Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Appendectomy and the Risk of Parkinson's Disease: A Korean Nationwide Study

Kye Won Park, MD, PhD,[1] Hyeong Taek Woo, MD, PhD,[2] Yun Su Hwang, MD, PhD,[3] Seung Hyun Lee, MD, PhD,[4] and Sun Ju Chung, MD, PhD[5,*]

Abstract: Background: The vermiform appendix is considered a potential reservoir for the abnormal α-synuclein aggregate in Parkinson's disease (PD). Previous epidemiologic evidence on the association between appendectomy and PD risk remains inconclusive, especially outside the Western world.
Objectives: To investigate the association between appendectomy and PD risk in Korea.
Methods: Among 703,831 eligible adult subjects in the National Health Insurance Service sample cohort, we identified 16,122 patients who underwent appendectomy. The rest formed the control group. PD risk was assessed using time-dependent Cox regression analyses.
Results: The appendectomy group did not have altered risk of PD compared with the control group in either unadjusted [hazard ratio (HR) 1.32, 95% confidence interval (CI) 0.97–1.80, $P = 0.08$] or adjusted model (HR 1.42, CI 0.88–2.30, $P = 0.15$). No further statistical difference appeared when stratified by sex.
Conclusions: Appendectomy is not associated with altered risk of PD in the Korean population.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by diverse motor and non-motor symptoms.[1] Gastrointestinal (GI) dysfunctions, such as dysphagia and constipation, are particularly common in PD and can precede the overt manifestation of motor symptoms. The pathological hallmarks of PD is the presence of cytoplasmic inclusion within neuronal cell bodies which consist mainly of α-synuclein protein.[1] Abnormal α-synuclein aggregates are frequently detected in the enteric nervous system (ENS) throughout the GI tract of PD subjects.[2] Given these backgrounds, Braak and colleagues postulated that microbial products in the gut that encounter the ENS could trigger the aggregation of α-synuclein and initiate sporadic PD by spreading the aggregated α-synuclein to the central nervous system via the vagus nerve.[3] Among the lengthy GI tract, the appendix is known to contain abundant α-synuclein and lacks a barrier between blood and ENS.[4] However, previous epidemiologic investigations upon the association between appendectomy and the future development of PD have yielded conflicting results so far.[5,6] Furthermore, none of the studies was carried out in Asian countries, where the gut microbiota exhibits a distinct composition compared to Western populations.[7] For example, a randomized crossover trial examining the effects of typical Korean and Western food patterns on gut microbiota composition demonstrated that the Korean diet promoted greater microbiota diversity compared to the Western diet.[8] Another study observed that the different ethnic individuals sharing a geographical location show different microbiota composition, possibly due to different genetic susceptibility and diet patterns.[9] In this regard, our study aimed to investigate the association between appendectomy and PD risk in a nationwide manner, in previously under-explored Asian population.

Methods

Data Source

The data for this study was obtained from the National Health Insurance Service-National Sample Cohort (NHIS-NSC).[10]

[1]Pacific Parkinson Research Centre, University of British Columbia, Vancouver, British Columbia, Canada; [2]Department of Preventive Medicine, Keimyung University School of Medicine, Daegu, Korea; [3]Department of Neurology, Jeonbuk National University Medical School and Hospital, Jeonju, Korea; [4]Department of Neurology, Seoul Medical Center, Seoul, Korea; [5]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

***Correspondence to:** Dr. Sun Ju Chung, Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea; E-mail: sjchung@amc.seoul.kr
Keywords: appendectomy, Parkinson's disease, gut brain Axis.

Received 10 October 2023; revised 1 February 2024; accepted 17 March 2024.
Published online 2 May 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.14031

The NHIS-NSC represents approximately 1 million individuals who were followed up from 2002 to 2015, randomly selected from a public insurance system that covers almost entire Korean population. The dataset contains demographic information and medical claim information which includes disease codes based on the International Classification of Disease 10th revision (ICD-10), procedure codes, and prescription codes.

Study Participants

Among the total cohort, we excluded individuals with age under 20 and those who had PD diagnosis before the study entry. The appendectomy exposed group was identified with the procedure code Q2860 (appendectomy), Q2861 (appendectomy, uncomplicated), Q2862 (appendectomy, perforated), and Q2863 (resection of appendiceal abscess and peri-appendiceal abscess drain). Individuals without any appendectomy procedure codes were classified to the control (unexposed) group. If a subject had a diagnosis of PD prior to or within the first 12 months of an appendectomy code occurrence, the subject was classified into the control group considering the lag time of the chronic progressive disease.

