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Helicobacter pylori infection is associated with worse severity of Parkinson's disease

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ABSTRACT

Background: Some studies have suggested that chronic *Helicobacter pylori* (HP) infection can aggravate the neurodegenerative process in Parkinson's disease (PD), and targeted intervention could potentially modify the course of this disabling disease. We aimed to study the impact of HP infection on motor function, gastrointestinal symptoms, and quality of life in a large cohort of PD patients.
Methods: 102 consecutive PD patients underwent ^{13}C urea breath testing and blinded evaluations consisting of the Unified Parkinson's Disease Rating Scale (UPDRS) including "On"-medication motor examination (Part III), objective and quantitative measures of bradykinesia (Purdue Pegboard and timed gait), Leeds Dyspepsia Questionnaire, and PDQ-39 (a health-related quality of life questionnaire).
Results: 32.4% of PD patients were HP-positive. HP-positive patients were older (68.4 ± 7.3 vs. 63.8 ± 8.6 years, $P = 0.009$) and had worse motor function (UPDRS Part III 34.0 ± 13.0 vs. 27.3 ± 10.0, $P = 0.04$; Pegboard 6.4 ± 3.3 vs. 8.0 ± 2.7 pins, $P = 0.04$; and timed gait 25.1 ± 25.4 vs. 15.5 ± 7.6 s, $P = 0.08$). In the multivariate analysis, HP status demonstrated significant main effects on UPDRS Part III and timed gait. The association between HP status and these motor outcomes varied according to age. Gastrointestinal symptoms and PDQ-39 Summary Index scores did not differ between the two groups.
Conclusions: This is the largest cross-sectional study to demonstrate an association between HP positivity and worse PD motor severity.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, but its etiology remains elusive and at present only symptomatic treatments exist. Recent advances have suggested that complex interactions between genetic predispositions and exposure to environmental factors, such as toxins and infectious agents, may underlie the selective – but widespread and multisystemic – loss of neurons in PD, and a fundamental role of the gastrointestinal (GI) system in the etiology and progression of PD has been hypothesized [1–13].

Helicobacter pylori (HP), a bacterium found on the luminal surface of the gastric epithelium, induces chronic inflammation of the underlying mucosa [14,15]. More than half of the world's human population has HP infection, with the highest prevalence found in Asian countries [14,15]. Infection is usually acquired during childhood and tends to persist indefinitely unless treated [14,15]. Although the great majority of HP-infected individuals will not have any clinically significant complication, this infection has been implicated in a wide variety of GI and extra-GI disorders [16].

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Several studies of HP eradication in PD patients showed promising results with improvement of motor symptoms (particularly motor fluctuations) post-treatment [17–22]. However, only two studies [19,23] attempted to correlate, in a cross-sectional manner, the presence of HP infection with worse PD severity. These studies were limited by small sample size [18–20,22,23], open-label design [19,20,22], and/or the use of non-validated assessments of motor function [17,21,23]; several have been reported in abstract form only [20,22,23]. Thus, a recent Cochrane review concluded that further studies are required to address the gaps in knowledge regarding the role of HP infection in PD [24], and screening PD patients for HP status has yet to enter routine clinical practice. A role for small intestinal bacterial overgrowth (SIBO) in PD has also been proposed recently [4,5,25]. It is known that SIBO can occur as a sequela of HP infection as well as of gut dysmotility [26]. We therefore aimed to study the potential impact of HP infection on motor, GI symptomatology and quality of life aspects of PD, taking SIBO into account.

2. Patients and methods

2.1. Study population

Eligible patients with PD were recruited consecutively from the University of Malaya Neurology Clinic, Malaysia, during routine outpatient visits between July 2012 and March 2013, as described previously [5]. The study received ethics approval from the Medical Ethics Committee, University of Malaya Medical Centre and written informed consent was obtained from all patients. Eligible patients were ≥18 years of age and diagnosed by a Movement Disorders Neurologist (SYL) with PD, according to the Queen Square Brain Bank criteria. Exclusion criteria were: history of having received HP eradication therapy (whether or not this treatment was successful); a history of gastric lesions or major abdominal/pelvic surgery; conditions preventing reliable completion of study assessments; and prior functional neurosurgery or treatment with apomorphine infusion. Recruitment was delayed if patients had used antibiotics in the preceding four weeks; used anti-acid, prokinetic or laxative agents in the preceding two weeks [15]; or were initiated on dopaminergic medications within the last three months. Patients did not pay for any of the study procedures and were given a small honorarium (equivalent to USD15) to help cover the cost of traveling to the hospital.

