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Review Article

## Parkinson's disease and appendix: a hidden kinship

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### ABSTRACT

Parkinson's disease is now recognized as the second most prevalent neurodegenerative disorder after Alzheimer's disease. More than 8.5 million people worldwide are estimated to have Parkinson's, and its frequency is rising swiftly because of global population aging. The disease is primarily marked by abnormal protein clumps, called Lewy bodies, found in the brain. Numerous studies have connected Parkinson's disease to the gut, suggesting that gastrointestinal issues like appendicitis could increase the likelihood of developing Parkinson's later in life. A review of several studies on the link between Parkinson's disease and gastrointestinal disorders shows that Parkinson's often follows such disorders, though genetics, the environment, and an individual's immune system also contribute. Some studies, however, report that early appendectomy may lower the risk of Parkinson's or delay its onset in people with a family history of the disease. This review examines the evidence on the relationship between the appendix and Parkinson's disease, presenting data on how the appendix may influence the development of PD. We conclude that while the appendix is not the only factor in Parkinson's disease, it may play an important role in its development.

**Keywords:** Parkinson's disease, Vermiform appendix,  $\alpha$ -synuclein, Gut-brain axis, Lewy bodies, Gastrointestinal involvement

### INTRODUCTION

The role of the appendix in the human body has been a topic of continuous debate and is often described as a vestigial organ. The presence of gut-associated lymphoid tissue in the lamina propria of the appendix has led to the belief that it serves a function in immunity, although the specific nature of this has never been identified.<sup>1</sup> A recent study has suggested that the appendix may serve as a storage house for microbial gut flora. Thus, it is suggested to play a major role in systemic diseases like Crohn's disease and Parkinson's disease. Parkinson's disease (PD) is the most common neurodegenerative movement disorder. It is neuropathologically characterized by the presence of Lewy bodies composed of  $\alpha$ -synuclein.  $\alpha$ -synuclein pathology spreads to the brain via the dorsal motor nucleus of the vagus nerve (Savica R et al, 1752-1758 (2009)). Another cause of Parkinsonism is the parkin

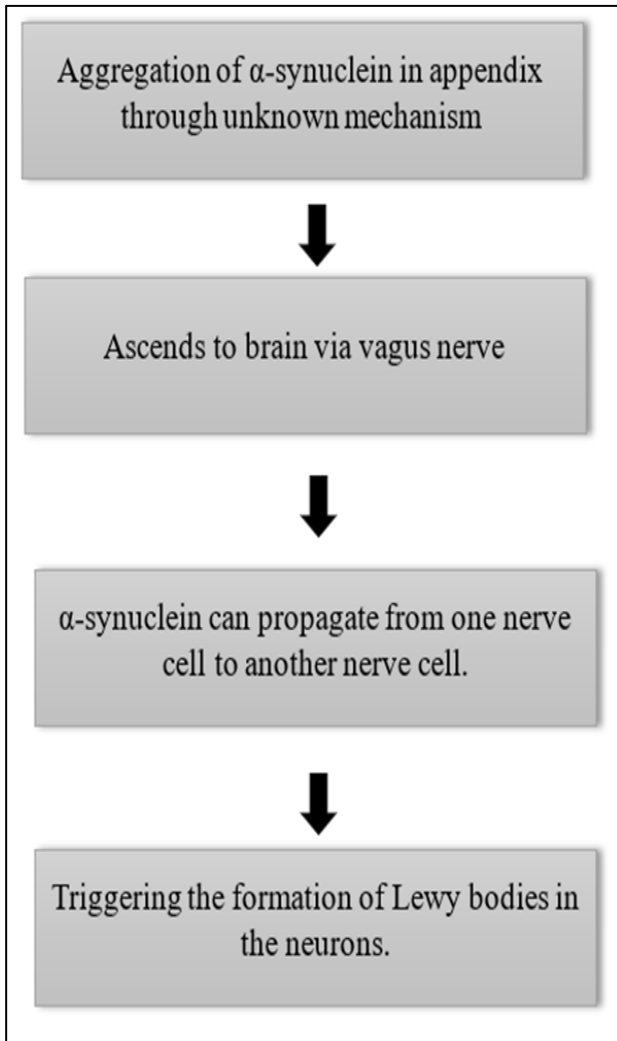
protein encoded by the PARK2 gene. The parkin protein plays a crucial role in association with an autosomal recessive form of PD. The Parkin protein plays a crucial role in the ubiquitin-proteasome system, which is responsible for degrading damaged or unnecessary proteins.<sup>2</sup>

Mutations in the PARK2 gene can lead to a loss of parkin function, resulting in the accumulation of harmful proteins in cells, particularly in neurons. This accumulation of proteins contributes to the neurodegeneration seen in Parkinsonism.<sup>3</sup> PD is characterized by motor dysfunctions as well as gastrointestinal symptoms and mental impairment. As the research goes on, growing evidence of PD association with the gastrointestinal system makes it a significant association.<sup>4</sup> One of the underlying pathomechanism of this is  $\alpha$ -synucleinopathy, which is found in the appendix. The assumption about Parkinsonism

associated with the appendix, as  $\alpha$ -synuclein, which accumulate in the appendix, is disseminated to the brain via the vagus nerve. Apart from the appendix, it is also said to be accumulated in the retina, colon, etc. So here, the question arises whether removal of the appendix, i.e. appendectomy, increases or decreases or has no association with risk of PD or delays its onset.