We have set newly diagnosed PD as the outcome. The diagnosis of PD was defined based on the presence of the G20, which corresponds to the ICD-10 code for idiopathic PD, and the V124 codes. V124 code is a registration code used for enrolling PD patients in a government program that offers co-payment reduction up to 90% for rare intractable diseases. To apply for this code, clinical manifestations consistent with PD should be confirmed by a neurologist or a neurosurgeon. We assumed that individuals who met the clinical criteria for PD would have been prescribed with anti-Parkinson medication for a certain duration. Therefore, our study only included individuals who had prescription history of any of the following anti-Parkinson medication for at least 30 days; amantadine sulfate, benztropine mesylate, levodopa, benserazide, carbidopa, ropinirole, selegiline, trihexyphenidyl, pramipexole, entacapone, rotigotine, rasagiline, opicapone, and safinamide. Follow-up terminated at whichever came first, the date of PD diagnosis, date of death, or the termination of the NHIS-NSC follow-up.

Baseline demographic information in this study included age at study entry, sex, comorbidities (hypertension (HTN) and diabetes mellitus (DM), defined by ICD-10 code I10–I13 and E10–E14, respectively), and smoking status (ever-smoker or never-smoker). Smoking status was obtained according to the national health checkup data collected within 2 years of their study entry. These demographic variables were selected based on expert opinions and data availability, considering their potential confounding effects.[1,11]

Statistical Analysis

Baseline demographics were compared using student's *t*-test for continuous variables and with chi-square test for categorical variables. Cox proportional-hazards regression analyses were employed to test the association between appendectomy and risk of PD. We employed univariate and multivariate models adjusted for potential confounders (age, sex, comorbidities, and smoking status). Sex-stratified analyses were additionally conducted. All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, United States). The study was approved by the Institutional Review Board of Asan Medical Center. The data supporting the findings of this study are available upon approval for use by the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do).

Results

We identified 16,122 appendectomy cases and 687,709 controls according to the inclusion and exclusion criteria. The mean (standard deviation) age of appendectomy case was 39.0 (14.3) years, which was younger than the control [41.5 (14.4) years]. The case group was less prevalent in HTN and DM compared with the controls (Table 1).

The PD incidence rate was 41 occurrences in 95,994 person-years in the case group and 2434 occurrences in 9,565,293 person-years in the control group, resulting in an overall annual incidence of 25.61 per 100,000 individuals. The case group did not show altered risk of PD compared with PD in both unadjusted model [hazard ratio (HR) 1.32, 95% confidence interval (CI) 0.97–1.80] and adjusted model (HR 1.42, CI 0.88–2.30) (Table 2). There was no further statistical difference in PD occurrence when stratified by sex. Regarding the covariates, older age was a non-modifiable risk factor for PD occurrence in all models, as anticipated. Smoking exhibited an overall protective effect against PD (HR 0.75, CI 0.64–0.89), particularly in male (HR 0.72, CI 0.60–0.88), whereas DM showed an overall risk effect for PD (HR 1.67, CI 1.38–2.02), particularly in female subjects (HR 1.96, CI 1.54–2.49) (Table 2).

Discussion

By utilizing a large nationwide cohort of more than 0.7 million Korean individuals, we found that subjects with appendectomy history do not have altered risk for PD compared with those without. This finding aligns with a recent large-scale meta-analysis conducted in Western societies, which concluded that appendectomy status is not associated with the risk or onset of PD in Western societies.[12] Braak's hypothesis on the pathogenesis of PD emphasizes the role of the gut microbiome in spreading the pathologic α-synuclein from the gut to the brain.[3] Studies have found that the composition and diversity of the gut microbiota are significantly influenced by the diet pattern and ethnicity, even when geographically co-localized.[8,9] To the best of our knowledge, our study provides the first epidemiologic evidence against appendectomy as decreasing the risk of PD outside the Western world. The observed lack of epidemiologic association, including our own work, may serve as evidence against the hypothesis that the appendix serves as the reservoir to spread the α-synuclein pathology to the brain. It rather supports the idea

TABLE 1 *Baseline demographics of the appendectomy case group and the control group*

	Appendectomy case	Control	*P*
N	16,122	687,709	-
Male, n (%)	7989 (49.6)	338,957 (49.3)	0.51
Age (years), mean ± SD	39.0 (14.3)	41.5 (14.4)	<0.01
Hypertension, n (%)	1006 (6.2)	49,848 (7.3)	<0.01
Diabetes Mellitus, n (%)	292 (1.8)	21,894 (3.2)	<0.01
Smoking status			0.99
Ever-smoker, n (%)	2287 (40.4)	92,597 (40.4)	
Never-smoker, n (%)	3371 (59.6)	136,516 (59.6)	

Abbreviation: SD, standard deviation.

