Parkinsonism and Related Disorders xxx (2014) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Risk of Parkinson's disease following severe constipation: A nationwide population-based cohort study

Chin-Hsien Lin [a], Jou-Wei Lin [b, c], Ying-Chun Liu [d], Chia-Hsuin Chang [b, d, *], Ruey-Meei Wu [a, **]

[a] Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
[b] Department of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Cardiovascular Center, National Taiwan University Hospital Yun-Lin Branch, Dou-Liou City, Yun-Lin County, Taiwan
[d] Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 18 July 2014
Received in revised form
20 September 2014
Accepted 22 September 2014

Keywords:
Constipation
Parkinson's disease
Population study
Non-motor symptoms
Pre-motor symptoms

ABSTRACT

Introduction: Constipation is a non-motor symptom of Parkinson's disease (PD). We investigated the association between the severity of constipation and subsequent risk of PD in a population-based sample.

Methods: 551,324 participants free of PD, dementia, and stroke were retrospectively ascertained between January 1, 2005 and December 31, 2005 using the Taiwan National Health Insurance Research Database. The association between constipation at the beginning of the study and the incidence of PD was examined using a Cox regression model. Information regarding comorbidities and concomitant medications use was adjusted in the proportional hazards models.

Results: After an average follow-up of 5.5 years, 2336 incident PD cases were diagnosed. The crude incidence rate of PD per 1,000,000 person-days was 1.57 for subjects without constipation and 4.04, 5.28, and 12.67 for mild, moderate, and severe constipation, respectively. After adjusting for age, sex, comorbidities, and concomitant medication use, patients with constipation were more likely to develop PD than subjects without constipation; the adjusted hazard ratio (aHR) was 3.28 (95% CI: 2.14–5.03), 3.83 (2.51–5.84), and 4.22 (2.95–6.05) for individual constipation severity categories. Constipation severity was also associated with an increased likelihood of PD in the time-varying analysis; the aHR was 2.84 (2.43–3.33), 5.22 (4.61–5.92), and 10.47 (9.46–11.58) for mild, moderate, and severe constipation, respectively ($P < 0.0001$). After excluding PD patients diagnosed within 3 years of constipation, the association remained significant.

Conclusions: Our study suggests that the severity of constipation is associated with a future diagnosis of PD in a dose-dependent manner.

1. Introduction

Parkinson's disease (PD) is a multi-centric neurodegeneration process with both motor and non-motor symptoms, which correlate with advancing age and disease severity [1]. Some non-motor symptoms, such as depression, constipation, olfactory problems, and rapid eye movement sleep behavior disorder, can occur early in the disease process and may precede motor symptoms by up to 20 years [2]. Research into these non-motor symptoms during PD development may advance our understanding of the pathophysiology of PD and lead to earlier diagnosis and improved management.

Constipation is one of the most common non-motor symptoms of PD [3–5]. PD-related constipation may come from Lewy body deposition in the enteric nervous system or the dorsal motor nucleus of the vagus nerve, which are among the earliest affected regions in PD [6]. Increasing numbers of studies have evaluated the temporal relationship between the frequency of bowel movements and the future risk of PD. In the male Honolulu–Asia Aging cohort study with a 24-year follow-up period, infrequent bowel

* Corresponding author. Department of Medicine, College of Medicine, National Taiwan University, Taipei 100, Taiwan. Tel.: +886 972651770.
** Corresponding author. Tel.: +88623123456x65337; fax: +88623418395.
E-mail addresses: chiahsuin123@yahoo.com.tw (C.-H. Chang), robinwu@ntu.edu.tw (R.-M. Wu).

http://dx.doi.org/10.1016/j.parkreldis.2014.09.026
1353-8020/

movements, as assessed by self-report bowel habit questionnaire, were associated with an increased risk of PD and with a reduced neuronal density in the substantia nigra [3,7]. A subsequent case–control study reported a greater risk of PD among individuals with a history of constipation, as assessed through review of medical records, as early as 20 years before the onset of motor symptoms [4]. Another cohort study using the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS) reported similar findings, but the association was not significant beyond 6 years follow-up in the NHS cohort [5]. Given that these studies have suggested that constipation may be an early, premotor symptom of PD, using a population-based study, we set out to explore further the hypothesis that the severity of constipation preceding motor symptoms of PD is associated with future disease risk.

