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Inflammatory bowel disease and risk of Parkinson's disease in Medicare beneficiaries

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ABSTRACT

Introduction: Gastrointestinal (GI) dysfunction precedes the motor symptoms of Parkinson's disease (PD) by several years. PD patients have abnormal aggregation of intestinal α-synuclein, the accumulation of which may be promoted by inflammation. The relationship between intestinal α-synuclein aggregates and central nervous system neuropathology is unknown. Recently, we observed a possible inverse association between inflammatory bowel disease (IBD) and PD as part of a predictive model of PD. Therefore, the objective of this study was to examine the relationship between PD risk and IBD and IBD-associated conditions and treatment.

Methods: Using a case-control design, we identified 89,790 newly diagnosed PD cases and 118,095 population-based controls >65 years of age using comprehensive Medicare data from 2004-2009 including detailed claims data. We classified IBD using International Classification of Diseases version 9 (ICD-9) diagnosis codes. We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the association between PD and IBD. Covariates included age, sex, race/ethnicity, smoking, Elixhauser comorbidities, and health care use.

Results: PD was inversely associated with IBD overall (OR = 0.85, 95% CI 0.80–0.91) and with both Crohn's disease (OR = 0.83, 95% CI 0.74–0.93) and ulcerative colitis (OR = 0.88, 95% CI 0.82–0.96). Among beneficiaries with ≥2 ICD-9 codes for IBD, there was an inverse dose-response association between number of IBD ICD-9 codes, as a potential proxy for IBD severity, and PD (p-for-trend = 0.006).

Conclusion: IBD is associated with a lower risk of developing PD.

1. Introduction

Gastrointestinal (GI) dysfunction precedes the onset of motor symptoms in Parkinson's disease (PD) by several years [1]; however, the etiology of GI dysfunction in PD and the role of GI pathology in the central nervous system (CNS) manifestations of PD are not well understood. Proposed theories for the mechanism of PD related GI dysfunction include abnormal protein aggregation with consequent degeneration of the enteric nervous system, destruction of the motor nucleus of the vagus nerve known to control the parasympathetic output to the GI tract, and/or chronic inflammation [2–6]. Abnormal α-synuclein aggregates in the intestine may propagate via the vagus nerve into the CNS, potentially contributing to the accumulation of α-synuclein in the brain. Supporting this hypothesis, patients who have undergone truncal vagotomy may have a lower risk of developing PD [7]. Furthermore, chronic intestinal inflammation may allow for rapid mobilization of abnormal protein between the gut and the brain [8].

Inflammatory bowel diseases (IBD) predominantly affect the GI tract but can also be associated with systemic inflammation and extraintestinal manifestations [9]. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which can differ in distribution in the gut and depth of inflammation. More severe disease may require immunosuppressant agents, biologic medications, and/or surgery. Given the potentially critical role of GI pathology in PD pathogenesis, there is reason to suspect that IBD or its

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treatments may impact PD risk. Recently, we observed a possible inverse association between IBD and PD while developing a predictive model of PD [10]. Therefore, in the present work, we hypothesized that patients with IBD would have a lower risk of developing PD than comparable controls without IBD, and that IBD-associated treatments such as GI surgery or immunosuppressant use may also be associated with a lower PD risk.

2. Methods

2.1. Protection of human subjects

This study was approved by the Washington University IRB and Centers for Medicare & Medicaid Services (CMS). All records were de-identified prior to release from CMS.

2.2. Study design

We constructed a population-based case-control study using 2009 Medicare base file (BASF) and inpatient, outpatient, physician/supplier, skilled nursing facility, home health care, and durable medical equipment claims data from age-eligible Medicare beneficiaries in 2004–2009 as detailed previously [10]. We required all cases and controls to be enrolled in Medicare Part A and/or B without health maintenance organization coverage, live in the U.S., and to be age-eligible for Medicare for at least two years (age $\geq$ 66 years, 11 months) at PD diagnosis or control reference date. Those who met these criteria, had an International Classification of Diseases version 9 (ICD-9) code 332 or 332.0 in 2009 and no prior year, and did not have an ICD-9 code for secondary or atypical parkinsonism, were included as incident PD cases (N = 89,790). Controls (N = 118,095) were a random sample of remaining beneficiaries with none of the above ICD-9 codes in 2004–2009 and meeting the same inclusion criteria. The case-control study was originally formed to develop a predictive model of PD, and we avoided matching so that model coefficients for known PD risk factors would be unbiased when applying the model to future cohorts. The inclusion and exclusion criteria were designed to ensure complete ascertainment of incident PD cases, the selection of comparable controls, and that both were population-based samples rather than disability- or clinic-based samples.

