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Meta-analysis of Association between *Helicobacter pylori* Infection and Epilepsy

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Abstract

Despite recent research focus on the association between *Helicobacter pylori* (*H. pylori*) infection and epilepsy there is no consensus about the findings. To obtain a more comprehensive estimate of the association we conducted a meta-analysis to determine the prevalence of *H. pylori* infection in epilepsy patients and healthy controls. PubMed, EMBASE, Cochrane Library, Web of Science, Google Scholar and CINAHL were searched to identify eligible studies. Four studies were selected for inclusion, involving 418 cases (232 patients with epilepsy and 186 controls). Overall, the prevalence of *H. pylori* infection in patients with epilepsy was higher than that in control groups. (46.98% vs. 26.34%, OR = 2.58, 95% CI: 1.15-5.82, P = 0.02). Subgroup analysis revealed that the levels of *H. pylori* infection in epilepsy patients was greater than that in control group by using ELISA (OR = 5.36, 95% CI: 2.62-10.95, P < 0.00001), but it was not statistically significant difference when using ^{13}C urea breath test (OR = 1.36, 95% CI: 0.75-2.46, P = 0.32). Our analysis demonstrated that the association between *H. pylori* infection and epilepsy is a significant positive correlation. Whether *H. pylori* infection is a risk factor for epilepsy should thus be addressed in large-scale and prospective studies.

Keywords

Epilepsy, Helicobacter pylori, Prevalence, Meta-analysis

Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium and mainly associated with chronic gastritis, peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma [1,2]. Furthermore, some reports have discerned a relationship between *H. pylori* infection and extra-gastrointestinal diseases such as cirrhosis, pancreatic cancer, coronary heart disease, stroke, migraine, Alzheimer's disease and Multiple sclerosis [3-8]. As these results remain controversial, the interactions between *H. pylori* and humans are suggested to be extremely sophisticated [9].

Recently, there has been some research interest in the association between *H. pylori* infection and epilepsy. Several studies evaluating the possible association between *H. pylori* infection and epilepsy have been published [10-15]. Some studies have reported a significant positive correlation between *H. pylori* infection and epilepsy [11,12]. However, others have failed to determine any association between *H. pylori* infection and epilepsy [10,13]. In 2011, Asadi-Pooya et al. [14] reported that treating *H. pylori* infection in patients with refractory epilepsy did not significantly change the seizure frequency. To obtain a more comprehensive estimate of the association we conducted a meta-analysis to determine the prevalence of *H. pylori* infection in patients with epilepsy and controls.

Methods

Literature search

A systematic search of PubMed, EMBASE, Cochrane Library, Web of Science, Google Scholar and CINAHL was performed to identify potentially relevant publications from the date of database origination through August 2016. They were searched for abstracts using the terms ("*Helicobacter pylori*" [Mesh] OR "*Campylobacter pylori*" [Title/Abstract] OR "*Campylobacter pyloridis*" [Title/Abstract] OR "*Campylobacter pyloris*" [Title/Abstract] OR "*Helicobacter nemestrinae*" [Title/Abstract]) AND ("Epilepsy" [Mesh] OR "Epilepsies" [Title/Abstract] OR "Seizure Disorder" [Title/Abstract] OR "Seizure Disorders" [Title/Abstract] OR "Seizures, Epileptic" [Title/Abstract] OR "Epileptic Seizures" [Title/Abstract] OR "Epileptic Seizure" [Title/Abstract] OR "Seizure, Epileptic" [Title/Abstract] OR "Single Seizure" [Title/Abstract] OR "Seizure, Single" [Title/Abstract] OR "Seizures, Single" [Title/Abstract] OR "Single Seizures" [Title/Abstract] OR "Epilepsy, Cryptogenic" [Title/Abstract] OR "Cryptogenic Epilepsies" [Title/Abstract] OR "Cryptogenic Epilepsy" [Title/Abstract] OR "Epilepsies, Cryptogenic" [Title/Abstract] OR "Status epilepticus" [Title/Abstract] OR "Aura" [Title/Abstract] OR "Auras" [Title/Abstract] OR "Awakening Epilepsy" [Title/Abstract] OR "Epilepsy, Awakening" [Title/Abstract]). There was no language restriction. Two investigators independently selected all titles and abstracts identified by the initial search.

