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The role of appendectomy in the development of Parkinson's disease: a retrospective study in a teaching hospital in Jordan

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Abstract

Background: Parkinson's disease is a degenerative brain disease related to the accumulation of an abnormally aggregated alpha-synuclein protein. A hypothesis was presumed that this protein will be transported retrogradely from the gastrointestinal tract ultimately leading to the disease. Various epidemiologic studies have shown conflicting results. This study reports the prevalence of appendectomy in Jordanian parkinsonian patients and compares it to controls seen at one major teaching hospital in Jordan. This is a retrospective study of 266 patients compared to a control group of 500 patients randomly selected from the hospital. The prevalence of appendectomy in the 2 groups was studied.

Results: The rate of appendectomy in patients and controls was 26/266 (9.8%) and 27/500 (5.4%), respectively (relative risk 1.30, odds ratio 1.81, χ^2, $p = 0.026$). Appendectomy in the patients was independent of gender (χ^2, $p = 0.297$). Also, there was no difference in patients with and without appendectomy regarding their age, age at diagnosis of PD, and duration of use of levodopa ($p = 0.827$, 0.960, and 0.688, respectively, Student t test). The mean duration from appendectomy to the diagnosis of the disease varied widely 23 ± 18.7 years, range −12–59 years.

Conclusions: Appendectomy occurred significantly more frequent in patients with Parkinson's disease than in control. There was no difference regarding the age of onset of disease in the patients with and without appendectomy. Though the appendix in this study seems to have a protective role against the development of the disease, the relationship is quite complex requiring prospective in-depth evaluation.

Keywords: Parkinson's disease, Appendectomy, Jordanian, Brain-gut axis

Background

Parkinson's disease (PD) is the most common sporadic degenerative movement disorder. Although James Parkinson described the disease in 1817 [1], its diagnosis is still based on a set of clinical criteria which currently requires the presence of bradykinesia, rigidity, and tremor [2, 3] precluding certain exclusion criteria and red flags [4]. The understanding of PD etiology and pathogenesis has evolved over the previous decades. The documentation of loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) was a milestone in the solving of the multifaceted puzzle of PD. The discovery of inherited cases of PD in a minority of patients 5–15% [4] and the knowledge of the function of some of the dysfunctional or mutated genes with advanced histopathological techniques lead to the consideration of the pathogenesis related to the accumulation of misfolded

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protein in Lewy bodies which are considered the pathological marker of PD [3, 5–7]. Alpha synuclein (Asyn) when misfolded gets aggregated and this leads to a cascade of events preceding the premature destruction of the dopaminergic neurons of the SNpc [8]. Non-motor manifestations of PD like anosmia, constipation, depression, dementia, sleep disturbances, and other autonomic dysfunction suggest that PD is not restricted to SNpc, but rather a multisystem disease involving other parts of the central and peripheral nervous system [9]. The discovery of Asyn in the mucosa of the gastrointestinal tract [10, 11], particularly in the vermiform appendix, proposes a possible link between the gut and the brain: the gut-brain axis [12]. New attention to the importance and function of the appendix proved that it has a significant role in the immune system of the gut, the microbiome, and the possibility of being a port of transfer of misfolded branched Asyn protein by a prion-like process through the vagus nerve to the brainstem then to be disseminated to the brain reaching different areas explaining the different clinical and pathological findings [8, 10, 13]. A significant laboratory and animal study supported this gut-brain axis hypothesis [12]. Truncal vagotomy may be associated with a lower incidence of PD [14]. Clinical interest for the relationship between appendectomy which is a frequent procedure typically performed in early adulthood [10] and the future development of PD has been reported in the last few years. Many such clinical observations and studies have been published with variable conclusions ranging from preventive or delaying [15–17], neutral [18–20], to accelerating/increasing [21, 22] the risk of occurrence of PD in patients who underwent appendectomy in their early adulthood. These conflicting findings may be interpreted as a possible protective, neutral, or pathological role of the appendix in the development of sporadic PD. Here, this retrospective study investigated if patients with the clinical diagnosis of PD had a significantly different prevalence of appendectomy compared to a control group and if those PD patients with appendectomy differed from PD patients without appendectomy regarding the onset of their disease.

