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Clinical Study

Association between *Helicobacter pylori* infection and dementia

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ABSTRACT

Dementia is the severe loss of global cognitive ability in a previously healthy person. This study examined the relationship between *Helicobacter pylori* infection (*HP*-I) and non-Alzheimer's dementia (non-AD) using a nationwide population-based dataset. The International Classification of Diseases, Ninth Revision (ICD-9) codes for dementia were used to define dementia patients; in addition, we examined the association of dementia with other comorbidities. Patients aged ⩾40 years with newly diagnosed *HP*-I (ICD-9 code 041.86) during 1998–2010 were identified as the *HP*-I cohort. The comparison cohort consisted of people aged ⩾40 years without *HP*-I (non-*HP*-I) randomly selected from the database at a ratio of 1:4 in the same time period. The controls were frequency matched according to the age (every 5 years), sex, and index year of patients in the *HP*-I cohort. Follow-up was performed for all patients until the date of dementia diagnosis (ICD-9 codes 290.0–290.4, 294.1, 331.0–331.2), date of withdrawal from the Taiwanese National Health Insurance program, date of death, or until December 31 2010. Compared with patients without *HP*-I, *HP*-I patients were 1.60-fold (95% confidence interval [CI] 1.32–1.95) more likely to develop non-AD. There was no statistical association between *HP*-I and AD. The adjusted hazard ratio of dementia increased from 1.48 (95% CI 1.22–1.79) for patients who had *HP*-I once to 2.19 (95% CI 1.13–4.25) for patients who had *HP*-I two or more times. Our study revealed that *HP*-I may be a critical risk factor for the development of non-AD. Further investigation, including clinical trials, to examine the microbe–dementia connection may provide further proof of the association between *HP*-I and dementia.

1. Introduction

Dementia is a health problem among elderly people in Taiwan. Several risk factors are associated with dementia, including aging, the presence of the apolipoprotein E4 allele, and socioeconomic status. Factors associated with vascular dementia (VaD) include hypertension, diabetes, head injury, and depression [1]. Elderly people with low education levels have a high risk of developing dementia. Understanding the types of dementia, including Alzheimer's dementia (AD), VaD, and that associated with parkinsonism, requires evaluation of potential environmental factors. Environmental factors are crucial in the etiology of dementia and are associated with dementia incidence [2]. In one recent study, *Helicobacter pylori* (*HP*) infection (*HP*-I) was associated with VaD in a case–control study of 30 patients [3], which demonstrated that antibody titers against *HP* were correlated with AD and VaD. However, the mechanism for this remains unclear. Possible mechanisms include neurotoxicity, defective immune regulation, and apoptosis [4–6]. Other studies have suggested that *HP* influences the pathophysiology of AD by releasing various proinflammatory cytokines [7–9], mimicking the molecular structure of host antigens [10], producing reactive oxygen metabolites and circulating lipid peroxides [11], or influencing apoptosis [4], which contribute to endothelial damage implicated in vascular disorders, such as VaD.

To our knowledge no studies have focused on the association between *HP*-I and dementia in an ethnic Han Chinese population [12,13]. The purpose of this study was to verify the association

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between *HP*-I and dementia in the Taiwanese population and to examine the relative risk of dementia in patients with and without *HP*-I.

2. Methods

2.1. Data sources and study population

In March 1995, the Taiwanese government implemented the National Health Insurance (NHI) program, which provides general health insurance to nearly the entire Taiwanese population. By the end of 2009, the insurance program had established contracts with 97% of clinics and hospitals in Taiwan [14]. We performed a cohort study by using medical information from the nationwide population-based data released by the National Health Research Institutes (NHRI) for 1996–2010. With approval from the NHRI, we used scrambled patient identification numbers to interlink files, including inpatient claims and beneficiaries' registration status. The available sociodemographic data consisted of sex, birth date, occupation, and place of residence. Diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012).

2.2. Study patients

In this retrospective cohort study, patients aged ⩾40 years with newly diagnosed *HP*-I (ICD-9 code 041.86) during the period 1998–2010 were identified as the *HP*-I cohort. The index date was defined as the date of *HP*-I diagnosis. The comparison cohort consisted of people aged ⩾40 years without *HP*-I in the same time period randomly selected from the database at a ratio of 1:4 (*HP*-I to non-*HP*-I). The controls were frequency matched according to the age (every 5 years), sex, and index year of patients in the *HP*-I cohort. Patients who were diagnosed with dementia (ICD-9 codes 290.0–290.4, 294.1, 331.0–331.2) before the index date, or had missing sex and age data were excluded from the study. Follow-up was performed for all patients until the date of dementia diagnosis, date of withdrawal from the NHI, date of death, or December 31 2010. History of hypertension (ICD-9 codes 401–405, 997.91), diabetes (ICD-9 code 250), acute myocardial infarction (ICD-9 code 410), head injury (ICD-9 codes 850–854, 959.01), and depression (ICD-9 codes 296.2, 296.3, 300.4, and 311) were identified based on hospital admission diagnoses before the index date.

