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Short Communication

Helicobacter pylori and the Central Nervous System: Neurophysiopathology and therapeutic Strategies in Psychiatry

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Abstract

The Helicobacter pylori (*H. pylori*) bacterium is a Gram-negative bacillus recognized in humans as responsible for a multitude of benign or malignant gastric diseases. Its identification in 1982 was the result of the valuable work of two Australian scientists and researchers, John Robin Warren and Barry James Marshall, who were awarded the Nobel Prize in Physiology or Medicine in 2005. Gastric infection with *H. pylori* is recognized as one of the most widespread chronic bacterial infections globally.

INTRODUCTION

The Helicobacter pylori (*H. pylori*) bacterium is a Gram-negative bacillus recognized in humans as responsible for a multitude of benign or malignant gastric diseases [1]. Its identification in 1982 was the result of the valuable work of two Australian scientists and researchers, John Robin Warren and Barry James Marshall, who were awarded the Nobel Prize in Physiology or Medicine in 2005 [2]. Gastric infection with *H. pylori* is recognized as one of the most widespread chronic bacterial infections globally. Approximately half of the world's population is estimated to be infected with different strains of *H. pylori*, with significant genetic disparities based on geographical and ethnic data [3]. In most cases, the transmission of the *H. pylori* bacterium occurs during childhood within the same family environment and can happen through oral-oral or fecal-oral routes. The spiral shape of the bacillus and its flagella facilitate its extreme mobility and its ability to colonize the gastric mucosa persistently, while its urease activity provides it with the ability to alter the epithelium and neutralize the extreme acidity of the gastric environment. Furthermore, numerous bacterial factors give *H. pylori* virulence characteristics, including vacuolating cytotoxin (VacA), the pathogenicity island (CagA), membrane protein (OipA), and protein (DvpA). *H. pylori* can thus cause acute or chronic gastritis, gastroduodenal ulcers, malignant stomach tumors, occult bleeding leading to iron deficiency with or without anemia, vitamin malabsorption, and immune thrombocytopenic purpura in adults [4]. Scientific publications addressing the subject of extra-gastric impacts caused by *H. pylori* in humans shed light on various physiopathological hypotheses and clinical effects related to the involvement of various tissues and organs, particularly the central nervous system. The role of *H. pylori* in psychotic symptoms in individuals genetically predisposed to schizophrenia has been suggested by authors [5], who hypothesized an alteration in the function of cerebral dopaminergic receptors and the neurotoxic effect of inflammatory markers induced by this bacterium. The connection between *H. pylori* and depression was suspected in a Chinese cross-sectional study involving women with infection [6]. A non-randomized prospective study aiming to determine the prevalence of *H. pylori* and anxious and depressive symptoms in patients with functional dyspepsia showed that over half of them were infected with the bacterium, and about one-third suffered from anxiety-depressive disorders [7]. A cross-sectional study involving Ethiopian children and adults with dyspepsia showed an increased prevalence of depression among subjects infected with *H. pylori* [8]. A narrative review also supports the hypothesis that *H. pylori* can influence the development of Alzheimer's disease, possibly through the bacterium's access to the brain through oral or nasal routes or by the passage of infected monocytes through the blood-brain barrier [9]. Additionally, by studying the effects of vacuolating cytotoxin

(VacA) released by *H. pylori* in mice, researchers concluded that the bacterium could induce anorexia and anxiety by migrating through the blood-brain barrier and activating the pituitary hormone ACTH (Adreno Cortico Tropic Hormone) receptors [10]. In a comprehensive review of the scientific literature, other authors have suggested the involvement of various physiopathological mechanisms in the neurological symptoms observed in patients infected with *H. pylori*, such as dysfunction of the gut-brain axis, alteration of the microbiota, modification of the production of intestinal neuropeptides, and the existence of neuroinflammation induced by the release of pro-inflammatory cytokines [11]. These mechanisms are also considered implicated in several neurological pathologies, including migraine, multiple sclerosis, and Alzheimer's and Parkinson's diseases. More recently published studies suggest a link between chronic *H. pylori* infection and the onset of inflammatory processes in the central nervous system through cellular and murine experimental models [12]. The authors demonstrated the role of outer membrane vesicles in activating the immune system in the tissues where they are released. The pathogenicity of *H. pylori* is partly explained here by the virulence factors contained in these vesicles, such as urease, the pathogenicity island (CagA), and vacuolating cytotoxin (VacA). In their work, the authors observed an increase in the production of pro-inflammatory cytokines such as interleukins 1β and 6, tumor necrosis factor (TNF-α), and inducible nitric oxide synthase (iNOS) when microglial cells were cultured in the presence of these vesicles. Furthermore, the authors suggest indirect virulence on the brain by *H. pylori* through iron, folate (vitamin B9), and cyanocobalamin (vitamin B12) malabsorption, as well as the emergence of an imbalance in the intestinal microbiota. Dysbiosis, considered capable of affecting the synthesis of tight junction proteins (Zonulin-1 and Claudin-5) and the action of adhesion molecules (Cadherins) in the intestine, increases intestinal permeability and consequently weakens the blood-brain barrier.

