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TREATMENT OF HELICOBACTER PYLORI INFECTION AND RISK OF PARKINSON'S DISEASE IN DENMARK

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Abstract

Objective—It has been speculated that gastrointestinal infection with *Helicobacter pylori* (HP) contributes to development of Parkinson's disease (PD). We used nationwide Danish registers to investigate this hypothesis.

Research Design and Methods—We identified 4,484 patients with a first time PD diagnosis between 2001–2008 from the Danish National Patient Register (DNPR) and 22,416 population controls from the Danish Civil Registration System (CRS). Information on drug use was obtained from the National Prescription Registry (NPR). We used logistic regression to compute odds ratios (OR) for the association between treatment for HP and risk of PD.

Results—Prescriptions for HP eradication drugs and proton pump inhibitors (PPI) five or more years prior to the diagnosis of PD were associated with a 45% and 23% increase in PD risk, respectively. Hospitalizations and outpatient visits for gastritis and peptic/duodenal ulcers, however, were not associated with PD.

Conclusions—Our population-based study suggests that chronic HP infections and/or gastritis contribute to PD or that these are PD related pathologies that precede motor symptoms.

Keywords

Helicobacter pylori; Parkinson

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by a progressive loss of dopamine-producing substantia nigra cells, which leads to a broad spectrum of motor and non-motor features including tremor, muscle rigidity, slowing of physical movement, and autonomic impairment including gastrointestinal dysfunction, which may precede the motor symptoms [1]

Helicobacter pylori (HP) plays a causal role in a variety of human diseases including chronic gastritis, peptic ulcer disease, and gastric cancer [2]. Gastric ulcers have been associated with PD since the 1960s [3, 4]. HP has been suggested to play a role in the development of

parkinsonism, as both diseases share certain characteristics, such as familial aggregation and association with water sources [5, 6]. A small case-control study reported a five-fold higher level of HP-antibodies in patients older than 80 years with parkinsonian features [7]. In another study, PD patients were three times more likely to be test-positive for HP serology than controls, and the patients' siblings were also more likely to be both seropositive and show signs of parkinsonism [8]. Finally, eradication of HP-infections has been shown to ameliorate symptoms of PD [9].

In both human and animal models of PD, neuroinflammation appears to be contributing to neurodegeneration with activation of microglia as the CNS resident immune cells [10]. Among PD patients, microglia might respond to a proinflammatory stimulus and release neurotoxic substances, which contribute to neurodegeneration [11]. Peripheral inflammation, such as HP infection[12], can trigger microglia activation through the humeral pathway when circulating proinflammatory or leukocytes cross a disrupted blood-brain barrier [13, 14] or noxious chemical produced by HP can be transmitted through vagal afferent pathways and affects neurons in the brainstem as indicated by animal studies [15]. Alternatively, auto-antibodies against dopaminergic neurons found in the cerebrospinal fluid and/or blood PD patients [16] may represent molecular mimicry from an HP infection [17].

In the present study, we linked unique databases, i.e., the Danish National Patient Register (DNPR) and the National Prescription Registry (NPR) – as part of a large population-based case control study. We explored whether HP-eradication treatment is more or less common in PD patients prior to the diagnosis of PD compared with population controls. We also investigated associations between medical treatment for peptic ulcers and gastritis and hospitalizations and clinic visits for PD.

SUBJECTS AND METHODS

Study Population

Denmark's National Health Service provides free and equal access to healthcare for the entire population[18]. Health service related events are recorded in various national databases, including the DNPR and the NPR. Information from both registries can be linked to each other by use of the unique 10-digit number assigned to all residents in Denmark since 1968 by the Danish Civil Registration System (CRS)[19].

Using the DNPR, PD cases were ascertained from all hospitalizations for PD since 1977 and all clinic visits - including out-patient clinics - since 1995[20].

