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# Presence of *Helicobacter pyloriamong* Patients with Resen Ischemic Stroke and its Relationwith Severity of Stroke

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## Abstract

Stroke is acute focal brain dysfunction due to vascular disease. Stroke is the third most common cause of death in the world. Acute occlusion of an intracranial vessel causes a reduction in blood flow to the brain region it supplies. Several studies were done on *H. pylori* infection, that reported association between *H. pylori* and endothelial dysfunction, chronic inflammation, dyslipidemia, impaired glucose metabolism, metabolic syndrome, peripheral vascular disease, and coronary artery disease. This study aims to find whether there is an association between *H. pylori* infection and resent atheroembolic ischemic stroke and if there is any effect on the severity of ischemic stroke.

This study was carried out in the Middle Euphrates neurological screen center (MENC) in Al-Najaf city for a period of fourteen months (from January 2015 to February 2016). This study includes one hundred patients presented with newly diagnosed ischemic stroke (fifty males and fifty female) and one hundred control (patients who are consulted Middle Euphrates neurological screen center for diseases rather than stroke, fifty males and fifty female). The ages of all persons in this study ranging from 40 to 60 years. A brain CT scan (plain) was obtained for all hundred patients that presented with stroke, and acute atheroembolic ischemic stroke was confirmed. For all persons in this study, full history and physical examination were done, blood pressure was measured, the serological method was used in the investigation of *H. pylori* infection, then, investigated for fasting blood sugar, lipid profile, electrocardiography, and echocardiography. The presence of *H. pylori* in patients with ischemic stroke was (56%), while (44%) in controls, however, the difference was statistically not significant ($p > 0.05$). There is a significant association between *H. pylori* and resent atheroembolic ischemic stroke in diabetic patients. There is no statistically significant association between *H. pylori* infection and the severity of recent ischemic stroke. This study concluded that there is no significant relationship between *H. pylori* infection and ischemic stroke after the stratification of other cofounder risk factors.

**Keywords:** *Helicobacter pylori*; Brain CT scan;Ischemic stroke

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## Introduction

Stroke is focal brain dysfunction due to vascular disease. Stroke is divided into ischemic and haemorrhagic. Stroke is also divided according to the duration and evolution of symptoms into a transient ischemic attack. The main third rift cause of death in the world is Stroke [1]. The acute obstruction of an intracranial vessel leads to blood flow reduction in the brain. The volume of blood flow reduction is a role of the collateral flow of blood, and that depends on the anatomy of the vascular individual tubule, which could be changed by disease, the places of occlusion, and blood pressure. A reduction in blood-flow to nil bring about the brain tissue death throughfour to ten mints, while less than sixteen to eighteen ml per 100 g tissue/minute could cause infarction in an hour, on the other hand, the values less than twenty mL per 100 g tissue/minute could cause ischemia wanting infarction except if extended for many hours or days [2].

*Helicobacter pylori*, also called Campylobacter pyloridis, is a gram -ve microaerophilic-rod present mainly in the deeper section of the mucous-gel which coating the gastric-mucosa or in between the gastric epithelium and mucus layer [3]. It may pertain to the epithelium of gastric, however with ordinary circumstances don't evidence invading to cells [4]. Strategically, it's designed to live in the offensive medium of the stomach. It's ~0.5–3 μm long, S-shape form and with many coated flagella. In the beginning, *H. pylori* were residing within the antrum, however, with time, emigrates to the more proximal segments of the stomach [5]. The spread of *H. pylori* alters through the world and that mainly depends on the universal scale of living in that area. In the developing countries, eighty percent population could be infected, while in industrialized countries it is 20%-50% [6]. The infection with *H. pylori* occurs by its transportation from person to others may through the oral-oral or/and fecal-oral way. The danger of *H. pylori* is decreasing in developing countries. The infection rats in the USA has declined by more than fifty percent throughout the past thirty years. Always the infection by *H. pylori* is linked with deep-spread active gastric infection, however only ten to fifteen percent of an infected person related to peptic-ulceration [7]. The reasons for this variance are not known exactly, but it is likely because of an association of host and itself bacteria [8]. The infection by *H. pylori* is still discussed as an important factor associated with atherosclerosis although a century-old hypothesis [9]. The infection makes a chronic inflammatory status