In the field of the physiopathology of neuropsychiatric disorders induced by *H. pylori*, published scientific research allows us to admit that chronic inflammatory processes are capable of causing or aggravating a depressive episode, even making it chronic or resistant to antidepressants, particularly through the harmful action of pro-inflammatory cytokines on neuronal function [13]. On the other hand, iron deficiency found in psychiatric patients is considered a factor that promotes the onset of certain psychiatric symptoms or disorders such as anxiety, depression, or schizophrenia [14]. The physiopathological mechanisms likely to explain the symptomatology in these patients thus appear to be multiple, such as the action of vacuolating cytotoxin (VacA) on the brain, the alteration of iron and/or vitamin B9 and/or B12 metabolism, the imbalance within the microbiota (dysbiosis) affecting both intestinal permeability and the synthesis of intestinal neurotransmitters, and finally, the release of pro- inflammatory cytokines induced by the presence of *H. pylori* in the gastric environment. In turn, these cytokines are recognized as capable of reducing the intracerebral synthesis of serotonin and melatonin by diverting tryptophan metabolism toward the kynurenine pathway, while simultaneously causing the production of quinolinic acid known to have a neurotoxic effect [15].

In the clinical practice domain, patients suffering from various neuropsychiatric disorders have, like the rest of the population, a risk of chronic *H. pylori* infection. Nevertheless, they can be considered particularly beneficial for the search for gastric infection by this bacterium given the various links observed and described in the scientific literature between *H. pylori* and neuropsychiatric disorders. According to the recommendations of the French Health Authority [4], the search for *H. pylori* is indicated, notably in patients with iron-deficiency anemia without a found cause or resistant to orally administered iron treatment, or chronic dyspepsia with a normal gastroscopy, or idiopathic vitamin B12 deficiency. Depending on the clinical situation, this search can be performed by fundic and antral biopsies (immunohistochemical study), or by a carbon-13-labeled urea breath test (stable and non-radioactive isotope of carbon 12) detecting the activity of *H. pylori* urease, or by detecting bacterial antigens in stools with a mixture of monoclonal antibodies, or by measuring specific Immunoglobulins (IgG) in the plasma. In cases where bacterial serology is positive, the confirmation of the infection must be performed using one of the other methods mentioned earlier. The treatment of gastric infection by *H. pylori* in psychiatric patients is not urgent and should be done orally, outside of any pregnancy and when psychiatric disorders have favored optimal adherence to antibacterial treatment. Indeed, the eradication treatment of *H. pylori*, which may be guided by the antibiogram, will involve triple or quadruple therapy, and its effectiveness will depend on the quality of the patient's therapeutic adherence. It is also necessary to consider the possible interactions between these treatments and prescribed psychotropes, as well as the risk of developing psychiatric disorders, such as sleep disturbances, anxiety, depression, manic episodes, or even iatrogenic psychotic symptoms, especially when treated with clarithromycin. Eradication of the bacterial infection should be checked at least four weeks after the end of the treatment using a carbon-13-labeled urea breath test or gastric biopsies. The verification of this eradication is even more necessary when psychiatric disorders are likely to compromise the good adherence to the antibacterial treatment in question. Any iron or vitamin B9 and B12 deficiencies must be treated as these vitamins are involved in the synthesis of neurotransmitters such as serotonin, melatonin, dopamine, and norepinephrine. Checking for the disappearance of all these biological abnormalities in a second step is necessary to optimize the chances of neuropsychiatric symptom remission. Patients who present psychiatric disorders associated with *H. pylori* infection and who, at the same time, suffer from nutritional deficiencies or resistant chronic depressive syndrome or functional dyspepsia (considered psychogenic in nature) may see their neuropsychiatric symptoms regress after the eradication of *H. pylori*. It appears crucial here to encourage collaborative work and information sharing between the psychiatrist and the gastroenterologist, aiming to strengthen the chances of clinical

remission on a neuropsychiatric scale. Future research aimed at assessing the various impacts of *H. pylori* in the field of mental health is required, given that the infection by this bacterium affects nearly half of the world's population. The field of mental health now appears indebted to Australian researchers who identified *H. pylori* more than forty years ago, and whose work currently stimulates a broad reflection on the role of this bacillus in the neurophysiopathology and therapeutic management of patients suffering from multiple psychiatric disorders.

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