**Letters to the Editor**

**Helicobacter pylori** may be involved in cognitive impairment and dementia development through induction of atrophic gastritis, vitamin B-12–folate deficiency, and hyperhomocysteinemia sequence

Dear Sir:

We read with considerable interest the article by Haan et al (1), which concluded that homocysteine (Hcy) is an independent risk factor for both dementia and cognitive impairment without dementia (CIND) in a cohort of Latin Americans residing in California and, moreover, higher plasma vitamin B-12 concentrations may reduce the risk of Hcy-associated dementia or CIND.

The background prevalence of Helicobacter pylori serum positivity in this population (Hispanic Mexicans) is ≈60% (2, 3). In particular, 79% of Hispanic volunteers residing in Los Angeles were shown to harbor *H. pylori* in gastric biopsy samples and all had histologic gastritis (4).

In this respect, although degenerative diseases of the central nervous system (CNS), including Alzheimer disease (AD), have an increasingly greater effect in elderly populations, their association with *H. pylori* infection has not been thoroughly researched. This issue was recently addressed in 2 studies (5, 6). A higher seropositivity for anti-*H. pylori* immunoglobulin (Ig) G antibodies was reported in AD patients than in age-matched controls (5). However, this serologic test has limitations because it does not discriminate between current and old infections (7). Such a distinction is essential because current *H. pylori* infection induces humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with components of nerves (7) and thereby affect or perpetuate neural tissue damage. Moreover, eradication of *H. pylori* infection might delay AD progression, particularly at early disease stages. On the basis of histologic analysis of gastric mucosa biopsy samples for the documentation of *H. pylori* infection, we investigated whether *H. pylori* infection is associated with AD by introducing the histologic method that is established as the actual gold standard for diagnosis of *H. pylori* infection (7). In our cohort of Greek patients, 88% of the AD patients had histologically proven *H. pylori* infection, whereas the rate of infection was significantly lower in the anemic control group (46.7%) (6). Moreover, histologic multifocal chronic gastritis (body and antrum atrophy) was observed in the vast majority of our patients as compared with controls (6, 7). These patterns of *H. pylori*–related chronic gastritis have also been reported by others (7). Importantly, an increased serum Hcy concentration has been shown in our AD patients (7). Chronic gastritis, as a result of *H. pylori* infection, can lead to malabsorption of vitamins (B-12) and folate, which results in the failure of methylation by 5-methyl-tetrahydrofolic acid and, hence, in the accumulation of Hcy (7). Elevated Hcy, in turn, could trigger endothelial damage and result in atherothrombotic disorders and AD. In this respect, investigators reported that *H. pylori*–induced chronic atrophic gastritis or atrophic gastritis per se decreases serum vitamin B-12 and folate concentrations, thereby increasing Hcy—a potent contributor to vascular disorders; serum Hcy concentrations correlated inversely with serum vitamin B-12 and folate concentrations and positively with atrophic scores (7). Hcy appears to be an independent risk factor not only for dementia and AD, as mentioned by Haan et al, but also for vascular disease. It is thought to be implicated in endothelial damage and neurodegeneration via oxidative injury in these diseases (7); oxidative damage has also been described in the brain of subjects with mild cognitive impairment (MCI), which suggests that oxidative damage may be one of the earliest events in the onset and progression of AD. It has been shown that the serum Hcy concentration correlates with the severity of dementia, and it is a significant predictor of the severity of dementia (7). From another vantage point, *H. pylori* infection is actually associated with vitamin B-12 deficiency or iron deficiency anemia, whereas eradication of *H. pylori* infection is associated with the reversal of vitamin B-12 deficiency or of iron deficiency and an improvement in anemia (8).

Extending our findings, we investigated 63 consecutive patients with amnestic MCI, and 35 anemic controls who underwent upper gastrointestinal endoscopy and histologic and serologic examinations (9). The prevalence of *H. pylori* infection was 88.9% in MCI patients and 48.6% in controls, as confirmed by biopsy (P < 0.001; odds ratio: 8.47; 95% CI: 3.03, 23.67). Mean serum anti-*H. pylori* IgG concentration and plasma total Hcy titer were also higher in MCI patients than in controls. When compared with the anemic participants, MCI patients had histologic multifocal (body and antral) gastritis more often. Interestingly, the positivity status for *H. pylori* serology appeared to correlate with cognitive deterioration in our *H. pylori*–positive MCI patients (9).