Methods

Patients with clinical diagnosis of PD in our hospital over the last 5 years (2014–2019) who were followed at the outpatient neurology clinics were studied. Their charts were reviewed by our research team and their clinical diagnosis was confirmed by the neurology clinic note. Their response to levodopa was also documented. Patients who had at least 1 year of follow-up were studied. Their contact information was collected and they were contacted by the research team, and after taking their consent, they were interviewed mainly over the phone and asked if they had a history of appendectomy, the reason behind it (to mark if appendix removal was due to appendicitis or incidentally), the date and age of the procedure, the age of diagnosis of PD and the duration of levodopa treatment which is the gold standard drug to treat these patients, other surgical procedures in addition to their gender, and age if alive or date of their death (from a family member). We randomly chose 500 adult patients who were seen at the hospital in the same period with no history of PD and reviewed their charts and contacted them for a history of appendectomy and other surgeries/interventions. In addition, it was documented that they were not diagnosed with PD or were prescribed levodopa for any reason by checking their pharmacy records. This study was approved by our institutional review board (IRB).

Statistical methods

We used SPSS package version 22, USA, to analyze our data. The following variables were collected for PD patients: age, gender, age at PD diagnosis, age at appendectomy, duration of levodopa treatment, and other surgeries. For control subjects, we recorded their age, gender, appendectomy, and other surgical interventions. For continuous variables, we used descriptive statistics and calculated mean, range, and standard deviations. For categorical variables, we calculated frequencies. The Pearson chi-square test (χ^2) was used to assess for the difference of appendectomy between PD patients and control and to look for the dependence of appendectomy on gender. Also, relative risk (RR) and odds ratio (OR) of having appendectomy in PD patients compared to the control group were calculated. An independent sample t test was used to look for differences between PD patients with and without appendectomy regarding age, age of onset of PD symptoms, and duration of levodopa use. A p value of < 0.05 was considered significant. We used a regression model to assess for the significance of age, gender, or category of being a PD patient or control and the odds of having appendectomy.

Results

The study included 266 patients with PD who had the needed information. Table 1 shows the characteristics of PD patients compared to control and Table 2 shows the characteristics of PD patients with and without appendectomy.

PD patients were slightly older than control patients v70.7 ± 11.4 vs 68.1 ± 9.2, 55–96 ($p = 0.001$). Otherwise, there was no difference in gender distribution. We did not study other possible confounding risk factors pertinent to PD like smoking and exposure to pesticides as our main interest was not the incidence of PD but rather the effect of appendectomy on PD and to know if

Table 1 Comparison between PD and control patients

	Control (n = 500)	PD (n = 266)	p value
Age (M ± SD, range) years	(68.1 ± 9.2, 55–96)	(70.7 ± 11.4, 37–96)	0.001¥
Gender (M/F %)	50%/50%	57.1%/42.9%	0.068*
Appendectomy *n* (%)	27 (5.4%)	26 (9.8%)	0.023* OR 1.81, 95% CI 1.08–3.04 RR 1.30, 95% CI 1.00–1.71

¥ *t* test, *Pearson χ^2 test, PD vs control patients; *CI* confidence interval, *SD* standard deviation, *M/F* male/female, *OR* odds ratio, *RR* relative risk

patients with PD had more appendectomies compared to non-PD patients. There were more appendectomies in PD patients compared to control patients 9.8% vs 5.4% (RR 1.30, 95% CI 1.00–1.71 and OR 1.81, 95% CI 1.08–3.04, p = 0.026, Fisher exact test). On regression analysis for the odds of having appendectomy using age, gender, and category (PD vs control), only category was significant with the following odds ratios: Exp(B) of 1.97, 1.00, and 0.94 for the category, gender, and age, respectively (p values 0.018, 0.97, and 0.23, respectively). When comparing PD patients with appendectomy to those PD without appendectomy, there was no significant difference regarding their age, age of onset of PD as manifested by the motor manifestations, and the duration of use of levodopa. Appendectomy was independent of gender and both groups had similar exposure to other surgeries and interventions. Age at appendectomy was relatively late 40.1 ± 18.7 (40–88) and the time to PD was 23 ± 18.4 (−12–59) years. Two patients had their appendectomy after the diagnosis of PD, one of them after 6 years and the other after 12 years, and one patient had incidental appendectomy while others were suspected to have acute appendicitis. This finding did not affect our results since we excluded the 3 patients.