2. Methods

2.1. Data source and study population

A single-payer and compulsory National Health Insurance program was implemented in Taiwan in 1995 and enrollment was 99% by 2010. The Taiwan National Health Insurance (NHI) database includes complete outpatient visits, hospital admissions, prescriptions, disease and vital status for 99% of the country's population (approximately 23 million). The current analyses linked several large computerized claims datasets with the National Death Registry through the use of birth dates and civil identification numbers unique to each beneficiary. From the source population, we conducted a retrospective cohort study of patients aged 20 years and older between January 1, 2005 and December 31, 2005. Patients aged more than 100, lack of continuous insurance coverage in 2004, and prior history of colorectal cancer diagnosed in 2003–2005 were excluded. We also excluded patients with prior diagnosis of PD, psychiatric or bipolar disorder (to exclude those with future risk of drug-induced parkinsonism) or cerebrovascular diseases (to exclude those with future risk of vascular parkinsonism) 2 years before entering the study. The constipation status was determined between January 1 and December 31, 2004, one year before including participants in the study. Patients were followed between January 1, 2005 (study commencement), to the earliest occurrence of the outcome (diagnosis of PD), last hospital discharge date, date of the last outpatient visit, or December 31, 2010 (Supplementary Fig. 1). The protocol was approved by the National Taiwan University Hospital (NTUH) Research Ethics Committee.

2.2. Ascertainment of constipation

Because participants' symptoms were not recorded in the claims database, we defined participants with constipation by the presence of the following criteria: 1) a diagnoses of constipation, 2) ever used laxative drugs to treat constipation (anatomical therapeutic chemical [ATC] classification system code A06A) between January 1 and December 31, 2004. Only occurrences of constipation documented in the claims database before the beginning of the study were accepted as exposure.

To assess the severity of constipation, we collected additional information on prescribed drug types, dates of prescriptions, supply days, and total number of tablets as derived from the outpatient pharmacy prescription database. Subjects with constipation were classified as mild (less than three prescriptions for laxatives within 1 year), moderate (equal to or more than 3 but less than 12 prescriptions for laxatives within 1 year), or severe (equal to or more than 12 prescriptions for laxatives within 1 year) based on the tertiles of the total number of laxative prescriptions in 2004.

2.3. Ascertainment of PD

The outcome of interest was defined as having any hospital discharge diagnosis or any outpatient diagnosis by neurologists of PD (ICD-9-CM code 332). A previous validation study using a hospital administrative database reported a positive predictive value of more than 90% when using this definition [8]. To evaluate the accuracy of the PD diagnostic criteria in our study, a validation study performed at the National Taiwan University Hospital, a tertiary referral center, found that the criteria specificity was 94.8% [9].

2.4. Covariates and adjustments

We used inpatient and outpatient diagnosis and prescription files during the 12-month period before cohort entry to ascertain patient histories of medical comorbidities (See Supplementary Table 1 for ICD-9-CM codes) and use of medications (See Supplementary Table 1 for ATC codes). Smoking history was unavailable, so we used a diagnosis of chronic obstructive pulmonary disease as a proxy for heavy smoking.

2.5. Statistical analysis

Baseline characteristics are presented in Table 1. For study participants with different severities of constipation, we estimated the crude incidence rates and 95% confidence intervals (CIs) for PD on a Poisson distribution in each category.

