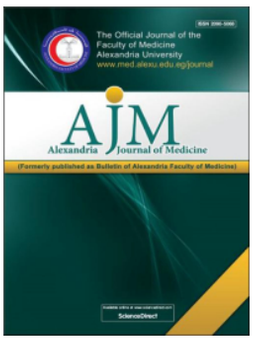

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Evaluation of *Helicobacter pylori* infection as a potential risk factor of acute ischemic cerebrovascular stroke

Helicobacter pylori Infection Increases Risk For Stroke.

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ABSTRACT

Background: *Helicobacter pylori (H. pylori)* is a very common gastrointestinal infection that varies clinically from asymptomatic to overt peptic ulcer disease. Although *H. pylori* had been linked to ischemic heart disease, still scanty of data available about *H. pylori* link to ischemic cerebrovascular stroke.

Object: Evaluation of *H. pylori* Infection as a Potential Risk Factor of Acute Ischemic Cerebrovascular stroke.

Method: In a case control study, we recruited 150 ischemic stroke patients (group A) further subdivided into two subgroups atherosclerotic ischemic stroke (group A1) and cardioembolic stroke (group A2), also asymptomatic 95 patients recruited as non-ischemic control group (group B). All subjects were investigated for chronic *H. pylori* infection using both serum *H. pylori* IgG antibody test and urea breath test. Statistical analysis was done for obtained data.

Results: Significant higher prevalence of *H. pylori* infection was found among atherosclerotic stroke group (group A1) 61.4% versus non atherosclerotic group (A2) 40% and control group (B) 35.8% (P value 0.003), furthermore, significant higher prevalence when comparing group A1 (atherosclerotic stroke) and control group B (P1 value 0.001), still non-significant higher prevalence when comparing group A2 (cardio embolic stroke group) and control group B (P2 value 0.618).

Conclusion: Chronic *H. pylori* infection is a curable potential risk factor for ischemic atherosclerotic stroke. However, further studies needed to investigate the beneficial effect of *H. pylori* treatment on ischemic stroke.

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KEYWORDS
Helicobacter pylori; ischemic stroke; cerebrovascular stroke; urea breath test; *H. pylori*

1. Introduction

Helicobacter pylori is a gram-negative spiral organism that is considered as most common infection affecting human gastrointestinal tract, infection mostly happen during childhood, and can lasts lifelong unless eradicated by antibiotics [1,2].

H. pylori infection can be asymptomatic or causes chronic gastritis, peptic ulcer disease, and gastric cancer, and also there is association between *H. pylori* infection and ischemic heart disease [3].

Ischemic stroke is a leading cause of morbidity and mortality worldwide, stroke has heterogeneous subtypes caused by atherosclerotic or non-atherosclerotic mechanisms [4]. According to Trial of Org 10,172 in Acute Stroke Treatment (TOAST), ischemic stroke was classified into large-vessel atherothrombosis, cardio embolism, small-vessel disease, other determined causes, or undetermined causes [5].

Large vessel atherothrombosis results from the formation of atherosclerotic plaques in the inner wall of a large vessels (common carotid arteries split, the start of the vertebral arteries, middle cerebral artery), however, athero-embolism and cardioembolic occurred when a thrombus forms on the wall of a blood vessel or from the heart then breaks apart and sheds into pieces of clot, then carried to be impacted in smaller arterial branches, cardio-embolization happen when blood clots can form within the heart because of intracardiac stasis of blood (e.g. atrial fibrillation) or because of adhering to a thrombogenic device or lesion (e.g. an implanted prosthetic valve) [6].

Small-vessel disease stroke caused by occlusive disease involving the microcirculation of the brain affecting Common sites for small vessels include deep areas of the hemispheric white matter [7].

Other determined causes include stroke caused by extracranial arterial dissections, nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders [8].

