome that shares symptoms found in Parkinson's disease. It has been suggested that a peripheral immune response characterized by the presence of proinflammatory cytokines such as IL-8, IL-1 β , and TNF- α in the bloodstream induces a disruption of the blood-brain barrier and promotes microglia-mediated inflammation and neurotoxicity^[19-21]. Several studies have established that that proinflammatory factors associated with chronic gastrointestinal disease can induce brain inflammation and the death of dopaminergic neurons and could eventually be responsible for parkinsonism^[22-24]. Dobbs *et al*^[25] proposed that *H. pylori* infection predisposes to autoimmunity that results in neuronal damage leading to eventual parkinsonism. This was based on the observation of an age-associated increase in the levels of antibodies against *H. pylori* in Parkinson's patients, but this association is not clear, and other investigations are required to clarify it.

ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative disease characterized by both synaptic loss and neuronal death as a result of extracellular and intracellular accumulation of β -amyloid deposits and neurofibrillary tangles in brain regions important for memory and cognitive processes^[26]. The inflammatory response plays an important role in the pathophysiology of Alzheimer's disease. Higher levels of *H. pylori*-specific IgG antibody, IL-8 and TNF- α have been found in cerebrospinal fluid (CSF) of cognitively impaired Alzheimer's disease patients infected with *H. pylori*^[27,28], and it has been proposed that the inflammatory response induced by *H. pylori* may be involved in the development of Alzheimer's disease. This is consistent with some studies that observed an improvement in parameters of cognitive and functional status and the survival rate of Alzheimer's disease patients after eradication of *H. pylori*^[29,30]. However, Alzheimer's disease was independent of *H. pylori* status in a Japanese population^[31].

H. pylori-induced chronic atrophic gastritis causes a decrease in serum vitamin B concentration, thereby increasing the concentration of homocysteine^[26]. It has been shown that the serum homocysteine concentration correlates with the severity of dementia. Homocysteine-induced oxidative damage has been described in the brain of subjects with mild cognitive impairment, suggesting that oxidative damage may be one of the earliest events in the onset and progression of Alzheimer's disease^[30].

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is an acute inflammatory autoimmune neuropathy, presenting as a progressive motor weakness usually beginning in the legs, and can be triggered by a preceding bacterial or viral infection. Molecular mimicry of host structures by antigens present in the gastrointestinal pathogens *Campylobacter jejuni* and *H. pylori* are thought to be connected with the development of the autoimmune sequelae observed in Guillain-Barré syndrome^[32,33]. In a case-control study, it was found that serum anti-*H. pylori* IgG of patients was significantly higher than that of controls, that CSF anti-*H. pylori* IgG was positive in 80% of patients and in 20% of controls and that the CSF IgG titer was also significantly higher in patients than controls^[34]. Furthermore, specific IgG antibodies to vacuolating cytotoxin A (VacA) of *H. pylori* have been detected in the CSF of patients with Guillain-Barré syndrome. The sequence homology found between VacA and human ATPase A subunit suggests that antibodies to VacA bind to ion channels in Schwann cells, resulting in demyelination of motor neurons in these patients^[35]. Moreover, high levels of serum anti-*H. pylori* IgG antibodies closely correlate with a more advanced clinical status, and elevation of anti-*H. pylori*-specific IgG antibodies is associated with involvement of the proximal parts of peripheral nerves in patients with acute inflammatory demyelinating polyradiculoneuropathy, the most commonly observed subtype of Guillain-Barré syndrome^[32]. Most studies have included only a small sample, so more research is needed to confirm the association between *H. pylori* infection and Guillain-Barré syndrome.

MULTIPLE SCLEROSIS

Multiple sclerosis is the most common inflammatory demyelinating disease of the central nervous system. The association between *H. pylori* infection and multiple sclerosis is a controversial issue and there are few studies that address the problem. *H. pylori* infection is significantly less frequent in patients with conventional multiple sclerosis than in healthy controls or patients with opticospinal multiple sclerosis^[36]. However, *H. pylori* infection seems to be one of the risk factors for the development of anti-aquaporin 4 (AQP4) antibody-positive multiple sclerosis, and the eradication of *H. pylori* may be a possible adjunct therapy^[37]. Neuromyelitis optica is an inflammatory disease selectively affecting the optic nerves and spinal cord. Chronic persistent infection may contribute to the development of neuromyelitis optica through molecular mimicry between human AQP4 and bacterial AQP. In addition, *H. pylori* neutrophil-activating protein (HP-NAP) contributes to the pathology by inducing migration and activation of neutrophils^[37].

ISCHEMIC STROKE

The pathophysiologic mechanism for the majority of

ischemic strokes is occlusion of carotid or cerebral vessels. Infection with *H. pylori* as a risk factor for stroke is still an unresolved issue because of conflicting results. However, a recent meta-analysis showed that chronic infection with *H. pylori* and the presence of CagA-positive strains are statistically significant risk factors for ischemic stroke, especially for noncardioembolic ischemic stroke^[38,39]. Similarly, CagA-positive strains of *H. pylori* are significantly associated with atherosclerotic stroke in patients with an active infection^[34].

The mechanisms of the high risk for ischemic stroke conferred by chronic *H. pylori* infection are still not understood. It has been hypothesized that *H. pylori* activates platelets and affects coagulation, and it has been shown that six months after eradication of *H. pylori* infection, the plasma levels of total cholesterol, low-density lipoprotein-cholesterol, fibrinogen, and IL-8 were significantly lower than those in *H. pylori*-positive stroke patients and controls^[40].

CONCLUSION

Most neurological diseases are the result of a combination of multiple factors, but the systemic inflammatory response and the production of autoantibodies are common components and determinants in the onset, evolution, and outcome of these diseases. Future studies need to focus on determining the molecular mechanisms by which inflammatory mediators induced by *H. pylori* act on the brain, tipping the balance toward a pathological condition.

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