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The relationship between *Helicobacter pylori* infection and Alzheimer's disease in Japan

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Conflict of interest None.

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Abstract

Although two studies have indicated a possible link between Alzheimer's disease (AD) and *Helicobacter pylori* (*H. pylori*) infection, these were reported from Europe, where the prevalence of *H. pylori* infection is not very high. In this study, the prevalence of *H. pylori* infection was examined in AD patients in Japan, where there is a high prevalence of *H. pylori*. Consecutive patients referred to the Memory and Dementia Outpatient Clinic from August 2002 to March 2009 were studied. *H. pylori* infection status was determined by measuring urinary levels of anti-*H. pylori* antibody (RAPIRUN®). Multiple stepwise logistic regression analyses were used to examine the associations of AD with the main predictor variables. Of the 917 patients who visited the clinic, 385 were diagnosed as having AD. Ninety-seven patients did not have dementia and were considered controls. On univariate analysis, average age and the proportion of males were significantly higher in AD patients than in controls. There was no difference in the prevalence of *H. pylori* infection between patients with AD and controls (62.0% vs. 59.7%, $p = 0.67$, crude odds ratio (OR), 1.10). Multiple logistic regression analysis showed that older age and male sex, but not *H. pylori* status, were significantly associated with AD ($p < 0.001$, $p = 0.01$, $p = 0.83$, respectively). The prevalence of *H. pylori* infection did not differ between AD patients and controls among Japanese subjects. The high prevalence of *H. pylori* in controls may contribute to the discrepancy with previous reports.

Keywords

Alzheimer's disease; *Helicobacter pylori*; Urine test

Introduction

Alzheimer's disease (AD) is a progressive, age-related, neurodegenerative disorder that is the most common form of dementia, affecting ~20 million people worldwide (6–8% of the population aged 65 years and approximately 30% of the population aged 85 years or over); the number of patients with AD is expected to increase with increased life expectancy [1, 26, 29, 31]. In its earlier stages, the disease is characterized by progressive impairments of memory, visuospatial skills, complex cognition, language, and personality. Later, patients present with global amnesia and slowing motor function, with death typically occurring within 9 years after the initial diagnosis [6].

Helicobacter pylori (*H. pylori*), a curved, spiral-shaped, gram-negative bacterium, was first described in 1983 as a bacterium in the stomach of patients with gastritis and peptic ulcer diseases [19]. *H. pylori* infection occurs mostly during childhood and generally remains in the stomach for life. Chronic *H. pylori* infection is accepted as the major cause of chronic gastritis, peptic ulcer, and gastric cancer [30]. *H. pylori* has also been associated with extradigestive disorders [15, 20, 23], such as functional vascular disorders caused by vascular dysregulation, atherosclerosis [33], hypertension, cardiovascular and/or cerebrovascular ischemia, and stroke [27]. All of these have been recognized as risk factors for AD, mainly by impairing the blood-brain barrier, a common denominator associated with various degrees of dementia, including AD [5, 8, 22,32]; these conditions contribute to the clinical manifestations and worsening of AD [24].

There are only two previous reports about the prevalence of *H. pylori* infection in AD patients. Both reports documented a high prevalence of *H. pylori* infection in AD patients [16, 18]. However, both were reported from Europe, where the prevalence of *H. pylori* infection is not very high [7]. In this study, the prevalence of *H. pylori* infection was examined in AD patients in Japan, where there is a relatively high prevalence of *H. pylori* infection.

Methods

All subjects provided their written, informed consent, and the Ethics Committee of Oita University approved the study.

Study population

Patients who visited the Memory and Dementia Outpatient Clinic at the Department of General Medicine in Oita University Hospital from August 2002 to March 2009 were studied. Almost all patients visited the clinic because of family concerns about dementia.

The diagnosis of probable AD was established according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-AD-RDA) [21]. All patients completed a screening battery that included the mini-mental state examination (MMSE) and the Hasegawa Dementia Scale-Revised (HDS). Clinical assessments were based on a standardized format consisting of a neurological and physical examination, magnetic resonance imaging (MRI) of the brain, and blood chemistries to exclude other metabolic causes for cognitive decline. MRI was conducted as a diagnostic neuroimaging technique to confirm temporal lobe and hippocampal formation atrophy; it was also used to exclude other causes of dementia (e.g., stroke, tumor, frontal–temporal dementia). Patients with vascular, lewy body, frontal–temporal, and other types of dementia were excluded from the study. Patients with mixed type dementia (AD plus vascular dementia) were also excluded. In addition, patients with known or subclinical thyroid disorders, patients with depression, patients with a history of *H. pylori* eradication therapy, and patients who had received antibiotic regimens in the previous 4–6 weeks were excluded.

Evaluation of *H. pylori* status

Helicobacter pylori status was evaluated using a rapid urine test (RAPIRUN® *H. pylori* antibody, Otsuka Pharmaceutical Co., Tokyo, Japan) according the manufacturer's instructions. The reported sensitivity, specificity, and accuracy of the kit in the Japanese population have been reported to be 92.0, 93.1, and 92.3%, respectively [34]. Antibodies in the urine from each patient were immediately measured after the sample collection. A skilled technician measured and analyzed all urine samples blinded to patient information.

Statistical analyses

All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Statistical analyses were done using the chi-square test to compare discrete variables, the Mann–Whitney *U*-test and the *t*-test to compare continuous variables. Differences in prevalence were analyzed for three age groups (<69 years, 70–79 years, and >80 years) using the Mantel–Haenszel method. To match age and sex, multiple backward stepwise logistic regression analyses were used to examine the associations of AD with the main predictor variables. Predictor variables for AD consisted of age (continuous variable), sex (dichotomous variable), and *H. pylori* status (dichotomous variable). For each variable, the odds ratio (OR) and 95% confidence interval (CI) were calculated. A two-tailed *p*-value of <0.05 was considered significant.