Undetermined causes include those patients with ≥2 conflicting risk factors of ischemic stroke or cryptogenic stroke patients whom a complete screening workup for cardiac conduction or structural

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abnormalities, intracranial or extracranial large-artery stenosis, coagulopathy, and other conditions do not reveal any cause. [9]

Although many risks factors for ischemic stroke already known as diabetes, hypertension, hyperlipidemia, smoking, male gender, as well as chronic infection and inflammatory processes may consider as modifying stroke risk still, they explain only little, as much of stroke risk still unexplained. [10,11]

Little data available about relation between chronic *H. pylori* infection and ischemic stroke, so we conducted this study to evaluate chronic *H. pylori* as independent risk factor for ischemic stroke.

2. Patients and methods

This study was done at Tanta University Hospital from June 2019 to June 2020, we had recruited our two groups of patients as follows:

Ischemic Stroke (group A): 120 patients had a first time cerebrovascular stroke within last 72 h and were admitted to neurological department of Tanta University Hospital for treatment, stroke was diagnosed and classified according to World Health Organization criteria as patients with > 50% stenosis of the extracranial carotid or an intracranial artery were defined to have large artery stroke, patients known to have small artery occlusion if they had a clinical lacunar syndrome associated with CT changes or a typical clinical syndrome despite normal CT scans define small arteries stroke[12], patients with electrocardiographic or echocardiographic evidence of embolic stroke were defined as cardioembolic stroke, we excluded from this group patients with non-ischemic stroke or hemorrhagic stroke, patients with recurrent stroke, patients with stroke of other determined etiology, and also patients with stroke of undetermined etiology were excluded from this study.

All patients of group A were subjected to full clinical examination, and cerebral infarction was confirmed by CT scan or MRI scan, this group further subdivided into two subgroups:

Group A1 (70 stroke patients with atherosclerotic disease): whether large artery or small artery stroke.

Group A2 (50 stroke patients with cardioembolic stroke): detected by electrocardiogram or echocardiogram.

Non ischemic Control group (group B) 95 patients: age matched, asymptomatic patients randomly recruited during routine checkup as outpatients at medical clinic at Tanta University Hospital. We excluded patients with previous stroke, those turned out to have cardiac or atherosclerotic disease. All patients were subjected to history taking and full clinical examination.

From both groups, we excluded patients with previous *H. pylori* treatment. Patients (both groups) were subjected to full clinical examination and laboratory evaluation including liver functions, renal functions, lipid profile, fasting blood glucose (FBG), post prandial blood glucose (PPBG), glycosylated hemoglobin (HbA1c), inflammatory marker as C-reactive protein CRP and erythrocyte sedimentation rate ESR . The carotid and vertebral arteries were assessed by color flow B-mode Doppler ultrasound to assess atherosclerotic disease and 12 leads electrocardiogram ECG to assess cardiac diseases or atrial fibrillation, also echo cardiogram was performed to all patients.

All patients were subjected to *H. pylori* testing including testing for serum IgG antibody to *H. pylori* Serum IgG using enzyme linked immunosorbent assay (ELISA). Also all patients were subjected to urea breath test as each patient underwent a 13 C-urea breath test (UBT) by drinking 100 mg of 13 C-urea in water after an overnight fast, then breath samples were collected before and 20 min after the administration of 13 C-urea. Patients with both tests positive were considered to be *H. pylori* positive and patients with both tests negative were considered to be *H. pylori* negative. W excluded patients with positive one test (patients from both groups that had positive antibodies and negative urea breath test).

Patients were considered as hypertensive if they had blood pressure ≥140/90 for two separate measures or they were on regular medications for more than 6 months, likewise they considered diabetic if they were on regular medications (insulin or non-insulin) or had fasting blood glucose ≥ 126 mg% and post-prandial blood glucose ≥200 mg% for two measures or HbA1c ≥ 6.4, also considered as hyperlipidemic if serum cholesterol level ≥200 mg%, obesity was considered if body mass index (BMI ≥25).

The data were collected and analyzed statistically to evaluate relation between *H. pylori* and ischemic stroke.

3. Statistical analysis

The data were analyzed using Statistical Program for Social Science (SPSS) version 20.0 Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

- A one-way analysis of variance (ANOVA) to compare between more than two means.
- Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
- Multivariate regression analysis was used to compare multiple variable stroke risk factors.

