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Review paper

Helicobacter pylori Induced Neurological Disease and Therapy

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ABSTRACT

About 50% of people worldwide are infected with the gut pathogen *Helicobacter pylori*. The chance of developing gastric cancer and duodenal and stomach ulcer disease is greatly increased by *H. pylori* infection, which also causes chronic inflammation. An *H. pylori* infection typically induces alterations to the gut bacteria and a prolonged inflammatory response, other than from the immediate release of several inflammatory substances, such as chemokines, growth-regulated oncogene, and cytokines. which can be ingested and have an effect throughout the body. If detectable levels of inflammatory mediators remain at both the systemic and local levels, the gut-brain axis or blood-brain barrier will probably to become altered. These proinflammatory factors can cause ischemic stroke, multiple sclerosis, Devic syndrome, Guillain-Barre syndrome, Bickerstaff brainstem encephalitis, Alzheimer's disease, and migraines. They can also cause brain inflammation and the loss of neurons. Included in this overview are the neurological diseases caused by *H. pylori*, their eradication, and customized treatments.

1. Introduction

Our health depends on our gut microbes, and a dysbiosis in the microbiome has been connected to a number of diseases. Additionally, current research reveals a connection between disrupted gut microbiota and neurological illnesses (Amorim et al., 2018). Numerous health issues, such as rheumatoid arthritis, inflammatory bowel disorders, asthma, and cancer, among others, have been linked to changes in the gastrointestinal microbiota (Carding et al., 2015). Additionally, research indicates that neurological conditions like depression, anxiety, Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS) can all be affected by changes in the gastrointestinal system (Zhu et al., 2020). The gut microbiota can send signals to the brain via several pathways, collectively referred to as the microbiome-gut-brain axis. The neuronal route, the endocrine route, the metabolic route, and the immunological route are every component of the microbiome-gut-brain axis, that includes the communication connect-

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-ions between the gut microbes and the brain. The stomach, intestine, and liver are all colonized by the species *Helicobacter* of gram-negative bacteria (Liu al., 2022; Fox et at., 1994). Although there are significant regional variations, over fifty percent of the world's population is infected with the gram-negative, spiral-shaped *H. pylori* bacterium (Öztekin et al., 2021). In addition to gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT), cancer, and adenocarcinoma, neurological disorders have also been related to *H. pylori* infection (Sanders et al., 2002). *H. pylori* has evolved to be able to inhibit effector T-cell reactions, regulate innate immune receptors, prevent the host's immune response, and endure the hostile circumstances found in the gut. *H. pylori* infection causes both innate and acquired immune reactions to be triggered, but the host is unable to eradicate eliminated of the bacteria, leaving the patient with a chronic, lifelong infection (Amieva et al., 2008; Lina et al., 2014). Pro-inflammatory factors may be released directly as a result of the host's triggered immune reaction against particular bacterial virulence factors. *H. pylori* results in neutrophils, macrophages, dendritic cells, T and B cells to penetrate the stomach mucosa and induces the secretion of interleukin (IL) 8, -6, -1β, -10, and -12, tumor necrosis factor (TNF), cytokines, chemokines and interferon (IFN) γ in the blood, which may reach the circulation induce neuroinflammation and toxicity. The secretion of several neurotransmitters, including acetylcholine, adrenaline, noradrenaline, serotonin, and dopamine, is another effect of *H. pylori* infection (White et al., 2015; Gorlé et al., 2021). Axonal/neuronal damage, the creation of free radicals, and modifications to the gut peptides VIP and c-fos are further consequences of *H. pylori* infection. Also, *H. pylori* can cause breakdown in the blood-brain barrier (Kountouras et al., 2014). Also, *H. pylori* may generate neurotoxin effects and activate inflammatory processes in the nerves, disrupting the gut-brain axis (Budzyński et al., 2014). The objective we had with this review was to illustrate the state of current knowledge in the field with respect to CNS conditions carried on by *H. pylori* disease in additional to methods for treating and eradicating this infection.