with other combinations of dyslipidemia, hyperhomocysteinemia, hypercoagulability, a decline of glucose metabolism, and endothelial dysfunction which contribute to the pathogenesis of atherosclerosis. Literature has shown that a positive relationship between cytotoxic which related to gene-Apositive *H. pylori* strains with diseases of vascular (e.g. coronary artery and stroke diseases) [10]. In this regard, a new emerging theory is the Infection of mediated genetic modulation. Minick and Fabricant are worked on infection and atherosclerosis in the laboratory animals had made the ground for pioneer and unique research in that field[11]. The chronic infection makes T1 a Helper cell-mediated inflammatory response, which has a critical function in atherosclerosis. Also, a sign of infection and inflammation were investigated as the danger agent for atherosclerosis [12].

Infection-related chronic inflammation of vascular could result in dysfunction of endothelial. Tousoulis D, et al. (2001) was the first research group proposed an endothelial dysfunction inflammatory pathway[13]. C-reactive protein and molecule of inflammatory adhesion (e.g. intracellular adhesion molecule-1) are an increase in patients infected by *H. pylori* infection, proposing that there is a link between endothelial dysfunction and infection[14]. The chronic infection leads to the release of inflammatory cytokines such as interleukin and tumor necrosis factor-α which can affect microvascular vasomotor functions then vasoconstriction and finally endothelial dysfunction [15]. Using antibiotics to the removal of *H. pylori* infection leads to a decrease in cytokines concentration [16]. *H. pylori* causes atrophic gastritis, that related to malabsorption of B12 and folic acid. Shortage of these vitamins leads to hyper homocysteinaemia because of reduction of re-methylation pathway [17]. Therefore, it might have a functionin the pathogenesis of earlyatherosclerosis [18]. Senmaru T, et al. (2012) concluded that carotid intima media thickness washigher with *H. pylori* patients which associated with atrophic gastritis [19]. Also, they found that *H. pylori* positive patients have higher homocysteine than controls. Gillum RF, et al. (2004) suggested that *H. pylori* association of seropositivity with CAD in diabetic patients [20]. Also, they showed that CAD and cerebrovascular diseases were associated more with *H. pylori* infected diabetic patients.

## Patients and Methods

This study is a case control study was carried out in Middle Euphrates neurological screen center in Al-Najaf city for a period of fourteen months (January 2015 - February 2016).This study includes one hundred patients presented with newly diagnosed atheroembolic ischemic stroke (fifty males and fifty female) and one hundred control (fifty males and fifty female). The ages of all persons in this study ranging from 40 to 60 years. Consent was obtained from all persons in this study.

### Inclusion criteria

Acute neurological deficit in patients with 40-60 years old that not explained on other bases, CT scan positive for ischemia and those with negative CT scan had been followed for 2-3 days to confirm diagnosis, otherwise excluded from the study.

### Exclusion criteria

Previous history of ischemic stroke, Intra cerebral bleeding on brain CT scan (plain), sub arachnoid bleeding on brain CT scan (plain), space occupying lesionon brain CT scan (plain), cardioembolic ischemic stroke (not by atheroembolism), and transientischemicattack. Brain CT scan (plain) was obtained for all 100 patients that presented with stroke, and acute ischemic stroke was confirmed.Severity ofischemic stroke was determined byNational institutes of health stoke scale at base line [21] (Table 1). Serological method was used in investigation of *H. pylori* infection . Two milliliters samples of venous blood had been drawn from all persons in this study, then, the samples centrifuged and used for serological diagnosis of *H. pylori* by kits (One step *H. pylori* Test Device/ABON kits). After taking full history and performing complete physical examination, including blood pressure, routine investigations that include blood glucose, fasting lipid profile, and EC.