Study selection

The inclusion criteria were as follows: (1) The studies had to be case-control, cross-sectional or case-cohort in design; (2) studies that provided the raw data on *H. pylori* infection in both the epilepsy
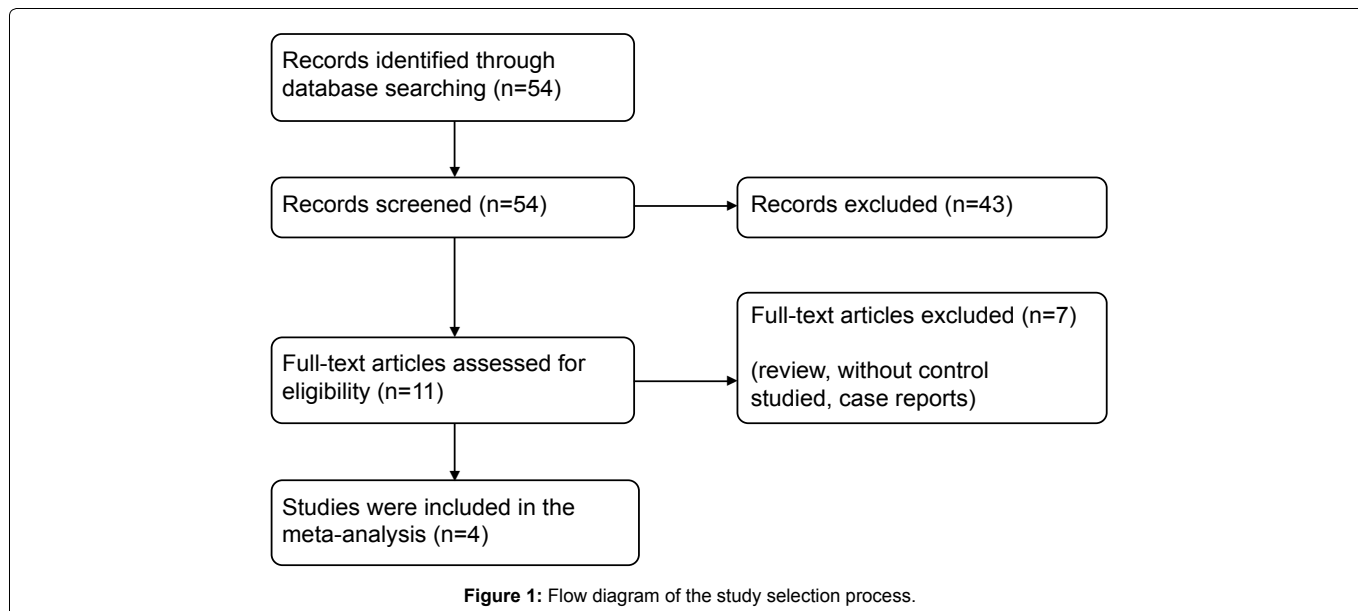
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Figure 1: Flow diagram of the study selection process.

Table 1: Characteristics of the 4 included studies.

Reference	Year	Country	Study design	Specimen	Method	H. pylori (+) in epilepsy group (%)	H. pylori (+) in control group (%)	H. pylori (+) in epilepsy classification	P value
Asadi-Pooya	2012	Iran	Case-control	Breath	^{13}C-UBT	35/62 (56.45%)	14/33 (42.42%)	IGE: 21/34; TLE: 14/28 The difference was not significant (P = 0.3)	0.3
Okuda	2004	Japan	Case-control	Serum	ELISA	19/75 (25.33%)	5/71 (7.04%)	IGE: 9/22; ILE: 10/53 The difference was not significant	< 0.05
Ozturk	2007	Turkey	Case-control	Serum	ELISA	37/47 (78.72%)	13/35 (37.14%)	Poor prognosis: 18/24 Good prognosis: 19/23 The difference was not significant (P > 0.05)	< 0.001
Razak	2012	Malaysia	Case-control	Breath	^{13}C-UBT	18/48 (37.50%)	17/47 (-36.17%)	Generalised epilepsy: 5/19 Partial epilepsy: 13/29 The difference was not significant	0.893

H.pylori- Helicobacter pylori; IGE- idiopathic generalized epilepsy; TLE- temporal lobe epilepsy; ILE- idiopathic localization-related epilepsy; ELISA- enzyme-linked immunosorbent assay; ^{13}C-UBT- ^{13}C urea breath test.

group and the control group. Studies were excluded if: (1) The studies had no control groups; (2) The articles were review articles, laboratory studies, or studies of animals. To ensure homogeneity in data the two investigators performed the data extraction independently.