2. *H. pylori* and Neurological Disease

Since the early 1990s, numerous researchers have observed that the stomach area is not the only part of the body that is affected by *H. pylori* infection. Gravina et al. (2018) provided evidence that H. pylori influences a wide range of hematological, cardiovascular, allergic, metabolic, neurological, ocular, cutaneous, and hepatobiliary functions. Another research by Sticlaru et al. (2019), found that *H. pylori*-positive patients had higher myenteric nervous plexus densities and surface areas as well as compared to the control group, more gastrointestinal glial cells and neural cell bodies in the stomach. The long-term effects of *H. pylori*-induced dysbiosis have an impact on how the neural system functions. More over half of all people on earth have *H. pylori* in their stomachs, despite significant regional variances (Sablet et al., 2011). In *H. pylori* infections, the chemokines and cytokines (IL-8, MCP-1, GRO-, IL-1, and TNF-), which are produced by stomach epithelial cells or directly by bacteria such as *H. pylori* neutrophil-activating protein, VacA, and urease, are responsible for inflammation (Baj et al., 2020). The *H. pylori* VacA protein is an important element in the etiology of gastric cancer. It, in the process, may affect the functioning of the BBB, as VacA affects bone marrow-derived mast cells (BMD-MCs), leading to to in the ensuring of an essential amount of pro-inflammatory cytokines these as the interleukins IL-1, IL-6, IL-8, IL-1β, IL-10, IL-12, interferon (IFN) γ, and TNF-α, associated in microglitis and direct neurotoxicity (Wroblewski et al., 2010). A few of the effector functions that immune cells carry out at the location of infection include the production of cytokines (IL-1, TNF-, IL-6, IL-12, IFN-), chemokines (IL-8, MCP-1), proteolytic enzymes, oxide nitric (NO), and reactive oxygen species. (ROS)TNF- impairs the BBB's integrity by inducing matrix metalloproteinases to become active (Kountouras et al., 2017). *H. pylori*-NAP (HP-NAP), a pro-inflammatory protein that frequently appears in people with *H. pylori*-related gastritis, promotes neutrophil migration and stimulation (Yang et al., 2022). Because of the BBB's damage and increased permeability brought on by extended exposure, the CNS experiences demyelinating, inflammatory, and edematous processes (Bagheri et al., 2018). The HPA axis is triggered and the neuroendocrine-immune system is disturbed which is related to an increase in cortisol and adrenaline secretion. These effects of the released inflammatory mediators on the brainstem and hypothalamus functions (Budzyński et al., 2014). Multiple other neurotransmitters, including acetylcholine, noradrenaline, dopamine, adrenaline,

and serotonin, have been shown to be released as a result of *H. pylori* disease (Meng et al., 2016). Because of problems with medication absorption, systemic inflammation, and molecular mimicry, H. pylori infection has been linked to the emergence and progression of neurological diseases (Kountouras et al., 2017). These conditions include depression, Devic Syndrome, Guillain-Barre syndrome, Multiple sclerosis, ischemic stroke, Bickerstaff Brainstem Encephalitis, Alzheimer's disease and migraine.

2.1 Alzheimer's Disease

Alzheimer's disease is a deteriorating, age-related neurological condition that harms and attenuates brain cells. The leading prevalent cause of dementia is Alzheimer's disease. Numerous studies emphasize the connect among *H. pylori* and extra digestive circumstances including functional vascular disorders caused on by vascular dysregulation, atherosclerosis, hypertension, cardiovascular as well as cerebrovascular ischemia, and stroke, all of which possess been discovered as at-risk factors for AD (Kountouras et al., 2006). The high levels of IgG HP in AD could be one of the mechanisms that is able to activate the cascade of inflammation in the AD brain. Kountouras et al. (2002) study suggests that *H. pylori* infection promotes platelet and platelet-leukocyte aggregation. Since platelets are a source of amyloid, the primary component of senile plaques, which are believed to be a key event in the aetiology of AD. Proinflammatory cytokines and vasoactive substances including IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α, interferon-γ), eicosanoids, and acute phase proteins (fibrinogen, C-reactive protein), which are all involved in AD, are released in high quantities (Malaguarnera et al., 2004). As a result of HP infection, it causes in circulating lipid peroxides and reactive oxygen metabolites that are involved in the pathogenesis of AD. It shows that apoptosis in AD is influenced by HP infection. Roubaud Baudron et al., (2013), reported after 20 years of *H. pylori* infection, there is a 1.5 times higher chance of getting dementia. Beydoun et al. (2013) conducted investigations examining the relationship between *H. pylori* seropositivity and cognitive function in US younger and older persons during normal ageing. The connection between Hp-I and ApoE 4 polymorphism in the pathophysiology of AD and potentially glaucoma ('ocular' AD) was highlighted by Kountouras et al. (2016). His research shows that AD patients, particularly those who are Hp-positive as opposed to Hp-negative, have higher levels of ApoE.