2.3. Assessment of IBD and covariates

We extracted ICD-9 diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes and Current Procedural Terminology (CPT) codes from all available claims data up to the PD diagnosis/control reference date. We created a dichotomous variable for each code observed in 2004–2009 prior to this date. We classified the beneficiary as having IBD if they had $\geq$1 of the following ICD-9 codes: 555.0–555.9, 556.0–556.9. We sub-classified IBD into CD (555.0–555.9) or UC (556.0–556.9) [11,12]. We also identified beneficiaries with at least two codes on separate dates for IBD as a method of improving accuracy and stability of IBD diagnosis. We calculated the total number of occurrences of an IBD ICD-9 code, as a proxy for IBD severity, in order to consider a dose-response relationship between IBD and PD. We then classified all beneficiaries as having a condition known to be associated with IBD [11] if they had any of the following ICD-9 and/or CPT codes: arthropathy (713.1), pyoderma gangrenosum (686.01), erythema nodosum (695.2), oral aphthous ulcers (528.2), cholangitis (576.1), or fistulae (ICD-9 537.4, 565.1, 569.81, 596.1, 599.1, 619.1, 46.72, 46.74, 49.73, 46.76, 48.73, 48.93, CPT codes 45800, 45820, 45825, 45805, 43880, 44640, 44650, 46706). We included these diagnoses to ensure a consistent association with PD. We also identified procedure codes for an ileostomy or colectomy, surgical procedures commonly used to treat IBD. Because IBD is commonly treated with immunosuppressants, we investigated whether immunosuppressants were associated with a lower risk of PD. We identified HCPCS, CPT, and ICD-9 codes associated with steroid (e.g., long-term use of steroids, systemic corticosteroids, dexamethasone, methylprednisolone, and hydrocortisone) and immunosuppressant use (e.g., infliximab, daclizumab, adalimumab, rituximab, azathioprine, methotrexate, and cyclosporine). We categorized immunosuppressant use into traditional, biologic, and steroid. Traditional immunosuppressants are commonly used synthetic disease modifying agents which include methotrexate, azathioprine, and cyclosporine. Biologics are newer immunosuppressant medications made from live biological systems and categorized based on their mechanism of action. We did not have Medicare Part D (prescription coverage) claims data to verify immunosuppressant use and were only able to ascertain immunosuppressant use through Medicare Part A/B.

We calculated age and obtained sex and race from the 2009 BASF. We calculated the probability of having ever regularly smoked (a continuous variable, hereafter “smoking probability”) for all cases and controls. We estimated the latter by assigning beneficiaries with a code specific to tobacco (ICD-9 V15.82, ICD-9 305.1, CPT 99406, CPT 99407) a probability of 100%. We calculated other participants' probability using a logistic regression predictive model for ever/never smoking that we developed within another nationwide, population-based dataset [13]. This model had 17 predictor variables, which we made in the Medicare dataset from >600 ICD-9 codes. We applied this predictive model to our Medicare data and validated smoking probability against (1) tobacco-specific codes before factoring them in, (2) county level smoking [14], and (3) diagnoses associated with smoking but in Medicare data only [10]. We defined comorbidities using a modified Elixhauser index, a validated measure of medical comorbidities when using claims data [15]. Finally, we counted the total number of unique types of providers/diagnosis codes seen in 2004–2009 to quantify beneficiaries' use of medical care, which can bias associations between two medical conditions [16]. The smoking, Elixhauser, and use of care variables were based on all claims data up to the PD diagnosis/control reference date.

2.4. Statistical analysis

We used logistic regression, with PD as our outcome variable, to determine the associations between PD and each medical condition or treatment. We reported the odds ratio (OR) and respective 95% confidence interval (CI) as an estimate of relative risk. We adjusted for age (continuously as two linear splines), race (seven categories), sex, and probability of ever smoking *a priori* because of their known associations with PD [17]. We adjusted for comorbidities using the Elixhauser index and total number of types of providers seen. For models of PD and IBD-associated conditions/treatments, we stratified by presence of IBD status, since associated conditions/treatments could be present in other disease processes. Finally, we performed three sensitivity analyses. First, we used stringent PD diagnostic criteria to identify incident PD requiring at least one ICD-9 code from a neurologist or $\geq$3 PD codes in 2009 [10]. Second, we restricted analyses to those without constipation given that constipation can be a symptom of PD and may have masked IBD symptoms. Third, we applied three-year exposure lag, similar to a prior study of autoimmune diseases and PD [18].

3. Results

Our PD cases demonstrated typical demographic associations

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