Colonic diverticular disease: A new risk factor for Parkinson's disease?

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ABSTRACT

Background: Colonic diverticular disease is a chronic gastrointestinal disorder. Previous studies have suggested that chronic gastrointestinal tract is involved in the pathophysiology of Parkinson’s disease. Object: This study investigated the potential link between colonic diverticular disease and risk of Parkinson’s disease. Methods: Data in this nationwide population-based cohort study were obtained from the National Health Insurance Research Database. Patients with colonic diverticular disease were identified from among 23.22 million insured Taiwanese residents who had been diagnosed between 2000 and 2005 and were aged ≥20 years (n = 23367). The comparison cohort included patients without colonic diverticular disease, matched by sex, age, and all comorbidities with the colonic diverticular disease patients cohort (n = 23367). Using univariable and multivariable Cox proportional hazard regression models, we estimated the adjusted hazard ratio (aHR) for PD with a 95% confidence interval (CI) after adjusting for age, sex, and all of comorbidities. Results: The risk of Parkinson’s disease was higher in the CDD cohort than in the comparison cohort (HR = 1.27, 95% CI = 1.10–1.47). Compared with patients aged ≥65 years without CDD, the CDD patients in the equal age group had a 1.25-fold increased risk of PD (95% CI = 1.07–1.46). Conclusion: Colonic diverticular disease may be associated with an increased risk of Parkinson’s disease. Thus, the risk of this neurodegenerative disease should be considered in patients with colonic diverticular disease.

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1. Introduction

Progress in understanding the role of gastrointestinal dysfunction in Parkinson’s disease (PD) has substantially increased in the past decade [1]. Several studies have indicated that the enteric nervous system might be the conductor of α-synuclein (α-Syn) propagation toward the central nervous system (CNS) [2]. α-Syn, a neuronal protein encoded by SNCA (synuclein, alpha, non-A4 component of amyloid precursor) [3], is one of the key proteins implicated in the pathogenesis of PD and the main component of Lewy bodies [4]. α-Syn has been demonstrated in nerve fibers of the colonic submucosa in early-stage PD patients and even before the onset of motor symptoms [5]. Furthermore, the involvement of gastrointestinal system in PD plays an important role during the disease course as source of non-motor symptoms, as constipation [2]. Therefore, it is worthwhile to investigate if chronic gastrointestinal diseases might be linked to the development of PD.

Here, we studied a common disease of this group: the colonic diverticular disease (CDD).

It is important to first define some key terms. Colonic diverticulosis is the presence of sac-like protrusions (i.e., diverticula)
formed when the colonic mucosa and submucosa herniate through defects in the muscle layer of the colon wall [6]. Approximately 20% of colonic diverticulosis develops the typical related symptoms. The symptomatic condition is labelled CDD [6].

15% of CDD patients ultimately develop diverticulitis, which indicates the macroscopic inflammation of diverticula with related acute or chronic complications [7].

The underlying pathological mechanisms causing the formation of colonic diverticula remain unclear, but are likely caused by complex interactions among factors of age, diet, genetic factors, abnormal motility due to autonomic dysfunction, and changes in the colonic structure [6].

We expect to find an increased risk of PD in CDD patients due to several factors that may link the two conditions. Firstly, the aSyn pathology in enteric neurons [8,9] causes autonomic dysfunction and, consequently, the low gastrointestinal mobility. The latter was typically found in pre-motor PD patients [10]. The resulted high intraluminal pressure is the main cause of developing diverticula before the clinical onset of PD. Furthermore, the abnormal intestinal microbiota in PD patients [11] plays a double role in this scenario. Indeed, it was found to promote the Lewy body pathology, and consequentially the hypomobility of gastrointestinal tract, as well as intestinal inflammation. The latter is another contributory factor to develop CDD [6].

2. Methods

2.1. Data source

The data were obtained from the Taiwan National Health Insurance Research Database (NHIRD).

The Taiwan National Health Insurance (NHI) program was established in 1995 through a consolidation of the 13 existing social health insurance programs into a nationwide, single-payer health insurance program. The Taiwan NHI program is a compulsory insurance program for Taiwanese residents, covering 99.9% of 23 million residents in 2014.