Higher amounts of amyloid deposition and earlier onset are associated with APOE-4, The biggest hereditary risk factor for Alzheimer's disease (AD) (Battista et al., 2016). According to several studies, the bacteria may enter the brain through circulating monocytes that have been infected with *H. pylori* via the oral-nasal-olfactory pathway (Doulberis et al., 2018). Recent research by Uberti et al. (2022) described *H. pylori*'s urease as a significant virulence factor also for the emergence of AD, with HPU's pro-inflammatory activities and immune system activation generating neuroinflammation and tau phosphorylation.

2.2 Parkinson's Disease

The disease that results in progressive neurodegeneration is the second most common, the accumulation of the intracellular protein synuclein is an indicator of Parkinson's disease (PD), which results in the death of dopaminergic neurons in the substantia nigra pars compacta. The small intestine's infection with Helicobacter pylori (HP) is a one of the factors in the development of PD was first proposed by Altschuler et al. (1996). According to the research by Rahne et al. (2013), symptoms fluctuations also decreased in PD patients who tested positive for HP. A different neurological illness called parkinsonism has symptoms similar to those of Parkinson's disease. By rupturing the blood-brain barrier, proinflammatory cytokines found in the blood, such as TNF, IL-1, IL-1, IL-6, and IL-8, cause neurotoxicity. According to some research, proinflammatory cytokines linked to chronic gastrointestinal conditions have the ability to cause inflammation in the brain and the degeneration of dopaminergic neurons, which may ultimately lead to parkinsonism (Dobbs et al., 1999).

Neuroinflammation seems to be causing neurodegeneration together with activation of the CNS-resident immune cells, the microglia (Villarán et al., 2010). Microglia in PD patients respond to a proinflammatory stimulation by releasing neurotoxic chemicals, which accelerate neurodegeneration. Microglia are activated via the humeral pathway when circulating proinflammatory or leukocytes breach the blood-brain barrier during an HP infection (Perry et al., 2010). Animal studies have shown that the unpleasant chemical produced by HP can also

affect neurons in the brainstem by being transmitted through vagal afferent pathways (Park et al., 2022). The blood group antigens expressed by *H. pylori* LPS are the same ones that are present in the stomach mucosa of humans. During infection, auto-antibodies against LPS that bind to host Lewis's antigens may be produced. As a result, they locate targets in gastric glycoproteins and cause autoimmune inflammation (Degen et al., 1995). Additionally, these antibodies against neurons in CNS fluid or blood of PD patients as a molecular imitation from an HP infection (Ahn et al., 2023). Through meta-analysis, Xiaoli Shen et al. (2017) demonstrated the connection between Parkinson's disease and *H. pylori* infection. Levodopa, the drug used for Parkinson's disease, its absorption in the digestive system may vary as a result of HP infection (Altschuler et al., 1996). Due to the inflammation and disruption of the duodenal mucosa caused by duodenal *H. pylori* infection, levodopa bioavailability and motor symptoms is affected (Narożańska et al., 2014), because levodopa mainly absorbed in the upper intestine (Mridula et al., 2017). According to studies, levels of IgG were significantly greater in Parkinson's disease patients with H. pylori infections than in the control group, but levels of IgA were noticeably lower (Nagayama et al., 2015).

