Acute stimulation challenge, but no efficacy data on the use of chronic directional DBS compared to standard ring DBS. Nevertheless, our findings may provide valuable input into the planning of appropriate clinical trials, which are now needed to establish the theoretical advantages of directional DBS in clinical practice and on a group level, but should also take into account possible disadvantages of the expanded parameter space, such as increased programming burden.

References


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Appendectomy in Mid and Later Life and Risk of Parkinson’s Disease: A Population-Based Study

Connie Marras, MD, PhD,1,2,4 Anthony E. Lang, MD,1 Peter C. Austin, PhD,2,4 Cindy Lau, MSc,2 and David R. Urbach, MD, MSc2,3,4

1Morton and Gloria Shulman Movement Disorders Center, Toronto Western Hospital and the Edmond J. Safra Program in PD, Toronto, Ontario, Canada, University of Toronto, Toronto, Ontario, Canada
2The Institute for Clinical Evaluative Sciences and the University of Toronto, Toronto, Ontario, Canada
3Toronto General Research Institute, University Health Network, Department of Surgery, Toronto, Ontario, Canada
4Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

ABSTRACT

Introduction: Pathogenic movement of alpha-synuclein from the gut to the brain in PD has been proposed. The appendix has a relatively high density of alpha-synuclein deposition in neurologically healthy individuals. We investigated the incidence of PD after appendectomy.

Methods: Using cause-specific hazards regression models, we compared persons over 35 years of age who had undergone appendectomy with two groups of age- and sex-matched individuals having had: (1) a cholecystectomy and (2) neither procedure. Subsequent diagnoses of PD were identified.

Results: Among 42,999 individuals undergoing appendectomy, no difference in risk of PD was identified compared to cholecystectomy (hazard ratio = 1.004; 95% confidence interval: 0.740–1.364). Compared with no procedure, individuals with appendectomy had a higher incidence of PD within 5 years, but no significant difference in risk thereafter.

Conclusion: In our study, appendectomy in mid or late life does not appear to be associated with a reduced risk of PD. © 2016 International Parkinson and Movement Disorder Society

Key Words: Parkinson’s disease; appendectomy; etiology

It has been proposed that the initiating events of Parkinson’s disease (PD) may occur outside the central nervous system (CNS), with secondary spread to the brain through a prion-like process. The gastrointestinal tract is a candidate for a location of initiating events. In people without PD, Gray and colleagues found that alpha-synuclein immunoreactivity was most abundant in the appendiceal lamina propria compared to the gastric mucosa or other parts of the right colon, colocalized with neural markers, and was close to the luminal surface of the appendix, putting it in close proximity to any pathogen or triggering event within the gut. The lack of a blood-tissue barrier in the appendiceal mucosa would facilitate contact between a blood-borne agent and the enteric nervous system and exogenous agents contacting the host.
within the gastrointestinal tract can also act as a trigger for alpha-synuclein deposition.\(^5\)

Interestingly, a trend toward a reduced risk of PD has been found after truncal vagotomy.\(^6\) Importantly, the appendix receives particularly dense innervation from the dorsal motor nucleus of the vagus, the CNS terminus of the enteric nervous system. Thus, the appendix is a particularly interesting candidate for an enteric origin of the pathogenic process of PD. In a cohort of PD patients, a later onset was found among those who had had an appendectomy.\(^7\) We undertook a large cohort study examining the risk of PD among individuals who had and had not had an appendectomy. We hypothesized that appendectomy and earlier age at the time of the procedure would be associated with a lower incidence of PD.

