Research Article

A study of Helicobacter pylori infection in patients of ischemic cerebrovascular stroke

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ABSTRACT

Background: The objective of the study was to study the prevalence and association of Helicobacter Pylori infection in patients of ischemic cerebrovascular stroke. Observational analytic cross sectional study.

Methods: Seroprevalence of infection by H. pylori was assessed by History, examination, CT scan Brain, Rapid Urease Test and Elisa in 39 patients with acute cerebral ischemia and 30 age and sex matched control subjects selected randomly from general population with similar socio economic status. The presence of carotid plaques instability was evaluated by color doppler ultrasound.

Results: Hypertension (61.54%) and previous history of cerebral ischemia are clinically significant leading cause of cerebral ischemia among the patients (p < 0.05). The prevalence of infection was more common (66.66%) in cases than control (40%). The difference is statistically significant (p < 0.05) and this remains significant after controlling other risk factors including socio-economic status. There is no significant association found between H. pylori seropositivity and carotid plaque surface irregularity (x2 = 0.649, P > 0.05).

Conclusions: Our results support the hypothesis of an association between infection with H. pylori and acute cerebral ischemia and there is no significant association found between H. pylori seropositivity and carotid plaque instability.

Keywords: Cerebrovascular, Helicobacter pylori, Ischemic, Infection, Stroke

INTRODUCTION

There has been increasing evidence that in addition to established risk factors, markers of inflammation and chronic infectious diseases may be linked to stroke and other ischemic vascular diseases.1 H. pylori is a gram-negative spiral bacterium that can cause gastritis, peptic ulcer, and gastric cancer but often remains asymptomatic. After infection, which occurs mostly in childhood via fecal-oral or oral-oral pathways, it persists in the gastric mucus layer. The infection induces a serum antibody response, which persists during the entire lifetime. Socioeconomic factors influence the age and rate of infection with H. pylori and low socioeconomic status in childhood appears to be associated with H. pylori seropositivity.

The mechanism underlying an association between H. pylori and vascular disease in uncertain. H. pylori results in a low grade chronic inflammatory response and it has been suggested that this may promote atherogenesis by altering some cardiovascular risk factors including haemostatic factors and lipids.

It is well known that carotid plaque instability plays a major role in the development of atherosclerosis, Lesions are associated with increased inflammatory response. Infection with H. pylori induces gastric inflammation in most subjects and has been associated with increased production of cytokines such as tumor necrosis factor (TNF-α), interferon (INF-γ) and interleukin (IL1-6-8). The strong inflammatory response elicited by cytotoxic H. pylori may induce plaque instability through the
immune mediated release of cytokines and other substances endowed with proinflammatory properties.

We performed a case control study (1) to confirm the association between H. pylori and ischemic cerebral stroke and (2) to assess the association between H. pylori and carotid plaque irregularity.

METHODS

We investigated 39 consecutive patients who were hospitalized for ischemic cerebral stroke and 30 ages - and sex-matched control subjects randomly selected from general population. Exclusion criteria included inability to give informed consent and hemorrhagic cerebral stroke. All patients underwent Computed Tomography, Extracranial (carotideal and vertebral) colour Doppler imaging, rapid urease test and ELISA for anti H. pylori antibodies (IgG). Each case was evaluated with detailed history regarding age, family history, high blood pressure, diabetes smoking habits, source of drinking water e.g. municipal tap water, ground water as well as filtered water and alcohol intake. Their socio-economic status was asessed by asking subjects, for the number of year in school, per capita income and their profession. The subject was also interviewed about the daily use of NSAIDS and proton pump inhibitor.

Carotid color doppler ultrasound

The carotid trunk was identified using both B-mode and pulsed wave color Doppler ultrasonography. The plaque was defined as a protrusion into the vessel lumen of at least 2 mm. The degree of stenosis was measured along the longitudinal axis and the patients were divided in two groups 50 – 74% or > 75% of vessel diameter. Plaques were considered stable or instable according to the features of their surface; smooth, irregular (height variations < 2 mm) or ulcerated (discrete depression > 2 mm in width extending into the media.