Results

A total of 917 patients visited the Memory and Dementia Outpatient Clinic (298 men, 619 women; mean age 74.4 ± 10.4 years) and were included in the study. Of these, 385 were diagnosed as having AD (114 men, 271 women; mean age 78.5 ± 6.4 years). Ninety-seven patients did not have dementia and were considered controls (17 men, 80 women; mean age 70.4 ± 9.8 years). The MMSE score was 20.4 ± 3.8 in AD patients and 26.6 ± 1.6 in controls ($p < 0.01$).

On univariate analysis, the average age was significantly higher in AD patients than in controls ($p < 0.01$) (Table 1). The ratio of males was significantly higher in AD patients than in controls (29.6% vs. 17.5%, $p = 0.01$). There was no difference in prevalence of *H. pylori* infection between AD patients and controls (62.0% vs. 59.7%, $p = 0.67$, crude OR 1.10). Mantel-Haenszel analysis was performed to match the age. Even when patients were categorized into the three age groups (<69 years, 70–79 years, and [80 years), the prevalence of *H. pylori* infection did not differ among the age groups (Mantel–Haenszel analysis, $p = 0.84$) (data not shown).

Results from the multiple logistic regression analysis examining associations of explanatory factors with diagnosis are shown in Table 2. Older age and male, but not *H. pylori* status, were significantly associated with AD ($p < 0.001$, $p = 0.01$, $p = 0.83$, respectively).

Discussion

Although the early events underlying AD remain uncertain, the possibility that microorganisms can cause AD has recently been addressed [11], with infiltration of the brain by pathogens acting as a trigger or co-factor for AD in the cases of herpes simplex virus type 1 and *Chlamydophila* [9,12]. These pathogens may cause the neurological damage that results in AD by eliciting inflammation. A recent report showed that systemic inflammation was associated with accelerated, delirium-independent cognitive decline in the patients with AD [10]; systemic infection may adversely affect microglia, and thereby indirectly the neurons they support [25].

Two studies from Europe showed a positive relation between AD and *H. pylori* infection [16, 18]. Malaguarnera et al. [18] showed that the presence of AD was significantly associated with high *H. pylori* IgG levels in 30 AD Italian patients. In Greece, Kountouras et al. investigated 50 AD patients and reported that *H. pylori* infection, determined by histology in addition to serological examination, was significantly associated with AD as compared to patients with iron deficiency anemia [16]. Interestingly, Kountouras et al. [14] also reported that the cognitive and functional status parameters in AD patients were improved in patients in whom *H. pylori* eradication was successful, but not in the other patients. This also suggests the positive association *H. pylori* and AD. However, these studies examined the effect of *H. pylori* eradication enrolled a small number of AD patients (i.e., 30 patients [18] and 50 patients [16]) and were reported from countries where the prevalence of *H. pylori* infection was relatively low (e.g., the prevalence of *H. pylori* infection was 46.7% in the report by Kountouras et al. [16]). Therefore, we examined the relationship between AD and *H. pylori* in Japan, where there is a high prevalence of *H. pylori* infection [13, 28], and we found for the first time that there was no relation between AD and *H. pylori*. To the best of our knowledge, this is the first report analyzing a large number of AD patients in a country with a high prevalence of *H. pylori* infection.

Our study has several limitations. First, this study was in a referral population. Therefore, the patients in controls might also be destined to develop AD in future. Although the information for follow up was not enough, no patients in controls develop AD in the next

few years (data not shown). Prospective study is necessary to clarify the relationship between *H. pylori* infection and AD. Second, urinary antibody was used to detect *H. pylori* infection in this study. For this urinary kit, an *H. pylori* antigen was extracted from a strain that had been isolated and cultivated from Japanese patients with atrophic gastritis, which contributes to the test's high accuracy in Japanese subjects [34]. However, the advanced atrophy and intestinal metaplasia is no longer ideal for the growth of *H. pylori* [2, 4]. Therefore, a negative *H. pylori* antibody test does not rule out the possibility of previous exposure to infection, especially in the elderly. It is possible that this is the reason for the low prevalence in controls (59.7%) compared with a previous study [3, 13, 17]. Differences of subjects and method of examination may also affect the different prevalence. Further studies that include evaluation of endoscopic findings such as atrophy or intestinal metaplasia are necessary.

In conclusion, *H. pylori* status was independent of AD in Japan, probably due to the high prevalence of *H. pylori* infection even in controls. It is necessary to examine the effect of *H. pylori* eradication therapy in the early stage of AD to prove the relationship between AD and *H. pylori* infection.

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Table 1

Comparisons between AD patients and controls

	AD		Controls		*p*-Value
	(*n* = 385)	(%)	(*n* = 97)	(%)	
Age (years)	78.5 ± 6.4	–	70.4 ± 9.8	–	<0.001 *
Male	114	(29.6%)	17	(17.5%)	0.01 *
H. pylori-positive	239	(62.0%)	58	(59.7%)	0.67

* AD versus controls

Table 2

Multivariate analyses of the risk for AD by age, sex, and *H. pylori* status

	Adjusted odds ratio	**95% Confidence interval**	***p*-Value**
Age (per 1 year)	1.15	1.11–1.19	<0.001
Sex (male)	2.21	1.19–4.10	0.011
H. pylori status (positive)	0.94	0.56–1.58	0.835