In this study, we used the hospitalization claims data of all enrollees (23 million residents) in Taiwan, which contained information on beneficiary registry, dates of admission and discharge, disease record, and discharge status.

The disease record system in the NHIRD is based on the codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The database renews the data annually.

Before releasing the data for research, the Taiwan government encrypts the original identification number and provides a scrambled, anonymous number for each insured person to link their data. This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012).

2.2. Study population

This study investigated the risk of PD in CDD patients, employing a CDD cohort and a comparison cohort.

The CDD cohort comprised patients who had been newly diagnosed with CDD (ICD-9-CM 562.1) between 2000 and 2005 and were aged ≥ 20 years. The index date of the CDD patients was the initial CDD diagnosis date. Furthermore, we divided the CDD cohort into the following two subgroups: the diverticulosis subgroup (only with ICD-9-CM 562.10 and/or 562.12) and diverticulitis subgroup (only with ICD-9-CM 562.11 and/or 562.13, both 562.11 and 562.13, or both 562.10 and 562.12).

For the comparison cohort, we sampled patients without CDD from the NHIRD, frequency matching by sex, age (per 1 years), and all of comorbidities (including diabetes mellitus, hyperlipidemia, hypertension, dementia, depression, anxiety, head injury, stroke, and constipation) at a ratio of 1:1 with the CDD cohort. For age-matched subjects in the comparison cohort, we randomly assigned a month and day in the index year of the matched case index date.

We excluded patients with missing information (age and/or sex) or with having a history of PD (ICD-9-CM 332) before the index date in both cohorts. All patients in each cohort were followed-up until the occurrence of PD, withdrawal from the NHI program, or December 31, 2013.

Age and sex were considered as covariates in this study.

In addition, we considered PD-associated comorbidities as the confounding factors of the study. Comorbidity was defined as a history of a given comorbidity before the index date. The PD-associated comorbidities comprised diabetes mellitus (DM, ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401–405), dementia (ICD-9-CM 290, 294.1, and 331.0), depression (ICD-9-CM 296.2, 296.3, 300.4, and 311), anxiety (ICD-9-CM 300.00), head injury (ICD-9-CM 910.2, 800, 801, 803, 804, 850–854, and 959.01), stroke (ICD-9-CM 430–438), and constipation (ICD-9-CM 564.0).

Of note, these specific PD-associated comorbidities have been selected according to previous literature as confounding factors to avoid the bias caused by comorbidities [12].

All insurance claims were scrutinized and coded by medical reimbursement specialists and peer reviewed according to the standard diagnosed criteria in this study. Doctors or hospitals that commit errors in diagnoses or coding are severely prosecuted. Therefore, the diagnoses and coding of CDD, PD, and all comorbidities in the study were considered as highly reliable.

2.3. Statistical analysis

We determined the mean and standard deviation for age as well as the number and percentage for sex and comorbidities in the CDD and comparison cohorts.

We evaluated the difference in distribution between the two cohorts by using a two-sample t-test for age and a chi square test for sex and comorbidities.

The incidence density of PD in each group was estimated by dividing the number of PD events by the total follow-up time (per 1000 person-years).

The Kaplan–Meier method was applied to plot cumulative incidence curves for each cohort, and the log rank test was used to assess the difference in curves between these two cohorts. The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using univariable and multivariable Cox proportional hazard models to evaluate the risk of PD in patients with and without CDD, as well as those with various CDD subtypes. The multivariable Cox regression models were adjusted for age, sex and all of comorbidities (including diabetes mellitus, hyperlipidemia, hypertension, dementia, depression, anxiety, head injury, stroke, and constipation).

Data management and statistical analyses were performed using SAS software, Version 9.4 (SAS Institute, Cary, NC, USA). The cumulative incidence curve was plotted using R software. The significance level was set at less than 0.05 for the two-side p value testing.

3. Results

In total, we included 23367 and 23367 patients in the CDD and comparison individuals, respectively; the mean age (57.8 years) and sex ratio (male: 56.8%) were similar between the cohorts (Table 1).

After frequency matching, both the CDD and comparison
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