Table 1. Characteristics of the stroke patients and control populations, F: ANOVA test, X2: Chi-square test.

		Group-A1 (atherosclerotic stroke) (n = 70)	Group-A2 (cardioembolic-stroke) (n = 50)	Group B Non ischemic Control group (n = 95)	Test	P value
Age	**Range**	50–75	40–65	40–75	F: 1.625	0.426
	Mean ±SD	62.12 ± 6.52	59.91 ± 7.19	61.39 ± 7.09		
Gender	Male (%)	45 (64.3%)	29 (58%)	50 (52.6%)	X^2: 2.247	0.325
	Female (%)	25 (35.7%)	21 (42%)	45 (47.4%)		
HTN	**n (%)**	69 (98.6%)	30 (60%)	30 (31.6%)	X^2: 75.368	0.001*
DM	**n (%)**	55 (78.6%)	26 (52%)	40 (42.1%)	X^2: 22.267	0.001*
Obesity	**n (%)**	40 (57.1%)	30 (60%)	20 (21.1%)	X^2: 30.381	0.001*
Smoking	**n (%)**	45 (64.3%)	29 (58%)	45 (47.4%)	X^2: 4.849	0.088

HTN = hypertension, DM = diabetes mellitus, significant P < 0.05.

Table 2. *H. pylori* prevalence among studied groups.

		Group-A1 (atherosclerotic stroke) (n = 70)	Group-A2 (cardioembolic-stroke) (n = 50)	Group B Control group (n = 95)	X^2:	P value	P1	P2
H. pylori	**Positive (%)**	43 (61.4%)	20 (40%)	34 (35.8%)	11.382	0.003*	0.001*	0.618
	Negative (%)	27 (38.6%)	30 (60%)	61 (64.2%)				

H. pylori positive = urea breath test positive and IgG positive, P1 = Group-A1 & Group B, and P2 = Group-A2 & Group B.

4. Results

Table 1 shows demographic data and comorbidities of studied groups, and we found no significant difference regarding age and gender distribution among groups; however, there was a significant higher percentage in comorbidities (diabetes, hypertension, and obesity) in stroke groups with p < 0.05.

Table 2 shows significant higher prevalence of *H. pylori* infection among atherosclerotic stroke group (group A 1) 61.4% versus cardioembolic group (A2) 40% and non-ischemic control group (B) 35.8% (P value 0.003); furthermore, significant higher prevalence founded when comparing group A1 and control group B (P1 value 0.001), still non-significant higher prevalence when comparing group A2 and control group B (P2 value 0,618).

Table 3 shows significant positive CRP prevalence among studied stroke groups (P value 0.001), likewise positive CRP prevalence in group A1 versus control group B (P1 value 0.001). Still non-significant prevalence when comparing group A2 and control group B (P2 value 0.087).

Table 4 shows a significant prevalence of comorbidities (DM and hyperlipidemia) and inflammatory markers among *H. pylori* positive populations, also significant prevalence found when comparing *H. pylori* positive population in group A1 and control group B; however, non-significant relation found when comparing *H. pylori* positive population in group A2 and control group.

Table 5 shows a significant over all association between *H. pylori* and ischemic stroke as well as other stroke risk factors (diabetes mellitus, hypertension, and obesity).

5. Discussion

In the present study, we found a significant association between *H. pylori* infection and overall ischemic stroke risk; moreover, significant higher risk found between atherosclerotic ischemic stroke and *H. pylori* infection. However, no significant association was found between cardioembolic stroke and *H. pylori* infection.

Table 3. Inflammatory markers prevalence among studied groups.

		Group-A1 (atherosclerotic stroke) (n = 70)	Group-A2 (cardioembolic-stroke) (n = 50)	Group B non ischemic control group (n = 95)	$X^{[2]}$:	P value	P1	P2
CRP positive	**n (%)**	55 (78.6%)	23 (46%)	30 (31.6%)	36.068	0.001*	0.001*	0.087
High ESR	**n (%)**	40 (57.1%)	29 (58%)	45 (47.4%)	2.192	0.334	0.214	0.224

CRP positive = C reactive protein > 10 mg/L, High ESR = erythrocyte sedimentation rate >22 mm/h for men and > 29 mm/h for women, P1 = Group-A1 & Group B, P2 = Group-A2 & Group B.

