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RESEARCH

HELICOBACTER PYLORI INFECTION IS AN AVOIDABLE RISK FACTOR FOR PARKINSON'S DISEASE

Abstract

Introduction: : Gram-negative bacteria such as Helicobacter pylori (HP) are becoming increasingly implicated in the etiology of Parkinson's disease (PD). This study aimed to investigate the association between PD and HP infections.

Materials and Method: Eighty-three patients with PD and age- and sex-matched healthy control subjects with no history of PD were enrolled. Patients with secondary Parkinsonism and severe cognitive impairment were excluded. All patients were staged according to the Hoehn and Yahr scale. We obtained 10 mL venous blood samples from all patients and controls. The plasma was separated, and samples were stored at −200°C. IgG antibodies developing against HP were investigated using the ELISA method. Values >5 IU/ml were considered positive.

Results: Eighty-three patients and 81 controls were included in the study. HP IgG was positive in 87% of the patient group and in 74% of the control group. The median antibody titer in the patient group was higher than that in the control group (p=0.0019). No significant relation was observed between disease severity and IgG positivity (p=0.947). However, a moderate correlation was observed between disease severity and mean IgG level (r=0.277, p=0.011). HP IgG positivity (OR 3.15, 95% CI 1.23–8.07, p=0.002), a family history of PD (OR 2.57, 95% CI 1.02–4.13, p= 0.03), and male gender (OR 2.05, 95% CI 0.95–6.99, p= 0.02) increase the likelihood of PD.

Conclusion: HP infections may trigger various abnormal or enhanced immunological processes in patients diagnosed with PD; these abnormal immunological activities are probably involved in the disease pathogenesis.

Keywords: Parkinson disease, Helicobacter pylori, Disease severity

ARAŞTIRMA

PARKİNSON HASTALIĞI İÇİN ÖNLENEBİLİR BİR RİSK FAKTÖRÜ OLARAK HELİCOBACTER PYLORİ ENFEKSİYONU

Öz

Giriş: Helicobacter pylori (HP) gibi Gram-negatif bakteriler Parkinson Hastalığı'nda (PH) etiyolojik etmen olabilir. Bu çalışmada PH ve HP enfeksiyonu arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Parkinson Hastalığı tanısı olan 83 hasta ve yaş-cinsiyet uyumlu olan sağlıklı kontrol grubu çalışmaya alındı. Sekonder parkinsonizm tanısı olan ve ağır bilişsel etkilenmesi olan hastalar çalışma dışı bırakıldı. Tüm hastalar Hoehn Yahr skalasına göre klinik olarak evrelendirildi. Çalışma grubundan 10 ml venöz kan örnekleri toplandı ve plasma ve serumları ayrılarak, örnekler -200°C\'de muhafaza adildi. HP'ye karşı oluşan IgG'ler ELİSA yöntemiyle bakıldı ve değerin >5 IU/ml\'in üzerinde olması pozitif olarak değerlendirildi.

Bulgular: Çalışmaya 83 hasta grubu ve 81 sağlıklı kontrol grubu dahil edildi. Parkinson hastalığı olan grupta %87, kontrol grubunda %74 oranında HP IgG pozitifliği saptandı. Hasta grubunun ortalama antikor titresi kontrol grubuna göre anlamlı olarak daha yüksekti (p=0.0019). Hastalık şiddeti ve IG pozitifliği arasında korelasyon saptanmadı (p=0.947). Ancak, hastalık şiddeti ile ortalama IgG düzeyleri arasında orta derecede korelasyon saptandı r=0,277, p=0.011). HP IgG pozitifliğinin (OR 3.15, 95% CI 1.23–8.07, p=0.002), ailede PH öyküsü olmasının (OR 2.57, 95% CI 1.02–4.13, p= 0.03) ve erkek cinsiyetin (OR 2.05, 95% CI 0.95–6.99, p= 0.02), PH olma olasılığını anlamlı biçimde artırmış olduğu saptandı.

Sonuç: : HP enfeksiyonu, çeşitli immünolojik yolaklar üzerinden PH 'yı tetikleyebilir ve bu anormal immün reaksiyonlar hastalık patogenezinde olasılıkla rol oynamaktadır.

Anahtar sözcükler: Parkinson hastalığı; Helicobacter pylori; Hastalık şiddeti

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide (1). It was first described by James Parkinson in 1817, although the etiology has remained unclear for the following 200 years. Genetic and numerous environmental factors are involved in the development of the condition, as with similar neurodegenerative diseases (2). Recent research has suggested that infections may be involved in the etiology of PD (3-6). Cytomegalovirus, Epstein Barr virus, Herpes Simplex Type I, Borrellia burgdorferi, Chlamydia pneumoniae, and Helicobacter pylori (HP) are some of the main causative agents (7). HP infections are widespread, infecting as much as 50% of the world population. Factors such as prevalence of HP infections increase with age. Lower socioeconomic status, contact with contaminated water, and living in overcrowded environments increase the prevalence of infections and reduce the age of infection by this agent (1). HP is a gram-negative bacterium that settles in the gastric epithelium. Due to urease production, it is resistant to gastric acid and can thus lead to chronic inflammation. Although it is commonly acquired during childhood, HP can result in chronic infections. Although it causes no clinical problems, it may nevertheless contribute to various gastrointestinal and extra-gastrointestinal diseases (8-11). The aim of this study was to investigate the potential association between PD and HP.