Discussion

The relationship between the gastrointestinal tract and the nervous system is quite established based on basic laboratory and clinical studies [23]. This relationship is complex and multifaceted although the real interaction is still speculative. There is a significant evidence to support a relationship between the appendix and PD [10]. Previous clinical studies and observations regarding this relationship have been conflicting. This may be related to the different methods and patients in these studies. Here, in this study, patients with PD had a higher prevalence of previous appendectomy compared to control, but—interestingly enough—those PD patients with appendectomy did not differ from those without appendectomy regarding the age of the onset of their disease. If the appendix had a protective role and when it becomes inflamed (the main reason for appendectomy), it leads to a change in GI microbiome and perhaps alters the normal structure of Asyn to the pathologic form that in turn will be transported by the vagus nerve to the brainstem ultimately leading to the most common form of CNS synculeopathies namely PD [10, 24, 25]. This speculated sequence of events will be expected to lead to earlier onset of PD which was not the case in our patients. We may be quite wrong in this speculation and what we see reflects the small number of our control group and that they were not well matched to the PD patients as their age at least was slightly younger than PD patients. We assumed PD have started at the time of motor manifestations. Indeed, once these manifestations occur, almost 60% of the SNpc neurons have already degenerated [26]. The onset in most patients starts as mild non-motor symptoms like anosmia and constipation, and if there was an appropriate study of these non-motor manifestations, this would have shown if they started significantly earlier than those PD patients without appendectomy. The time interval between appendectomy and the onset of PD was quite variable 23 ± 18.4 years which makes the relationship rather unlikely or more complex and indirect, so a second hit or triggering factors may be needed [10]. Other previous studies also concluded that appendectomy was associated with a higher prevalence of PD. In a study using Danish medical and administrative registries of 265,758 appendectomy patients compared to 1,328,790 control patients,

Table 2 Comparison between PD patients with appendectomy and those PD patients with no history of appendectomy

	PD (n = 240)	PD appendectomy (n = 26)	p value
Age (mean ± SD, range)	70.7 ± 11.3(37–96)	70.2 ± 12.4 (47–91)	0.827¥
Gender (M/F %)	58.3%/41.7%	46.2%/53.8	0.23*
Age at diagnosis	64.5 ± 11.8	64.7 ± 13.5	0.95¥
Duration of LD use (mean ± SD, range)	6.1 ± 4.8 (1–25)	5.91 ± 3.3 (1–15)	0.71¥
Other surgeries %	45%	65%	0.05*

¥ *t* test, *Pearson χ^2 test, *M/F* male/female, *PD* Parkinson's disease, *LD* levodopa, *SD* standard deviation

Sevesson and colleagues found a small increase in the risk of having PD in those with appendectomy (hazard ratio of 1.14, 95% CI 1.03–1.27) after more than 20 years post-appendectomy follow-up [21]. In another large study of a huge database including more than 62 million patients and almost half a million of appendectomy patients, Shirif and colleagues concluded that the relative risk to develop PD was 3.19, 95% CI 3.10 to 3.28, $p < 0.0001$ regardless of gender or ethnicity. They could not determine the duration between appendectomy and PD onset [22]. Other studies showed a preventive or protective effect of appendectomy on the development of PD. In a large study from Sweden, Liu and colleagues found a 16% lower risk of PD in patients who underwent appendectomy compared to control after studying 78, 650 PD patients, each one compared to 40 non-PD control individuals matched for gender and year of birth [15]. In another small study like ours including 295 patients with PD, Mendes and colleagues found that patients with appendectomy had a later onset of PD than in those without appendectomy who had PD onset after the age of ≥55 years but has no effect on the age of onset on the entire cohort or those with the younger onset of PD [16]. In a well-conducted epidemiological and pathological study of the appendix in two independent datasets involving more than 1.6 million persons and 91 million persons after a year of observation, Killinger and colleagues found that appendectomy was associated with a lower incidence of PD especially in people living in rural areas. They also found that lysate of the human appendix tissue led to rapid cleavage and aggregation of Asyn [17]. Other studies did not suggest a clear relationship between appendectomy and PD incidence. Marras and colleagues studied the relationship between mid- and later-life appendectomy and the risk of PD, compared to patients who had cholecystectomy or no surgery. They found no increase in the incidence of PD in appendectomy compared to cholecystectomy (hazard ratio = 1.004; 95% confidence interval 0.740–1.364) and slightly higher incidence compared to the no surgery patients in the first 5 years postoperatively but not later. This may be related to already existing non-motor PD in such patients [27]. Other epidemiologic studies considered the first 5 years as a washout period [28]. In a retrospective study from Turkey comparing 69 PD patients with appendectomy and 770 PD without appendectomy, Yilmaz and colleagues found no effect of appendectomy on the onset, duration, or severity of PD and that the age of appendectomy (less or more than 20 years) did not affect the risk of developing PD [28]. Palacios and colleagues studied 2 large cohorts of women and men in the nurses' health study and the health professional's follow-up study; in the pooled analysis of both groups, self-reported appendectomy was not related to the risk of PD with a hazard ratio of 1.08 (95% confidence interval 0.94, 1.23). The risk for women who reported appendectomy for appendicitis rather than incidental appendectomy was higher with a hazard ratio of 1.23 (95% confidence interval 1.00, 1.50). All in all, the study suggested limited or no association between appendectomy and the risk of PD [29]. Finally, in a meta-analysis of studies of PD and appendectomy, Lu and colleagues concluded that appendectomy had no significant effect on the incidence of PD with a relative risk of 1.02, 95% CI 0.87–1.20, $I^2 = 83.1\%$, $p = 0.789$ [21]. So, this study supports those studies indicating a positive relationship between appendectomy and the risk of developing PD. The possible reason is that all our patients except one had appendicitis as the cause of their appendectomy and that was seen in the nurses' health study. Again, this study adds to the uncertainty about the relationship of appendectomy and PD as those patients with appendectomy did not differ from those PD without appendectomy in the age of onset or severity of disease as reflected by the duration of use of levodopa. It is important to mention that the duration of levodopa use does not necessarily indicate disease duration or severity as its use is typically guided by patient symptoms and their effect on daily life activities. Levodopa use reflects the presence of motor symptoms which may not indicate the onset of the disease as non-motor symptoms may have appeared much earlier. The strength of our study comes from the well-documented PD diagnosis, one center study, and as it is the first that comes from our region which will add to data coming from the other regions in the world. The limitations of our study include the relatively small number of patients and controls compared to other major studies. There were 648 surveyed candidate patients with PD, but only it included 266 who were reported here. The main reason for being not included in the study was the inability to contact them, even though they did not differ from studied patients regarding their age, gender, or duration of PD. Another limitation was the lack of study of other PD risk factors like smoking or exposure to pesticides. There was as well no attempt to correlate the progression of PD non-motor symptoms especially gastrointestinal, the total or motor score of UPDRS, or Hoehn and Yahr staging between patients with and without appendectomy. Despite these limitations, we still believe that this study confirms the need for a well-conducted international prospective study of patients with appendectomy including studies that detect preclinical PD or PD in the premotor stage.

