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Association of *Helicobacter pylori* with Parkinson's Disease

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Background and Purpose Parkinson's disease (PD) is a major neurological disorder that requires lifelong treatment, and the combined presence of *Helicobacter pylori* (*H. pylori*) infection can increase the required anti-PD medications. We aim to investigate the effect of *H. pylori* infection in Indian PD patients.

Methods We prospectively recruited 36 PD patients from December 2007 to January 2011. All patients underwent a detailed neurological evaluation and serological examination for *H. pylori* infection. Seropositive and seronegative patients were considered to be the cases and controls, respectively. All patients who were seropositive received triple therapy for 2 weeks. Outcome measures of the mean 'off' Unified Parkinson's Disease Rating Scale (UPDRS)-III score, mean 'on' UPDRS-III score, mean onset time, mean 'on' duration, and mean daily 'on' time were measured at baseline and at a 3-week follow-up.

Results *H. pylori*-IgG positivity was present in 18 (50%) PD patients. The prevalence of men (72.2% vs. 33.3%), mean duration of disease (13.8 vs. 12.5) and mean levodopa equivalent daily dose (824 mg vs. 707 mg) were significantly higher among *H. pylori* positive patients than in controls (p<0.0001). Controls had a significantly longer 'on' duration and daily 'on' time, and better 'on' UPDRS-III scores. Seropositive patients took a significantly longer time to turn 'on' after a levodopa challenge. At the 3-week follow-up, *H. pylori* eradication significantly improved the mean 'on' UPDRS-III score, onset time, 'on' duration, and daily 'on' time.

Conclusions *H. pylori* infection was present in 50% of Indian PD patients. *H. pylori* seropositivity was associated with a poor response to levodopa and increased medication usage, while eradication therapy was associated with better patient outcomes.

Key Words Parkinson's disease, *H. pylori* infection, prevalence, triple therapy, Indian patients.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease defined mainly by a progressive loss of dopamine-producing substantia nigra cells, and it produces both motor and non-motor symptoms.[1] The worldwide distribution of PD occurrence is uneven, with a crude prevalence rate of 6–328 per 100,000 population in India.[2,3] The risk of developing PD increases with age, and the mean age at onset is approximately 65 years.[4]

There are various studies suggesting a role of *Helicobacter pylori* (*H. pylori*) infections in the development of PD as well as a worse motor function and requirement for increased levodopa dosage.[1,5] *H. pylori* is a ubiquitous Gram-negative bacterium that infects about half of the world's population and is associated with peptic ulcers.[6,7] The reported prevalence of *H. pylori* seropositivity in India is 50–77%, and its eradication may impact the morbidity experienced by PD patients.[8] However, no supporting data are currently available from the Indian subcontinent. The aim of the present study was to identify the role of *H. pylori* infection in PD in Indian patients and its effect on anti-PD medication.

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METHODS

Study population

We prospectively recruited 36 PD patients over a 3-year period from December 2007 to January 2011 at the department of neurology, Nizam's Institute of Medical Sciences, which is a tertiary-care hospital in South India. The protocol of this study was approved by the Institutional Ethics Committee, and informed consent was obtained from all patients before they entered the study.

Inclusion criteria

The inclusion criteria for PD patients were as follows: PD diagnosed based on United Kingdom Parkinson's Disease Brain Bank Criteria,[9] a Hoehn and Yahr score of 2–4 as determined by a movement-disorder specialist, a disease duration of at least 3 years, currently receiving levodopa therapy, and presence of motor fluctuations and normal cognition (Montreal Cognitive Assessment score of >25).

Exclusion criteria

Patients with secondary parkinsonism, Parkinson-plus syndromes, severe cognitive impairment, psychiatric abnormalities, or dysphagia were excluded, as were those with a history of gastric lesions, gastric surgery, prior intake of anti-*H. pylori* medications anytime during their lifetime, history of antibiotic use during the last 6 months, or use of antacids, H2-receptor antagonists, proton-pump inhibitors, domperidone, prokinetic drugs, or any drug potentially affecting gastrointestinal motility and integrity during the last 2 months.