**Table 1:** National Institutes of Health Stroke Scale (NIHSS)*.

| Tested Item | Title | Responses and Scores | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| 1A | Level of consciousness | Alert | Drowsy | Obtunded | Coma/ Unresponsive |
| 1B | Orientation questions (2) | Answers both correctly | Answers 1 correctly | Answers neither correctly | - |
| | i. Current month | | | | |
| | ii. His/her age | | | | |
| 1C | Response to commands (2) | Performs both tasks correctly | Performs 1 tasks correctly | Performs neither | - |
| 2 | Gaze | Normal Horizontal movements | Partial gaze palsy | Complete gaze palsy | - |
| 3 | Visual fields | N visual field defect | Partial hemianopia | Complete hemianopia | Bilateral hemianopia |
| 4 | Facial movement | Normal | Minor Facial weakness | Partial Facial weakness | Complete unilateral palsy |
| 5 | Motor function (arm) | No drift | Drift before 5 seconds | Falls before 10 seconds | No effort against gravity |
| | a. Left | | | | |
| | b. Right | | | | |
| 6 | Motor function | No drift | Drift before 5 seconds | Falls before 10 seconds | No effort against gravity |
| | (leg) | | | | |
| | a. Left | | | | |
| | b. Right | | | | |
| 7 | Limb ataxia | N ataxia | Ataxia in 1 limb | Ataxia in 2 limbs | - |
| 8 | Sensory | No Sensory loss | Mild Sensory loss | Severe Sensory loss | - |
| 9 | Language | Normal | Mild aphasia | Severe aphasia | Mute or Global aphasia |
| 10 | Articulation | Normal | Mild dysarthria | Severe dysarthria | - |
| 11 | Extinction or inattention | Absent | Mild (loss 1 sensory modality lost) | Severe (loss 2 modalities) | - |

Where: *o: No stroke symptoms, 1-4: Minor stroke, 5-15: Moderate stroke, 16-20: Moderate to severe stroke and 21-42: Sever stroke.

## Statistical analysis

SPSS, version 22,2013 was used for statistical analysis. Descriptive statistics were expressed as frequencies (No.)and proportions (%). Chi square test was used to assess the association between categorical variables, Fisher's exact test was used as an alternative when the chi square was inapplicable.Level of significance was tested at ≤0.05, to be considered as significant association. Multiple regression analysis for the relationship between variable risk factors and ischemic stroke was used. Multiple regression analysis for the relationship between variable risk factors and ischemic stroke was used. Multiple logistic regression analysis applies when there is a single dichotomous outcome and more than one independent variable. The regression analysis was coded as 0 and 1, where 1 means present, and 0 means null.Finally, results presented in tables with an explanatory paragraph for each using Microsoft office Word, 2010 software for windows.

## Results

A total of 100 stroke patients and 100 controls were enrolled in this study, both groups were matched for age (40-60 years) and gender (males and females were equally presented), (Pvalue=1.0).As it shown in table,*H. pylori*was more frequent among stroke patients than controls (56%) *vs.* (44%), however the difference was statistically insignificant, (P>0.05) (Table 2). Hypertension, diabetes mellitus, ischemic heart diseases, dyslipidemia and smoking were significantly more frequent among the stroke patients than controls, in all comparisons, (P<0.05).

For more precise assessment of the relationship between *H. pylori* and stroke and to exclude the confounding effect other risk factors, the comparison was made after stratification of the studied groups according to the presence of these risk factors. The findings of this assessment and analysis are shown as the followings: The below tableshows the relationship between *H. pylori* and stroke in the studied groups stratified by gender, no significant association had been found between *H. pylori* and stroke neither among males nor females, (P>0.05) (Table 3). No significant association had been found between *H. pylori* and stroke after stratification for hypertension, (P>0.05) (Table 3). In the table there was a statistically significant association between severity of stroke and *H. pylori* infection didn't reach the statistical significance, (P>0.05).