Conclusion

Our study showed that appendectomy occurred significantly more frequent in patients with PD compared to

non-PD (control group) with a possible significant effect and increased relative risk of 1.3 of appendectomy on the incidence of PD in our population like some previous studies. Further studies are needed for a better understanding of the pathogenesis and progression. This insight may open new ways of its treatment through a better understanding of the relationship between the gut, mainly the appendix and the brain.

Abbreviations

PD: Parkinson's disease; Asynch: Alpha synuclein; SNpc: Substantia nigra paras compacta; LD: Levodopa; RR: Relative risk; OD: Odds ratio; IRB: Institutional review board; SPSS: Statistical Package for the Social Sciences; UPDRS: Unified Parkinson's disease rating scale; Exp(B): Exponential B in logistic regression analysis

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Authors' contributions

SD: idea generation, data analysis and writing of the initial manuscript, revision, and acceptance of the final manuscript. AS, RH, and TD participated in idea generation and data collection. AD participated in idea generation and data analysis. All authors have read and approved the final manuscript.

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Availability of data and materials

The data set used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Jordan university review board (IRB)/Faculty of medicine research committee decision # 8023/2019/67.
All patients gave *a verbal consent* as this was a retrospective study with an interview of the patient and a review of his medical file. No interventions were applied on the participants, and the institution review board approved the study based on this verbal consent.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