### Patients and Methods

#### Sources of Data

The 14 million residents of Ontario, Canada, are insured under a health insurance plan that includes physician and hospital services. Individuals age 65 or older are additionally eligible for prescription drug coverage. Diagnostic and procedure information was obtained from (1) the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which records diagnoses contributing to hospitalizations and procedures performed during the hospital stays from 1988 to the present, (2) the National Ambulatory Care Reporting System consisting of data on emergency room visits (2000–present), (3) the CIHI Same-day Surgery database, consisting of data on institution-based ambulatory surgical procedures (1991–present), and (4) the Ontario Health Insurance Plan (OHIP) physician billing database (consisting of information on inpatient and outpatient physician services, including a physician-assigned diagnosis code for each visit; 1992–present). The Registered Persons Database contains date of birth, sex, and dates of death (1988–present). The Ontario Drug Benefit (ODB) database (1990–present) records data on all outpatient prescription claims paid for by the

---

### TABLE 1. Baseline characteristics of patients who had an appendectomy, cholecystectomy, or no procedure

| Table 1: Baseline characteristics of patients who had an appendectomy, cholecystectomy, or no procedure |
|---|---|---|---|
| **Appendectomy Cohort (n = 42,999)** | **Cholecystectomy Cohort (n = 42,995)** | **Control Cohort (n = 42,999)** |
| **Unperforated (n = 28,150)** | **Perforated (n = 14,849)** | **Control Cohort (n = 42,999)** |
| **Age, years** | **Mean ± SD** | **Median (IQR)** | **Mean ± SD** | **Median (IQR)** | **Mean ± SD** | **Median (IQR)** |
| **Female** | 48.85 ± 11.92 | 46 (40–55) | 50.13 ± 12.33 | 47 (40–57) | 50.10 ± 12.36 | 47 (40–57) |
| **Male** | 6.686 ± 46.3 | 7,981 (53.7) | 21,878 (50.9) | 21,117 (49.1) | 21,879 (50.9) | 21,120 (49.1) |
| **Age, years, categories (%)** | | | | | | |
| **35–44** | 12,964 (46.1) | 12,964 (46.1) | 12,964 (46.1) | 12,964 (46.1) | 12,964 (46.1) | 12,964 (46.1) |
| **45–54** | 7,762 (27.6) | 4,362 (29.4) | 12,124 (28.2) | 12,124 (28.2) | 12,124 (28.2) | 12,124 (28.2) |
| **55–64** | 3,989 (14.2) | 2,713 (18.3) | 6,702 (15.6) | 6,702 (15.6) | 6,702 (15.6) | 6,702 (15.6) |
| **65–74** | 2,168 (7.7) | 1,732 (11.7) | 3,900 (9.1) | 3,900 (9.1) | 3,900 (9.1) | 3,900 (9.1) |
| **75–84** | 1,047 (3.7) | 938 (6.3) | 1,985 (4.6) | 1,985 (4.6) | 1,985 (4.6) | 1,985 (4.6) |
| **≥85** | 220 (0.8) | 180 (1.2) | 400 (0.9) | 400 (0.9) | 400 (0.9) | 400 (0.9) |
| **No. of ADGs in the past year** | **Mean ± SD** | **Median (IQR)** | **Mean ± SD** | **Median (IQR)** | **Mean ± SD** | **Median (IQR)** |
| **Female** | 4.79 ± 3.03 | 4.45 ± 2.92 | 6.26 ± 2.80 | 6.26 ± 2.80 | 6.26 ± 2.80 | 6.26 ± 2.80 |
| **Male** | 4 (3–7) | 4 (2–6) | 6 (4–8) | 6 (4–8) | 6 (4–8) | 6 (4–8) |
| **No. of outpatient visits in the past year** | **Mean ± SD** | **Median (IQR)** | **Mean ± SD** | **Median (IQR)** | **Mean ± SD** | **Median (IQR)** |
| **Charlson Index (%)** | | | | | | |
| **0** | 6,312 (22.4) | 2,394 (16.1) | 11,984 (27.9) | 5,789 (13.5) | 5,789 (13.5) | 5,789 (13.5) |
| **1** | 988 (3.5) | 590 (4.0) | 2,166 (5.0) | 1,197 (2.8) | 1,197 (2.8) | 1,197 (2.8) |
| **2** | 696 (2.5) | 368 (2.5) | 1,152 (2.7) | 812 (1.9) | 812 (1.9) | 812 (1.9) |
| **3** | 477 (1.7) | 264 (1.8) | 780 (1.8) | 751 (1.7) | 751 (1.7) | 751 (1.7) |
| **Missing** | 19,665 (69.9) | 11,233 (75.6) | 26,913 (62.6) | 34,450 (80.1) | 34,450 (80.1) | 34,450 (80.1) |
| **Income quintile (%)** | | | | | | |
| **1 (lowest)** | 5,034 (17.9) | 2,585 (17.4) | 8,298 (19.3) | 8,164 (19.0) | 8,164 (19.0) | 8,164 (19.0) |
| **2** | 5,554 (19.7) | 2,831 (19.1) | 8,488 (19.7) | 8,440 (19.6) | 8,440 (19.6) | 8,440 (19.6) |
| **3** | 5,574 (19.8) | 2,993 (20.2) | 8,853 (20.6) | 8,562 (19.9) | 8,562 (19.9) | 8,562 (19.9) |
| **4** | 5,660 (20.1) | 3,188 (21.5) | 8,938 (20.8) | 8,543 (19.9) | 8,543 (19.9) | 8,543 (19.9) |
| **5 (highest)** | 6,223 (22.1) | 3,168 (21.3) | 8,203 (19.1) | 8,857 (20.6) | 8,857 (20.6) | 8,857 (20.6) |
| **Missing** | 105 (0.4) | 84 (0.6) | 215 (0.5) | 433 (1.0) | 433 (1.0) | 433 (1.0) |
| **Long-term care (%)** | 71 (0.3) | 59 (0.4) | 100 (0.2) | 246 (0.6) | 246 (0.6) | 246 (0.6) |
| **History of dementia (%)** | 284 (1.0) | 215 (1.4) | 511 (1.2) | 589 (1.4) | 589 (1.4) | 589 (1.4) |

