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Research Article

Helicobacter Pylori and Psychiatric Disorders: Comorbidity and Therapeutic Perspectives

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ABSTRACT

Our observational study aims to investigate the extent of comorbidity between gastric infection caused by the bacillus *Helicobacter pylori (H. pylori)* and patients receiving psychiatric outpatient care. The study carried out by a psychiatrist includes adult patients who have received various psychotropic treatments for their different psychiatric disorders. The study, which lasted for three consecutive years, included 291 patients who underwent a blood test for iron status and measurement of plasma levels of vitamins B9 and B12. The investigation for *H. pylori* infection was motivated by the presence of treatment-resistant Depressive Episode, treatment-resistant Iron Deficiency, or Dyspepsia. The presence of the bacterium was confirmed through gastric biopsy or a Carbon-13 urea breath test. Analysis of data from 291 adult patients showed an infection rate of 32.3% by the bacillus *H. Pylori*. Eradication of the bacteria associated with oral supplementation with iron and/or vitamins B9 and B12 when necessary, resulted in a favorable response in 74% of positive *H. pylori* subjects who maintained their psychiatric follow-up. The reported improvement in neuropsychic symptoms included the reduction or disappearance of multiple symptoms, such as apathy, anhedonia, anxiety, sadness, cognitive complaints, feelings of derealization, and sleep disorders. The physiological mechanisms underlying the benefits of the treatment could be diverse, including on the one hand the regression of neuroinflammatory processes responsible for the hijacke of tryptophan metabolism towards the kynurenine pathway and the production of quinolinic acid, and on the other hand, the deleterious effects of vacuolating cytotoxin (VacA) on the brain.

INTRODUCTION

The family *Helicobacteraceae* which is part of the Epsilon subdivision of *Proteobacteria* is dominated by the genus *Helicobacter*. Its type species is the germ *Helicobacter pylori (H. pylori)* which is a Gram-negative bacillus and recognized as a pathogenic agent responsible for a multitude of gastrointestinal diseases in humans [1]. Its identification is the result of two Australian biologist researchers' work, Barry James Marshall and John Robin Warren, who were awarded the Nobel Prize in Medicine and Physiology in 2005 for their discovery of this bacterium in the gastric mucosa in 1982 [2,3]. The prevalence of *H. pylori* infection reaches half of the global population, although there is significant genetic, geographic, and ethnic disparity [4]. In France, the prevalence is estimated to be between 15% and 30% of the population [5], and transmission usually occurs during childhood through oral-oral or fecal-oral routes, such as contact with saliva, vomiting, feces, or sharing utensils within the family circle. *H. pylori*

primarily affects the stomach mucosa, but its virulence can also affect intra and extra-gastric tissues and organs through various biological mechanisms. Indeed, the bacterium's urease activity allows it to proliferate in the acidic environment of the mucus (pH <2), while its spiral shape and flagella promote its extreme mobility and its ability to alter and colonize the mucosa for a long time. Moreover, depending on the strains involved, multiple bacterial factors are found, which provide *H. pylori* with virulence characteristics, including the DvpA protein, the pathogenicity island (CagA), the OipA membrane protein, and the Vacuolating Cytotoxin (VacA). *H. pylori* can induce inflammatory and nutritional pathologies such as acute or chronic atrophic gastritis, gastro-duodenal ulcers, gastric adenocarcinoma and MALT lymphoma, appetite and weight disorders, occult chronic digestive bleeding leading to iron deficiency or anemia, vitamin malabsorption, and immune thrombocytopenic purpura in adults [5]. The literature on extra-gastric disorders caused by this bacterium provides numerous insights into the remote impact of this bacterium on various tissues and organs, including the brain. In a study investigating the potential role of *H. pylori* in psychotic symptoms in individuals genetically predisposed to schizophrenia [6], the authors proposed various hypotheses, such as the alteration of dopamine receptor function and the neurotoxic effect of inflammatory markers induced by the bacterium. The link between *H. pylori* and depression was suggested in women in a Chinese cross-sectional study involving patients infected with the bacterium [7]. A non-randomized prospective study aimed at determining the prevalence of *H. pylori* and anxiety-depressive symptoms among patients with functional Dyspepsia showed that more than half of them were infected with *H. pylori*, with approximately one-third experiencing anxiety-depressive disorders [8]. A cross-sectional study involving Ethiopian children and adults with Dyspepsia indicated an increased prevalence of depression according to the PHQ-9 evaluation questionnaire among *H. pylori*-infected subjects [9]. By studying the impact of *H. pylori* treatment in patients with fibromyalgia, authors [10] observed a significant regression of tender points in infected patients after three weeks of anti-infective treatment, but no notable effect on their sleep disorders, anxiety, and mood. Our study aims to observe, on the one hand, the extent of *H. pylori* infection in patients monitored in private psychiatric consultations, and on the other hand, the impact of eradicating the germ on the evolution of neuropsychiatric symptoms. Later, we will discuss the physiopathological hypotheses involved in neuropsychiatric symptoms and provide therapeutic conclusions.