**Table 2:** Relationship between risk factors and stroke.

| Variable | | Stroke(n=100) | | Control (n=100) | | Total | P value |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | |
| *H. pylori* | Positive | 56 | 56.0 | 44 | 44.0 | 100 | 0.09* |
| | Negative | 44 | 44.0 | 56 | 56.0 | 100 | |
| Hypertension | Yes | 66 | 60.6 | 43 | 39.4 | 109 | 0.001* |
| | No | 34 | 37.4 | 57 | 62.6 | 91 | |
| DM | Yes | 52 | 62.7 | 31 | 37.3 | 83 | 0.003* |
| | No | 48 | 41.0 | 69 | 59.0 | 117 | |
| IHD | Yes | 38 | 67.9 | 18 | 32.1 | 56 | 0.002* |
| | No | 62 | 43.1 | 82 | 56.9 | 144 | |
| Dyslipidemia | Yes | 86 | 67.7 | 41 | 32.3 | 127 | <0.001* |
| | No | 14 | 19.2 | 59 | 80.8 | 73 | |
| Smoking | Yes | 78 | 63.9 | 44 | 36.1 | 122 | <0.001* |
| | No | 22 | 28.2 | 56 | 71.8 | 78 | |

Where: * - Significant, p<0.005.

**Table 3:** Relationship between H. pylori and Stroke stratified by gender, Hypertension, Diabetes Mellitus, IHD, Dyslipidemia and Smoking.

| Hypertension | *H. pylori* | Stroke (n = 100) | | Control(n=100) | | Total | *P* |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| Yes | Positive | 47 | 67.10% | 23 | 32.90% | 70 | 0.059 |
| | Negative | 19 | 48.70% | 20 | 51.30% | 39 | |
| No | Positive | 9 | 30.00% | 21 | 70.00% | 30 | 0.31 |
| | Negative | 25 | 41.00% | 36 | 59.00% | 61 | |
| **Diabetes Mellitus** | | | | | | | |
| Yes | Positive | 40 | 72.7 | 15 | 27.3 | 55 | 0.008* |
| | Negative | 12 | 42.9 | 16 | 57.1 | 28 | |
| No | Positive | 16 | 35.6 | 29 | 64.4 | 45 | 0.34 |
| | Negative | 32 | 44.4 | 40 | 55.6 | 72 | |
| IHD | | | | | | | |
| Yes | Positive | 23 | 71.9 | 9 | 28.1 | 32 | 0.46 |
| | Negative | 15 | 62.5 | 9 | 37.5 | 24 | |
| No | Positive | 33 | 48.5 | 35 | 51.5 | 68 | 0.21 |
| | Negative | 29 | 38.2 | 47 | 61.8 | 76 | |
| **Dyslipidemia** | | | | | | | |
| Yes | Positive | 49 | 71 | 20 | 29 | 69 | 0.39 |
| | Negative | 37 | 63.8 | 21 | 36.2 | 58 | |
| No | Positive | 7 | 22.6 | 24 | 77.4 | 31 | 0.52 |
| | Negative | 7 | 16.7 | 35 | 83.3 | 42 | |
| **Smoking** | | | | | | | |
| Yes | Positive | 44 | 65.70% | 23 | 34.30% | 67 | 0.49 |
| | Negative | 31 | 59.60% | 21 | 40.40% | 52 | |
| No | Positive | 12 | 36.40% | 21 | 63.60% | 33 | 0.37 |
| | Negative | 13 | 27.10% | 35 | 72.90% | 48 | |

Where: * - Significant, p<0.005.

*H. pylori* and stroke in diabetic group while not in non-diabetic, this indicated that diabetic patients with *H. pylori* are more likely to have stroke than non-diabetic (Table 3). No significant association had been found between *H. pylori* and stroke after stratification for IHD, (P>0.05) (Table 3). Similarly, no significant association had been found between *H. pylori* and stroke after stratification for dyslipidemia or smoking, (Table 3; P>0.05).

Multiple logistic regression analysis revealed that no significant association had been found between *H. pylori* and stroke after adjustment for other risk factors, however, as a secondary outcome of the study, dyslipidemia and smoking were significantly associated with stroke, (OR=6.74, P=0.001) and (OR=2.46, P=0.01), respectively and the higher risk associated with dyslipidemia (Table 4). As it shown in the below table, *H. pylori* positive patients were relatively more likely to have moderate to severe or severe stroke than *H. pylori* negative group; (8.9%) *vs.* (6.8%) and (10.7%) *vs*. (9.1%), respectively (Table 5). However, the association between

**Table 4:** Results of multiple regression analysis for the relationship between risk factors and stroke.

| Covariate | ß | OR | 95% C.I. for OR | P |
|---|---|---|---|---|
| H. pylori | 0.16 | 1.17 | 0.59 - 2.3 | 0.65 |
| Smoking | 0.90 | 2.46 | 1.21 - 4.99 | 0.01* |
| Hypertension | -0.13 | 0.88 | 0.41 - 1.89 | 0.74 |
| DM | 0.39 | 1.48 | 0.73 - 3.03 | 0.28 |
| IHD | 0.48 | 1.61 | 0.77 - 3.38 | 0.20 |
| Dyslipidemia | 1.91 | 6.74 | 3.21 - 14.2 | 0.001* |

Where: * - Significant, p<0.005.

