

Article

Parkinson's Disease

# Gastrointestinal dysfunction in Parkinson's disease

*After decades of focus on the motor impairments of Parkinson's disease (PD), the past years have shown a resurgence of interest in non-motor symptoms, including gastrointestinal dysfunction. It is now well recognised that gastrointestinal symptoms, particularly constipation, are amongst the most prominent and troublesome early manifestations of PD. The fact that alpha-synuclein aggregations can be found in the gastrointestinal tract of patients with early or even prodromal PD lends weight to the idea that PD may start in the gut, at least in some patients.*

# Gastrointestinal dysfunction in Parkinson's disease

Reviewed by Prof. Lim Shen-Yang

Neurologist and Professor at the University of Malaya,  
Kuala Lumpur, Malaysia

Published: 17.01.2023

Parkinson's disease is often defined as a degenerative condition of the brain,<sup>1</sup> but it is the neuronal connections outside of the brain, particularly those of the gastrointestinal tract, that have become a focus of interest in PD in recent years.<sup>2-4</sup> The gastrointestinal tract is innervated by the largest part of the peripheral nervous system, an autonomous network of neurons known as the enteric nervous system (ENS).<sup>5,6</sup> The ENS communicates with the central nervous system (CNS) but can operate independently, which is why it is sometimes called 'the second brain'.<sup>6</sup>

The gut-brain axis is a bidirectional communication system between the CNS and the ENS. This axis is comprised of two main communication pathways – humoral factors such as cytokines, hormones, and bacterial metabolites from the gut microbiome, and the vagal nerve (Figure 1).<sup>5,7</sup> The ENS contains neuronal and glial cells that are similar to those found in the CNS, sharing many features, including neurochemistry.<sup>5,8,9</sup>

Parkinson's disease gives rise to an array of gastrointestinal symptoms and clinical manifestations, which include gastroparesis (slowed gastric emptying) and impaired absorption, dysphagia (difficulty swallowing) and drooling, and constipation.<sup>10</sup>

Gastrointestinal symptoms directly contribute to weight loss and low body mass index, complicate clinical management and significantly impact the prognosis of patients with PD.<sup>10,11</sup> Gastrointestinal disturbances also greatly impact quality of life and are a common reason for emergency room visits and hospitalisations.<sup>12</sup> The time of onset and severity of gastrointestinal dysfunction varies between patients, but almost every patient with PD will eventually suffer these symptoms.<sup>10</sup> Gastrointestinal symptoms often occur at an early stage in PD and, in some cases, can even precede motor symptoms by decades.<sup>13</sup>