2.3 Multiple Sclerosis

A chronic inflammatory disease called multiple sclerosis (MS) is defined by lesions of the central nervous system (CNS), which can result in neurological defects as well as serious physical or mental impairment (Goldenberg et al., 2012). Although its reliable pathogenesis is still unknown, it is hypothesized that environmental factors, among others, may be involved. *H. pylori* infection may contribute to the etiopathogenesis of several autoimmune diseases, including MS, according to studies. Atrophic gastritis was the most common histopathological finding in MS patients whose suffered from H. pylori infection; inquisitive these patients also had other autoimmune-related conditions like ulcerative colitis (Gavalas et al., 2007; Kira et al., 2019). *H. pylori* eradication may be a possible adjuvant therapy because it appears to be one of the risk factors for the onset of multiple sclerosis associated with anti-aquaporin 4 (AQP4) antibody positivity (Sellner et al., 2010). The inflammatory condition neuromyelitis optica particularly affects the spinal cord and optic nerves. Human AQP4 and bacterial AQP exhibit molecular mimicry, which may contribute to the development of optic neuritis in chronic recurrent infections (Montecucco et al., 2003). Additionally, *H. pylori* neutrophil-activating protein (HP-NAP) contributes to the disease through promoting neutrophil migration and activation (Polenghi et al., 2007; Jaruvongvanich et al., 2016). Specifically, when it comes to how infections function as a shield against the onset of autoimmune illnesses, we base our decisions on the 'hygienic theory'. Meta-analyses have looked into the beneficial function of *H. pylori* infection in MS (Yao et al., 2016). There were 1553 instances of MS and 1553 healthy controls after only 9 of the 82 identified data were included. In this meta-analysis, the prevalence of *H. pylori* infection was statistically lower in MS patients than in normal controls. *H. pylori* infection statistically decreased the severity and the quantity of pathogenic T lymphocytes in the central nervous system in three separate investigations on mice with experimental autoimmune encephalitis (EAE), a mouse model of MS (Ranjbar et al., 2019). A sample of MS patients' seropositivity for *H. pylori* was also evaluated, and it was found to be significantly lower than in a group of healthy people (Cook et al., 2014). The hypothesis that *H. pylori* infection plays a preventive function in MS is backed up by this experimental study. The recovery to equilibrium between the Th1, Th17, and Treg lymphocyte subsets is one of the numerous pathways associated with the suggested mechanism of protection by *H. pylori* infection in EAE and MS (Liston et al., 2009; Gravina et al., 2018). These pathways are particularly linked to IL-10 functions and CCR6-CCL20 interaction. It seems that MS people are more probable to contract HP infection. If verified, this may suggest either a shared component that increases susceptibilities to both MS and HP infection or that HP may be a cause of MS. The pathophysiology and treatment of MS may be significantly affected if a causative relationship between Hp infection and MS is later found to exist.

2.4 Guillain–Barré Syndrome

Acute autoimmune demyelinating condition of the peripheral nerves called Guillain-Barré syndrome (GBS) typically arises from an infection (Wijdicks et al., 2017). GBS is recognized by progressively paralysing the limbs in a distal-proximal pattern but might lead in life threatening implications. *Campylobacter jejuni*, *Mycoplasma pneumoniae*, and *H.*

pylori are the primary sources of GBS, but it can also be brought on by Haemophilus influenzae, and influenza A virus, cytomegalovirus, Epstein-*Barr* virus, *Zika* virus, *Hepatitis* virus, HIV (Jacobs et al., 1998). According to recent studies, COVID-19 viral infection can lead to GBS (Sriwastava et al., 2021). Additionally, it is an uncommon side effect in people who receive the COVID-19 vaccination from Johnson & Johnson or AstraZeneca. Remarkably usual type of GBS is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Miller Fisher syndrome (MFS), acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy are additional, less common types of GBS (AMSAN). A previous infection, high CSF protein, and an anti-GQ1b antibody are every sign of the MFS variant referred to as BBE (Dimachkie et al., 2013).