MATERIALS AND METHOD

The research was designed as a multicenter cohort study. All patients and all healthy control subjects provided verbal informed consent to participate in the study. Approval for the research project was granted by the Samsun Training and Research Hospital ethical committee.

1.1.Participants

Eighty-three patients meeting the UK Parkinson's Disease Society's brain bank diagnostic criteria were included in the study. Eighty-one healthy control subjects were matched with the patients in terms of age and sex. We excluded patients with secondary Parkinsonism or severe cognitive impairment, subjects treated with antibiotics for HP within the previous year, and individuals with a history of inflammatory or neoplastic diseases. All patients underwent Hoehn and Yahr scale disease staging. The research was approved by the local ethical committee. Informed written consent was obtained from all patients and healthy controls.

1.2. Procedures

We obtained 10 mL venous blood samples from all members of the patient and control groups. The plasma was separated, and samples were stored at −200°C. IgG antibodies against HP were investigated using the ELISA method (DiaPro, Italy). Values ≥5 IU/ml were considered positive.

2. Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 16.0 for Windows was used for all statistical analyses, and p values <0.05 were considered statistically significant for all results. The chi-square test was used to compare categorical variables, and p values were calculated using Fisher's test where necessary. For data with non-normal distributions, the mean values for two independent groups were compared using the nonparametric Mann–Whitney U-test. Pearson correlation analysis was used to determine the direction and level of correlation between variables, and variables considered to affect one another were subjected to multiple regression analyses. The association between the odds of PD and HP IgG positivity was assessed using a mutually-adjusted multivariate logistic regression model, controlling for potential confounders and providing an odds ratio (OR) and corresponding 95% confidence interval (95%CI).

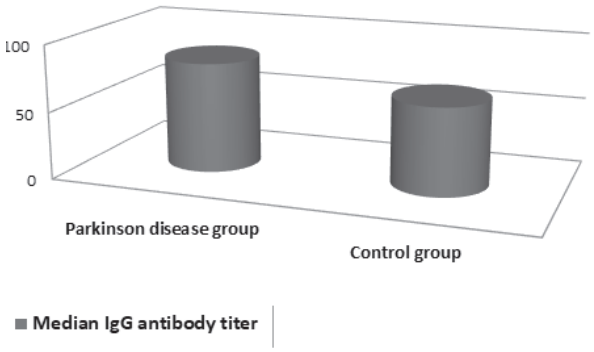
RESULTS

Eighty-three patients (F/M, 34/49) and 81 controls

(F/M, 45/36) were included in this study. The mean age of the patient group was 68.73±8.6 (45–86) years, and the mean age of the control group was 69.26±8.42 (50–87) years. The difference in age between the patient and control groups was not statistically significant (p>0.05). HP IgG was positive in 73 subjects (87%) in the patient group and in 60 (74%) in the control group. This difference between the two groups was statistically significant (p=0.028). The median antibody titer in the patient group was higher than that in the control group. The difference between the patient and control groups was significant (82.17±92.15 IU/ml and 64.84±88.99 IU/ml, respectively) (p=0.019) (Figure 1).

Mean duration of disease in the patient group was 7.7±6.22 (1–30) years. No correlation was determined between duration of disease and mean IgG (r=0.137). The patient group was examined in terms of IgG positivity, based on tremor or bradykinesia onset characteristics. Bradykinesia predominated at onset in 36 of the 73 patients who were positive for HP IgG antibody, while tremor predominated in 37. Onset involved tremor in six of the 10 IgG antibody negative patients, while onset predominantly involved bradykinesia in four. No statistically significant difference was determined between the two groups (p=0.29).

Figure 1. Median IgG titer of both groups.



Familial PD was observed in 15 members of the patient group, but was not present in 68 patients. HP IgG positivity was present in 14 of the 15 patients with familial PD, and IgG positivity was present in 59 of the 68 patients without familial PD. The difference was not statistically significant (p=0.42). HP positive IgG values according to the Hoehn–Yahr scale are presented in Table 1. No significant relationship was observed between disease severity (as indicated by Hoehn–Yahr score) and IgG positivity (p=0.947). However, a moderate correlation was observed between disease severity and mean IgG level (r=0.277, p=0.011). When a mutually-adjusted multivariate logistic regression model was constructed for both groups, HP IgG positivity was determined to increase the likelihood of PD (OR 3.15, 95% CI 1.23–8.07, p=0.002). Additionally, factors such as a family history of PD (OR 2.57, 95%CI 1.02–4.13, p= 0.03) and male sex (OR 2.05, 95%CI 0.95–6.99, p= 0.02) also increased the likelihood of PD.