We identified 17,213 PD cases in the DNPR in the period 1986–2008 who (1) had a valid CRS number; (2) were over 35 years of age at the time of diagnosis; and (3) had not emigrated from Denmark. Information on date of death or emigration was obtained from the CRS[19]. In order to allow for a sufficient latency period between HP related diseases and PD, only cases that were registered with a primary diagnosis of PD (*International Classification of Diseases (ICD), 10th revision*, code G20) between January 2001 and December 2008 were included in our analyses. Furthermore, to more accurately define the "earliest date of a PD diagnosis", we backdated the primary PD diagnoses to the first prescription of PD drugs (Anatomical Therapeutic Chemical (ATC) code N04B)[21] since the establishment of the NPR in 1995[22], if the drug use preceded the PD diagnosis. PD cases whose backdated diagnosis date was *prior* to 2001 were excluded. We further excluded PD patients who had never received a PD drug prescription.

We then individually matched five randomly selected controls from the CRS by sex and year of birth to each case, using incidence density sampling[23]. The date of PD diagnosis

served as the index date for control selection. This yielded a final study population of 4,484 PD cases and 22,416 controls. Finally, we obtained a full hospital history from 1977 for all cases and controls, and computed the Charlson comorbidity score (CCS), with a lag-time of five years prior to index date as an indicator of baseline morbidity. The CCS is a weighted index, which has been adapted for use with ICD-10 administrative data, takes into account both the number and the seriousness of comorbid diseases[24]. The index is based on 19 chronic conditions, each with an assigned weight from 1–6 according to the relative risk of dying within one year. We divided the CCS into 3 groups: CCS 0 =no comorbidity; CCS 1 = low comorbidity, and CCS 2 = high comorbidity.

The study protocol was approved by the Danish Data Protection Agency (No 2002-41-2112) and the UCLA human subject review board.

Assessment of HP-related diagnoses and HP eradication drug use

Information on diagnoses of HP-related diagnoses prior to the index date was extracted from the DNPR, including peptic ulcers (ICD8 codes: 531–534; ICD-10 codes: K25-K28) and gastritis (ICD-8 code: 535; ICD-10 code: K29).

The NPR holds data on all dispensed prescriptions from pharmacies in Denmark, including type and quantity of drugs prescribed according to the ATC classification system[21], date of dispensing at the pharmacy, and the patient's CRS number[22]. Prescription data for HP eradication and gastritis drugs for all study subjects prior to the index date were extracted, including proton pump inhibitors (PPI) (ATC, A02BC), amoxicilin (J01CA04), clarithromycin (J01FA09), amoxicilin + clarithromycin (J01CR02) and metronidazol (P01AB01). We defined HP eradication treatment as one of the following combinations prescribed in the same month: 1) PPI plus amoxicilin and clarithromycin, or 2) PPI plus metronidazol and clarithromycin, as defined by the Danish Society for Gastroenterology Guidelines. PPI prescriptions were defined as any filling of one or more prescriptions during the relevant period prior to the index date; non-users were defined as study subjects without any prescriptions for HP treatment combinations or PPI alone.

Statistical Analysis

We used unconditional logistic regression analysis to calculate odds ratios and 95% confidence intervals for the association between peptic ulcers and gastritis diagnoses and treatment and risk of PD, with adjustment for age (continuous), sex, and chronic obstructive pulmonary disease (COPD) (ICD-8 codes: 490.00, 491.00, 491.01, 491.03; ICD-10 code: J44), as a proxy for heavy smoking. Co-morbidities registered before the index date, classified as CCS[24].

To further preclude the possibility of having included prevalent PD cases, for our primary analyses, we advanced (lagged) the index date for HP-eradication drug prescriptions or diagnosis of HP-related diagnoses (using ICD-codes) by 5 years; i.e., we excluded all first HP-eradication treatments and HP-related diagnoses within a 5 year period prior to the index date. In addition, we performed non-lagged analyses of PD. We lagged COPD by 5 years to capture the general health status of subjects prior to the index date. In secondary analyses, we stratified by age at first diagnosis (< 60, >60 years) and sex. Furthermore, we conducted sensitivity analyses excluding cases (and their corresponding controls) and controls who had been prescribed non-steroid anti-inflammatory drugs (NSAID), defined as prescriptions for aspirin (ATC: B01AC06, N02BA01, N02BA51) or non-aspirin NSAID (M01A) within one month of the HP or gastritis treatment to circumvent the influence of acute upper gastro-intestinal irritation due to these drugs.