**Table 5:** Relationship between Severity of stroke and *H. pylori* infection.

| H. pylori | Minor | Moderate | Moderate to severe | Severe | Total | P |
|---|---|---|---|---|---|---|
| Positive | 16 | 29 | 5 | 6 | 56 | 0.97 |
| | 28.6% | 51.8% | 8.9% | 10.7% | | |
| Negative | 13 | 24 | 3 | 4 | 44 | |
| | 29.5% | 54.5% | 6.8% | 9.1% | | |
| Total | 29 | 53 | 8 | 10 | 100 | |
| | 29.0% | 53.0% | 8.0% | 10.0% | | |

## Discussion

With atherosclerotic pathways catalyzing, *H. pylori* infection might be a danger agent for ischemic stroke. Single infectious factor is low related to stroke however progressive chronic infectious exposures have been related to the danger of stroke [22]. The potential mechanisms may include activated of macrophage plaque de-stabilization, elevated expression of different adhesion molecules and inflammatory cytokines, localized hypercoagulability, change gene expression, and a molecular mimicry [23]. Infection by *H. pylori* is related to low in High-density lipoprotein cholesterol and high in total cholesterol, low density lipoproteincholesterol and triglyceride levels [24]. The present study concluded that there was no statistical correlation neither in-between *H. pylori* infection and ischemic stroke, nor the severity of ischemic stroke. *H. pylori* infection was (56%) in patients with acute atheroembolic ischemic stroke, while (44%) in controls.These findings were agreed with Gabrielli M, et al. (2004) anda Korean Yang X, et al.(2011) were found that there was no significant association between *H. pylori* infection and ischemic stroke [25,26].

The results of the present study disagreed, on the other hand, that reported by Heuschmann PU, et al. (2001) found positive correlation between prevalence of *H. pylori* infection and ischemic stroke [27]. However, it is worth mentioning, that patients with ischemic stroke who had diabetes mellitus were more likely to have *H. pylori* infection (p=0.008), this may explain by that diabetic patients had been associated with reduced response of T cells, neutrophil function, and disorders of humoral immunity which reversed by strict insulin control [28].

KayarY, et al. (2015) reported that there was a significant association between infection with *H. pylori* and insulin resistance [29]. Upala S, et al. (2016)reported that there was significant association between metabolic syndrome and *H. pylori* infection [30].

Several studies were presented that there was relationship between *H. pylori* infection and ischemic heart disease [31]. Vijayvergiya R, et al. (2015) reported that patients with ischemic heart disease had higher IgG seropositivity in relation to controls [32]. The present study found that moderate sever and sever stroke were relatively more likely to have *H. pylori* infection, however, the difference was statistically insignificant. For our knowledge, no medical researchers had been done on the association between *H. pylori* infection and severity of ischemic stroke. The difference in the results of these different studies was due to variation in the cofounder risk factors like hypertension, diabetes mellitus, ischemic heart disease, smoking, and dyslipidemia. also due to variation in size of samples, the studied population, prevalence of *H. pylori*, the study design, and ethnical variation between the studied groups. Limitations of the study were restriction in time led to small samples size, and findings of the current study could not be generalized on total population, because the study conducted in tertiary center does not represent to the total population.

## Conclusion

In this case-control study, there is neither association was found between the prevalence of *H. pylori* infection and ischemic stroke, nor the severity of ischemic stroke. So that further large case-control studies with extended duration of time are required to show the relationship between the prevalence of *H. pylori* infection and ischemic stroke, and whether there is an effect on the severity of ischemic stroke.

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