Neurological Manifestations of *Helicobacter pylori* Infection: Epiphenomenon or Immunologic Incident?

JP Anthony O’Connor, Colm A. O’Morain

Department of Gastroenterology, Trinity College Dublin, Ireland

The topic of the extragastric manifestations of *Helicobacter pylori* (*H. pylori*) infection continues to capture the attention of many researchers all over the world. The humble gastric pathogen has been linked to multiple conditions, including cardiovascular diseases, lung diseases, hematologic diseases, eye and skin diseases, hepatobiliary diseases, diabetes mellitus and neurological disorders. It is proposed that *H. pylori* may cause some of its pathogenic effects via direct gastric mucosal damage and, some others, via the immunological response evoked by the host. The role of *H. pylori* in neurological diseases has been a hot topic in the scientific literature over the last number of years. The suggested mechanisms have been manifold. *H. pylori* has long been proposed as a co-factor in the development of atherosclerosis. The basis for this is that pro-inflammatory cytokines lead to accelerated atherosclerosis, especially amongst CagA-positive strains. A primary care based case control study suggested higher prevalence of *H. pylori* infection amongst stroke patients which reached statistical significance only in CagA-positive strains. However, it has never been illustrated that *H. pylori* infection can reduce the risk of stroke. Other studies have suggested a role for *H. pylori* in the development of Alzheimer’s dementia (AD). In one such study, *H. pylori* plasma IgA and IgG levels were noted to be significantly increased in AD patients compared to those of normal controls. However, the *H. pylori* IgA levels were observed to be equally increased in both vascular dementia and AD patients. There may be a degree of difficulty in the differential diagnosis between AD and vascular dementia and a mixed picture is common. A study in Greece showed that successful eradication of *H. pylori* led to a significantly lower mortality rate in patients with AD. A small number of studies have suggested that *H. pylori* may be responsible for idiopathic Parkinsonism. A study examining the effect of *H. pylori* eradication showed improved stride length and maintenance of gait integrity for 2 and 3 years post eradication. Other studies suggest improvement in motor function when *H. pylori* is eradicated due to better absorption of L-dopa. Other associations have also been made such as migraine in both adults and children. In epilepsy, the presence of *H. pylori* has been associated with the development of the condition and a poor prognosis. Antibodies to *H. pylori* have also been detected in cerebrospinal fluid of patients with Guillain-Barré syndrome (GBS). It is proposed that GBS is most closely associated with VacA-positive strains of *H. pylori* with a specifically increased risk of the Miller-Fisher variant of the condition.

One of the most interesting neurological associations with *H. pylori* infection has been with demyelinating disease. Some studies have actually suggested that *H. pylori* may be a protective factor against multiple sclerosis (MS). Others, however, have associated *H. pylori* with another demyelinating condition, acute inflammatory demyelinating polyradiculoneuropathy. The same authors have hypothesized that MS may be the common denominator between systemic and multiple sclerosis. The variable role played by *H. pylori* in the pathogenicity of MS may be predicated on ethnicity.

In this issue of *Immuno-Gastroenterology*, Boziki et al. were the first to show immunomodulatory properties of *H. pylori* (namely the *H. pylori*-SS1 antigen, common in humans) in mice with an experimental model of MS, with an ensuing T-cell proliferation being noted. The clinical implications for this are unclear and, as the authors outline, may be different in a long-term chronic infection model compared to when seen with systemic immunization. This could be a significant development in the understanding of the role played by *H. pylori* infection in neurological diseases. Hitherto, the association of *H. pylori* with neurological diseases was clouded by the role of atherosclerosis and the difficulties inherent in selecting out specific syndromes in often multifactorial clinical cases. The illustration of immune properties of *H. pylori* in the mechanism of a neurological disease with a widely accepted immunological base may offer clarity. Questions however still remain and as *H. pylori* does not possess bacterial aquaporin (AQP), the authors’ hypothesis that molecular mimicry between human AQP4 and *H. pylori* AQP may induce anti-AQP4 autoimmunity may need further robust assessment. The widespread acceptance of *H. pylori* as a neurological pathogen has been somewhat weakened by the multiplicity of conditions it is associated with. To many observers the notion that a bacterium known to live only in gastric tissue with such a diverse array of neurological diseases, such as migraine, AD, cerebrovascular disease, demyelination, parkinsonism and GBS has been a confusing one. The most recent Maastricht IV consensus guidelines for the management of *H. pylori* infection published earlier this year state that the evidence available shows no unequivocal causative association between *H. pylori* and other extragastric disorders, including cardiovascular and neurological disorders. The demonstration of an immunomodulatory
reaction in an immunologic disease will hopefully set in motion a series of studies that will shed much needed light on this field. We commend the authors on their enterprise and await with interest further studies in the area.

Conflicts of interest

The authors declared no conflicts of interest.

References