2.3. Statistical analysis

The demographic and clinical characteristics of *HP*-I patients and non-*HP*-I comparison controls were identified using the total numbers (proportions) of categorical variables and the means (± standard deviation [SD]) of continuous variables. Differences were examined using the χ^2 test for categorical variables and the *t*-test for continuous variables. The sex-specific, age-specific, and comorbidity-specific incidence density rates of dementia were calculated in person-years. The *HP*-I cohort to non-*HP*-I cohort incidence rate ratio (IRR) with 95% confidence intervals (CI) was determined using a Poisson regression.

Multivariate Cox proportional hazard analysis was used to estimate the hazard ratio (HR) of dementia, and the 95% CI among patients with *HP*-I were compared with those of non-*HP*-I patients. In the models, age, sex, and comorbidities were controlled. Both crude HR and multivariate adjusted HR were used to measure the risk of developing dementia. We used the SAS statistical package (version 9.1; SAS Institute, Cary, NC, USA) to conduct statistical analyses. Statistical significance was defined as two-sided $p < 0.05$.

3. Results

The cohort consisted of 16,793 *HP*-I patients and 67,172 non-*HP*-I controls for the period of 1998–2010. The mean ages of the *HP*-I and non-*HP*-I cohorts were 63.6 (SD, 13.4) and 63.2 (SD, 13.5) years, respectively (Table 1). Approximately 62% of the patients were male. Most patients were 40 to 65 years old (52.9% in both cohorts). Patients with *HP*-I had a higher prevalence of all baseline comorbidities ($p < .0001$). Table 2 presents the incidence rate in both cohorts and the *HP*-I to non-*HP*-I IRR of dementia according to demographic factors and comorbidity. The *HP*-I cohort had a higher incidence of dementia than the non-*HP*-I cohort (28.3 *versus* 17.2 per 10,000 person-years, IRR = 1.64, 95% CI 1.56–1.73), with an adjusted HR of 1.51 (95% CI 1.25–1.82). Sex-specific analysis showed that the incidence rates of men and women were 29.5 and 26.4 per 10,000 person-years, respectively, in the *HP*-I cohort. In men, the *HP*-I cohort showed a 1.67-fold significantly higher risk of developing dementia compared with the non-*HP*-I cohort (95% CI 1.32–2.12). Comparing the *HP*-I cohort with the non-*HP*-I cohort, the incidence rate increased with age, but the IRR of dementia decreased with age. Moreover, older patients (65 to 80 years of age) in the *HP*-I cohort showed a significantly higher risk of developing dementia than older patients in the non-*HP*-I cohort did (adjusted HR = 1.89, 95% CI 1.46–2.45).

Most of the comorbidities were associated with an increased incidence of dementia. Analyzing the association of *HP*-I with comorbidities showed that *HP*-I patients with most types of comorbidities had a higher risk of developing dementia than the non-*HP*-I cohort did (adjusted HR of hypertension = 1.50, 95% CI 1.14–1.97; adjusted HR of diabetes = 1.91, 95% CI 1.29–2.82). The *HP*-I cohort had a higher risk of dementia than the non-*HP*-I cohort did (adjusted HR = 1.51, 95% CI 1.46–2.45) in the multivariate Cox model (Table 3). The adjusted HR of dementia was higher for elderly patients (65 to 80 years of age, adjusted HR = 44.8, 95% CI 30.4–66.1) than for those aged between 40 and 65 years. Among the comorbidities, the risk of developing dementia was greatest for patients with depression (adjusted HR = 2.86, 95% CI 1.87–4.37). Compared to patients without *HP*-I, the adjusted HR increased from 1.48 (95% CI 1.22–1.79) for patients with one infection to 2.19 (95% CI 1.13–4.25) for patients with two or more infections (p for trend <.0001) (Table 4). We analyzed the distribu-

Table 1
Demographic characteristics and comorbidity in patients with and without *Helicobacter pylori* infection

Variable	*Helicobacter pylori* infection		*p* value
	No n = 67,172	Yes n = 16,793	
Sex			
Female	25804 (38.4)	6451 (38.4)	0.99
Male	41368 (61.6)	10342 (61.6)	
Age, mean (SD)[#]	63.2 (13.5)	63.6 (13.4)	0.001
Stratified age			
40–65	35548 (52.9)	8887 (52.9)	0.99
65–80	23038 (34.3)	5759 (34.3)	
80+	8586 (12.8)	2147 (12.8)	
Comorbidity			
Hypertension	11056 (16.5)	4925 (29.3)	<0.0001
Diabetes	5824 (8.67)	2914 (17.4)	<0.0001
Head injury	2963 (4.41)	1417 (8.44)	<0.0001
Depression	549 (0.82)	473 (2.82)	<0.0001

[#] Chi-square test; two sample *t*-test.
SD = standard deviation.

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