In additional sensitivity analyses aimed at reducing PD misclassification, we excluded cases (and their matched controls) and all controls diagnosed with dementia (ICD-8 codes: 29009–29011, 29018–29019, 29309; ICD-10 codes: F00.X, F03, G30) or cerebrovascular disease (ICD-8 codes: 430–438; ICD-10 codes: I60–I69, G45–G46) two years prior to PD diagnosis of the index case. We further excluded cases (and their matched controls) and all controls with neuroleptics (ATC code N05AA, N05AB, N05AC, N05AD, N05AF, and N05AG) use in the six months preceding PD diagnosis.

Results

Both cases and their controls were on average 70.8 years of age (SD=10.6) at the index date. We identified more males than females with a diagnosis of PD. Five years prior to the index date, cases had a slightly higher CCS, but less COPD than controls (Table 1).

Between 1995 and the index date, 2.4 % (643) of our study population (138 cases, 505 controls) had ever received a prescription for any HP eradication treatments as defined above. Relying on HP-eradication treatments to identify participants with HP infection, we observed moderate size associations with PD (OR=1.46, 95% CI, 1.21– 1.77), which remained almost unaltered when we only assessed those prescribed HP-eradication treatments five or more years prior to PD risk (Table 2). An increased risk of PD was also observed among those who were prescribed PPI alone, for both the 0-year lag (OR=1.26, 95% CI 1.16–1.36) and the 5-year lag (OR=1.23, 95% CI 1.11–1.37) prior to PD.

Stratification by sex and age and taking into account prescriptions for aspirin and non-aspirin NSAIDs within a month of the HP or PPI treatments did not alter the risk estimates. The sensitivity analyses excluding dementia, cerebrovascular diseases and neuroleptic use only changed the risk estimates minimally (data not shown).

In further analyses of HP-related and gastritis diagnoses, we estimated a 22% increase in the risk of developing PD (OR=1.22, 95% CI, 1.04 – 1.43) among those with gastritis, but not with an ulcer diagnosis. Finally, lagging by five years prior to PD diagnosis changed all associations toward unity (Table 3).

Discussion

In our population-based case-control study, we found that use of HP eradication and gastritis drugs five years and more prior to PD were both positively associated with risk of PD, but we did not find any associations between gastritis or peptic ulcers and PD risk. These observations support previous reports that found a higher risk of PD among patients with HP positive serology compared with healthy controls [8].

HP-infection is the most widespread gastrointestinal infection in the world and depends on age and socio-economic status. In Denmark 20 % of the population is colonized with HP [25] and these infections may be more frequent among elderly individuals. Colonization with HP may be asymptomatic, but often leads to gastritis with symptoms of upper abdominal pain and discomfort and peptic ulcers with as many as 75% found to be infected [26]. While HP-infection have also been associated with gastric cancer, and primary B-cell mucosa-associated lymphoid tissue lymphoma of the stomach [2], the high mortality rate of patients with these cancers precludes studies of PD.

In our study we did not detect an increased PD risk following gastritis or peptic ulcer diagnoses, whereas we observed positive associations between use of HP-eradication drugs and gastritis treatment with PPI and risk of PD. While we cannot exclude that some antibiotics may have been prescribed for non-HP infections, we believe that the specific

combination of these antibiotics and PPI prescribed in the same month is a valid measure for HP-infection. The discrepancy in the number of patients diagnosed in the DNPR versus treatment according to the NPR reflects the fact that only a fraction of upper gastro-intestinal disease is diagnosed during a hospital admission or visit. The majority of patients with symptoms of upper gastro-intestinal disease are likely to be diagnosed and treated by general practitioners or private sector specialists. Thus, information on drug use by the appropriate ATC codes is a more reliable indicator of these disorders.

