**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.

**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, consequentially, 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].

**METHODS**

**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).

**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 310.2, 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.

**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.

**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 cohorts had similar the percentages of sex, age, and all of comorbidities.

The median (range) of follow-up period were 9.54 (0.003–13.96) years and 9.29 (0.003–13.99) years for comparison cohort and CDD cohort, respectively. As shown in Figure 1, the cumulative incidence was significantly higher in the CDD cohort than in the comparison cohort (*p*<0.001).

The incidence of PD was only 1.71 per 1000 person-years in the patients without CDD and 2.00 per 1000 person-years in the CDD patients (Table 2).

After adjustment for sex, age, and all of comorbidities, the risk of PD in the CDD cohort was 1.27-fold higher than that in the comparison cohort (95% CI = 1.10–1.47, p-value = 0.001).

Stratified by sex, the results showed that males with CDD were associated with increased risk of PD than in those without CDD (HR = 1.30, 95% CI = 1.07–1.58, p-value = 0.008).

Stratified by age groups, the results showed that patients with CDD had a higher risk of PD compared with subjects without CDD in the age group of 65 years and above (adjusted HR = 1.25, 95% CI = 1.07–1.46, p-value = 0.004).

In the individuals with comorbidity, the CDD patient was significantly associated with higher risk of PD than non-CDD subject (HR = 1.36, 95% CI = 1.12–1.66, p-value = 0.002). However, there was no risk difference between CDD group and non-CDD group in the individuals without any comorbidities (HR = 1.18, 95% CI = 0.96–1.46, p-value = 0.11).

Table 3 illustrates the risk of PD in different CDD subtypes.

After adjustment for sex, age, and all of comorbidities, compared with the patients without CCD, the patients with diverticulitis and diverticulosis had a 1.20-fold (95% CI = 1.01–1.44, p-value = 0.04) and 1.34-fold (95% CI = 1.13–1.59, p-value <0.001) increased risk of PD, respectively.

**DISCUSSION**

Our results revealed that CDD patients in Taiwan have a significantly higher overall risk of PD. Our data were obtained from the NHIRD, which covers 99.9% of the Taiwanese population and is contracted by 97% of Taiwanese hospitals. Therefore, our findings can be generalized.

Each patient in the CDD cohort was frequency matched according to age, sex, and index year with a person without CDD from the general population.

Prior studies have reported mixed results regarding the association between PD and comorbidities [12].Our data also showed that the percentage of comorbidities, according to previous PD studies, namely DM, hyperlipidemia, hypertension, dementia, depression, anxiety, head injury, and stroke, were significantly higher in the CDD cohort than in the comparison cohort. Therefore, we adjusted the HR with these comorbidities. The risk of PD in patients with CDD was 2.00 per 1000 person-years.

In addition, compared with the patients without CDD, the CDD patients aged ≥65 years had a 1.25-fold increased risk of PD.

Furthermore, male patients with CDD had a 1.30-fold increased risk of PD. This finding may be attributable to the neuroprotective effect of estrogens; however, their role remains controversial [13].

Interestingly, the risk of PD was increased both in patients with diverticulosis (1.20-fold) as well as with diverticulitis (1.34-fold) compared to the comparison cohort.

Our findings confirm the critical involvement of colon disease in early-stage PD.

The importance of non-motor features of PD has been increasingly recognized for several years [14].Several of these symptoms are caused by damage of peripheral autonomic ganglia due to α-Syn deposition in the Stage 1 of Braak theory [9]. Additionally, some studies explained the autonomic dysfunction also with a peripheral postganglionic sympathetic denervation [15, 16].

Interestingly, it has been showed that patients diagnosed with pure autonomic dysfunction developed PD nearly 15 years later the first diagnose [17].

The role of abnormal intestinal motility, result of autonomic dysfunction, in the developing of diverticula is controversial. It is well known that constipation leads to high intraluminal pressure and, consequentially, facilitates the development of diverticulosis [18]. However, Peery et al. observed that increased bowel frequency, rather than the expected decrease, was noted in patients with diverticulosis [19].

Sampson et al. showed that gut bacteria regulate movement disorders in mice and suggest that alterations in the human microbiome represent a risk factor for PD [11].It is found that the different intestinal microbiome is involved in modulation of inflammatory and immunological processes in the regional microglia, which are implicated in PD pathology [20]. The development of CDD which leads to the change the colonic flora may involve in this pathology.

Given the above evidences, our results supported the hypothesis that the altered colonic motility in PD patients and increased intraluminal pressure has an important role on the formation of diverticula. In this regard, there is the possibility that CDD is a representation of prodromal constipation related to PD.

To avoid this bias, we included the constipation as a comorbidity and observed that the risk of PD was still significantly higher for the CDD patient than for the age-matched comparisons (adjusted HR=1.25, 95% CI=1.11-1.41) even with the confounding factor of constipation.