Due to the relatively few number of PD cases compared to the number of covariates reflecting participants' baseline characteristics, we included disease risk score deciles as summary measures of these covariates in the regression model to adjust for baseline imbalance. Using a logistic regression model, we estimated individual PD risk scores using age, sex, underlying disease, concomitant medication use and numbers of medical resource use (outpatient visits and hospitalizations). We examined the association between constipation and PD by comparing the occurrence of PD across different constipation severity subgroups to the occurrence among subjects without constipation (i.e., no constipation diagnosis and no use of laxatives). We hypothesized that participants with more severe constipation and a higher cumulative use of laxative medications would have a greater risk for PD than those who did not use laxatives. In the main analysis, a Cox regression model with indicators for baseline constipation drug use was used to calculate hazard ratios (HRs). We also calculated each participant's cumulative number of prescriptions for these drugs during the follow-up period and treated them as time-dependent

Table 1
Baseline characteristics of study participants with and without diagnosis of PD in our study.

	Without PD $N = 548,988$	With PD $N = 2336$	P value
Patient characteristics			
Mean age, years (SD)	43.38 (15.67)	69.32 (10.97)	<0.001
Male, %	47.27	49.91	0.01
Comorbidity, %			
Diabetes mellitus	5.58	21.83	<0.001
Hypertension	10.68	38.48	<0.001
Ischemic heart disease	3.07	17.04	<0.001
Atrial fibrillation	0.27	1.24	<0.001
Peripheral arterial occlusion disease	0.40	1.84	<0.001
Chronic liver disease	4.42	9.50	<0.001
Chronic lung disease	5.18	15.41	<0.001
Chronic kidney disease	1.70	6.81	<0.001
Rheumatoid arthritis	1.52	3.04	<0.001
Osteoarthritis	6.45	24.87	<0.001
Cancer	1.29	3.34	<0.001
Seizure	0.33	0.47	0.22
Depressive disorder	1.62	4.71	<0.001
Anxiety	4.94	14.30	<0.001
Medication use, %			
Non-selective NSAIDs	69.90	73.72	<0.001
COX-2 selective NSAIDs	2.56	13.70	<0.001
ACE inhibitors	4.45	17.47	<0.001
Angiotensin receptor blockers	3.15	12.50	<0.001
Beta-blockers	9.91	30.44	<0.001
Calcium channel blockers	9.27	38.27	<0.001
Diuretics	5.86	22.99	<0.001
Insulin	0.34	1.54	<0.001
Sulfonylurea	4.05	16.44	<0.001
Metformin	3.50	14.47	<0.001
Thiazolidinediones	0.83	4.07	<0.001
Vitamin K antagonists	0.20	0.47	0.005
Non-aspirin anti-platelet agents	6.67	28.98	<0.001
Aspirin	8.35	25.77	<0.001
Histamine-2 receptor antagonists	18.65	23.84	<0.001
Proton pump inhibitors	2.01	5.14	<0.001
Nitrates	2.16	11.69	<0.001
Statins	3.32	11.99	<0.001
Fibrates	1.75	4.97	<0.001
Estrogen	3.66	2.95	0.07
Antidepressants	3.34	10.62	<0.001
Anti-epileptics	2.02	6.64	<0.001
Thyroid therapy	1.07	1.28	0.33
Resource utilization, mean (SD)			
Total number of outpatient visits	10.96 (11.99)	24.37 (19.44)	<0.001
Total number of outpatient visits due to cardiovascular-related disease	1.16 (3.55)	5.21 (6.57)	<0.001
Total number of hospitalizations	1.02 (0.26)	1.08 (0.52)	<0.001
Total number of hospitalizations due to cardiovascular-related disease	0.02 (0.17)	0.10 (0.43)	<0.001

SD: standard deviation.

Please cite this article in press as: Lin C-H, et al., Risk of Parkinson's disease following severe constipation: A nationwide population-based cohort study, Parkinsonism and Related Disorders (2014), http://dx.doi.org/10.1016/j.parkreldis.2014.09.026