ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-6

Alzheimer's & Dementia

Short Report

Helicobacter pylori and the risk of dementia: A population-based study

Lana Fani[a], Frank J. Wolters[a,b], M. Kamran Ikram[a,b], Marco J. Bruno[c], Albert Hofman[a,d], Peter J. Koudstaal[b], Sarwa Darwish Murad[a,c], M. Arfan Ikram[a,*]

[a]*Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[b]*Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[c]*Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands*
[d]*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

Abstract

Introduction: *Helicobacter pylori* infection might increase risk of dementia, but available evidence is inconsistent, and longitudinal studies are sparse. We investigated the association between *H. pylori* serology and dementia risk in a population-based cohort.

Methods: Between 1997 and 2002, we measured *H. pylori* serum IgG titers in 4215 nondemented participants of the Rotterdam Study with a mean age of 69 years. We determined the association between *H. pylori* at baseline and dementia incidence until 2015, per natural log (U/mL) increase in titer, and for seropositive/seronegative, using Cox models adjusting for cohort, sex, age, education, and cardiovascular risk factors.

Results: During a median follow-up of 13.3 years, 529 participants developed dementia, of which 463 had Alzheimer's disease. *H. pylori* was not associated with risk of dementia (hazard ratio [95% confidence interval] for antibody titer: 1.04 [0.90–1.21]; for seropositivity 1.03 [0.86–1.22]), or Alzheimer's disease.

Discussion: In this community-dwelling population, *H. pylori* was not associated with dementia risk.

Keywords: Alzheimer's disease; *Helicobacter pylori*; Dementia; Infection; Longitudinal

1. Introduction

Helicobacter pylori is a gram-negative bacillus that colonizes the stomach and is estimated to infect half of the world's population [1]. The bacterium is generally acquired during childhood by oral ingestion. In adults, the infection is usually chronic and will not heal without specific therapy. The clinical course, however, is highly variable. While in some individuals infections remain asymptomatic, others may develop serious gastric complications, such as ulcers or gastric carcinoma [2].

In addition, recent evidence suggests that *H. pylori* infection might be associated with extra-gastric diseases, including dementia [3–5]. This may be due to detrimental consequences of *H. pylori* associated anemia, inflammation, and hyperhomocysteinemia on vascular and neuronal health [6,7]. A recent systematic review and meta-analysis [8] showed a 71% increased risk of dementia with *H. pylori* infection, but heterogeneity across studies was high. This may relate to differences in (geographical) setting and study design, with current evidence mainly arising from cross-sectional studies. We aimed to investigate the association of *H. pylori* with dementia in a prospective population-based cohort study.

2. Methods

2.1. Design and study population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study among middle-aged and elderly individuals in the Netherlands [9]. A detailed description is provided in the online

Conflicts of interest: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

*Corresponding author. Tel.: +31107043489; Fax: +31107044657.
E-mail address: m.a.ikram@erasmusmc.nl

https://doi.org/10.1016/j.jalz.2018.05.005

Supplementary Material. Established in 1990, participants were invited every 4–5 years to undergo follow-up examinations at the research center. Between 1997 and 2002, a total of 7444 participants from two subcohorts visited the research center, of which 4215 dementia-free subjects provided blood samples for measurement of *H. pylori* titer (Supplementary Fig. S1).

The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, and written informed consent was obtained.

2.2. Assessment of anti-H. pylori antibodies

Blood was drawn at baseline. To obtain serum and plasma, tubes were centrifuged according to a protocol standardizing time and conditions from the drawing of blood to centrifugation. All samples were snap-frozen at −196°C using liquid nitrogen and stored at −80°C. Anti-*H. pylori* serum IgG antibody titers were measured in 2011 using commercial enzyme immunoassays (Pyloriset EIA-G III ELISA; Orion) as described earlier [10]. We used anti-*H. pylori* serum IgG antibody titers primarily as a continuous variable. In addition, seropositivity was defined as an anti-*H. pylori* IgG titer equal to or greater than 20 U/mL, according to the manufacturer's recommendation.