ADG = Aggregated Diagnosis Groups
provincial drug benefit plan for all individuals age 65 and older. These data sets were linked using unique encoded identifiers, which are derived from the resident’s health card number. All Canadian citizens, permanent residents, or landed immigrants living in Ontario are eligible for an Ontario health card.

### Inclusion Criteria

We identified individuals 35 years of age or older who had undergone appendectomy between 1 April 1997 and 31 March 2007. For each patient undergoing appendectomy, we identified 2 matched comparison individuals of the same sex within 5 years of age: (1) a person having had a cholecystectomy in the same year and never having had an appendectomy and (2) a person having had neither procedure. To determine the absence of procedures, we looked back to 1992, when the databases were established. The index date was designated as the date of the procedure or, for the nonprocedure group, within 1 year of the appendectomy date in their matched comparator. The agreement between Ontario administrative data and medical records is nearly perfect for appendectomy (kappa value of 0.98) and cholecystectomy (kappa = 0.97) in reabstraction studies.  

### Exclusion Criteria

Individuals were excluded if they had a diagnosis of parkinsonism within the 5 years preceding the index date, a vagotomy, or any resection of intestine, rectum, esophagus, or stomach any time preceding the index date. We excluded patients with a diagnosis of schizophrenia within 5 years preceding the index date to reduce the chance of including drug-induced parkinsonism. The diagnostic and procedural codes used are shown in the Supporting Information.

### Descriptive Variables and Covariates

Age and sex were obtained from the Registered Persons Database. Median neighborhood income was estimated based on the median income associated with postal codes from the 2006 Canadian Census. Using the Johns Hopkins Adjusted Clinical Group case-mix system, the number of Aggregated Diagnosis Groups (ADGs) in 1 year before cohort entry was used as a summary measure of comorbidity (http://acg.jhsph.org/index.php?option=com_content&view=article&id=55:describing-morbidity-burden&catid=37:system-components&Itemid=315). Residence in long-term care at baseline was obtained from OHIP and ODB, looking back 6 months before the index date. The diagnostic codes for dementia are listed in Supporting Table 1.