The most common cause of GBS is *C. jejuni*. Its harmful mechanism involves molecular mimicry between *C. jejuni* LPSs and peripheral nerve gangliosides. The most common cause of GBS is *C. jejuni*. Its harmful mechanism involves molecular mimicry between *C. jejuni* LPSs and peripheral nerve gangliosides. The surface antigens of *C. jejuni* contain sialic acid, a key element of human gangliosides. In one-third of the serotypes of *C. jejuni*, a high-molecular weight LPS sequence from *H. pylori* can be identified. The pathogenic connection has been proposed to be a molecular mimicry between peripheral nerve gangliosides and *H. pylori* LPS (Moran et al., 2001). Patients with GBS are more likely to have an infection with *H. pylori* because they have higher serum concentrations of anti-*H. pylori* IgG antibodies than individuals without the disease against (Chiba et al., 2002). IgG antibodies against VacA of *H. pylori* were discovered in the CSF of GBS patients, according to study by Chiba et al (Ho et al., 1995). Because VacA and the human ATPase A subunit share sequence homology, it's possible that VacA-specific antibodies can attach to ion channels in Schwann cells, demyelinating motor neurons in these patients. *H. pylori* infection may be involved in the pathophysiology of GBS, according to the current meta-analysis study by Efthimios Dardiotis et al. (2020). The study showed a significant correlation between GBS and H pylori antibodies, especially in CSF (Wijdicks et al., 2017). Additionally, it demonstrated that both CSF and serum levels of anti-*H pylori* IgG were considerably higher in GBS patients compared to controls. Some GBS, AMAN, and AMSAN variants are related to *C. jejuni* infection. There is still much to learn about the pathogenesis of GBS and its variants. According to theory, T cells that target peripheral nerve myelin proteins and antibodies that target myelin glycolipids cause autoallergic neuritis, which causes GBS. These antibodies are present in the serum of GBS individuals (Macko et al., 1996; Chiba et al., 2004). In CSF from 12 MFS patients, numerous studies found antibodies against natural *H. pylori* VacA. Previous studies have demonstrated the presence of *H. pylori* VacA-specific antibodies in the cerebrospinal fluid of MFS patients (Kusunoki et al., 2023). Ion channels in the node of Ranvier in MFS patients have sequence homology with membrane ion transport proteins, indicating the possibility of targeted antibodies against VacA of *H. pylori*. Further investigation is necessary to confirm an actual cause-and-effect relationship between *H. pylori* and GBS.

2.5 Bickerstaff Brainstem Encephalitis

Bickerstaff brainstem encephalitis (BBE) affects the peripheral and central nervous systems and is an uncommon case of autoimmune disease. BBE is considered a variant of other immune-mediated polyneuropathies, such as GBS and MFS (Bagaria et al., 2021; Yamamoto et al., 2012). Traditionally, BBE manifests as an acute triad of ataxia, encephalopathy, and ophthalmoplegia that usually follows an infection. The neurological symptoms were originated as by infection and typically concluded with the patients, similar to the random rebounds seen in GBS and MFS patients (Yuki et al., 1993). A study by Chiba et al. (1992) showed that an anti-GH1b antibody was present in MFS patients, shortly after that, BBE patients were also discovered to have the antibodies. The similarities between the three diseases were noted by Bickerstaff, despite the fact that they initially thought to be three separate diseases (Bickerstaff et al., 1957). Regardless of the fact that cases of BBE and MFS with anti-GM1b and anti-GalNAc-GD1a antibodies present but not anti-GH1b antibodies were similarly reported, "anti-GH1b antibody syndrome" was used to describe the overlap between BBE and MFS after the similarity was identified (Kountouras et al., 2005). Recent findings indicate to support the idea that BBE may be caused by *H. pylori*. It has been demonstrated that *H. pylori* can cause immune reactions that might set up to persist nerve injury, as seen in a number of neurodegenerative diseases, including GBS (Wingerchuk et al., 2007). The findings

of the Dardiotis et al. (2020) meta-analysis, which demonstrated a link between *H. pylori* infection and GBS, also lend credence to this conclusion (Jarius et al., 2010). As a consequence, we are able to presume that as both GBS and BBE have a similar pathophysiology, BBE may also be driven on by that pathogen.