2.3. Ascertainment of incident dementia

Participants were screened for dementia at baseline and subsequent center visits with the Mini–Mental State Examination and the Geriatric Mental Schedule organic level. Those with a Mini–Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study center with medical records from general practitioners and the regional institute for outpatient mental health care. A consensus panel headed by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R) and Alzheimer's disease (AD) (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association). Follow-up until January 1, 2015, was virtually complete (99.1% of potential person-years in the original cohort and for 97.0% of potential person-years in the extended cohort). Within this period, participants were censored at date of dementia diagnosis, death, loss to follow-up, or administrative censoring date, whichever came first.

2.4. Covariables

Potential confounding factors for dementia were chosen on the basis of previous literature [8,11]. In all models, we adjusted for cohort, sex, and age at baseline. In multivariate adjusted models, we additionally adjusted for education, smoking, systolic and diastolic blood pressure, anti-hypertensive drug use, body mass index, cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein E (APOE) ε carrier status, stroke, diabetes mellitus, ethnicity, and serum lipid–reducing agents at baseline. APOEε carrier status was corrected since a study has shown that *H. pylori* and ApoE 4 polymorphism may be associated with dysphagic symptoms in older adults [12]. Assessment methods of the covariates are described in the Supplementary Materials. Blood samples for determination of levels of hemoglobin, homocysteine, C-reactive protein (CRP), interleukin-6 (IL6), α1-antitrypsin (α1-AT), lipoprotein-associated phospholipase A2 activity, and fibrinogen were obtained at the research center.

2.5. Statistical analysis

Because of a skewed distribution of anti-*H. pylori* serum IgG antibody titers, we performed a natural log transformation. Differences in baseline characteristics between the *H. pylori*-positive and *H. pylori*-negative groups were assessed using Student's *t*-test and chi-squared test. We determined the association between *H. pylori* (continuously as well as dichotomized for seroprevalence) and risk of dementia, using Cox regression models, adjusting for age, sex, study cohort, education, and cardiovascular risk factors. The proportional hazards assumption was met.

We repeated analysis only for Alzheimer's disease and used higher cutoffs for seroprevalence (in steps of 5 U/mL from the manufacturer's recommended cutoff) to explore differential effects among individuals with more profound antibody response. We assessed interaction by age, sex, or medication use by stratification and testing for multiplicative interaction. In addition, we tested for multiplicative interaction between *H. pylori* titer and CRP to assess if there is a difference in dementia risk between more severely infected and less severely infected groups. Finally, we computed Pearson correlation coefficients for the association of *H. pylori* titer with levels of hemoglobin, homocysteine, and CRP, with homocysteine and CRP both natural log transformed. In addition to CRP, which was available for all participants, we also determined the correlation between *H. pylori* and four other inflammatory biomarkers that have previously been related to dementia risk [13] and were available in a subsample of approximately 500 participants with *H. pylori* measurement.

All analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY).

3. Results

Baseline characteristics of the study population are presented in Table 1. During a mean follow-up of 10.6 (±4.5) years and median follow-up of 13.3 years (interquartile

Table 1
Baseline characteristics of the Rotterdam Study cohort

	Study population for analysis (N = 4215)	*Helicobacter pylori* positive (N = 2088)	*H. pylori* negative (N = 2127)	*P*-value for difference
Age, years	68.4 (8.6)	69.3 (8.6)	67.5 (8.5)	<.001
Female	2288 (54.3)	1093 (52.3)	1195 (56.2)	.012
Caucasian ethnicity	4140 (98.2)	2056 (98.5)	2081 (97.8)	.161
Education				<.001
Primary education	537 (12.7)	325 (15.6)	215 (10.1)	
Lower/intermediate general education	1873 (44.4)	944 (45.2)	928 (43.6)	
Intermediate vocational education	1244 (29.5)	602 (28.8)	642 (30.2)	
Higher vocational education	561 (13.3)	217 (10.4)	342 (16.1)	
Smoking				.006
Never smoker	1335 (31.7)	615 (29.5)	719 (33.8)	
Former, now nonsmoker	2130 (50.5)	1077 (51.6)	1051 (49.4)	
Current smoker	759 (17.8)	396 (19.0)	357 (16.8)	
Systolic blood pressure, mm Hg	143.4 (21.2)	143.8 (21.2)	143.1 (21.2)	.284
Diastolic blood pressure, mm Hg	76.9 (11.2)	76.6 (11.3)	77.1 (11.1)	.117
Anti-hypertensive medication	1488 (35.3)	757 (36.3)	728 (34.2)	.178
Body mass index, kg/m^2	27.0 (3.9)	27.0 (3.8)	27.0 (4.0)	.495
Diabetes mellitus	579 (13.7)	276 (13.2)	304 (14.3)	.333
Cholesterol, mmol/L	5.8 (1.0)	5.8 (1.0)	5.8 (1.0)	.939
High-density lipoprotein, mmol/L	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)	<.001
Triglycerides, mmol/L	1.6 (0.8)	1.6 (0.8)	1.6 (0.8)	.537
Lipid lowering medication	572 (13.6)	291 (13.9)	288 (13.5)	.742
History of stroke	163 (3.9)	85 (4.1)	78 (3.7)	.549
Apolipoprotein E genotype				.701
ε3 homozygote	2478 (58.8)	1218 (58.3)	1264 (59.4)	
ε2/ε2 or ε2/ε3	587 (13.9)	299 (14.3)	288 (13.5)	
ε4/ε4, ε3/ε4 or ε2/ε4	1149 (27.3)	571 (27.3)	575 (27.0)	
H. pylori serum IgG antibody titers, U/mL	19.6 (11.5; 92.2)	94.0 (36.0; 238.9)	11.5 (10.2; 14.2)	<.001
H. pylori-positive seroprevalence	2088 (49.5)			