### Outcomes

PD was identified according to a previously published algorithm modified to exclude secondary and atypical parkinsonism codes. Under age 65, two PD OHIP International Classification of Diseases (ICD)-
8 or ICD-9/ICD-10 diagnostic codes (see Supporting table 1) within 1 year with at least 30 days between claims were required. For individuals 65 and older, one PD diagnostic code and one antiparkinson drug prescription (levodopa, dopamine agonist, monoamine oxidase type B inhibitor or catechol-O-methyl transferase inhibitor) within 6 months of each other were required. Previous validation work has estimated that the original algorithm has a sensitivity of 78% and specificity of 99%.

Follow-up

Follow-up began at the time of appendectomy or cholecystectomy or, for individuals who had undergone neither procedure, in the same year that their matched comparator underwent appendectomy. The observation window terminated at the first of (1) death, (2) start of a dopaminergic drug, (3) resection of any portion of the intestine, (4) diagnosis of schizophrenia, (5) use of metoclopramide, antipsychotic drugs, tetrabenazine, or reserpine, or (6) diagnosis of PD. Maximum follow-up was to 31 March 2014.

Statistical Analysis

Continuous variables were summarized as means (SDs) and medians (IQR), whereas categorical variables were summarized using frequencies and percentages. Formal statistical tests were not used for testing differences across groups. Cause-specific hazards regression models estimated the effect of appendectomy (vs. cholecystectomy or no procedure) on the cause-specific hazard of the occurrence of PD after accounting for the competing events listed above. These models stratified on the matched sets, allowing the baseline hazard function to vary across sets. The validity of the proportional hazard assumption was assessed by including an interaction between exposure status (appendectomy vs. control) and time. In the case of statistical significance of the interaction term, this term was used to estimate time-specific hazard ratios (HRs). Models were adjusted for median neighborhood income and ADGs. These analyses were repeated within strata of decade of age at the time of the procedure. In addition, a secondary model was fit in which the HR during the first 5 years of follow-up were allowed to differ from the HR after 5 years of follow-up, with the rationale that within the first 5 years of follow-up incident PD had likely begun before any procedure.

A secondary analysis was done excluding appendectomy procedures to which the surgeon assigned a procedural code indicating that the appendix had perforated.

All analyses were done using SAS software (version 9.4; SAS Institute Inc., Cary, NC). The study was approved by the research ethics board of Sunnybrook Health Sciences Center.

Results

A total of 42,999 individuals undergoing appendectomy were identified and matched to 42,995 individuals undergoing cholecystectomy and 42,999 individuals undergoing neither procedure. The groups were similar aside from higher comorbidity scores, which were highest in the cholecystectomy group and lowest in the no procedure group (Table 1). Median follow-up was 9.9, 10.2, and 10.4 years in the appendectomy, cholecystectomy, and no procedure groups, respectively. Median follow-up was approximately 10 years for all age strata under 75, but was shorter for older individuals because of death. Reasons for terminating follow-up are shown in Supporting Table 2. A total of 129 individuals in the appendectomy group, 172 individuals in the cholecystectomy group, and 93 controls met the criteria for PD during follow-up. Incidence rates per 100,000 person-years were 31 in the appendectomy group, 40 in the cholecystectomy group, and 21 in the control group. Age at first PD diagnostic code was above 55 in 84% of the appendectomy group, 86% of the cholecystectomy group, and 91% of the no procedure group. No significant difference in risk of PD was identified for individuals undergoing appendectomy compared to cholecystectomy, whether considering a uniform effect over the entire follow-up period (HR = 1.004; 95% confidence interval [CI]: 0.740–1.364; Table 2) or allowing the effect to differ before and after 5 years of follow-up (HR = 1.018; 95% CI: 0.677–1.531 during the first 5 years of follow-up vs. HR = 0.971; 95% CI: 0.632–1.492 after 5 years of follow-up). The proportional hazards assumption was not met for the comparison of appendectomy versus no procedure (P < 0.001). HRs estimated at time points revealed a higher risk of PD in the appendectomy group shortly after the procedure, which did not persist with increasing length of follow-up (Table 2).