DISCUSSION

Although the relationship between HP and PD has not yet been completely elucidated, the commonly accepted thesis is that HP has no direct impact on the disease. However, an immune response due to chronic inflammation caused by HP affects the central nervous system, particularly dopaminergic receptors located in the substantia nigra (12-16). Chen et al. observed that injection of IgG obtained from the sera of patients with PD into the substantia nigra in rats resulted in the destruction of cells producing tyrosine hydroxylase (15). In addition, endotoxins of gram-negative bacteria, including HP, may increase the production of inflammatory cytokines, such as TNFα, and stimulable nitric oxide synthase in cultured microglia and astrocytes (13). Inflammatory cytokines, such as ILβ, TNFα, and INF-ϒ, and nitric oxide, derived from microglia and non-neuronal cells may lead to the degeneration of dopaminergic neurons (17-18).

Table 1. IgG positivity rates according to the Hoehn-Yahr scale.

	HP IgG positive above 5		Total
	Negative (%)	Negative (%)	
Only unilateral involvement, usually with minimal or no functional disability (1)	1 (10.0%)	10 (13.7%)	11 (13.3%)
Bilateral or midline involvement without impairment of balance (2)	3 (30.0%)	16 (21.9%)	19 (22.9%)
Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent (3)	4 (40.0%)	24 (32.9%)	28 (33.7%)
Severely disabling disease; still able to walk or stand unassisted (4)	2 (20.0%)	21 (28.8%)	23 (27.7%)
Dependent on bed or wheelchair unless aided (5)	0 (0.0%)	2 (2.7%)	2 (2.4%)
Total	10 (100.0%)	73 (100.0%)	83 (100.0%)

The blood and/or cerebrospinal fluid of PD patients has been observed to contain antibodies against sympathetic and dopaminergic neurons. Systemic inflammation occurring because of the development of antibodies may accelerate neurodegeneration, and treating infections may help improve patients' clinical conditions (12-20). Chronic HP infections can disrupt the blood–brain barrier and result in microglial activation, and increase the incidences of neuronal destruction and mortality (16). In the light of this information, we examined the relationship between the presence of HP antibodies and IgG titer and PD. The level of HP IgG antibodies was higher in the patient group than in the healthy control group. The mean IgG titer was significantly higher among patients with PD. Previous studies have reported lower rates of HP positivity, whereas the values obtained in our study were considerably higher (5,21). We also determined higher levels of HP antibody elevation in our control group. The variation among studies in terms of HP IgG antibody positivity may be attributed to factors that may vary between countries, including lifestyle differences, eating habits, and genetic disposition. One meta-analysis published in 2017 reported an OR of 1.59 for patients with PD and HP. Subgroup analysis revealed a higher OR in Asia than in Europe (1.99 and 1.55, respectively) (22). In another meta-analysis, HP infection was identified as a risk factor in terms of PD, and a decrease in UPDRS scores, indicating severity of PD, was achieved with HP eradication (23). In our study, when all potential confounding factors were added together, HP increased the risk of PD 3.15-fold. The risk also increased in males, and among subjects with a family member with PD.

HP infection has long been known to cause gastrointestinal diseases such as chronic gastritis and peptic ulcer. However, studies in recent years have also shown that it may also predispose to neurological diseases such as cerebrovascular disease, multiple sclerosis, and Alzheimer's (24,25,26). The eradication of HP infection, also regarded as a societal problem, may be beneficial

Table 2. Impact of some factors in parkinson's disease

	Odds Ratio (OR)	P
HP IgG positive	3.15	0.017
Age	1.01	0.644
Male gender	2.05	0.043
Family history of PD	2.57	0.04
Total	835	100.0

in reducing the development of severity of neurological disease that frequently also entails socioeconomic burdens.

HP infections may trigger various abnormal or enhanced immunological processes in patients diagnosed with PD, and these abnormal immunological activities are probably involved in the pathogenesis of the disease. This association has been described as significant in previous studies. However, two questions remain unanswered. The first concerns the identity of the underlying pathophysiological mechanism. Secondly, it is unclear whether infection accelerates the disease process or initiates it. If this association is scientifically proven among patients with HP, antibiotic treatment may reduce the prevalence of PD or decelerate the progression of existing PD.

CONCLUSION

This study investigated the association between the presence of IgG as a serological indicator of HP infection and PD. However, the processes underlying this association were not investigated and our findings suggest a significant association. However, we were unable to conclude that HP infection represents a risk factor for PD. Further, more detailed studies with longer follow-up periods in which the processes involved in PD, HP infection, and immunological changes are closely monitored are required to confirm this association.

CONFLICTS OF INTEREST:

None.

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