METHODS

This is an observational study conducted by a psychiatrist in an urban setting, including adult patients who have received treatment for various psychiatric disorders. The study was carried out over a period of three years, from January 2020 to December 2022. The search for *H. pylori* infection among patients was motivated by the presence of one or more of the following clinical criteria: a Depressive Episode resistant to two antidepressants prescribed successively at optimal doses, a Iron Deficiency (with or without anemia) resistant to one first treatment with oral iron, and Dyspepsia sometimes attributed to psychogenic causes and related to the patient's anxiety state. We collected data from 291 patients, including 199 women and 92 men, aged between 18 and 88 years, with a mean age of 43 years old. The psychiatric diagnoses motivating the patients' treatment included the following disorders according to the International Classification of Diseases, 10th edition (ICD-10): Social Phobia, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, Mood Disorder, Eating Disorders, Mental and Behavioral Disorders due to psychoactive substance use, Schizoaffective Disorder, Non-organic Psychosis, and Non-organic Insomnia. The patients had received psychiatric treatment ranging from a few months to several years, either at their own request or upon referral by their general practitioners. The psychiatric care provided to the patients included either psychodynamic psychotherapy alone or in combination with the prescription of psychotropic medications from different classes (antidepressants, anxiolytics, mood stabilizers, antiepileptics, antipsychotics, and hypnotics). Additionally, all patients underwent blood test including a complete iron status (ferritin, iron, calculation of the Transferrin Saturation Coefficient (TSC)), as well as vitamin B9 and vitamin B12 levels. Patients considered to have resistant Iron Deficiency were those with serum ferritin levels below 100 ng/ml or a TSC below 30% after an initial attempt of oral iron treatment. Patients considered to have vitamin B9 or B12 deficiency or

insufficiency were those with serum levels below 11 nmol/l and 150 pmol/l, respectively. None of the patients had undergone bariatric surgery or had a known previous diagnosis of *H. pylori* gastric infection. The positive or negative diagnosis of *H. pylori* infection was determined either by gastroscopy with antral and fundic biopsies (immunohistochemical study), a carbon-13-urea breath test (mass spectrophotometry using stable and non-radioactive carbon isotope) to detect the bacterium's urease activity, or plasma measurements of specific IgG antibodies when the previous methods were difficult to perform for some patients. No patient underwent stool antigen detection (monoclonal antibody mixture). Subjects considered currently infected were those with a positive result in either of the diagnostic methods (biopsy showing the presence of the bacterium or a carbon-13 urea breath test result greater than 5.5 U/1000). Non-infected subjects were those with negative results in either of the previous methods or when the immunological assay (specific IgG) was negative. In terms of treatment, following the new Maastricht consensus report, experts recommend prescribing first-line quadruple therapy for 10 or 14 consecutive days in countries where macrolide resistance exceeds 15%, such as France [11]. In our study, the *H. pylori* eradication protocol was initiated by a gastroenterologist or another general practitioner, and it involved either bismuth-based quadruple therapy for 10 days (consisting of omeprazole, bismuth salts, tetracycline, and metronidazole) or non-bismuth-based triple therapy for 14 days (consisting of a proton pump inhibitor, amoxicillin, and clarithromycin). An efficacy assessment was subsequently performed for all infected patients more than four weeks after completing the eradication protocol, either through gastric biopsies or a carbon-13-urea breath test. Patients who showed resistance underwent gastroscopy for biopsy and received treatment guided by antibiogram results.

RESULTS

We collected data from 291 patients who had benefited from *H. pylori* testing according to the clinical criteria defined in our study. We found 107 subjects (36.8%) with resistant Depressive Episode, 109 subjects (37.4%) with resistant Iron Deficiency (with or without anaemia), and 75 subjects (25.8%) with Dyspepsia (Figure 1). In each patient category tested for *H. pylori* infection, we analyzed the number and percentage of patients infected with the bacterium. In the category with treatment-resistant Depressive Episode (107 subjects), 34% of patients were found to be infected. In the category with treatment-resistant Iron Deficiency (109 subjects), 30% were found to be infected, and in the category with Dyspepsia (75 subjects), 33% were found to be infected with *H. pylori* (Figure 2).