Abbreviation: N, number of subjects.

NOTE. Data presented as mean (standard deviation) for continuous variables and number (percentages) for categorical variables. *H. pylori* serum IgG antibody titers are presented as median (interquartile range).

NOTE. Differences in baseline characteristics between the *H. pylori*-positive and *H. pylori*-negative groups were assessed using Student's *t*-test and chi-squared test.

range of 5.9) with 47,664 person-years, 529 individuals were diagnosed with dementia, of which 463 had AD.

Serum antibody titer of *H. pylori* was not associated with risk of dementia (hazard ratio, 95% confidence interval, per log unit increase: 1.04, 0.90–1.21). Similarly, *H. pylori* seroprevalence was not associated with dementia risk (hazard ratio 1.03, 0.86–1.22). These results were similar for AD (Table 2) and robust for different antibody titer cutoffs defining seroprevalence (Online Supplementary Fig. S2). Risk estimates tended to be higher in older participants and in men, and albeit interaction terms were not statistically significant (P = .383 and P = .142, respectively; Supplementary Fig. S3). We observed no significant interaction between *H. pylori* serum IgG titer or use of antibiotics and anti-acids on dementia risk (P = .449) (Supplementary Fig. S3), nor with CRP (P = .974). Antibody titers of *H. pylori* showed only very weak correlation with concurrent levels of hemoglobin, homocysteine, and CRP (r = 0.004 and P = .835, r = 0.086 and P < .01 and r = 0.053 and P = .001, respectively). Finally, interleukin-6, α1-AT, lipoprotein-associated phospholipase A2 activity, and fibrinogen showed no meaningful correlations with *H. pylori* (r = 0.039 for IL6; r = 0.080 for α1-AT; r = –0.067 for lipoprotein-associated phospholipase A2 and r = 0.004 for fibrinogen; all P > .05).

4. Discussion

In this prospective cohort study, we found no association between *H. pylori* infection and risk of all-cause dementia or AD.

There are only two other longitudinal studies performed on this association, which show a hazard ratio of 1.46 (confidence interval 1.01–2.11) [14] and 1.51 (confidence interval 1.25–1.82) [15] for developing dementia. These findings are in contrast with our results, but several potential explanations, including methodological differences, may clarify this contrast. For instance, the community-based PAQUID cohort study performed in France [14] had an older study population (65 years and older) compared with our

Table 2
Helicobacter pylori infection and the risk of dementia: Longitudinal results

	All dementia n/N = 529/4215 HR, 95% CI	Alzheimer n/N = 463/4215 HR, 95% CI
Model I		
H. pylori serum IgG, per log(U/mL)* increase	1.07, 0.92–1.23	1.11, 0.94–1.30
H. pylori seroprevalence, positive versus negative	1.03, 0.87–1.23	1.08, 0.89–1.31
Model II		
H. pylori serum IgG, per log(U/mL)* increase	1.04, 0.90–1.21	1.06, 0.90–1.25
H. pylori seroprevalence, positive versus negative	1.03, 0.86–1.22	1.06, 0.87–1.29

Abbreviations: n, number of cases; N, number of persons at risk; HR, hazard ratio; CI, confidence interval.