2.6 Devic Syndrome

Devic's disease, also known as neuromyelitis optica (NMO) (Jarius et al., 2010). The optic nerve and spinal cord are the two areas of the central nervous system that are most commonly affected by this severe, demyelinating, idiopathic disease. NMO serum indicators are antibodies to aquaporin-4 (AQP4-Ab or NMO-IgG). According to research by Jarius et al. (2010), in 80% of patients with NMO, second-generation recombinant diagnostic assays may identify anti-AQP4-Ab, and these findings support anti-AQP4-Ab's involvement in the immunopathogenesis of NMO. According to the research by Wei et al. (2009), one of the risk factors for the onset of AQP4 appears to be *H. pylori* infection. When the blood-brain barrier becomes permeable, anti-AQP4 antibody enters the CNS and has a strong affinity for orthogonal array AQP4 particles. We can hypothesise that chronic infection brought on by *H. pylori* may promote in the emergence of NMO.

2.7 Depression

H. pylori has been linked to psychiatric disorders like depression by the brain-gut axis, but Quraan et al. (2019) demonstrated that it also plays a part in immunity. Out of 54 patients with functional dyspepsia and *H. pylori* infection, Ünal et al. (2013) discovered that 22 have at least one psychiatric condition, with depression being the most common in about 13 patients. They advised that patients who experience symptoms after *H. pylori* removal but do not respond to treatment to be evaluated for psychiatric illness because it will affect their recovery. According to Kabeer et al. (2017), who used the PHQ-9 scale to assess the severity of the patients' sadness, 55% of them had *H. pylori*, 56% of them had depression, and 29% had both. This screening tool was also employed by Matiwos et al. (2022) to show that persons who have *H. pylori* diseases have a greater frequency of positive probable case of depression scores.

2.8 Migraine Headache

Migraines are headaches that occur in waves and are triggered by a neurological condition also known as migraine. Particularly in people who experience migraines without an aura, severe infections like *H. pylori* have been related to migraines. The traditional theory of vasoconstriction and vasodilatation has given way to a fundamental neuronal dysfunction in the etiology of migraines. In China, *H. pylori* eradication in people with liver cirrhosis led to a decrease or disappearance of headache complaints. According to the research by Tunca et al. (2004), migratory patients had higher rates of *H pylori* positivity than controls that were not moving elsewhere (Wingerchuk et al., 2007). Infection with the bacterium *H. pylori* increases the chance of developing migraines. This study investigates if eradicating the bacterium can lessen the frequency, duration, and intensity of clinical bouts of the disease. There is a significant difference in the mean OD value of both antibodies to *H. pylori* between the case and control groups, according to study by Hosseinzadeh et al. (2011), on IgG and IgM antibodies to *H. pylori* in sufferers of migraine headaches (Ansari et al., 2015). Therefore, *H. pylori* infection is significantly associated with migraine frequency and intensity, and *H. pylori* treatment dramatically reduces migraine frequency and intensity. According to several case-control studies including 84 patients and 49 healthy people, concluded that elimination of this bacterium may be able to stop the progression and intensity of migraine headaches (Su et al., 2014). *H. pylori* infection and migraine headache are positively correlated, according to the same findings compiled by Faraji et al. (2012). The inflammatory condition carried on by the bacterium appears to change the pathophysiology of migraines brought on by neuroendocrine release such as serotonin, SP, and VIP (Harris et al., 2001). IL-10 plasma levels have been found to be higher during migraine attacks, and some investigations have shown that HP infection is linked to higher IL-12 and IL-10 levels. These results suggested that IL-10 activated by HP may increase migraine intensity. There is now no evidence to warrant a systematic investigation of the infection in migraineurs, thus this is still an active area of research.

2.9 Ischemic Strokes

The majority of ischemic strokes are caused by carotid or cerebral vascular obstruction, which is their pathophysiologic cause (Zoppo et al., 2000). Due to contrasting results, the challenge of *H. pylori* infection as a risk factor for stroke is still up for discussion. A recent meta-analysis discovered that CagA-positive strains and persistent *H. pylori* infection are statistically significant risk factors for ischemic stroke (Cremonini et al., 2004). Individuals who are actively infected, *H. pylori* strains that are CagA-positive are substantially related to atherosclerotic stroke. The causes of the chronic *H. pylori* infection's elevated risk for ischemic stroke are yet known. It encompasses been showed that six months after the elimination of the *H. pylori* infection plasma levels of IL-8, fibrinogen, total cholesterol, and low-density lipoprotein were significantly lower than those in *H. pylori*-positive stroke patients and controls, promoting the theory that *H. pylori* causes blood coagulation by triggering platelets (Bastiani et al., 2008; Ribaldone et al., 2016).