Serological data

From all the cases serum samples were taken and subjected to ELISA test for IgG against Helicobacter pylori by Biochem Immunosystems Italia S.P.A. Elagen Helicobacter pylori IgG. Cut off value were decided by the reading of OD (Optical density) value of calibrator 3 which was found to be 1.220. This corresponded to a titre of 15 AU/ML. An OD value greater than this indicated a positive result. A graph was plotted using OD values of 5 calibrators which was found to be a straight line. This was used to determine the AU (Arbitrary Units) values by plotting the OD values. Analysis - The entire data was later on tabulated and analysed statistically.

Rapid urease test (rut)

This was performed using rapid urease kit, “Helikocheck” of the RMD Crystals Research Pvt. Ltd. India the test was considered positive when the yellow colour of the indicator became bright pink or red within 24 hours of placing the biopsy sample in the urease medium.

Data analysis

We used the x² test to compare categorical variables. P values <0.05 were considered significant. We decided to include the following variables in the multivariate model; age, sex, the generally accepted stroke risk factors (hypertension, smoking, diabetes mellitus, previous cerebral ischemia. Data was analyzed using SPSS software. To describe nominal data, simple percentages were used. Mean and standard deviations were used to describe normally distributed data from the subjects. The Spearman rank correlation test was used to determine the relationship between different continuous variables.

RESULTS

Demographic variable are present in Table 1. H. pylori seropositivity was higher in patients (26/39; 66.66%) than control subjects (12/30; 40%). This association remained significant after adjustment for age, sex and social status and source of water intake.

Table 1: Demographic variables.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>39</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age (Year)</td>
<td>47.87 ± 9.66</td>
<td>46.67 ± 8.82</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Female gender</td>
<td>14/39 (35.89%)</td>
<td>8/30 (26.66%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>H. pylori seropositivity</td>
<td>26/39 (66.66%)</td>
<td>12/30 (40%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Municipal Tape Water</td>
<td>25/39 (64.10%)</td>
<td>18/30 (60%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Socio Economic Status</td>
<td></td>
<td></td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Hypertension, diabetes mellitus, previous cerebral ischemia and family history of stroke and smoking was more in patients than control subjects while history of alcohol was more in control group. The table also shows that hypertension (61.54%) and previous cerebral ischemia were clinically significant among the patients (p < 0.05) (Table 2).

No significant association was found between H. pylori infection and plaque surface irregularity (87% of H. pylori seropositivity in patients with irregular plaque versus 61.29% in patients without) (Table 3).
Table 2: Multivariate analysis of risk factor for cerebral ischemia.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group I</th>
<th>Group II</th>
<th>χ² test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>11 (36.66%)</td>
<td>24 (61.54%)</td>
<td>4.20</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2 (6.66%)</td>
<td>6 (15.38%)</td>
<td>1.26</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Previous cerebral ischemia</td>
<td>1 (3.33%)</td>
<td>8 (20.51%)</td>
<td>4.4038</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Family History of stroke</td>
<td>9 (30%)</td>
<td>11 (28.21%)</td>
<td>0.0257</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Alcohol</td>
<td>4 (13.33%)</td>
<td>3 (7.69%)</td>
<td>0.5964</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (50%)</td>
<td>27 (69.23%)</td>
<td>2.63</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Table 3: Correlation between H. pylori seropositivity and carotid plaque irregularity.

<table>
<thead>
<tr>
<th>H. pylori</th>
<th>Irregular Plaque (n = 8)</th>
<th>Regular Plaque (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>7 (87%)</td>
<td>19 (61.29%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1 (13%)</td>
<td>12 (38.71%)</td>
</tr>
</tbody>
</table>

Superficial gastritis was most prevalent findings (17/39; 43.58%) followed by normal histology (13/39; 33.33%) as second common findings.

