Helicobacter pylori infection: a risk factor for ischaemic cerebrovascular disease and carotid atheroma

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Abstract

Objectives—Chronic Helicobacter pylori infection has been associated with ischaemic heart disease although the mechanism by which it mediates this effect remains unclear. The objective was to determine whether it is also a risk factor for ischaemic cerebrovascular disease.

Methods—A total of 238 patients and 119 controls were studied. Patients were characterised into stroke subtypes based on pathogenic mechanisms and carotid atheroma load was estimated using duplex ultrasound. H pylori seropositivity was determined on serum samples.

Results—H pylori seropositivity was more common in cases (58.8% v 44.5%, p=0.01). The odds ratio for cerebrovascular disease associated with seropositivity was 1.78 (95% confidence interval 1.14–2.77), and this remained significant after controlling for other risk factors including socioeconomic status (1.63 95% CI 1.02–2.60). H pylori seropositivity was associated with large vessel disease (odds ratio 2.58 (95% CI 1.44–4.63), p=0.001) and lacunar stroke (odds ratio 2.21 (95% CI 1.44–3.40), p=0.02) but not stroke due to cardioembolism or unknown aetiology (odds ratio 1.16 (95% CI 0.66–2.02), p=0.5). Mean (SD) carotid stenosis was greater in patients seropositive for H pylori (37.3 (29.7) v 27.9 (26.2)%), p=0.01). There was no difference in the prevalence of seropositivity between patients with stroke and transient ischaemic attack (59.6% v 58.6%, p=0.9).

Conclusion—Chronic H pylori infection is an independent risk factor for ischaemic cerebrovascular disease and may act, at least in part, by increasing atherosclerosis.

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Keywords: cerebral ischaemia; Helicobacter pylori; homocysteine; folate
patients with well characterised ischaemic cerebrovascular disease. We hypothesised that it might be associated with large vessel atheroma and therefore stroke caused by large vessel disease, and therefore examined the relation between seropositivity and different stroke subtypes, as well as the association between seropositivity and mean internal carotid artery stenosis determined on high resolution carotid duplex ultrasound.

Methods
Two hundred and eighty eight consecutive white patients presenting with non-haemorrhagic stroke or transient ischaemic attack presenting to a neurological cerebrovascular disease service in south London, UK, were studied. Patients with asymptomatic disease or venous thrombosis were not included. A white control population was recruited from spouses of the same patients with cerebrovascular disease. We used spouse controls to improve controlling for socioeconomic status; there has been concern that the relation between H pylori and cardiovascular disease may be explained by socioeconomic factors which themselves are related to cardiovascular risk.11 It has been shown that spirochete tend to have similar childhood and parental socioeconomic status.12 A ratio of two patients to each control was studied for two reasons: firstly, the larger group of patients allowed sufficient sample sizes for subgroup analysis of the relation between seropositivity and different stroke subtypes. Secondly, not all spouses were alive and therefore one to one matching was not possible. Therefore the first 72 male and 47 female controls presenting were enrolled. Controls were excluded if they had clinical cerebrovascular disease (two cases) but were included if they had ischaemic heart disease or vascular risk factors. In both patient and control groups hypertension was defined as either a systolic blood pressure>160 mm Hg, or a diastolic pressure>95 mm Hg, or current treatment with antihypertensive drugs. A diabetic patient was defined as non-insulin or insulin dependent. Social class was recorded and subjects were divided into class 1, 2, 3a, 3b, 4, or undefined.

Duplex ultrasound was performed using an Acuson XP colour flow imager. Internal carotid artery stenosis was calculated from a combination of Doppler data (ICA systolic/CCA diastolic ratio) for stenoses greater than 50%, and using the B mode modality to measure the ratio of maximum plaque thickness to luminal diameter for lesser degrees of stenosis. Mean carotid stenosis was calculated from the mean of left and right common/internal carotid artery stenosis.