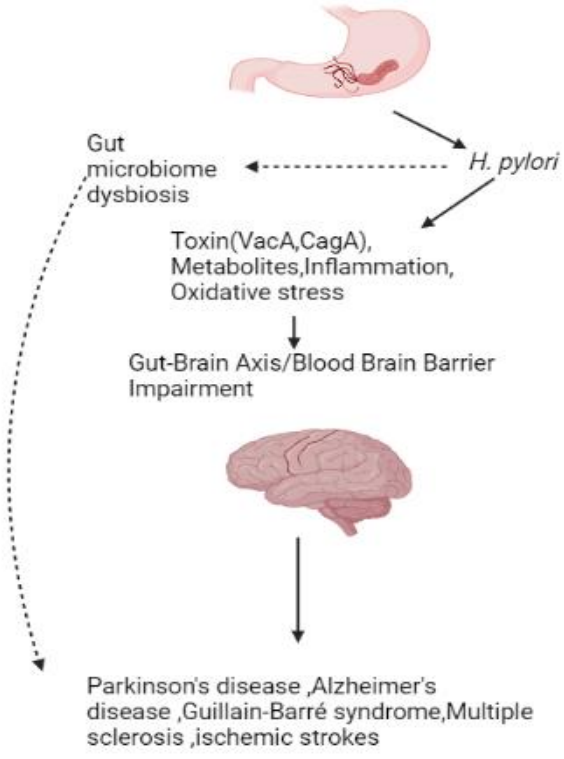

Fig. 1. H. *pylori* and neurological disease: Diagram showing how the evolution of various neurological diseases may be influenced by H. pylori infection migrating along the gut-brain axis

3. Treatment for *H. pylori*

H. pylori causes an uncomplicated stomach infection because they are a common antibiotic-susceptible bacteria (Mégraud et al., 2007). Studies of antibiotic treatment for various infections have traditionally been carried out and assessed in circumstances of clearly characterised drug susceptibility. Antimicrobial resistance causes quick changes in guidelines and practise for numerous infectious illnesses. *H pylori* has been an outlier in that findings have been interpreted without taking drug resistance patterns or its effects into consideration, and treatment plans with various dosages, durations, and composition are frequently contrasted (Graham et al., 2000). Reactive oxygen and nitrogen species are abundant in the microenvironment created by *H. pylori*-induced inflammation, which increases the risk of DNA degradation and somatic mutations (Jain et al., 2021).

The probability of developing gastric cancer increases with *H. pylori* infection, particularly when that infection is caused by more dangerous strains that are CagA-positive (Brenner et al., 2002). Insistent findings have been obtained when attempting to connect a specific *H. pylori*-related illness with a single putative virulence factor because the majority of virulence factors are typically present in combination in the more virulent strains (Graham et al., 2015). No specific disease has been attached to any of the known virulence factors. They may be best thought of as indicators of the intensity of inflammation, though, as they are often related to an increase in the inflammatory response. There are no avirulent strains of *H. pylori*; all of them produce stomach inflammation and disease. Although the risk of gastric cancer differs between the most and least virulent strains, it is advised that all *H. pylori* infections be treated, independent of virulence factor (Robinson et al., 2007).

4. Eradication Therapy

In order to reduce the occurrence of gastric cancer as well as make it less prevalent, it is crucial to prevent *H. pylori* infections (Fuccio et al., 2010). Antimicrobial resistance causes modifications in guidelines and practise for numerous infectious diseases. *H. pylori* has been atypical in that outcomes have been interpreted without considering medication resistance patterns or its effects into consideration, and treatment plans with different dosage, durations, and composition are frequently compared. In East Asian countries, *H. pylori* eradication therapy lowers the risk of gastric cancer in both healthy individuals

and those who have gastric neoplasia, according to new research by Liou et al. (2020). Additionally, it indicates that mortality linked to stomach cancer has decreased. He found 10 RCTs, of which three randomly assigned 1841 patients with gastric neoplasia and seven recruited 8323 healthy participants. Eradication treatment decreased the incidence of gastric cancer and the mortality from gastric cancer, but it possessed no effect on all-cause mortality in healthy people.

