High prevalence of Helicobacter pylori infection in Malaysian Parkinson’s disease patients

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Background: Studies have reported a higher prevalence of Helicobacter pylori (H. pylori) infection in Parkinson’s disease.

Objectives: To determine the frequency of H. pylori in patients with Parkinson’s disease compared to controls and its effect on symptom severity and quality of life.

Methods: A cross-sectional comparative study involving 29 Parkinson’s disease patients and 23 controls. The 13C-urea breath test was used to diagnose H. pylori. Symptom severity and quality of life were assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) and 39-item Parkinson’s Disease Questionnaire (PDQ-39), respectively.

Results: The frequency of H. pylori infection was 48.3% in the Parkinson’s disease group and 21.7% in controls (P=0.048). This became more significant (P=0.012) when we excluded relatives of H. pylori-positive patients from the control group. There was no association between Hoehn and Yahr stages, UPDRS and PDQ-39 scores, and H. pylori.

Conclusion: H. pylori infection is more prevalent in the Malaysian Parkinson’s disease population compared to controls (48.3% versus 21.7%). However, symptom severity and quality of life was not related to H. pylori infection.

Keywords: Parkinson’s disease, Helicobacter pylori, prevalence, 13C-urea breath test

Introduction

An association between Helicobacter pylori (H. pylori) and Parkinson’s disease (PD) was first noted when a high prevalence of duodenal and gastric ulcers was observed among PD patients.1 It was suggested that H. pylori might play a part in the biosynthesis of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or MPTP-like substances, which are directly neurotoxic to dopaminergic neurons.2 H. pylori has structural similarities to the plant seed cycad, which is believed to be neurotoxic.3 Cycad is known to cause amyotrophic lateral sclerosis/parkinsonism–dementia complex among populations in Guam4,5 and Japan’s Kii Peninsula.6

Studies have shown that H. pylori infection leads to poorer motor function,7,8 and eradication leads to improvement in stride length.7 Eradication of H. pylori also correlated with a reduction in inflammatory markers,9,10 leading some authors to hypothesize that H. pylori infection leads to a chronic inflammatory process resulting in the destruction of dopaminergic neurons.

Studies in patients with PD have shown that levodopa absorption in the duodenum is affected by H. pylori.11 Impaired gastric motility in advanced PD can also delay the transit and absorption of levodopa. One study showed that H. pylori-infected PD patients who received eradication therapy had consistently higher serum levodopa levels compared to...
untreated controls. The treated group had prolonged response to levodopa and fewer motor fluctuations. The authors concluded that *H. pylori* infection impairs absorption of levodopa, and eradication therapy is a simple way to enhance levodopa absorption and clinical response.

There are no studies on the prevalence of *H. pylori* infection among Malaysian PD patients, despite its high prevalence in our population. Given the possible therapeutic benefits of *H. pylori* eradication in PD, we set out to determine the prevalence of *H. pylori* infection among our PD patients compared to age-matched controls and its effect on motor function and quality of life.

**Materials and methods**

This was a cross-sectional comparative study. Consenting PD patients aged ≥18 years were consecutively recruited from the outpatient clinic. Patients with secondary parkinsonism, Parkinson’s plus, history of antibiotic use within 6 months, and proton pump-inhibitor or H$_2$-antagonist use within 4 weeks of the urea breath test (UBT) and those who were unable to perform the UBT were excluded. An age- and sex-matched control group was recruited. Approval from the university research ethics committee was obtained prior to the study.

**Sample size**

The sample size for the study was calculated using the PS 3.0.7 (Power and Sample Size, 2009 release) Program by Dupont and Plummer from Vanderbilt University based on local data for probability of exposure among controls and cases.

**Study assessments**

**Baseline data**

Sociodemographic characteristics, previous antibiotic use, medical and medication history, and presence of gastrointestinal symptoms were recorded.

**PD-specific assessments**

PD severity was assessed using Hoehn and Yahr (H&Y) staging and the Unified Parkinson’s Disease Rating Scale (UPDRS). Quality of life was assessed using the 39-item Parkinson’s Disease Questionnaire (PDQ-39).

**UBT protocol**

Each subject was given 75 mg of the infrared isotope analyzer, $^{13}$C urea mixed in Tang™ orange drink. Breath samples were taken at 0, 10, 20, and 30 minutes, and were analyzed using a nondispersive isotope-selective infrared spectrometer. Interpretation of the results was based on IRIS software 2.3 for analysis of delta over baseline (DOB).

**DOB**

DOB is a measure of severity of *H. pylori* infection, as it correlates significantly with the total urease activity in the stomach. DOB has also been studied extensively and the value has been shown to be correlated with bacterial strain virulence, intensity of dyspeptic symptoms, and therapeutic efficacy. A DOB >4.0 was considered positive, while a DOB <2.5 was considered negative. Values between 2.5 and 4.0 were considered positive if the subjects had taken antibiotics, proton-pump inhibitors, or H$_2$ antagonists for 4–6 weeks prior to testing. Otherwise, patients were considered negative for *H. pylori*. The sensitivity and specificity of $^{13}$C-UBT are 98.3% and 98.6%, respectively.