Data acquisition and assessment

Standardized techniques were adapted for assessing risk factors along with socioeconomic strata.[10] Data were collected using face-to-face interviews and in physical and neurological examinations. The Hoehn and Yahr stage[11] and motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS)-III[12] were used to assess the motor severity of PD. Motor examinations were performed both at the practically defined 'off' state (12 hours without drugs) and 'on' state (best motor response after ingesting at least 1.5 times the levodopa dose being taken daily; a minimum of 200 mg of levodopa). The time from consuming levodopa to the onset of the 'on' time (onset time) was noted. After the levodopa challenge, the duration of the 'on' time ('on' duration) was noted. The individual levodopa daily dosage was noted and was not changed throughout the study period. The total 'on' time over 24 hours (daily 'on' time) was calculated by the patient from home diaries filled on the day prior to the visit, because this method has been generally employed in previous studies of motor fluctuations in PD.[12]

Evaluation of *H. pylori* by serological examination

Serum IgG antibodies to *H. pylori* were assessed using an enzyme-linked immunosorbent assay IgG antibody test in all patients. We used the EUROIMMUN kit (EUROIMMUN Co., Luebeck, Germany) for the diagnosis. Based on the current literature indicating that this cut-off value for the test has a sensitivity of 100% and a specificity of 94%, we considered values of >20 and ≤20 relative units per mL as positive and negative, respectively.

Cases and controls

PD patients were further divided into two groups based on IgG assessments: cases comprised PD patients who were *H. pylori*-IgG positive (*H. pylori* positive), while controls comprised PD patients who were seronegative for *H. pylori*-IgG (*H. pylori* negative).

Outcome measurement

All patients continued receiving their dopaminergic treatment at a constant dosage that was maintained for 3 weeks. *H. pylori* positive patients additionally received triple therapy with amoxycillin (1 mg twice daily), clarithromycin (500 mg twice daily), and omeprazole (20 mg twice daily) for 2 weeks. All patients were followed up at 3 weeks (i.e., 1 week after completing anti-*H. pylori* treatment in the *H. pylori* positive group). UPDRS-III scores in both the 'on' and 'off' states, the onset time, the 'on' duration, and the daily 'on' time were measured in all subjects at baseline and after 3 weeks. A gap of 1 week was allowed for assessing the actual effect of *H. pylori* eradication since antibiotics can modify and occasionally worsen the motor symptoms.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 16.0, SPSS Inc., Chicago, IL, USA). Descriptive statistical values (mean±standard deviation) were calculated for various continuous variables. The Mann-Whitney U test was used to assess the differences in various parameters between the *H. pylori* positive and *H. pylori* negative groups. The Wilcoxon paired rank-sum test was used to compare the effect of anti-*H. pylori* treatment on various parameters in the *H. pylori* positive group. All tests were two sided, and a probability value of $p<0.05$ was considered statistically significant.

RESULTS

The 10.3±36 PD patients included 19 (52.7%) men, and they

were aged 60.0 years, with an age range of 41–75 years. Twenty-one patients (55.5%) were hypertensive, 16 (44.4%) had diabetes, none of them smoked, and 7 (19.4%) consumed alcohol regularly. Two patients had a low socioeconomic status, and the educational status varied. Serological testing revealed *H. pylori*-IgG positivity in 18 (50%) patients.

Baseline (0 week)

We compared the various parameters at baseline between *H. pylori* positive and *H. pylori* negative patients. The prevalence of men was significantly higher among *H. pylori* positive patients than the controls (72.2% vs. 33.3%), as were the mean disease duration (13.8 years vs. 12.5 years) and the mean levodopa equivalent daily dose (824 mg vs. 709 mg). The levodopa challenge test found no significant difference in the mean levodopa dose between the two groups.

UPDRS-III scores in the 'off' state did not differ significantly between the two groups, but the mean UPDRS-III scores in the 'on' state were significantly higher and the onset time was significantly longer among patients with *H. pylori*-IgG positivity, while the 'on' duration and daily 'on' time were significantly longer among *H. pylori* negative patients (Table 1).

Follow-up (3 weeks)

Patients with *H. pylori*-IgG positivity were assessed before treatment at 0 week and after treatment at 3 weeks. There was significant improvement in UPDRS-III 'on' scores, onset time, 'on' duration, and daily 'on' time after the anti-*H. pylori* treatment (Table 2). However, there was no significant difference between the various parameters tested at 0 and 3 weeks in the *H. pylori* negative group (Table 3).

Comparisons of the various parameters between *H. pylori*-IgG positive patients and controls at the end of 3 weeks re-