NOTE. Cox regression model I: Adjusted for age, sex and study cohort. Cox regression model II: Adjusted for age, sex, study cohort, education, smoking, systolic and diastolic blood pressure, anti-hypertensive drug use, body mass index (BMI), cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, APOEε carrier status, stroke, diabetes mellitus, ethnicity, and serum lipid–reducing agents.

*Natural log transformed because of right skewed distribution.

cohort of 55 years and over. Because we show a tendency for an increased risk in older age groups (Supplementary Fig. S3), an older cohort may indeed show an effect of *H. pylori* on dementia. Also, the PAQUID cohort selected their study sample on being followed up for 20 years, thereby selecting the survivors, which is more susceptible to selection bias. The other longitudinal study is a Taiwanese registry study [15] using medical information from a nationwide population-based data set. The study population was aged ≥40 years and followed during 1998–2010. In this retrospective cohort study, dementia diagnosis was therefore based on registries instead of multiple-stage designs with in-person screening for dementia diagnosis, making dementia diagnosis less reliable. In addition, results are prone to confounding due to the inherent shortcomings of the NHRI database. Also, participants with newly diagnosed *H. pylori* were identified with ICD-9 codes, potentially including the symptomatic *H. pylori* cases which may be more virulent and thereby observing a stronger effect of *H. pylori* on dementia risk in the overall population.

There are also potential biological explanations for the differences across studies, such as geographical differences. Studies have found that the rate of colonization with cagA(+) *H. pylori* strains has become very low in the Netherlands [16,17]. CagA is a highly antigenic protein that is associated with a prominent inflammatory response [18]. This finding suggests that the *H. pylori* infections in the Netherlands may have low virulence in general compared with other countries, leading to fewer complications. For example, in studies comparing dyspeptic patients, studies indeed report higher prevalence rates of cagA+ strains in France (88%) [19] and Taiwan (99%) [20] compared with 78% in the Netherlands in 1996 [21] with a Dutch study from 2013 showing a sharp age-specific decline in CagA+ from 38% to 14% in randomly selected blood donors [17]. This might be reflected in the higher risk estimates in older participants in our study, who would have been exposed more to these highly virulent strains in earlier years, suggesting a cohort effect. Thus, infection-induced cognitive decline can be supported by this finding.

Mechanistically wise, there are several hypotheses regarding the *H. pylori* and dementia association. Prior studies have suggested altered tau phosphorylation [18], vitamin B deficiency (and consequent hyperhomocysteinemia) [7,22], systemic inflammation [23,24], and anemia [25] as potential mechanisms by which *H. pylori* could increase risk of dementia. Although no studies have directly assessed these factors as potential intermediates, the lack of any correlation between *H. pylori* and homocysteine, inflammatory markers (CRP, IL6, α1-AT, lipoprotein-associated phospholipase A2 activity, and fibrinogen) and hemoglobin levels in our study might also support the notion of a less virulent *H. pylori* strain that is currently prevalent in the Netherlands. This in turn could explain why we did not observe an association of *H. pylori* with risk of dementia.

The role of infectious diseases in the development of dementia has been longer known with diseases such as neurosyphilis and acquired immunodeficiency syndrome being accepted infectious causes [26]. However, also more frequently occurring diseases such as herpes virus, toxoplasmosis, and cryptococcus have been shown to have a relationship with dementia [27]. It is postulated that because systemic infection can provoke the enhanced synthesis of inflammatory mediators in the brain, infectious diseases may promote the onset of dementia [28]. Thus, even more common infections which an individual is unable to resolve adequately could lead to chronic inflammation and subsequently neuroinflammation [29]. It is therefore important for future studies to identify such sources of inflammation and eventually identify individuals with increased susceptibility for infections for treatment and prevention purposes.