## PATHOGENESIS

One of the possible pathways that  $\alpha$ -synuclein can travel from the gut or appendix to the brain is given in figure 1.



**Figure 1: Flow chart of the possible pathophysiology of Parkinson's associated with the appendix.**

During research, it has been found that accumulation of aggregated  $\alpha$ -synuclein in the enteric nervous system is believed to be involved in the pathogenesis of PD. In prodromal PD and PD patients, there are higher levels of aggregated (proteinase K-resistant)  $\alpha$ -syn in the appendix compared to another GI tract region.  $\alpha$ -syn aggregates are also prevalent in the mucosa and enteric plexuses of the healthy human appendix. Aggregated  $\alpha$ -syn was shown to be present in all age groups of the healthy human appendix,

including young individuals (<20 years of age), and was observed in individuals with a normal appendix and those with an inflamed appendix.<sup>13</sup>  $\alpha$ -Syn aggregates were particularly enriched in nerve terminals of myenteric plexuses of the appendix, which are innervated by the vagus nerve, which can be a reason for the propagation of  $\alpha$ -Syn aggregates to the brain.<sup>13</sup>  $\alpha$ -Syn truncation products are enriched in Lewy bodies and can serve as potent seeds for rapid  $\alpha$ -syn aggregation in experimental models.<sup>14-17</sup>  $\alpha$ -Syn truncation products, i.e., the digested products identified in the appendix, contained an intact NAC-domain, which is necessary and sufficient for  $\alpha$ -syn aggregation.<sup>18,19</sup>

Elimination of the N- and/or C-terminal enhances aggregation kinetics of  $\alpha$ -syn in-vitro and in-vivo, suggesting that the prevalence of truncated  $\alpha$ -syn in the appendix likely makes this tissue prone to PD-relevant pathology.<sup>17-22</sup> Accumulation of  $\alpha$ -syn aggregates and of the N and/or C-terminal truncated  $\alpha$ -syn protocorms identified in the appendix is neurotoxic in the brain, leading to neuro degeneration.<sup>17</sup> The appendix lacks a blood tissue barrier, suggesting that appendectomy may reduce  $\alpha$ -synuclein aggregation in the appendix.<sup>7</sup> Some studies have found appendectomy to be associated with a reduction in risk for developing PD, while others have found no effect, or even increased risk.<sup>17-20,24-26</sup>  $\alpha$ -synuclein resides in the dorsal motor nucleus of the vagus nerve, the olfactory bulb, the enteric nervous system and the submandibular gland.<sup>8</sup> The process seems to start in the enteric nervous system or the olfactory bulb and spreads via rostro cranial transmission to the substantia nigra and further into the CNS.

## DISCUSSION

According to the information we reviewed, we found cases that showed positive association of PD with the appendix, negative association, and no association at all. However, it can be one of the reasons that aggravates the condition. The Kaplan-Meier plot showed the onset of PD for individuals with 0,1,2, or >2 relatives with PD. Patients with 3 or more relatives with PD had a much earlier onset ( $p=0.063$ ). This illustrates the genetic relationship between the onset of PD. Whereas in another study, patients who had undergone an appendectomy before Parkinson's were examined in the study. The study showed that an appendectomy postponed the age of Parkinson's onset in individuals with a family history of Parkinson's, with a p-value less than 0.01, which suggests that the result of the hypothesis test is highly significant. The patients were divided into three groups that is patient with appendectomy, patients without appendectomy and patients with a history of PD. For a Patient "with a family history of PD" who had an appendectomy, the median age of PD onset was 63.2, and for the patient without an appendectomy, the median age of PD onset was 58.4, i.e. comparatively early than the patient with an appendectomy. An appendectomy did not benefit the age of Parkinson's onset in a patient with "no family history". That is, for patients with appendectomy,

the median age of PD onset was 60.1, and for those without an appendectomy, the median age of PD onset was 59.2. This is quite similar in both cases with or without appendectomy.<sup>26</sup>

## CONCLUSION

PD cannot be solely associated with the appendix. It is considered that it is caused by a combination of both genetic and environmental factors. The Individual immune system also plays a major role in the occurrence of diseases, as bacterial or viral infections have been proposed as potential risk factors. Biological plausibility for the role of infectious agents is supported by the known neurotropic effects of specific viruses, the particular vulnerability of the substantia nigra, and even the promotion of alpha-synuclein aggregation. Essentially, all bacterial or viral infection act as a triggering factor leading the body to a vulnerable state and making it susceptible to the occurrence of diseases. Therefore, we conclude that PD is not fully associated with the appendix. Although the appendix plays a major role in the occurrence of the disease, as the data suggest, Various underlying factors may also be involved. Some of which may not yet be discovered connecting these factors reveals a linkage between them.

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