2.2. Clinical evaluations

Demographic and clinical data, including PD duration, body mass index (BMI), daily L-dopa equivalent units (LEU), and use of anticholinergic medication were recorded. GI symptoms were evaluated using a validated and self-administered Malaysian version of the Leeds Dyspepsia Questionnaire (LDQ) [27]. We administered the Unified PD Rating Scale (UPDRS), which consists of four subscales: Part I, which has 4 questions on mentation, behavior, and mood; Part II, which has 13 questions on activities of daily living; Part III, which has 14 questions on motor function; and Part IV, which has 11 questions on motor and other complications of the disease. PD motor severity was assessed using the UPDRS Part III and Hoehn and Yahr staging during the subjects' usual "On"-medication state in the morning by a trained clinician specializing in Movement Disorders (AHT). The UPDRS Part III evaluation was video-recorded so that the accuracy of the live ratings could be verified if necessary. During their "On"-medication state, patients also underwent timed tests of upper and lower limb function: (1) the Purdue Pegboard test (patients were instructed to insert as many pegs as possible in 30 s, first with the dominant hand, then with the non-dominant hand, followed by both hands simultaneously; the average of three trials was calculated); and (2) a timed gait test. Patients walked 14 m (7 m to and fro) as fast as they could, followed by a second walk after 5 min. A walking aid could be used depending on individual preference. The time and number of steps taken to complete the walk were recorded, and the average for both trials was calculated. Quality of life was evaluated using the PD Questionnaire (PDQ-39). Patients and research personnel performing the clinical assessments were blind to the results of HP testing. The motor and GI symptom assessments were conducted by different examiners, and all the UPDRS Part III ratings (administered by a single examiner, AHT) were done blinded to the results of the other motor assessments.

2.3. Breath testing procedure

H. pylori testing was performed using a ^{13}C UBT (Isotope-Selective Infrared Spectroscopy method), which has been shown to have a sensitivity of 91.0% and a specificity of 93.0% in our local population [15,28]. The technique involves the consumption of 75 mg of a ^{13}C urea solution after collection of a baseline breath sample. Breath samples are then collected 10, 20 and 30 min post-administration of ^{13}C urea, and the concentrations of isotope-labeled carbon dioxide ($^{13}CO_2$ and $^{12}CO_2$) analyzed using an IRIS® infra-red isotope analyzer (Wagner Analysen Technik, Bremen, Germany). A delta-over-baseline value (DOB) > 4% indicates HP positivity. Patients also underwent lactulose-hydrogen breath testing to detect SIBO; this component of the study has been reported separately [5].

2.4. Statistical analysis

Data were analyzed using SPSS for Windows Version 20.0. Quantitative data were expressed as means and standard deviations. Chi-square and independent *t*-tests were used to compare differences between groups. The *P* values for the multiple GI and motor outcomes were adjusted using the Benjamini–Hochberg method. Multiple regression analyses were used to examine the effects of HP status on motor function while accounting for potential confounding factors (age, PD duration, and SIBO status). Tests for multicollinearity, normality, and influential data points showed that the assumptions of the regressions were met. Preliminary checks were also conducted to look for any interaction effects between these independent variables; significant interactions were included in the regression model. $P < 0.05$ was the threshold for significance.

3. Results

103 patients fulfilled the inclusion criteria and agreed to participate in this study, however one patient was unable to complete the UBT and was excluded from further analysis. The patients' demographic and clinical characteristics are summarized in Table 1. The mean total LEU (mg/day) was 487.4 ± 370.4 in the ≤60 years group, 522.9 ± 447.5 in the 61–70 group, and 577.3 ± 408.7 in the ≥71 group ($P = 0.724$).

Thirty-three out of the 102 patients (32.4%) were HP positive. Compared with HP-negative patients, HP-positive patients were significantly older (68.4 ± 7.3 vs. 63.8 ± 8.6 years, $P = 0.009$). There were no significant between-group differences in other variables such as gender, smoking status, BMI, PD duration, total LEU, and use of anticholinergic medication. There was a higher prevalence of SIBO among HP-positive patients, but this difference was not significant (36.4% vs. 18.8%, $P = 0.084$). HP infection was more prevalent in patients of non-Malay race (34.3% of Chinese; 28.6% of Indians; 16.7% of Malays); and in those with lower levels of educational attainment (50.0% of primary-educated; 33.3% of secondary-educated; and 23.1% of tertiary-educated patients); however, none of these differences were statistically significant.

Table 1
Demographic and clinical characteristics.

Clinical characteristics	Overall cohort ($n = 102$)	HP positive ($n = 33$)	HP negative ($n = 69$)	*P* value
Age (years)	65.3 ± 8.5	68.4 ± 7.3	63.8 ± 8.6	0.009[a]
Gender (% male)	59.8	60.6	59.4	0.909
Race (%)				0.122
Chinese	65.7	69.7	63.8	
Indian	20.6	18.2	21.7	
Malay	11.8	6.1	14.5	
Others	2.0	6.1	0.0	
Education level (%)				0.238
Tertiary	26.0	18.2	29.0	
Secondary	48.0	48.5	46.4	
Primary	20.0	30.3	14.5	
None	6.0	3.0	7.2	
Smoking status (%)				0.844
Current smoker	1.0	0.0	1.4	
Ex-smoker	20.0	18.2	20.3	
Never-smoker	79.0	78.8	76.8	
BMI (kg/m^2)	23.6 ± 4.3	24.2 ± 5.4	23.4 ± 3.6	0.396
PD duration since diagnosis (years)	7.2 ± 5.3	7.8 ± 6.0	7.0 ± 4.9	0.459
Total LEU (mg/day)	527.6 ± 414.7	510.3 ± 308.6	535.8 ± 458.7	0.772
Use of anticholinergic medication (% yes)	25.5	27.3	24.6	0.775
SIBO status (% positive)	24.5	36.4	18.8	0.084

Abbreviations. BMI = body mass index; LEU = levodopa equivalent units; SIBO = small intestinal bacterial overgrowth.
[a] Denotes statistically significant between-group differences.