Several limitations of this study should be taken into account. First, the diagnostic test for detecting *H. pylori* infection has the disadvantage that antibodies are present in blood even after eradication of *H. pylori*. Therefore, current and past infection cannot be distinguished, so we cannot rule out the presence of information bias in the form of misclassification of the exposure. However, we do not expect that the association with incident dementia would be affected because the timing of infection may only be shifted for several months or years. An alternative for future studies would be the stool antigen test, which proves to be more accurate and still noninvasive than the serology test [30]. Second, considering the differences in virulence factors of the

bacterium and treatment strategies in different countries, our findings may not be generalizable to other geographical regions. To take differences in virulence factors into account, future studies could assess CagA phenotypes in *H. pylori*. Third, the invasiveness of lumbar puncture prevents cerebrospinal fluid (CSF) sampling in participants in the Rotterdam Study and therefore we have not been able to measure *H. pylori* IgG antibodies in CSF. Although CSF measurements are likely more reflective of pathology within the CNS, studies show a larger mean concentration of anti-*H. pylori* IgG concentrations both in CSF and serum in AD patients compared with controls [31,32]. This finding supports the systemic effect of the infection, which can be thus measured in serum. Finally, the length of time with the infection could not be accounted for in this present study, which may also contribute to the age-related trend for infection-induced cognitive decline that is observed.

In conclusion, we have found no evidence of an association between *H. pylori* infection and risk of all-cause dementia or AD in our Dutch population. This could be due to low virulence of *H. pylori* in the Netherlands. Future studies are warranted to further elucidate the role of common infectious diseases in the pathophysiology of Alzheimer's disease and thereby identifying novel targets for prevention and treatment.

Acknowledgments

The authors gratefully acknowledge the study participants of the Ommoord district and their general practitioners and pharmacists for their devotion in contributing to the Rotterdam Study. The authors also thank all staff that facilitated assessment of participants in the Rotterdam Study throughout the years. Special thanks to Frank J.A. van Rooij for managing the data.

This work was supported by the European Union's Horizon 2020 research and innovation programme [grant number 667375] ("CoSTREAM"); the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research (NWO) [grant numbers 948-00-010, 918-46-615]; the Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam.

The funding source had no role in study design, collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.05.005.

RESEARCH IN CONTEXT

1. Systematic review: Infection with *Helicobacter pylori* may increase risk of dementia, but evidence is inconsistent, and longitudinal studies are sparse.
2. Interpretation: We have found no association between *H. pylori* infection and risk of all-cause dementia or Alzheimer's disease in the Dutch community-dwelling population. Infection with *H. pylori* in our study was not associated with previously suggested mediators between infection and clinical disease, including hemoglobin, C-reactive protein, and homocysteine.
3. Future directions: Additional longitudinal studies are needed to determine the association between *H. pylori* infection and dementia risk, considering differences in geographical regions, virulence of *H. pylori,* and treatment strategies as potential sources of heterogeneity.

References

[1] Brown LM. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev 2000;22:283–97.
[2] Pellicano R, Ribaldone DG, Fagoonee S, Astegiano M, Saracco GM, Megraud F. A 2016 panorama of Helicobacter pylori infection: key messages for clinicians. Panminerva Med 2016;58:304–17.
[3] Goodman KJ, Joyce SL, Ismond KP. Extragastric diseases associated with Helicobacter pylori infection. Curr Gastroenterol Rep 2006; 8:458–64.
[4] Álvarez-Arellano L, Maldonado-Bernal C. Helicobacter pylori and neurological diseases: married by the laws of inflammation. World J Gastrointest Pathophysiol 2014;5:400–4.
[5] Doulberis M, Kotronis G, Thomann R, Polyzos SA, Boziki M, Gialamprinou D, et al. Impact of Helicobacter pylori on Alzheimer's disease: what do we know so far? Helicobacter 2018;23.
[6] Tchantchou F, Shea TB. Folate deprivation, the methionine cycle, and Alzheimer's disease. Vitam Horm 2008;79:83–97.
[7] Stettin D, Waldmann A, Strohle A, Hahn A. Association between Helicobacter pylori-infection, C-reactive protein and status of B vitamins. Adv Med Sci 2008;53:205–13.
[8] Shindler-Itskovitch T, Ravona-Springer R, Leibovitz A, Muhsen K. A systematic review and meta-analysis of the association between helicobacterpylori infection and dementia. J Alzheimers Dis 2016; 52:1431–42.
[9] Hofman A, Brusselle GG, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, et al. The Rotterdam Study: 2016 objectives and design update. Eur J Epidemiol 2015;30:661–708.
[10] Mayerle J, den Hoed CM, Schurmann C, Stolk L, Homuth G, Peters MJ, et al. Identification of genetic loci associated with Helicobacter pylori serologic status. JAMA 2013;309:1912–20.
[11] de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC Med 2015;13:132.