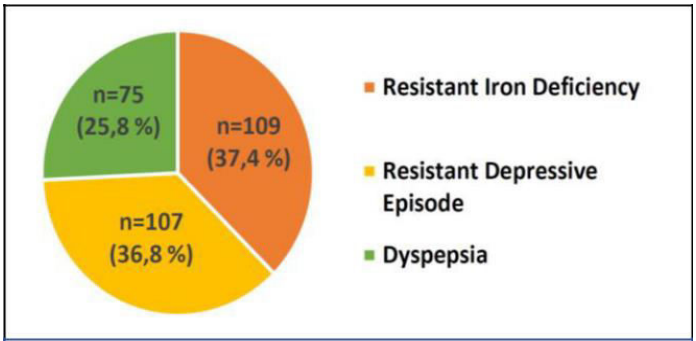

Figure 1: Patient categories and distribution according to clinical inclusion criterias (n=291).

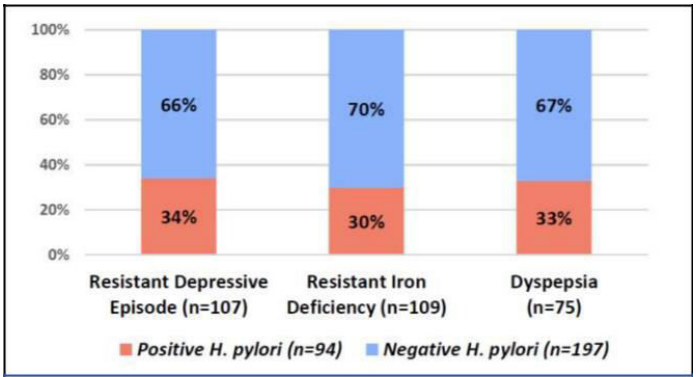

Figure 2: Infection rate according to the clinical categories defined in the inclusion criterias (n=291).

Furthermore, among the infected patients (94 patients, accounting for 32.3% of the total population studied), the eradication of the bacterium followed, if necessary, by oral supplementation of iron and/or vitamin B9 (folates) and B12 (cyanocobalamin) for several consecutive months, resulted in a favorable response in 49 patients (52.1%). 17 patients (18,1% of treated subjects) were considered non-responders after *H. pylori* eradication, and 28 patients (29.8% of treated subjects) could not undergo psychiatric evaluation after starting antibacterial treatment due to loss to follow-up. Hence, our findings show that 74% of the returning patients exhibited positive responses to the *H. pylori* treatment. This supports the link between *H. pylori* infection and psychiatric disorders

observed, aligning with our initial hypothesis that this bacterial infection is involved in these psychiatric disorders. More particularly, the 49 patients who achieved a favorable neuropsychiatric response reported a reduction or disappearance of apathy, anhedonia, anxiety, sadness, cognitive complaints, derealization sensations, and sleep disorders during their regular follow-up (Table 1).

Table 1: Evolution of neuropsychiatric symptoms after the eradication of *Helicobacter pylori*.

Patients treated for *H. pylori*	**Women N (%)**	**Men N (%)**	**Total N (%)**
Responding to treatment	27 (28,7)	22 (23,4)	49 (52,1)
Not Responding to treatment	7 (7,4)	10 (10,7)	17 (18,1)
Out of sight	20 (21,3)	8 (8,5)	28 (29,8)
Total	54 (57,4)	40 (42,6)	94 (100)