Table 4. Relation between *H. pylori* infection and other risk factors in studied groups.

	Group A1 *H. pylori* +ve (n = 43)		Group A2 *H. pylori* +ve (n = 20)		Group B *H. pylori* +ve (n = 34)					
	N	%	N	%	N	%	$X^{[2]}$:	P value	P1	P2
Gender Male	23	53.5	8	18.6	20	46.5	1.817	0.403	0.640	0.181
Female	20	46.5	12	27.9	14	32.6				
DM	35	81.4	11	25.6	18	41.9	8.201	0.017*	0.007*	0.884
Hyperlipidemia	31	72.1	9	20.9	11	25.6	12.609	0.002*	0.001*	0.353
Hypertension	28	65.1	13	30.2	15	34.9	3.976	0.137	0.065	0.138
ESR positive	30	69.8	13	30.2	10	23.3	13.568	0.001*	0.001*	0.011*
CRP positive	35	81.4	9	20.9	12	27.9	18.209	0.001*	0.001*	0.480

P1 = Group-A1 & Group B, P2 = Group-A2 & Group B:

Table 5. Multivariate analysis of stroke risk factors.

	Multivariate	
	OR (95% CI)	P value
HTN	**10.214 (5.389–19.360)**	**0.001***
DM	**2.856 (1.634–4.992)**	**0.015***
Obesity	**5.250 (2.846–9.685)**	**0.017***
Smoking	**1.787 (0.536–3.084)**	**0.106**
H. pylori	**1.983 (1.142–3.443)**	**0.035***

HTN = hypertension, DM = diabetes mellitus, significant P < 0.05.

Our findings were relatively consistent with some previous studies that reported elevated levels of IgG antibody for *H. pylori* among patients with large and small arteries stroke. [13] Similarly, we found a significant association between chronic *H. pylori* infection (confirmed by both IgG antibody and positive urease test) and atherosclerotic ischemic cerebrovascular stroke.

Studies did not find a significant relation between chronic *H. pylori* infection and cardioembolic stroke Similar to results given by. [14] Likewise, we did not find a significant relation between chronic *H. pylori* infection and cardioembolic stroke, which might be explained by hypothesized mechanisms of atherosclerotic and cardioembolic stroke and the relation between chronic *H. pylori* and atherosclerosis.

Many hypothesized mechanisms suggest that *H. pylori* can induce atherosclerosis by releasing cytotoxins, direct immune vascular damage, direct bacterial invasion [15]. Moreover *H. pylori* positive patients showed more evidence of systemic inflammation (higher CRP levels), which supports the hypothesis that *H. pylori* infection may induce generalized inflammation which is a known risk factor for atherosclerosis and atherosclerotic stroke. Our results also goes with this explanation as we found that CRP level was significantly positive among stroke groups when compared with non-ischemic control group; furthermore, CRP level was significantly positive among *H. pylori* infected stroke group. However, CRP level was non-significant in cardioembolic stroke group when compared with non-ischemic control groups.

On the other hand, some studies failed to find significant relation between seropositivity of *H. pylori* IgG and stroke risk; moreover, no significant relation was found between *H. pylori* infection and occurrence of cardiovascular event, [16,17] this conflict of results between studies might be due to different samples size, disease classification, and studies design.

Although smoking is a known risk factor for ischemic stroke, surprisingly we did not find significant association between smoking and ischemic stroke in *H. pylori* infected patients, which might be due to lack of calculation dose and duration of smoking as smoking index wasn't included in our statistical analysis.

Still some limitations in our study as it is not a prospective study and we did not investigate strain of *H. pylori* infection, so our recommendation is to carry out large prospective study to confirm the potential curable risk relation between *H. pylori* and ischemic stroke.

6. Conclusion

Our study suggested that *H. pylori* infection is a potential risk factor for ischemic atherosclerotic cerebrovascular disease.

Disclosure statement

No potential conflict of interest was reported by the author (s).

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