**Statistical analysis**

All data were analyzed using SPSS version 19.0 (IBM, Armonk, NY, USA) for Windows. Values of <0.05 were deemed significant.

**Results**

Of 57 eligible patients, only 29 were recruited, as 27 patients failed to show for the UBT and one had received recent antibiotic therapy. Twenty-three controls were recruited. Thirty-one males (59.6%) and 21 females (40.4%) were recruited. They consisted of 17 Malays (32.7%), 30 Chinese (57.7%), four Indians (7.7%) and one Indonesian (1.9%). The mean ages were 64.1 ± 11.6 years and 61.3 ± 8.4 years for the PD and control groups, respectively. The mean duration of PD from diagnosis was 5.8 ± 4.7 years. The demographic data of the study population are shown in Table 1.

**UBT**

We found significant differences in the frequency of *H. pylori* infection between patients and controls (48.3% vs 21.7%, $P=0.048$). When we excluded subjects who were closely related to PD patients (one subject in the PD group and three in the control group) and those with recent or past *H. pylori* infections, our subanalysis achieved greater significance ($P=0.012$) (Table 2).

Comparative analysis between *H. pylori*-positive and -negative PD patients showed no significant differences in terms of H&Y stages, duration of PD, PDQ-39, or UPDRS scores. When duration of PD was arbitrarily divided at 4 years, we observed that among those with <4 years of...
Table 1 Demographic data

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>PD group (n=29)</th>
<th>Control group (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.1 ± 11.6</td>
<td>63.1 ± 8.4</td>
<td>0.325*</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.59 ± 0.07</td>
<td>1.62 ± 0.07</td>
<td>0.082*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.04 ± 9.53</td>
<td>64.96 ± 10.10</td>
<td>0.742*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.38 ± 3.40</td>
<td>24.61 ± 3.37</td>
<td>0.435*</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (55.2)</td>
<td>15 (65.2)</td>
<td>0.463*</td>
</tr>
<tr>
<td>Female</td>
<td>13 (44.8)</td>
<td>8 (34.8)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>7 (24.1)</td>
<td>10 (43.5)</td>
<td>0.260†</td>
</tr>
<tr>
<td>Chinese</td>
<td>19 (65.5)</td>
<td>11 (47.8)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>3 (10.3)</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school or less</td>
<td>13 (44.8)</td>
<td>5 (21.7)</td>
<td>0.18†</td>
</tr>
<tr>
<td>Secondary school</td>
<td>14 (48.3)</td>
<td>13 (56.5)</td>
<td></td>
</tr>
<tr>
<td>University/college</td>
<td>2 (6.9)</td>
<td>4 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Master’s/ postgraduate</td>
<td>0 (0.0)</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Employment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>3 (10.3)</td>
<td>2 (8.7)</td>
<td>0.23†</td>
</tr>
<tr>
<td>Nonprofessional</td>
<td>7 (24.1)</td>
<td>11 (47.8)</td>
<td></td>
</tr>
<tr>
<td>Unemployed/ retired</td>
<td>19 (65.5)</td>
<td>10 (43.5)</td>
<td></td>
</tr>
<tr>
<td>Household income RM/month (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>5 (17.2)</td>
<td>0 (0)</td>
<td>0.03†</td>
</tr>
<tr>
<td>1,000–2,500</td>
<td>11 (37.9)</td>
<td>8 (34.8)</td>
<td></td>
</tr>
<tr>
<td>2,500–5,000</td>
<td>10 (34.5)</td>
<td>6 (26.1)</td>
<td></td>
</tr>
<tr>
<td>5,000–10,000</td>
<td>3 (10.3)</td>
<td>5 (21.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>0 (0)</td>
<td>4 (17.4)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Pearson chi-squared; †Fisher’s exact test; ‡independent t-test.
Abbreviations: PD, Parkinson’s disease; BMI, body mass index; RM, Ringgit Malaysia.

Disease, 35.7% were positive for H. pylori, while among those with disease duration of ≥4 years, 60% were positive (P=0.191) (Table 3).

Levodopa and H. pylori status

Total daily levodopa-dose requirements were divided into three groups (<400 mg, 400–799 mg, and ≥800 mg) and analyzed for H. pylori positivity. There appeared to be more H. pylori-positive patients in the group with the highest levodopa requirement. However, these results were not statistically significant (P=0.515).