Adjustment for use of aspirin and non-aspirin-NSAID did not alter the risk estimates for treatment or gastritis history. Since some NSAID, unlike the vast majority of PPI, are over-the-counter drugs and therefore not registered in the prescription database, we have some misclassification of NSAID use in our analyses. However, it is unlikely that NSAID-induced HP-negative cases of gastritis would be given HP-eradication treatment. NSAID use is potentially inversely associated with PD [27, 28] and is strongly associated with dyspepsia, gastritis and stomach and stomach and duodenal ulcers [29]. We were unable to fully control for smoking, although our adjustment for COPD, as a proxy for smoking, may at least have partly controlled for heavy smoking. Given the negative association of smoking and NSAID use with PD, this would have resulted in an attenuation of risk estimates, however, the adjustment for COPD did not change the risk estimates markedly.

A recent study reported that the incidence of gastrointestinal disorders, including gastritis and peptic ulcers, among PD patients was as high as 65 % and interpreted this to be associated with the adverse effects on PD-related outcomes, such as neurological symptoms, movement and urinary disorders, as well as higher rates of visits to the emergency rooms [30].

Several studies have suggested that inflammation plays an important role in the pathogenesis of PD [12, 31], through the release of proinflammatory cytokines and neurotoxic substances [32]. A similar hypothesis has been suggested in autoimmune diseases, such as rheumatoid arthritis [33] and systemic lupus erythematosus [34]. However, in a prior publication based on the same Danish data set, no association was observed between autoimmune diseases and PD [35].

Strengths of our study are the sampling strategy, with controls selected at random from the general population, and no non-participation and recall bias of disease history and drug due to the register approach using complete data from nationwide registers. We required that all PD cases had been admitted to hospital or visited an out-patient clinic at least once with a primary diagnosis of PD and whenever possible, we backdated the PD to the likely earliest diagnosis, using information on prescription for PD drugs. Limitations include some disease misclassification since primary PD diagnoses were identified from hospital records that may have included some cases of non-idiopathic Parkinsonism, and the possibility that the PD cases identified at the hospital setting were different in the exposure profile than PD patients diagnosed and treated in the primary health sector alone. Sensitivity analyses for dementia, cerebrovascular diseases and neuroleptics use suggested this bias to be minimal. We might have selected less healthy PD cases more likely to be hospitalized than Danish PD patients seen exclusively by private practitioners, without ever attending a specialty clinic before 2009. However, this method of identifying PD patients likely increased our diagnostic validity for idiopathic PD, since more erroneous diagnoses are made during the early disease stages. The slightly higher CCS and greater number of CVD drug prescriptions among our PD patients compared to controls 2 years prior to and at the index date (data not shown) supports, albeit only modestly, the possibility for a selection of less healthy PD patients. However, differences in general health status were not evident 5 years prior to PD diagnosis/index date. The universal coverage of most health care expenses in Denmark, including

partial reimbursement of costs for prescribed drugs, makes it less likely that anti-HP drug prescriptions or PD diagnoses were influenced by factors determining access to care. However, we may have missed HP cases that never received HP-eradication treatment.

Increased gastro-intestinal dysfunction is acknowledged in PD patients and may even precede the PD diagnosis by many years [36]. The symptoms may vary from early dyspepsia, upper abdominal pain, a sense of abdominal bloating, nausea, weight loss and constipation due to abnormalities in the autonomic and enteric nervous systems associated with PD [3, 4, 37]. It is therefore possible that the gastroparesis and delayed transit time in PD may lead to small-intestinal bacterial overgrowth, as this has been observed in other conditions associated with gastroparesis [38] thereby leading to more frequent HP-colonization as a complication of the disease rather than an aetiological risk factor.

It is also possible that abdominal symptoms of preclinical PD may lead to increased hospitalization and clinic visits thereby increasing the risk of being diagnosed with HP or receiving HP-eradication treatment. While we were not able to adjust for the use of HP-diagnostic tests in the two populations, it should be noted that the CCS did not indicate significant differences in the comorbidity of PD patients and controls five years prior to PD diagnosis.