TABLE 2 *Time-dependent cox regression analysis*

	Total		Male-only		Female-only	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Unadjusted model						
Appendectomy						
Control	1.00		1.00		1.00	
Case	1.32 (0.97–1.80)	0.08	1.20 (0.72–2.00)	0.48	1.41 (0.96–2.08)	0.08
Adjusted model[a]						
Appendectomy						
Control	1.00		1.00		1.00	
Case	1.42 (0.88–2.30)	0.15	1.24 (0.59–2.62)	0.57	1.59 (0.84–2.96)	0.15
Age (years)	1.11 (1.10–1.12)	<0.01	1.11 (1.10–1.12)	<0.01	1.11 (1.10–1.12)	<0.01
Sex						
Male	1.00		-	-	-	-
Female	1.01 (0.88–1.16)	0.91				
HTN						
No	1.00		1.00		1.00	
Yes	1.07 (0.93–1.24)	0.35	1.20 (0.95–1.50)	0.12	0.99 (0.82–1.21)	0.95
DM						
No	1.00		1.00		1.00	
Yes	1.67 (1.38–2.02)	<0.01	1.33 (0.98–1.82)	0.07	1.96 (1.54–2.49)	<0.01
Smoking						
Never-smoker	1.00		1.00		1.00	
Ever-smoker	0.75 (0.64–0.89)	<0.01	0.72 (0.60–0.88)	<0.01	0.88 (0.64–1.21)	0.42

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; PD, Parkinson's disease.
[a]Adjusted for age, sex (in total population), DM, HTN, and smoking status.

that pathology does not equal pathogenesis; that pathology is the consequence of many disorders but cause of none.[13] It is important to note that the null association should be interpreted as epidemiologic evidence to alleviate unnecessary concerns regarding appendectomy status among individuals who possess risk factors for PD.

We noted several associations between the covariates and PD. Smoking appeared to have a protective effect, while DM demonstrated a potential risk for PD occurrence, aligning with findings from prior epidemiological and mendelian randomization studies.[14–16] The observed disproportionate association based on sex may be influenced by our relatively smaller sample size compared to larger-scale studies. Additionally, including both type 1 and type 2 diabetes as covariates may have limited our statistical power to assess the association between true insulin resistance and PD. It's important to acknowledge that our primary focus was on testing the main association, and we should interpret these covariate associations with caution.

There are several limitations in our study. First, we relied on medical claim information to infer the diagnoses of PD, potentially lacking more reliable clinical diagnostic criteria. We tried to mitigate this limitation by utilizing the unique V124 code in Korea and anti-Parkinson medication history. Second, the follow-up duration was 13 years at best. Considering that the mean age of the appendectomy group was 39.0 years, it might not provide sufficient time to observe PD occurrence. However, recent epidemiological studies conducted on the entire population of South Korea between 2010 and 2015, reported an annual incidence of 22.4–27.8 cases per 100,000 individuals.[17] The incidence rate reported in our study aligns with this trend. Therefore, we infer that our study observed the impact of appendectomy not only on a minority of young-onset PD cases but on PD as a whole.

In conclusion, our study suggests that appendectomy performed earlier in life is not associated with altered risk of PD in the Korean population.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

K.W.P.: 1A, 1B, 1C, 2C, 3A
H.T.W.: 1C, 2A, 2B, 2C, 3B
Y.S.H.: 2C, 3B
S.H.L.: 2C, 3B
S.J.C.: 1A, 2C, 3B

Disclosures

Ethical Compliance Statement: The study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea. Informed patient consent was not necessary for this work utilizing public dataset. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: This study was supported by the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Republic of Korea (grant number: 2022IT0012).

Financial Disclosure for the Preceding 12 Months: K.W.P. received a research grant from the Korean Neurological Association. Otherwise, there is no additional disclosures to report. ■

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