Statistical analysis

Calculation of dichotomous variables was conducted using the odds ratio (OR) with the 95% confidence interval (CI) as the summary estimates to measure the strength of the association of *H. pylori* infection and Epilepsy. Heterogeneity was tested using the I^2 statistic test, which is a quantitative measure of inconsistency across studies. I^2 values of above 25%, 50% and 75% being considered to indicate low, medium, and high heterogeneity, respectively. Heterogeneity was also determined by Q-test, and it was considered indicative of significant heterogeneity when P values were less than 0.1. When the effects were assumed to be homogeneous ($I^2 < 50\%$) a fixed-effects model was used; otherwise, the random-effects model was more appropriate [16]. Statistical significance was set at P values of less than 0.05. The meta-analysis was performed using Review Manager 5.3 software.

Results

Identification of eligible studies

We identified 54 articles from PubMed, EMBASE, Cochrane Library, Web of Science, Google Scholar and CINAHL. Of these articles most were excluded after reading the titles and abstracts, mainly because they were reviews or were not relevant to the meta-analysis, leaving 11 that appeared to fulfill the inclusion criteria. Following more thorough scrutiny, an additional 7 articles were excluded. Finally, a total of 4 prospective articles including 232 cases

of Epilepsy and 186 participants were included in the meta-analysis [10-13]. A detailed flowchart of the selection process is presented in figure 1.
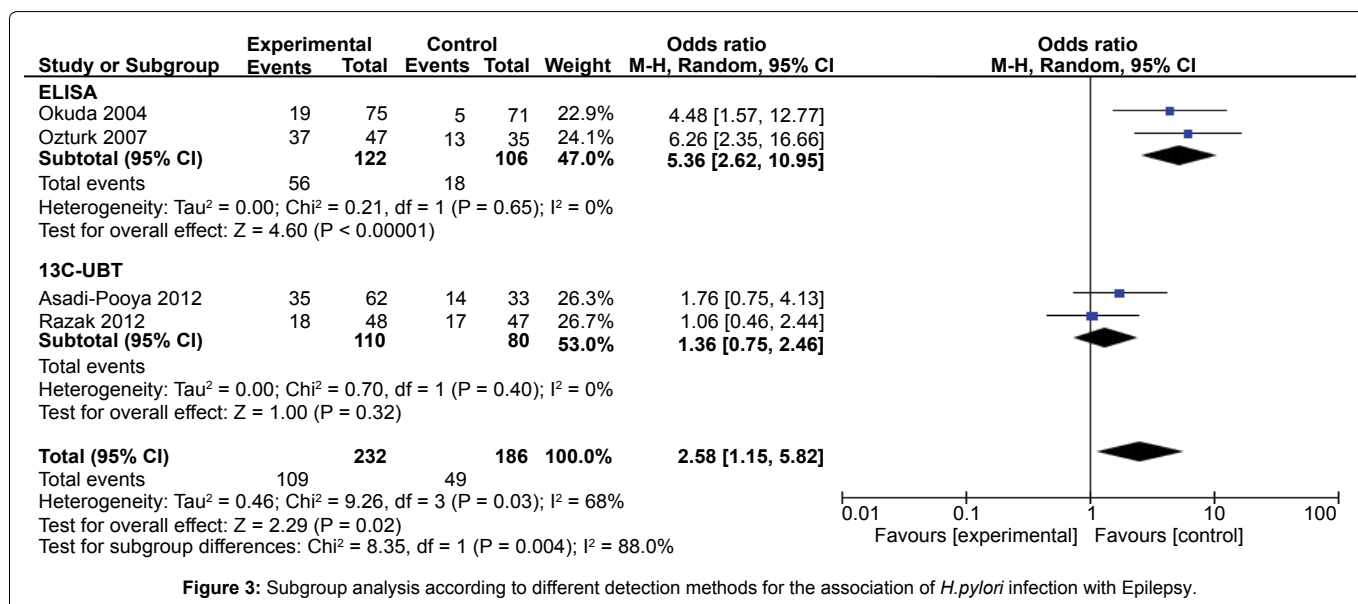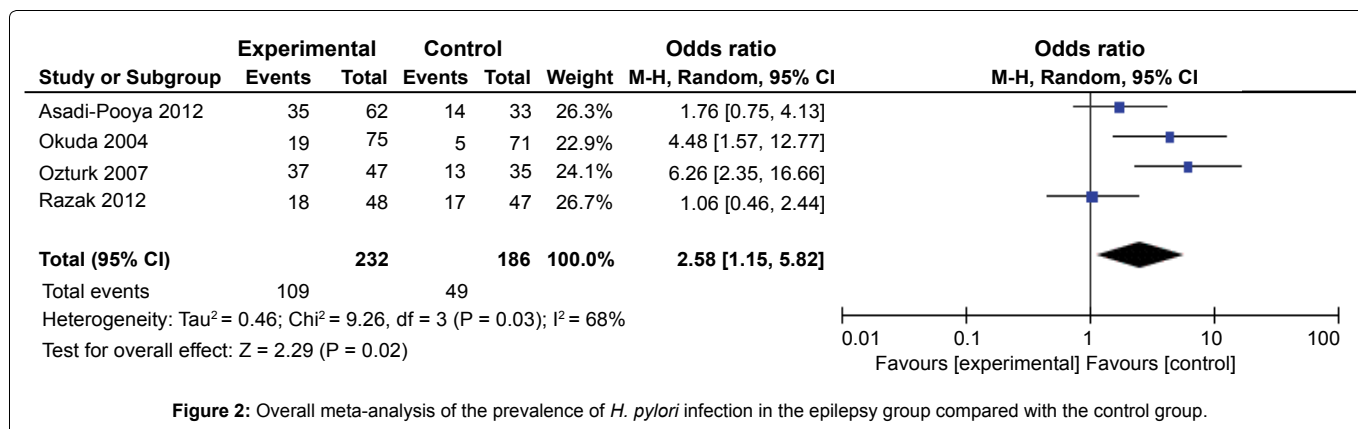
Study characteristics