[12] Kountouras J, Tsolaki F, Tsolaki M, Gavalas E, Zavos C, Polyzos SA, et al. Helicobacter pylori-related ApoE 4 polymorphism may be associated with dysphagic symptoms in older adults. Dis Esophagus 2016; 29:842.
[13] Darweesh SKL, Wolters FJ, Ikram MA, de Wolf F, Bos D, Hofman A. Inflammatory markers and the risk of dementia and Alzheimer's disease: a meta-analysis. Alzheimers Dement 2018.
[14] Roubaud Baudron C, Letenneur L, Langlais A, Buissonniere A, Megraud F, Dartigues JF, et al. Does Helicobacter pylori infection increase incidence of dementia? The Personnes Agees QUID Study. J Am Geriatr Soc 2013;61:74–8.
[15] Huang WS, Yang TY, Shen WC, Lin CL, Lin MC, Kao CH. Association between Helicobacter pylori infection and dementia. J Clin Neurosci 2014;21:1355–8.
[16] den Hoed CM, Vila AJ, Holster IL, Perez-Perez GI, Blaser MJ, de Jongste JC, et al. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. Helicobacter 2011;16:405–9.
[17] van Blankenstein M, van Vuuren AJ, Looman CW, Ouwendijk M, Kuipers EJ. The prevalence of Helicobacter pylori infection in the Netherlands. Scand J Gastroenterol 2013;48:794–800.
[18] Yamaoka Y. Mechanisms of disease: helicobacter pylori virulence factors. Nat Rev Gastroenterol Hepatol 2010;7:629–41.
[19] Jenks PJ, Megraud F, Labigne A. Clinical outcome after infection with Helicobacter pylori does not appear to be reliably predicted by the presence of any of the genes of the cag pathogenicity island. Gut 1998;43:752–8.
[20] Lai CH, Kuo CH, Chen YC, Chao FY, Poon SK, Chang CS, et al. High prevalence of cagA- and babA2-positive Helicobacter pylori clinical isolates in Taiwan. J Clin Microbiol 2002;40:3860–2.
[21] Weel JF, van der Hulst RW, Gerrits Y, Roorda P, Feller M, Dankert J, et al. The interrelationship between cytotoxin-associated gene A, vacuolating cytotoxin, and Helicobacter pylori-related diseases. J Infect Dis 1996;173:1171–5.
[22] Tchantchou F. Homocysteine metabolism and various consequences of folate deficiency. J Alzheimers Dis 2006;9:421–7.
[23] Shadfar S, Hwang CJ, Lim MS, Choi DY, Hong JT. Involvement of inflammation in Alzheimer's disease pathogenesis and therapeutic potential of anti-inflammatory agents. Arch Pharm Res 2015; 38:2106–19.
[24] Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci 2015; 16:358–72.
[25] Min JY, Min KB. The Folate-Vitamin B12 Interaction, Low Hemoglobin, and the Mortality Risk from Alzheimer's Disease. J Alzheimers Dis 2016;52:705–12.
[26] Hoepelman AI. Test for HIV and syphilis too in suspected early dementia. BMJ 2011;344:d8213.
[27] Almeida OP, Lautenschlager NT. Dementia associated with infectious diseases. Int Psychogeriatr 2005;17 Suppl 1:S65–77.
[28] Dunn N, Mullee M, Perry VH, Holmes C. Association between dementia and infectious disease: evidence from a case-control study. Alzheimer Dis Assoc Disord 2005;19:91–4.
[29] Sochocka M, Zwolinska K, Leszek J. The infectious etiology of Alzheimer's disease. Curr Neuropharmacol 2017;15:996–1009.
[30] Khalifehgholi M, Shamsipour F, Ajhdarkosh H, Ebrahimi Daryani N, Pourmand MR, Hosseini M, et al. Comparison of five diagnostic methods for Helicobacter pylori. Iran J Microbiol 2013;5:396–401.
[31] Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Grigoriadis N, et al. Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. Int J Neurosci 2009;119:765–77.
[32] Attallah AM, Toson EA, Ibrahim GG, Bakr NE. Detection of a Helicobacter pylori antigen in cerebrospinal fluid of patients with meningitis. J Immunoassay Immunochem 2007;28:25–33.