In conclusion, the results from our study suggest that HP-infections may increase the risk of PD. Whether this association is the result of a chronic infection leading to aggravated inflammatory pathophysiological insults or merely related to the disease due to degeneration of the autonomous and enteric nervous systems remains to be determined.

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Table 1

Demographic characteristics of study population, 2001–2008

	Parkinson's Disease Cases (n=4,484)	Population Controls (n=22,416)
Age, mean (std)	70.8 (10.6)	70.8 (10.6)
Sex (n, %)		
Female	9,038 (40.3)	1,808 (40.3)
Male	13,378 (59.7)	2,676 (59.7)
Age Group (n, %)		
30–40	28 (0.6)	140 (0.6)
41–50	181 (4.0)	905 (4.0)
51–60	549 (12.2)	2,743 (12.2)
61–70	1,236 (27.6)	6,180 (27.6)
71–80	1,651 (36.8)	8,254 (36.8)
81–90	803 (17.9)	4,014 (17.9)
>90	36 (0.8)	180 (0.8)
Charlson comorbidity score (n, %)^I		
0	3,365 (75.0)	16,839 (75.3)
1	567 (12.7)	2,915 (13.0)
COPD (n, %)^I		
No	4,415 (98.5)	21,954 (97.9)
Yes	69 (1.5)	462 (2.1)

^I 5 years prior to the index date or date of PD diagnosis

Table 2

Odds Ratio (and 95% CI) for having received helicobacter pylori eradication treatment¹ (zero and 5-year or more prior to having received a Parkinson's disease diagnosis

	Parkinson's Disease cases N	Population controls N	Odds Ratio (95 % CI) ²
HP eradication treatment			
<i>0-year lag</i>			
No	3,351	17,689	1.0
Yes	138	505	1.46 (1.21 – 1.77)
<i>5-year lag</i>			
No	3945	20193	1.0
Yes	64	227	1.45 (1.10 – 1.92)
Proton inhibitor only treatment			
<i>0-year lag</i>			
No	3,351	17,689	1.0
Yes	995	4,222	1.26 (1.16 – 1.36)
<i>5-year lag</i>			
No	3945	20193	1.0
Yes	475	1,996	1.23 (1.11 – 1.37)

¹ HP eradication treatment defined as: 1) Proton inhibitor plus amoxicillin and clarithromycin; or 2) Proton inhibitor plus metronidazol and clarithromycin for each combination the medication is prescribed within a one month window.

² adjusted for age and sex, and COPD (5-year lagged)

Table 3

Odds Ratio (and 95% CI) for having been hospitalized with an ulcer and/or gastritis zero and 5 or more years prior to Parkinson's disease diagnosis

	Parkinson's Disease Cases N	Population Controls N	Odds Ratio (95 % CI) ⁴
Ulcer and/or Gastritis diagnosis¹			
<i>0-year lag</i>			
No	4,108	20,682	1.0
Yes	376	1,734	1.10 (0.98 –1.24)
<i>5-year lag</i>			
No	4,257	21,268	1.0
Yes	227	1,148	1.0 (0.86 –1.15)
Ulcer diagnosis only²			
<i>0-year lag</i>			
No	4,108	20,682	1.0
Yes	232	1,141	1.04 (0.90 –1.20)
<i>5-year lag</i>			
No	4,257	21,268	1.0
Yes	138	755	0.92 (0.77 –1.11)
Gastritis diagnosis³			
<i>0-year lag</i>			
No	4,108	20,682	1.0
Yes	196	817	1.22 (1.04–1.43)
<i>5-year lag</i>			
No	4,257	21,268	1.0
Yes	117	535	1.10 (0.90–1.35)

¹ICD-8: 531-35 and/or ICD-10 K25-29

²ICD-8: 531, 532, 533, 534 and/or ICD-10: K25, K26, K27, K28

³ICD-8: 535 and/or ICD-10: K29

⁴adjusted for age and sex, and COPD (5-year lagged)