N: Number of patients treated; %: rate of positive patients

DISCUSSIONS

The prevalence of *H. pylori* infection within our observational study indicates that nearly one-third of psychiatric patients (32.3%) who underwent gastric testing were infected (94 subjects). We also found that approximately one-third of the patients were infected with *H. pylori* within each of the three tested patient categories. Our results show a significantly higher rate of infection by the bacterium than the global French population, reported between 15 and 30% [3]. These rates remain lower than those of the global population infected (over 50%), with a significant geographical variation to consider [4]. Furthermore, a reduction or disappearance of neuropsychiatric symptoms was found in 49 patients (accounting for 52.1% of the 94 treated patients) after the eradication of the bacterium and, if necessary, supplementation with iron and/or vitamins B9 and B12 for deficient patients. It was also observed that a normal or elevated serum ferritin level could be compatible with Iron Deficiency in certain infected patients with low serum iron and/or transferrin saturation levels below 30%. Regarding the physiopathological aspect, a narrative review confirms the hypothesis that *H. pylori* can influence the development of Alzheimer's disease in a pleiotropic manner [12]. The mechanisms of neurodegeneration suggested primarily involve the access of the bacterium to the brain through the oral-nasal route or the passage of infected monocytes through the blood-brain barrier. Additionally, by studying the effects of the VacA released by *H. pylori* in mice, researchers concluded that this bacterium could induce anorexia and anxiety by migrating through the blood-brain barrier and activating the adrenocorticotropic hormone (ACTH) receptor axis [13]. In an extensive review of international literature, authors have suggested the existence of various underlying mechanisms for the extra-gastrointestinal neurological symptoms induced by *H. pylori*, such as dysfunction of the gut-brain axis, alteration of the microbiota, modification of intestinal neuropeptide production, and neuroinflammation induced by the release of pro-inflammatory cytokines [14]. These mechanisms are thought to be involved in conditions such as multiple sclerosis, migraines, Alzheimer's disease, and Parkinson's disease. More recently published studies suggest a link between chronic *H. pylori* infection and neuroinflammation through cellular and murine experimental models [15]. The authors demonstrated the role of outer membrane vesicles (HP-OMV) in activating the immune system in the tissues where they are released. The pathogenicity of *H. pylori* is partly explained by virulence factors contained in these vesicles, such as urease, which neutralizes acidity and damages the gastric epithelium, the pathogenicity island (CagA), and the Vacuolating Cytotoxin (VacA). In their article, the authors observed an increase in the production of pro-inflammatory cytokines, such as interleukins (IL-1β and IL-6), Tumor Necrosis Factor (TNF-α), and inducible Nitric Oxide Synthase (iNOS), when microglial cells were cultured in the presence of these vesicles. An indirect virulence of *H. pylori* is suggested through malabsorption of iron, folates (vitamin B9), cyanocobalamin (vitamin B12), as well as the induction of dysbiosis. Dysbiosis affects the synthesis of tight junction proteins (Zonulin-1 and Claudin-5) and the action of adhesion molecules (Cadherins) in the intestinal tract, leading to increased intestinal permeability (leaky gut) and subsequent weakening of the blood-brain barrier. In our observational study, the favorable psychiatric improvement reported in the long or short term after *H. pylori* eradication could be explained by direct or indirect biological mechanisms, such as regression of inflammation induced by immune system activation, reduction of the detrimental effect of VacA on the brain, regression of intestinal hyperpermeability (leaky gut), and progressive normalization of ferritin levels and serum

levels of vitamins B9 and B12 in treated patients. Our initial hypotheses regarding the observed favorable response become even more plausible considering that the synthesis of monoaminergic neurotransmitters involved in neuropsychiatric symptoms (serotonin, dopamine, and norepinephrine) depends on the bioavailability of iron and vitamins B9 and B12, and that intracerebral production of 5-hydroxytryptamine (serotonin) can be reduced by neuroinflammatory processes that hijackes tryptophan metabolism toward the kynurenine pathway and generate the production of neurotoxic quinolinic acid [16]. Quinolinic acid (QUIN) is an endogenous N-methyl-D-aspartate receptor agonist synthesized from L-tryptophan via the kynurenine pathway and thereby has the potential of mediating N-methyl-D-aspartate neuronal damage and dysfunction [17]. The absence of a favorable response observed in the studied patients who underwent *H. pylori* eradication could be explained by the short evaluation period before the interruption of their psychiatric follow-up or the presence of various comorbidities of psychiatric, sleep-related, iatrogenic, metabolic, or other nature.

CONCLUSIONS

It is now well established that chronic inflammatory processes can contribute to or worsen a characterized depression, even rendering it chronic and resistant to chemical, psychotherapeutic, or other therapeutic approaches. Analyzing the results of studies published in scientific literature suggests the existence of various physiopathological mechanisms explaining the impact of gastric infection by *H. pylori* on the central nervous system. Our observational study conducted over three consecutive years in a psychiatric clinic, including

291 patients with treatment-resistant Depressive Episode, resistant Iron Deficiency, or Dyspepsia, indicates that more than one-third of them were infected with *H. pylori*. Eradicating the bacterium in infected patients proved beneficial for psychiatric symptoms in over half of the cases. Regression of inflammation induced by immune system activation, reduction of the deleterious effect of VacA on the brain, regression of intestinal hyperpermeability (leaky gut), and progressive normalization of ferritin levels and serum levels of vitamins B9 and B12 in treated patients are believed to be responsible for the improvement of neuropsychiatric symptoms in many patients. Future research exploring the significance of identifying pathogenic strains of this bacterium, as well as plasma measurement of VacA, may be useful in optimizing the management of patients infected with the bacterium. Multicenter studies with more objective selection and evaluation criteria are needed to confirm the involvement of *H. pylori* in the pathophysiology of neuropsychic disorders in some patients and to expand the therapeutic options in the management of patients suffering from chronic or treatment-resistant psychiatric disorders.

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