Considering the abovementioned data, we speculate that *H. pylori* infection might contribute, at least in part, to the pathogenesis of MCI and AD through induction of chronic atrophic gastritis, vitamin B-12–folate deficiency, and Hcy sequence. It would be of interest to know whether Haan et al took into account comparable data from participants in the Sacramento Area Latino Study on Aging (SALSA), who would be expected to have a high prevalence of *H. pylori* infection. Such data appear to be crucial in shedding light on *H. pylori* infection, which may influence the pathophysiology of the MCI-AD sequence by: 1) promoting platelet and platelet-leukocyte aggregation, also proposed to play pathophysiologic roles in AD development (7, 9); 2) releasing proinflammatory and vasoactive substances involved in a number of vascular disorders, including MCI, AD, and other AD-related neuropathies such as glaucoma, defined as “ocular AD” (7, 9, 10); 3) stimulating mononuclear cells to produce a tissue factor–like procoagulant that converts fibrinogen into fibrin (7); 4) causing the development of cross mimicry between endothelial and *Hp* antigens; 5) increasing the aforementioned Hcy, which has been implicated in endothelial damage and neurodegeneration via oxidative injury in these neurodegenerative diseases (7); 6) producing reactive oxygen metabolites and circulating lipid peroxides also involved in the pathophysiology of AD (7); and 7) influencing the apoptotic process, which is an important form of cell death in many...
neurodegenerative diseases including AD and possibly MCI (7). Nota-
ably, *H. pylori* is capable of inducing apoptotic effects through the mi-
 tochondrial apoptotic pathway involving activation of the proapoptotic
proteins Bax and Bak, activation of certain caspases, or through induc-
bile nitric oxide (7). Nitric oxide is a rapidly diffusing gas and a potent
neurotoxin that may contribute to the apoptotic neuronal cell death in
degenerative neuropathies (7).

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REFERENCES


Reply to J Kountouras et al

Dear Sir:

Kountouras et al raise interesting points about the potential relations between *Helicobacter pylori* infection, gastric function, vitamin B-12 absorption, and risk of cognitive impairment. Our research group has not specifically investigated *H. pylori* infection in the

Sacramento Area Latino Study on Aging (SALSA), but we did report previously on the cross-sectional association between gastric function and vitamin B-12 status in a nonrandom subsample of study subjects (1). Elevated serum gastrin (≥100 ng/L) is a sensitive predictor of moderate-to-severe atrophy of the gastric body (2). We observed elevated serum gastrin in ≈30% of the SALSA subjects, with a higher percentage (48%) of elevated values in those subjects with a deficient total plasma B-12 concentration (<148 pmol/L). Moreover, we observed a highly significant inverse association between gastrin and plasma vitamin B-12 concentrations (*P* < 0.0001).

The association between *H. pylori* infection and gastric function is complex. Initial, acute *H. pylori* infection results in reduced secretion of gastric acid (3). If the infection persists for several months, gastric acid secretion may normalize or increase (4). If the infection and gastritis are prolonged beyond several months, there is progression to gastric atro-

phy, and gastric acid secretion is again reduced. This *H. pylori-*induced reduction in gastric acid secretion impairs the capacity to release and absorb vitamin B-12 from animal source foods and may increase the risk of intestinal bacterial overgrowth. The bacteria may compete with the host for dietary vitamin B-12 and reduce the vitamin’s bioavailability. Finally, recent evidence has been presented that links previous *H. pylori* infection with subsequent development of autoimmune pernicious anemia (5). The pathogenesis of such an association may involve molecular mimicry by *H. pylori* of gastric mucosal antigen, which allows the organism to “fly below the radar screen” of host immune surveillance with subsequent risk of autoimmune consequences in a susceptible host (6).

Thus, it is reasonable to predict that *H. pylori* infection may con-
tribute to low vitamin B-12 status. Data from the National Health and Nutritional Examination Survey show that Mexican Americans 70 y of age and older experience a significantly higher prevalence of infection with *H. pylori* than do white non-Hispanics (74.0% compared with 54.8%) (7). The SALSA study involves a representative sample of the Mexican elderly population in the Sacramento area of California who are demographically similar to national samples of the same age and ethnicity (8). It is therefore likely that the SALSA population carries a high burden of *H. pylori* seroprevalence. It is possible that the relatively high prevalence of low plasma vitamin B-12 (6.5%) we observed in the SALSA cohort may be associated with prevalent infection by *H. pylori*. Whether the influence of gastric atrophy on vitamin B-12 status is of sufficient magnitude to affect cognitive function in the SALSA cohort is open to speculation. Because we did not find an effect of low plasma vitamin B-12 on dementia and CIND outcomes, the link between *H. pylori* and vitamin B-12 may not directly apply to these findings. We also have not yet examined the influence of related medications on vitamin B-12 or on cognitive status.

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