Table 4: Frequency of gastric antral histological features.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Histological Features</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>13 (33.33%)</td>
</tr>
<tr>
<td>2</td>
<td>Superficial gastritis</td>
<td>17 (43.58%)</td>
</tr>
<tr>
<td>3</td>
<td>Atrophic gastritis</td>
<td>6 (15.58%)</td>
</tr>
<tr>
<td>4</td>
<td>Intestinal metaplasia</td>
<td>5 (12.82%)</td>
</tr>
<tr>
<td>5</td>
<td>Capillary ectasia</td>
<td>3 (7.69%)</td>
</tr>
</tbody>
</table>

DISCUSSION

This study shows that H. pylori seropositivity is a risk factor for symptomatic cerebrovascular disease, independent of the other conventional risk factors measures. A concern in interpreting the relation between H. pylori seropositivity and vascular disease has been that H. pylori may merely be a marker for poor socioeconomic conditions which are themselves the causal risk factor for vascular disease. H. pylori seropositivity was higher in subjects with lower socioeconomic status in both cases (66.66%) as well as control group (46.66%). This can be attributed to the over crowding sharing of beds and consumption of food, prepared under unhygienic condition and usually poor patients with lower socio-economic status were coming to the government hospital and also being part of our study. Hypertension (61.54%) and the history of previous cerebral ischemia (20.51%) was the major risk factors and clinically significant among the patients. Epidemiological studies have shown that water source and exposure related to sewage disposal and exposure to animals are risk factors for infection. In present study there was no significant association found between H. pylori seropositivity and plaque surface irregularity. The relationship between the infection with Cag-A positive strains and atherosclerosis has been investigated by Pietroiusi and colleagues showing these strains to be strongly associated to atherosclerosis independently of the classical vascular risk factors. Histological examination of antral biopsies (taken during endoscopy) in all ischemic stroke patients showed that superficial gastritis was the most prevalent finding (17 out of 39, 43.58%) and second common finding among cases was normal histology 13 (33.33%).

It has recently been shown that H. pylori may be present at the level of the carotid plaques. Because CagA-positive strains elicit a strong local inflammatory response, it is possible that their presence may contribute to plaque instability and to the development of ischemic stroke through a local action. Some mechanisms may link chronic H. pylori infection with atherogenesis including a low grade acute phase response, free radical formation and immune mediated mechanisms. Serum markers of an acute phase response are raised in chronic H. pylori infection. Antioxidants have been shown to be decreased in subjects with H. pylori. This could result in lipid peroxidation, another possible mechanism linking H. pylori and atherogenesis. Cross reacting antibodies to heat shock proteins are a risk factor for carotid atherosclerosis. If further studies confirm that H. pylori is a risk factor for cerebrovascular disease this has important clinical implications. H. pylori infection can be eradicated by a short course of combination antibiotic therapy. If the association with stroke is causal its eradication may reduce the risk of subsequent stroke and other vascular events.

Irregularities of the atherosclerotic plaque reflect plaque instability that is closely associated with major ischemic events. Since the inflammation plays a major role in atherosclerosis and complicated lesions are associated with an increased inflammatory response. It has also been suggested that H. pylori, as well as Chlamydia pneumoniae, could directly provoke inflammation within the atherosclerotic plaques. H. pylori DNA has been found in carotid atherosclerotic lesions and has been associated with features of inflammation. Also, an autoimmune reaction could be postulated. A cross reactivity between anti-caga antibodies and vascular wall antigens has been recently demonstrated, suggesting that these antibodies may contribute to the inflammatory response cells within atherosclerotic lesions, which might eventually lead to plaque instability. Prospective data has demonstrated that infection with caga-positive strains significantly increases the risk of carotid...
atherosclerosis.7 Heuschmann et al, in their population-based case-control study found higher risk of ischemic stroke in *H. pylori* positive patients similar to the present study.8 Our proportion also seems close to the studies by Ponzetto et al, Mayr et al, Moayyedi et al.7,9,10

We also found high proportion (66.66%) of *H. pylori* on ELISA in ischemic stroke patients, which is concurrent to these studies. Masoud et al, in their case-control study of 91 cases of ischemic stroke and 80 normal healthy control cases found [66/91 (72.5%)] seropositivity (IgG) for *H. pylori* as compared to the control group [45/80(56.3%)].11 Their results are similar to our results in regard to seropositivity [26/39 (66.66%)].

**CONCLUSIONS**

Our results support the hypothesis of an association between infection with *H. pylori* and acute cerebral ischemia and there is no significant association found between *H. pylori* seropositivity and carotid plaque instability.

**Funding:** No funding sources  
**Conflict of interest:** None declared  
**Ethical approval:** The study was approved by the Institutional Ethics Committee

**REFERENCES**