Table 1. Comparison between *H. pylori* positive and negative in PD patients

Parameters	*H. pylori* positive (*n*=18)	*H. pylori* negative (*n*=18)	*p*
Men (%)	13 (72.2)	6 (33.3)	0.04
Mean age (SD) (in years)	59 (10.3)	61 (9.10)	
Age range (in years)	41–75	43–75	
Hypertension (%)	13 (55.5)	8 (44.4)	0.8
Diabetes (%)	9 (44.4)	7 (38.8)	0.6
Alcoholism (%)	3 (16.6)	4 (27.7)	0.2
Education (%)			
Graduates and higher	12 (66.6)	14 (77.7)	0.7
High school level	4 (22.2)	2 (11.1)	0.6
Below high school	2 (11.1)	2 (11.1)	0.5
Low socioeconomic status (%)	2 (11.1)	0	0.4
Mean PD duration (SD) (in years)	13.8 (5.3)	12.5 (2.5)	0.04
Mean total levodopa dose (SD) in mg	470.4 (207.8)	449.4 (217.5)	0.7
Mean levodopa equivalent daily dose	823.8 (240.6)	708.7 (250.5)	0.04
Mean levodopa dose used in levodopa challenge test	216.7 (37.3)	211.1 (31.4)	0.6
Mean 'off' UPDRS-III (SD) score	54.1 (5.2)	52.3 (11)	0.5
Mean 'on' on UPDRS-III (SD) score	22.3 (6.6)	17.9 (5.2)	0.03
Mean onset time in min (SD)	58.8 (18.4)	36.3 (10.5)	0.01
Mean 'on' duration in min (SD)	104.8 (35.7)	124.1 (16.8)	0.04
Daily 'on' time in min (SD)	461.1 (128.5)	583.6 (89.3)	0.002

H. pylori: *Helicobacter pylori*, PD: Parkinson's disease, SD: standard deviation, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2. Clinical symptoms before and after treatment of *H. pylori* in positive patients

Parameters	Before treatment at 0 week	After treatment at 3 weeks	*p*
Mean 'off' UPDRS-III score (SD)	54.1 (5.2)	49.6 (11.5)	0.3
Mean 'on' UPDRS-III score (SD)	22.3 (6.6)	15.3 (3.8)	0.0001
Mean onset time in min (SD)	58.8 (18.4)	45.6 (9.9)	0.007
Mean 'on' duration in min (SD)	104.8 (35.7)	114.1 (48.9)	0.001
Daily 'on' time in min (SD)	461.1 (128.5)	567.4 (208.9)	0.0001

H. pylori: *Helicobacter pylori*, SD: standard deviation, UPDRS: Unified Parkinson's Disease Rating Scale.

vealed no significant intergroup differences in any of the parameters (UPDRS-III 'off' and 'on' scores, onset time, 'on' duration, and daily 'on' time) (Table 4).

DISCUSSION

This study found *H. pylori*-IgG positivity in 50% of PD patients, which is consistent with other studies finding prevalence rates of 40–60% among PD patients.[1,5,13-16] The prevalence in our population is also similar to that in the general Indian population.[17] Studies from UK and China have shown that the prevalence of *H. pylori* is higher among PD patients, suggesting a causal role.[18,19] Schulz et al.[20] suggested that *H. pylori* infection can contribute to the degeneration of dopaminergic neurons by increasing cholesterol glucosides in a manner similar to cycad toxins.

Duration of disease

Our patients with *H. pylori* infection had a significantly longer disease duration compared to the *H. pylori* negative patients (p=0.04). A study from Malaysia also found that the prevalence of *H. pylori* infection was associated with a longer disease duration.[5] Poor gastric motility, worsening motor function, poor hygiene, and a growth-promoting effect of levodopa may result in PD patients with a longer disease duration being more prone to *H. pylori* infection.[21,22] A bidirectional association of *H. pylori* infection and PD thus seems to exist, resulting in severe morbidity.

Table 3. Comparison of various parameters in *H. pylori* negative group at baseline and 3 weeks without treatment group

Parameters	0 week	3rd week	*p*
Mean 'off' UPDRS-III score	52.3 (11)	53.7 (5.3)	0.27
Mean 'on' UPDRS-III score	17.9 (5.2)	16.7 (7.6)	0.28
Mean onset time in min	46.3 (10.5)	48.4 (7.6)	0.30
Mean 'on' duration in min	124.1 (16.8)	118.4 (34.3)	0.18
Daily 'on' time in min	583.6 (89.3)	560 (128)	0.4

H. pylori: *Helicobacter pylori*, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 4. Comparison of various parameters between *H. pylori* positive and negative groups at 3 weeks follow up

Parameters	*H. pylori* positive	*H. pylori* negative	*p*
Mean 'off' UPDRS-III score (SD)	49.6 (11.5)	53.7 (5.3)	0.1
Mean 'on' UPDRS-III score (SD)	15.3 (3.8)	16.7 (7.6)	0.4
Mean onset time in min (SD)	45.6 (9.9)	48.4 (7.6)	0.3
Mean 'on' duration in min (SD)	114.1 (48.9)	118.4 (34.3)	0.7
Daily 'on' time in min (SD)	567.4 (208.9)	560 (128)	0.8