Table 3 Relationship between staging, quality of life and UPDRS scores with Helicobacter pylori status

<table>
<thead>
<tr>
<th>Stage</th>
<th>Hoehn and Yahr, n (%)</th>
<th>PDQ39</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (7.1)</td>
<td>17 (13.7–35.25)</td>
</tr>
<tr>
<td>2</td>
<td>11 (78.6)</td>
<td>12 (7.75–16.50)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>11.0 (7.0–15.0)</td>
</tr>
<tr>
<td>4</td>
<td>2 (14.3)</td>
<td>11.79 ± 3.827</td>
</tr>
</tbody>
</table>

Notes: *Fisher’s exact test; †mean ± standard deviation, analyzed with paired t-test; ‡all other data are expressed as medians (interquartile range) and were analyzed with Mann–Whitney U-test.
Abbreviations: UPDRS, Unified Parkinson’s Disease Rating Scale; PDQ, Parkinson’s Disease Questionnaire; ADL, activities of daily living; H. pylori, Helicobacter pylori.

Discussion

The prevalence of H. pylori varies widely. This was a cross-sectional pilot study testing our hypothesis that H. pylori infection is higher in the PD population compared to non-PD population based on previously published data. Most studies reported rates between 40% and 93% in adults. Ethnicity is an important determinant, the lowest prevalence (1.9%–29.2%) being among Malays, followed by Chinese (26.7%–57.5%) and Indians (49.4%–52.3%). Our findings are therefore in keeping with locally published data.

Prevalence rates of H. pylori infection among PD patients in other countries were slightly higher than ours, ranging from 53.8% to 64%. This variation may be attributable
to such factors as timing and location of the study and study population characteristics.\textsuperscript{25}

One study,\textsuperscript{22} which used enzyme-linked immunosorbent assays to diagnose \textit{H. pylori}, demonstrated that 70\% of PD patients were positive for \textit{H. pylori} compared to 36\% of controls ($P < 0.02$). Serology has a specificity of 79\%–90\% and sensitivity of 76\%–84\%.\textsuperscript{27,28} UBT has sensitivity and specificity \textgreater{}95\%.\textsuperscript{30,31} Patients who have been positive for \textit{H. pylori} may remain seropositive for up to 4 years after eradication.\textsuperscript{26,28} Consequently, most studies using serology as a diagnostic test tend to overestimate \textit{H. pylori} prevalence.

We noted \textit{H. pylori} infection was higher in patients with a longer duration of PD. Although this was not statistically significant, the possibility that PD patients may have characteristics that put them at risk of acquiring \textit{H. pylori} infection should be considered. Possible reasons include poor gastric motility,\textsuperscript{32} levodopa, which has been shown to promote \textit{H. pylori} growth,\textsuperscript{33} and worsening motor function leading to poor personal hygiene. It has been well demonstrated that \textit{H. pylori} transmission is higher within close family members.\textsuperscript{34} When we took this into account and excluded the close family members from our sub-analysis, our findings gained further statistical significance (Table 2).

Our study did not demonstrate any relationship between \textit{H. pylori} positivity and H\&Y stages, PDQ-39, or UPDRS scores. One possible explanation could be that higher UPDRS scores led to higher levodopa requirements, thus masking any true association. We observed higher requirements in our \textit{H. pylori}-positive PD patients compared to their \textit{H. pylori}-negative counterparts. However, this trend did not meet statistical significance. Lee et al\textsuperscript{13} and Borgohain et al\textsuperscript{24} likewise found no significant differences in UPDRS scores between \textit{H. pylori} positive and negative patients. However, they observed significant difference in UPDRS scores after \textit{H. pylori} eradication.

We noted a trend of increased levodopa-dose requirements with higher DOB levels. Lee et al\textsuperscript{13} and Pierantozzi et al\textsuperscript{23} demonstrated that \textit{H. pylori} infection caused a reduction in levodopa absorption, which increased by 54\% after eradication therapy. Studies have shown that levodopa may also encourage \textit{H. pylori} growth.\textsuperscript{35} It has been demonstrated that \textit{H. pylori} cultured in levodopa- and noradrenalin-rich media grew faster than \textit{H. pylori} cultured in media resembling normal gastric milieu. This would suggest that \textit{H. pylori}-infected PD patients were less likely to achieve therapeutic levodopa levels, and would therefore have poorer control of their symptoms. Further studies need to be conducted to determine if this is true in vivo.

Another possible cause for a higher levodopa requirement in \textit{H. pylori}-infected PD patients is the development of atrophic gastritis, which has been shown to have an association.\textsuperscript{36} There is no published research regarding the presence of atrophic gastritis in PD patients.

Treating asymptomatic \textit{H. pylori} infection is not currently recommended.\textsuperscript{37,38,42} Screening is selected for those with symptoms or risk factors. For PD patients, however, it may be justified to screen for and treat \textit{H. pylori} infection, as this may improve serum levodopa levels and motor function. More studies are needed to demonstrate a clear benefit of eradication therapy for PD patients before we can suggest \textit{H. pylori} screening as part of treatment guidelines.

To summarize, we found that \textit{H. pylori} infection was significantly higher in Malaysian PD patients compared to controls. There was a trend of a higher daily levodopa-dose requirements and severity of \textit{H. pylori} infection. Our study found no association between presence of \textit{H. pylori} infection and H\&Y stages, PDQ-39, or UPDRS scores.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