Computed tomography, carotid ultrasound, and ECG were performed in all patients and echocardiography in about 40%. Magnetic resonance imaging and magnetic resonance angiography of both the extracranial and intracranial vertebralbasilar systems was performed in most patients with posterior circula-

Results

H PYLORI SEROPOSITIVITY AND CARDIOVASCULAR RISK FACTORS

Within the control population age was slightly but not significantly higher in H pylori positive patients (mean (SD) 66.5 (10.3) years v 64.4 (8.8) years, p=0.16). There was no relation between H pylori seropositivity and hypertension (p=0.14), smoking history (p=0.85).
Table 1 Characteristics of the cerebrovascular disease (CVD) and control populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CVD patients (n=238)</th>
<th>Controls (n=119)</th>
<th>Odds ratio (95% CI), p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.9 (9.8)</td>
<td>64.5 (9.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Male sex</td>
<td>144 (60.5)</td>
<td>72 (60.5)</td>
<td></td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>164 (68.9)</td>
<td>55 (46.2)</td>
<td>2.58 (1.64-4.06)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>147 (61.8)</td>
<td>47 (39.5)</td>
<td>2.47 (1.58-3.89)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (14.3)</td>
<td>10 (8.4)</td>
<td>1.82 (0.86-3.82)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>26 (10.9)</td>
<td>5 (4.2)</td>
<td>2.8 (1.05-7.48)</td>
</tr>
<tr>
<td>H. pylori seropositive</td>
<td>140 (58.8)</td>
<td>53 (44.5)</td>
<td>1.78 (1.14-2.77)</td>
</tr>
</tbody>
</table>

Values given indicate mean (SD) for age and proportion (%) for other data. Odds ratios are not corrected for other risk factors.

Table 2 Effect on the relation between H pylori and seropositivity of controlling for potential confounding risk factors

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.78</td>
<td>1.14-2.77</td>
<td>0.01</td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.77</td>
<td>1.14-2.77</td>
<td>0.01</td>
</tr>
<tr>
<td>and social class</td>
<td>1.79</td>
<td>1.15-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td>and diabetes</td>
<td>1.80</td>
<td>1.15-2.83</td>
<td>0.01</td>
</tr>
<tr>
<td>and smoking status</td>
<td>1.73</td>
<td>1.09-2.75</td>
<td>0.02</td>
</tr>
<tr>
<td>and hypertension</td>
<td>1.63</td>
<td>1.02-2.60</td>
<td>0.04</td>
</tr>
</tbody>
</table>

diabetes (p=0.3), male sex (p=0.69), or social class (p=0.72).

PATIENT STUDY
Table 1 shows the characteristics of the patient and control populations. The two populations were well matched for age. H pylori was significantly more common in cases than controls (58.8% vs 44.5%, odds ratio 1.78, 95% CI 1.14-2.77, p=0.01). The association was independent of age, sex, diabetes, smoking, hypertension, and social class (table 2) with an adjusted odds ratio of 1.63 (95% CI, 1.02-2.60, p=0.04). There was no difference in the prevalence of H pylori seropositivity between patients with stroke (109/186, 59.6%) and those with transient ischaemic attack without an infarct on CT (31/52, 58.6%, p=0.9). Hypertension and smoking history were also independent risk factors for cerebrovascular disease. Adjusted odds ratios (95% CI) were: hypertension 2.25 (1.40-3.62), p=0.0008; smoking history 2.52 (1.57-4.08), p=0.0001.

Mean (SD) percentage carotid stenosis was significantly higher in patients seropositive for H pylori (37.3 (29.7) vs 27.9 (26.2) %, p=0.01). This relation remained significant after controlling for other risk factors (p=0.048). Mean carotid stenosis was also significantly independent related to hypertension (p=0.006) and smoking history (p=0.0003).