H. pylori: *Helicobacter pylori*, SD: standard deviation, UPDRS: Unified Parkinson's Disease Rating Scale.

Motor symptoms of PD

Motor symptoms are the most important cause of morbidity among PD patients. UPDRS-III motor scores in the 'off' state did not differ between our *H. pylori* positive and *H. pylori* negative patients, suggesting similar disease severity. However, the response to levodopa in terms of the time to a response, response duration, and overall response to treatment was worse in the *H. pylori* positive group than in the *H. pylori* negative group. These findings are consistent with those of other studies.[16] *H. pylori* infection could affect levodopa absorption via numerous mechanisms.[23] It has been demonstrated that *H. pylori*-related gastritis reduces gastric acid secretion by releasing the proinflammatory cytokine interleukin-1b.[23] Levodopa is soluble in an acidic pH and is impaired by alterations in gastric acid. *H. pylori* also interferes with gastric myoelectric function, leading to gastric immotility and delayed gastric emptying, further reducing levodopa absorption. Other studies have shown that *H. pylori* may use levodopa for its growth. *In vitro* studies have shown that *H. pylori* grows faster in levodopa- and noradrenaline-rich culture media than in media similar to the normal gastric environment. All of these factors may act synergistically to impair intestinal levodopa absorption *in vivo*. Thus, *H. pylori* positive PD patients are prone to a poor levodopa response and fluctuations associated with erratic absorption.[23]

Therapeutic response

H. pylori positive patients were assigned to receive a standard *H. pylori* eradication treatment, after which there was significant improvement in the response to levodopa. *H. pylori* negative patients did not receive any eradication treatment and acted as controls, and they showed a similar response to levodopa when assessed after 3 weeks. Our results are similar to those of previously published studies. In a randomized control trial, Bjarnason et al.[24] found improvement in gait (stride length, torque-to-flex rigidity, and percentage body sway) among PD patients with *H. pylori* eradication compared to placebo. Weller et al.[25] found that eliminating infection in late parkinsonism can significantly improve motor symptoms and cachexia. Randomized control trials performed in different countries have shown improvements in the motor symptoms of PD (especially motor fluctuations) with *H. pylori* eradication.[15,16,26]

These improvements were probably due to improvement in the absorption of levodopa, since the levodopa absorption was found to be increased by 54% after *H. pylori* eradication therapy.[22] We also, found no significant difference between the seropositive and seronegative groups in various disease parameters after 3 weeks. This suggests that *H. pylori* acts

predominantly by impairing levodopa absorption, which is consistent with other findings.[23]

Limitations of study

This study is the first from the Indian subcontinent, and all patients were evaluated by a single movement-disorder specialist and all laboratory tests were performed at a single laboratory. We have shown that *H. pylori* seropositivity is common in Indian PD patients and that treatment definitely improves their outcome. However, the present study was subject to a few limitations. It was based on serological tests for detecting antibodies to a specific microorganism, whose presence would indicate that infection with the microorganism occurred at some point in time. Anti-*H. pylori* antibodies do not always imply the presence of an active infection, and so we may have overtreated our patients. Upper gastrointestinal endoscopy and biopsy as well as rapid urease treatment are suggested for all patients with antibody positivity,[27] but most of the PD patients in our clinic refuse this procedure. The urea breath test is a noninvasive technique, but 13C radioactive ligands are not available in our state and serology still remains the most commonly performed test worldwide.[28]

We applied a combination of amoxycillin, clarithromycin, and omeprazole for 2 weeks to all of the seropositive patients. We were unable to obtain tissue samples for the diagnosis and assessment of antibiotic sensitivity. Worldwide there is an increasing prevalence of resistant strains, although clarithromycin resistance is rare in Indian subjects.[29,30] Our study had an unblinded open-label design, and hence we cannot exclude a placebo effect. A placebo effect associated with an increase in striatal dopamine in anticipation of a reward can partly contribute to and falsely exaggerate the therapeutic effect in PD.[31]

Conclusion

This study found a 50% prevalence of *H. pylori* seropositivity among Indian PD patients and that this population exhibited a worse response to levodopa. The presence of *H. pylori* infection among PD patients may be missed completely due to the symptoms of dyspepsia and gastric irritation occurring as a nonmotor manifestation of PD or being considered a side effect of levodopa. Erratic absorption of levodopa and motor fluctuations in PD patients can significantly worsen their quality of life, reduce productivity, and increase anxiety and depression. Due to the effect that *H. pylori* infection has on levodopa function, it is important to recognize and treat this problem in countries where it is highly prevalent. The implication that *H. pylori* infection may predispose to neurodegeneration and cause PD is still largely unexplored. Large-scale and multicenter studies involving our population may provide an answer in the future.

Conflicts of Interest

The authors have no financial conflicts of interest.

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