The main characteristics of the 4 included studies are presented in table 1. Four studies involved 232 patients with epilepsy, with a total *H. pylori* infection rate of 46.98% (109/232). The sample size of the control groups was 186, of which 49 were *H. pylori*-positive (26.34%). Concerning the *H. pylori* measure methods, two studies used ELISA, and two studies used the ^{13}C urea breath test (^{13}C-UBT). Okuda, et al. [11] divided the epilepsy subjects into two subgroups: idiopathic generalized epilepsy (IGE) and idiopathic localization-related epilepsy (ILE). Ozturk, et al. [12] separated the Epilepsy patients into poor prognosis and good prognosis groups. Asadi-Pooya, et al. [10] determined the frequency of infection with *H. pylori* among two groups of patients with epilepsy: patients with idiopathic generalized epilepsy (IGE) and patients with temporal lobe epilepsy (TLE) due to mesial temporal sclerosis. Razak, et al. [13] investigated the association of *H. pylori* infection with generalised epilepsy and partial epilepsy.

Results of meta-analyses

Overall, the prevalence of *H. pylori* infection in patients with epilepsy was higher than that in control groups. (46.98% vs. 26.34%, OR = 2.58, 95% CI: 1.15-5.82, P = 0.02) (Figure 2). The heterogeneity was high (P = 0.03, $I^2 = 68\%$). We performed a subgroup analysis to further investigate the factors impacting the overall results.

Using stratified analysis based on different methods, the data

Study or Subgroup	Experimental		Control		Weight	Odds ratio M-H, Random, 95% CI	Odds ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Asadi-Pooya 2012	35	62	14	33	26.3%	1.76 [0.75, 4.13]	
Okuda 2004	19	75	5	71	22.9%	4.48 [1.57, 12.77]	
Ozturk 2007	37	47	13	35	24.1%	6.26 [2.35, 16.66]	
Razak 2012	18	48	17	47	26.7%	1.06 [0.46, 2.44]	
Total (95% CI)		**232**		**186**	**100.0%**	**2.58 [1.15, 5.82]**	
Total events	109		49				

Heterogeneity: Tau² = 0.46; Chi² = 9.26, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 2.29 (P = 0.02)

$0.01 \quad 0.1 \quad 1 \quad 10 \quad 100$
Favours [experimental] Favours [control]

Figure 2: Overall meta-analysis of the prevalence of *H. pylori* infection in the epilepsy group compared with the control group.