The prevalence of H pylori seropositivity in the different subgroups is shown in table 3. The association between H pylori seropositivity and cerebrovascular disease was significant for both large vessel disease and lacunar groups but not for cardioembolic/unknown. Mean degree of carotid stenosis in the different subgroups was large vessel 62.2 (9.0)%, lacunar 12.5 (13.9)%, cardioembolic/unknown 12.5 (13.8)%, tandem 52.0 (20.5)%.

There was no relation between H pylori seropositivity and either serum homocysteine or serum folate concentrations. Serum homocysteine was mean (SD): controls seropositive 19.2 (7.2) nmol/l v seronegative 20.7 (11.2) nmol/l, p=0.58; cases seropositive 22.16 (8.61) nmol/l v seronegative 26.19 (15.44) nmol/l, p=0.08. Mean (SD) serum folate was mean (SD) controls, seropositive 6.37 (4.42) µg/l v seronegative 6.90 (3.79) µg/l, p=0.63, cases seropositive 5.77 (4.03) µg/l v seronegative 5.97 (2.89) µg/l, p=0.77.

Discussion
This study shows that H pylori seropositivity is a risk factor for symptomatic cerebrovascular disease, independent of the other conventional risk factors measured. Consistent with our a priori hypothesis we found that there was a stronger independent association with both cerebrovascular disease caused by large vessel disease and with the degree of carotid stenosis. However, there was also a strong independent association with lacunar stroke indicating that the association is not totally explained by a proatherogenic effect. 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. However, the relation was independent of social class in this study. In addition we did not find an association between H pylori seropositivity and social class, an association which has been reported in previous studies. This may be due to the use of spouse controls which were designed to reduce any confounding by social class. The degree of association we found with cerebrovascular disease (a corrected odds ratio of 1.63) is of a similar degree to that seen in some previous studies in patients with ischaemic heart disease. In the control population we found no relation between H pylori seropositivity and hypertension, smoking history, cholesterol, or diabetes, in agreement with previous studies.

In our study H pylori seropositivity was associated with increased mean internal carotid artery stenosis. Furthermore the association between cerebrovascular disease and H pylori seropositivity was stronger when the analysis was confined to patients with large vessel disease (p=0.01).
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disease and this relation was independent of other risk factors. 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. Fibrinogen, leucocyte count, and C-reactive protein, all risk factors for cardiovascular disease, are raised in those seropositive for H pylori and point to a low grade inflammatory response. Free radical formation and immune mediated mechanisms may also be important. 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. H pylori produces 60 kDa heat shock proteins, which have a high degree of sequence homology with human 60 kDa heat shock proteins. An alternative explanation for the relation between cardiovascular disease and H pylori is via hyperhomocysteinaemia. Homocysteine concentrations are raised in the presence of low vitamin B12 and folate, and chronic gastric inflammation could result in malabsorption particularly of vitamin B12 and secondary hyperhomocysteinaemia. However, we found no association between H pylori seropositivity and either serum homocysteine or folate concentrations.

The association between H pylori and stroke cannot be accounted for solely by promotion of large artery atherogenesis. We found a similar independent association with lacunar stroke. The major risk factor for lacunar stroke both in our study and in many other studies is hypertension but the relation between H pylori and lacunar stroke was still significant after controlling for hypertension. Some studies have found an association between acute infections and stroke and its had been suggested that these induce a prothrombotic state. It is possible that chronic H pylori infection could have a similar effect. Alternatively it may also promote atherosclerosis in the small perforating vessels or at the point that they branch from the intracerebral arteries.

Identifying the importance of different pathogenic mechanisms in patients with stroke is complex as many patients may have more than one pathogenic process caused by shared risk factors. For example, hypertension is a risk factor for cardioembolic stroke via atrial fibrillation or myocardial infarction, carotid disease, or lacunar stroke. Furthermore, current diagnosis of the stroke subtype is subject to error. Therefore, further studies are required in patients with the underlying disease processes (for instance, large vessel atheroma) but without stroke—for example, the relation between H pylori and atheroma could be determined in asymptomatic patients with atheroma load quantified by duplex ultrasound as in our study.

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.

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