We recognized the strengths as well as some limitations of our study.

The strengths of our study were its population-based design, generalizability of findings, and use of population-based data and NHIRD records using a large sample size and having low loss to follow-up in the longitudinal design, including study and control cohorts. In addition, NHIRD covers a highly representative sample of Taiwan’s general population because the reimbursement policy is universal and operated by a single-buyer, the government in Taiwan.

We admit some limitations. Especially, the absence of information about life style of participants. Consequentially, there is a lack of record about the presence of risk factors for CDD including body mass index, smoking and alcohol status, intake of opioids or non-steroidal anti-inflammatory drugs. Notable, it was not possible to review the individual chart of participants due to government’s rules.

We aimed to investigate the effect of constipation. However, due to the insurance system only severe constipation who needed treatment have been included. We recognize that this is a potential weakness of our study, but it is also the strength. Indeed, minor symptom of constipation may be over looked.

In summary, our study suggested that CDD may be considered as another predictive risk factor for PD. However, future study would be crucial to investigate other physio-pathological factors (genetic and environmental) that may explain the association of these two diseases.

**REFERENCES**

[1] Pfeiffer RF. Gastrointestinal dysfunction in Parkinson’s disease. Lancet Neurol. 2 (2003) 107–116.

[2] Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol. 14 (2015) 625-639.

[3] Nussbaum RL, Polymeropoulos MH. Genetics of Parkinson's disease. Hum Mol Genet. 6 (1997) 1687-1691.

[4] Dehay B, Vila M, Bezard E, Brundin P, Kordower JH. Alpha-synuclein propagation: New insights from animal models. Mov Disord 31 (2016) 161-168.

[5] Shannon KM, Keshavarzian A, Mutlu E, Dodiya HB, Daian D, Jaglin JA, Kordower JH. Alpha-synuclein in colonic submucosa in early untreated Parkinson's disease. Mov Disord. 27 (2012) 709-715.

[6] Strate LL, Modi R, Cohen E, Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 107 (2012) 1486–1493.

[7] Elisei W, Tursi A. Recent advances in the treatment of colonic diverticular disease and prevention of acute diverticulitis. Ann Gastroenterol. 29 (2016) 24

[8] Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, van Hilten JJ. Patient-reported autonomic symptoms in Parkinson disease. Neurology. 69 (2007) 333–341.

[9] Braak H, de Vos RA, Bohl J, Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner’s and Auerbach’s plexuses in cases staged for Parkinson’s disease-related brain pathology. Neurosci Lett. 396 (2006) 67–72

[10] Derkinderen P, Rouaud T, Lebouvier T, Bruley des Varannes S, Neunlist M, De Giorgio R. Parkinson disease: The enteric nervous system spills its guts. Neurology. 77 (2011) 1761–1767.

[11] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF, Keshavarzian A, Shannon KM, Krajmalnik-Brown R, Wittung-Stafshede P, Knight R, Mazmanian SK. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell. 167 (2016) 1469-1480.

[12] Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology. 69 (2007) 1688–1695.

[13] Saunders-Pullman R. Estrogens and Parkinson disease: neuroprotective, symptomatic, neither, or both? Endocrine. 21 (2003) 81–87.

[14] Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson’s disease: diagnosis and management. Lancet Neurol. 5 (2006) 235–245.

[15] Braak H, Sastre M, Bohl JR, de Vos RA, Del Tredici K. Parkinson’s disease:lesions in dorsal horn layer I, involvement of parasympathetic and sympatheticpre- and postganglionic neurons. Acta Neuropathol 113 (2007) 421–429.

[16] Minguez-Castellanos A, Chamorro CE, Escamilla-Sevilla F, Ortega-Moreno A,Rebollo AC, Gomez-Rio M, et al. Do alpha-synuclein aggregates in autonomic plexuses predate Lewy body disorders? A cohort study. Neurology. 68 (2007) 2012–2018.

[17] Kaufmann H, Nahm K, Purohit D, Wolfe D. Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies. Neurology. 63 (2004) 1093–1095.

[18] Tursi A. Diverticulosis today: unfashionable and still under-researched. Therap Adv Gastroenterol. 9 (2016) 213-228.

[19] Peery AF, Sandler RS, Ahnen DJ, Galanko JA, Holm AN, Shaukat A, Mott LA, Barry EL, Fried DA, Baron JA. Constipation and a low-fiber diet are not associated with diverticulosis. Clin Gastroenterol Hepatol. 11 (2013) 1622–1627.

[20] Palma JA1, Kaufmann H. Autonomic disorders predicting Parkinson's disease. Parkinsonism Relat Disord. 20 (2014) Suppl 1:S94-8.

**Figure 1.** Cumulative incidence curves of Parkinson’s disease in CDD and comparison cohorts.

Abbreviations: PD, Parkinson’s disease; CDD, colonic diverticular disease.