A therapeutic paradox has arisen as a result of the sudden decrease in effectiveness of clarithromycin-containing regimens given that these are frequently the only treatments approved by regional regulatory bodies (Demir et al., 2009). New medication combinations that were promoted as superior as a result of this decline in effectiveness included sequential treatment. The novel 4-drug clarithromycin and metronidazole treatments (such as sequential, simultaneous, or hybrid regiments) all display comparable high levels of efficacy in the lack of clarithromycin resistance (Lin et al., 2018).

5. Customized Therapy

Healthcare providers only need to take consideration of drug accessibility, tolerance (such as whether patients might have allergies or the drugs have side effects), expense, and known or suspected patterns of resistance based on prior experience with the drug in the same community. The treatment for eliminating *H. pylori* is relatively simple. Only regimens that consistently produce >90%, preferably >95%, therapeutic success should be adopted, if at all possible (Harris et al., 2001). It is important to take into account information on the treatments to which each patient's illness is likely to be resistant or sensitive. There are currently various regimens that, when employed to annihilate susceptible strains, will reliably yield 95% or more therapeutic success per protocol. Amoxicillin, clarithromycin, metronidazole and tetracycline are the most frequently given antibiotics (Safavi et al., 2016). These include simultaneous therapy, sequential therapy, and levofloxacin triple therapy in addition to a 14-day course of clarithromycin or metronidazole triple therapy. Clarithromycin and metronidazole are first option because to the frequency of resistance to the two drugs functioning together. *H. pylori* infection is treated with proton pump inhibitors (Dickey et al., 1996; Feng et al., 2005). Lansoprazole, omeprazole, pantoprazole, rabeprazole, or esomeprazole are examples of proton pump inhibitors that are often recommended.

Bismuth quadruple therapy is used if the patient's infection does not recover after receiving this treatment (Graham et al., 2015). The above-mentioned combinations of antibiotics and proton pump inhibitors may occasionally include the medication bismuth subsalicylate. This medication protects the stomach lining. The patient should be transferred to a facility with experience treating resistant infections if either of the two treatment options fails to completely eradicate an infection. Alternatively, the illness should be cultured and tested for susceptibility. If local or regional medication susceptibility statistics are known, most therapy regimens may be predicted to have a certain result. There is no vaccine to prevent *H. pylori* infection yet, but a late-stage clinical research has produced encouraging findings (Sutton et al., 2019). Children who received the vaccination in this experiment had up to three years of *H. pylori* infection protection (Talebi et al., 2016).

6. Conclusion

Most gastrointestinal illnesses have been discovered to be caused by an infection with *H. pylori* as the underlying cause, including gastric ulcer, gastric cancer, acute or chronic gastritis, MALT, and functional dyspepsia. Any changes in the gut microbiota carried on through the generation of free radicals may be greatly impacted by *H. pylori* disease, alterations in neuropeptide expression, and neuronal damage that could result in neurological impairments. *H. pylori* may generate neurotoxin effects and activate inflammatory processes in the nerves, disrupting the gut-brain axis. So, the basic reason of CNS disease caused by *H. pylori* is breakdown of gut-brain axis. The neurological disorder related with *H. pylori* include depression, Devic Syndrome, Guillain-Barre syndrome, multiple sclerosis, ischemic stroke, Bickerstaff Brainstem Encephalitis, Alzheimer's disease and migraine. The *H. pylori* infection and migraine are thoroughly explained in this review because, until recently, it was unclear what the source of this association was. In this review discuss current eradication therapy and customized therapy of *H. pylori* infection. Several studies have been publications involving a potential connection between the *H. pylori* infection and central nervous system

disorders, but more research and a thorough assessment of this issue remains necessary.

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