1. Lees A. An essay on the shaking palsy. Brain. 2017;140(3):843–8. https://doi.org/10.1093/brain/awx035.
2. Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonafati V, et al. EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease. Eur J Neurol. 2013;20(1):16–34. https://doi.org/10.1111/ene.12022.
3. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276(5321):2045–7. https://doi.org/10.1126/science.276.5321.2045.
4. Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol. 2020;27(1):27–42. https://doi.org/10.1111/ene.14108.
5. Gasser T. Genetics of Parkinson's disease. Ann Neurol. 1998;44((Suppl) 1):53–7.
6. Hsu LJ, Sagara Y, Arroyo A, Rockenstein E, Sisk A, Mallory M, et al. Alpha-synuclein promotes mitochondrial deficit and oxidative stress. Am J Pathol. 2000;157(2):401–10. https://doi.org/10.1016/S0002-9440(10)64553-1.
7. Rocha EM, De Miranda B, Sanders LH. Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiol Dis. 2018;109:249–57. https://doi.org/10.1016/j.nbd.2017.04.004.
8. Scott DA, Tabarean I, Tang Y, Cartier A, Masliah E, Roy S. A Pathologic Cascade Leading to Synaptic Dysfunction in-Synuclein-Induced Neurodegeneration. J Neurosci. 2010;30(24):8083–95. https://doi.org/10.1523/JNEUROSCI.1091-10.2010.
9. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol. 2008;15(Suppl 1):14–20.
10. Killinger B, Labrie V. The appendix in Parkinson's disease: from vestigial remnant to vital organ? Bryan J Parkinsons Dis. 2019;9(Suppl 2):345–58.
11. Stokholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological α-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. Ann Neurol. 2016;79(6):940–9. https://doi.org/10.1002/ana.24648.
12. Chao Y-X, Gulam MY, Chia NSJ, Feng L, Rotzschke O, Tan E-K. Gut–brain axis: potential factors involved in the pathogenesis of Parkinson's disease. Front Neurol. 2020;11:849. https://doi.org/10.3389/fneur.2020.00849.
13. Visanji NP, Brooks PL, Hazrati L, Lang AE. The prion hypothesis in Parkinson's disease: back to the future. Acta Neuropathol Commun. 2013;1:2.
14. Svensson E, Horvath-Puho E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015;78(4):522–9. https://doi.org/10.1002/ana.24448.
15. Liu B, Fang F, Ye W, Wirdefeldt K. Appendectomy, tonsillectomy and Parkinson's disease risk: a Swedish register-based study. Front Neurol. 2020;11:510. https://doi.org/10.3389/fneur.2020.00510.
16. Mendes A, Gonçalves A, Vila-Chã N, Moreira I, Fernandes J, Damásio J, et al. Appendectomy may delay Parkinson's disease onset. Mov Disord. 2015;30(10):1404–7. https://doi.org/10.1002/mds.26311.
17. Killinger BA, Madaj Z, Sikora JW, Rey N, Haas AJ, Vepa Y, et al. The vermiform appendix impacts the risk of developing Parkinson's disease. Sci Transl Med. 2018;31:465.
18. Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of α-synuclein pathology: vagal highway or dead end? Mov Disord. 2019;34(3):307–16. https://doi.org/10.1002/mds.27556.
19. Yilmaz R, Bayram E, Ulukan, Altınok MK, Akbostancı MC. Appendectomy history is not related to Parkinson's disease. J Parkinsons Dis. 2017;7(2):347–52. https://doi.org/10.3233/JPD-171071.
20. Lu HT, Shen QY, Xie D, Zhao QZ, Xu YM. Lack of association between appendectomy and Parkinson's disease: a systematic review and meta-analysis. Aging Clin Exp Res. 2020;32(11):2201–9. https://doi.org/10.1007/s40520-019-01354-9.
21. Svensson E, Horváth-Puhó E, Stokholm MG, Sørensen HT, Henderson VW, Borghammer P. Appendectomy and risk of Parkinson's disease: a nationwide cohort study with more than 10 years of follow up. Mov Disord. 2016;31(12):1918–22. https://doi.org/10.1002/mds.26761.
22. Sheriff MZ, Mansoor E, Cooper GS. Parkinson's disease is more prevalent in patients with appendectomies: a national population-based study. Gastro. 2019;156(Suppl 1):409.
23. Spielman LJ, Gibson DL, Klegeris A. Unhealthy gut, unhealthy brain: the role of the intestinal microbiota in neurodegenerative diseases. Neurochem Int. 2018;120:149–63. https://doi.org/10.1016/j.neuint.2018.08.005.
24. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Esra Ilhan Z, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016;167(6):1469–80. https://doi.org/10.1016/j.cell.2016.11.018.
25. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T, et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014;128(6):805–20. https://doi.org/10.1007/s00401-014-1343-6.
26. Marsden CD. Parkinson's disease. Lancet. 1990;335(8695):948–9. https://doi.org/10.1016/0140-6736(90)91006-V.

27. Marras C, Lang AE, Austin P, Urbach DR, Lau C. Appendectomy in mid and later life and risk of Parkinson's disease: a population-based study. Mov Disord. 2016;31(8):1243–7. https://doi.org/10.1002/mds.26670.
28. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain. 1991;114(5):2283–301. https://doi.org/10.1093/brain/114.5.2283.
29. Palacios N, Hughes KC, Cereda E, Schwarzschild MA, Ascherio A. Appendectomy and risk of Parkinson's disease in two large prospective cohorts of men and women. Mov Disord. 2018;33(9):1492–6. https://doi.org/10.1002/mds.109.

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