We did not find a pattern of lower risk of PD with earlier age at the time of the procedure (see Supporting Tables 3 and 4). In a sensitivity analysis, we excluded individuals in the appendectomy group whose appendix had perforated and their matched comparators with the rationale that such an inflammatory event may negate any protective effect. This did not change the results (data not shown).

Discussion

In our large, population-based study, we did not find a lower incidence of PD after appendectomy compared to cholecystectomy or neither procedure. We did find a higher incidence of PD shortly after appendectomy compared to a control group having no procedure. Given the long presymptomatic phase of PD, it is likely that the pathological process was ongoing.
at the time of appendectomy in those developing PD within the first 5 years. It is possible that inflammation in the bowel could promote the ongoing aggregation and propagation of synuclein, resulting in a hastening of manifest disease. However, we hypothesize that the higher incidence is rather related to increased contact with the health care system around the time of the procedure, increasing the likelihood that parkinsonian signs will come to medical attention. This is consistent with the lack of such an association when cholecystectomy patients were used as a comparator group. The contrast highlights the importance of using an appropriate medical condition as the basis for sampling of a comparison group in such association studies.

Recently, Mendes and colleagues examined the relationship between age at onset within a group of 295 PD patients with and without self-reported appendectomy. Using a Cox proportional hazards model, they found no significant association between appendectomy and age at onset overall, although there was a later onset of PD in the appendectomy group within the subgroup of patients with age at PD onset over 55. In our cohort, 87% of the individuals meeting criteria for PD did so over the age of 55, and the proportion was highest in the no procedure group. Therefore, our data do not suggest an association between appendectomy and delayed PD onset within this older age group. Unlike the work by Mendes and colleagues, our study was not restricted to individuals who were known to develop PD over the follow-up period, an important assumption of the Cox proportional hazards model used in both studies. It is likely that our approach provides a less biased perspective on risk of PD related to appendectomy.

One limitation of our study was the lack of direct confirmation of PD diagnosis, which relied on administrative records. Missing cases of PD that were not yet diagnosed or diagnosed, but not yet treated, will reduce the number of cases and reduce precision. Inclusion of parkinsonism other than PD is inevitable, which would be expected to dilute any associations. However, previous validation studies identified PD as accounting for over 80% of the parkinsonism identified by the original algorithms, and we further excluded secondary and atypical parkinsonism codes for this study to increase specificity. Also, we did not have information on cigarette smoking, known to be negatively associated with PD. At least one study has suggested an increased risk of appendectomy in current smokers, which could thus result in a lower frequency of PD in the appendectomy group. This was not observed, however, in our study. As with any observational study, there is the possibility of unmeasured confounders biasing the results. The major limitation of our study was the maximum 17-year observation period. Older individuals who had had an appendectomy when they were young would not be captured by our study. Indeed, we expect some contamination of the control group with individuals who had had an appendectomy or cholecystectomy in early life, and such misclassification would tend to bias the results toward the null. Considering the long preclinical period for PD development, it may be important for appendectomy to occur early in life to have a meaningful protective effect, if it has any effect at all. Our study argues against an effect of appendectomy in mid or later life on later risk of PD.●

Acknowledgments: This work was funded by Physician Services Incorporated. This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. The funding agencies played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI. We thank Brogan Inc., Ottawa, for use of their Drug Product and Therapeutic Class Database. Dr. Austin is supported, in part, by a Career Investigator Award from the Heart and Stroke Foundation (Ontario office).

References

Supporting Data
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.