Study or Subgroup	Experimental		Control		Weight	Odds ratio M-H, Random, 95% CI	Odds ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
ELISA							
Okuda 2004	19	75	5	71	22.9%	4.48 [1.57, 12.77]	
Ozturk 2007	37	47	13	35	24.1%	6.26 [2.35, 16.66]	
Subtotal (95% CI)		**122**		**106**	**47.0%**	**5.36 [2.62, 10.95]**	
Total events	56		18				

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)

	Events	Total	Events	Total			
13C-UBT							
Asadi-Pooya 2012	35	62	14	33	26.3%	1.76 [0.75, 4.13]	
Razak 2012	18	48	17	47	26.7%	1.06 [0.46, 2.44]	
Subtotal (95% CI)		**110**		**80**	**53.0%**	**1.36 [0.75, 2.46]**	
Total events							

Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

	Events	Total	Events	Total			
Total (95% CI)		**232**		**186**	**100.0%**	**2.58 [1.15, 5.82]**	
Total events	109		49				

Heterogeneity: Tau² = 0.46; Chi² = 9.26, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 2.29 (P = 0.02)
Test for subgroup differences: Chi² = 8.35, df = 1 (P = 0.004); I² = 88.0%

$0.01 \quad 0.1 \quad 1 \quad 10 \quad 100$
Favours [experimental] Favours [control]

Figure 3: Subgroup analysis according to different detection methods for the association of *H.pylori* infection with Epilepsy.

revealed that the prevalence of *H. pylori* infection in epilepsy patients was greater than that in control group by using ELISA in two studies (OR = 5.36, 95% CI: 2.62-10.95, P < 0.00001), but it was not statistically significant difference when using ^{13}C urea breath test in other two studies (OR = 1.36, 95% CI: 0.75-2.46, P = 0.32) (Figure 3).

Discussion

The association between epilepsy and *H. pylori* infection is controversial [10-15]. In this meta-analysis we provide an overview of the relationship between *H. pylori* positiveity and epilepsy with a total of 418 subjects from four eligible studies. Overall the prevalence of *H. pylori* infection in epilepsy patients (46.98%, 109/232) was higher than in control individuals (26.34%, 49/186) (P = 0.02), indicating that *H. pylori* infection may be a risk factor for epilepsy.

Epilepsy may be triggered by immunological mechanisms as a result of *H. pylori* infections. Autoimmunity was recently suggested to be involved in the pathology of epilepsies [17]. Bartolomei, et al. [18] found that detection of anti-GM1 antibodies could allow identification of patients with partial epilepsy associated with an autoimmune response. *H. pylori* could indirectly influence the brain function due to the release of multiple cytokines such as IL-1,IL-6,TNF-α,which involved in the blood–brain barrier (BBB) disruption and pathogenesis of neuronal inflammatory damage in epilepsy [19,20]. Kountouras, et al. [20] have hypothesized that *H. pylori* might be a potential therapeutic target in epilepsy.

We conducted a further analysis based on different detection methods, the results showed that the prevalence of *H. pylori* infection in epilepsy patients was higher than that in control groups by using ELISA [11,12], but it was not statistically significant difference using ^{13}C-UBT [10,13]. The anti-*H. pylori* IgG-ELISA is a common method for detecting *H. pylori* seropositivity in clinics. It is well suitable for large-scale population surveys [21]. ^{13}C-UBT is a detection method based on the carbon dioxide and ammonia produced by *H. pylori* converting urea and has high specificity and sensitivity [21]. ^{13}C-UBT reveals the active (present) infection, whereas the serology can reveal the past infection. However, it may be impossible to directly compare the ^{13}C-UBT results due to the difference in UBT protocols across different clinical centers generated differences in breath sample collection times and intervals, as well as influences on delaying gastric emptying [21,22].

There are some limitations in our study. First, the analysis was conducted on a small number of case-control studies, and the cases included in these studies are also limited and lack of high-quality data. Second, the lack of individual data has limited further subgroup analyses of gender and epilepsy sub-type. Finally, some articles published in non-English languages might be missed.

In summary, the present study showed that the association between epilepsy and *H. pylori* infection is a significant positive correlation. Whether *H. pylori* infection is a risk factor for epilepsy should thus be addressed in large-scale and prospective studies.

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