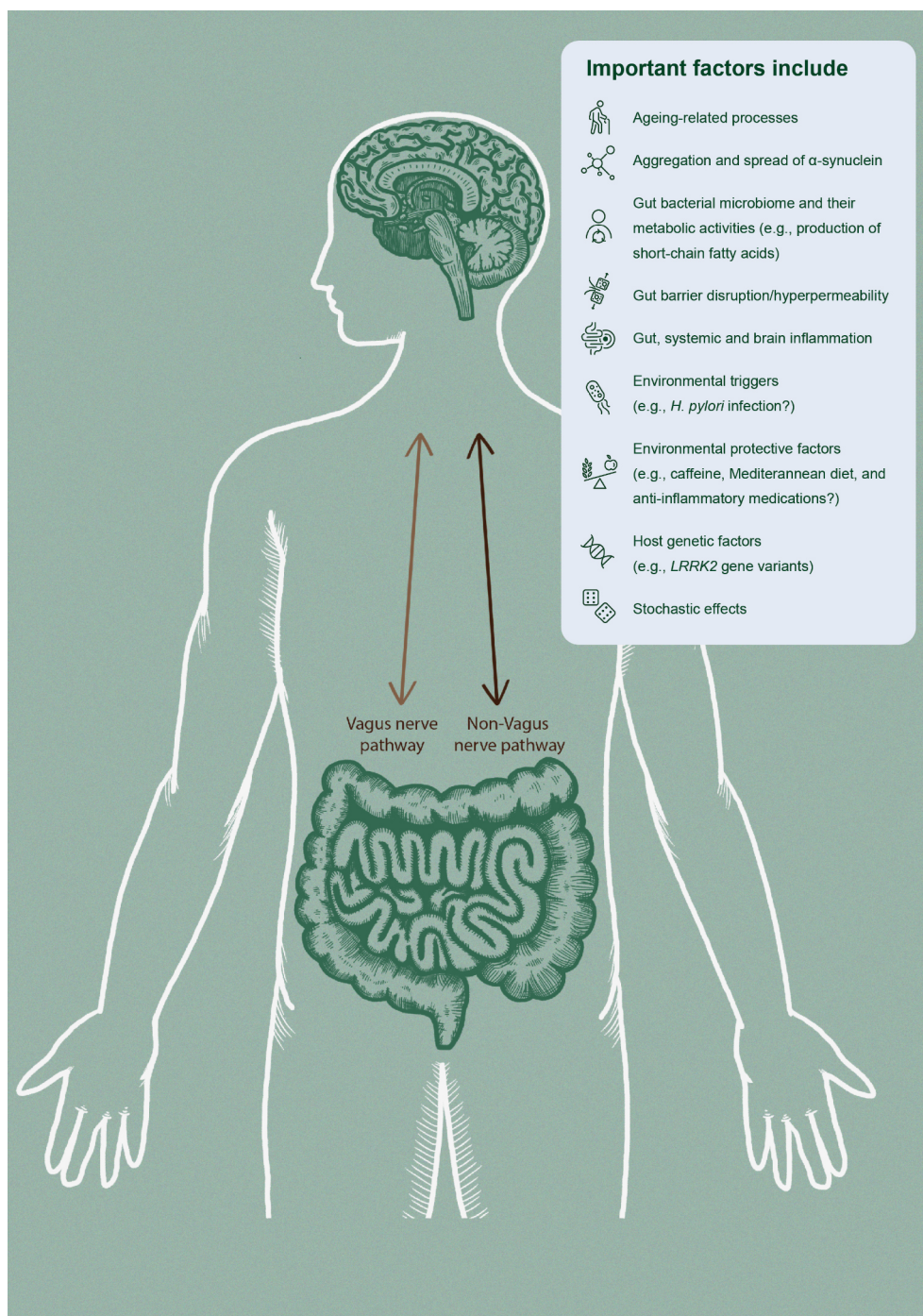


Figure 1. Bidirectional interplay between the brain and the gut includes the vagus nerve pathway, and non-vagus nerve pathways such as the bloodstream. Important factors associated with the development of PD include ageing-related processes, aggregation and spread of alpha-synuclein, gut bacterial microbiome and their metabolic activities, gut barrier disruption, inflammation, environmental influences, host genetic factors, and probably chance effects.



## Common gastrointestinal symptoms in PD

### Dysphagia

The reported prevalence of dysphagia in PD varies widely, but has been reported in 9–82% of patients.<sup>14</sup> Dysphagia in PD is associated with impairments in the brainstem, basal ganglia, and also cortical areas.<sup>15</sup> These impairments act to reduce the control of swallowing mechanisms in the oral, pharyngeal, and oesophageal phases.<sup>10</sup> Dysphagia is more commonly associated with male gender, advanced age, longer duration of disease, dementia, depression, and more severe motor symptoms.<sup>14</sup>

Drooling (sialorrhea), caused by insufficiency in swallowing saliva and unintentional mouth opening as part of the masked facial expression of PD, is a common effect of dysphagia.<sup>14</sup> In addition to the negative social and quality of life effects, dysphagia and drooling can cause difficulties with feeding and speech, leading to weight loss and dehydration and increased risk of aspiration pneumonia.<sup>14</sup>

### Gastroparesis

Gastroparesis is thought to be common in patients with PD, reported in up to 70–100% of patients, although the true prevalence is controversial, and it is not always symptomatic.<sup>2,3,16</sup> Gastroparesis is characterised by feeling full after ingestion of only a small amount of food, and is associated with a wide range of symptoms that include nausea, vomiting, and bloating.<sup>5</sup> These symptoms can lead to weight loss, malnutrition, and dehydration, with corresponding serious consequences for the patient.<sup>5</sup>

The pathophysiological abnormalities of gastroparesis involve both CNS and ENS abnormalities, particularly the parasympathetic system.<sup>5,10</sup> Medications used to treat PD may also delay gastric emptying, which may partly explain the progression of gastroparesis in advanced PD.<sup>3,12,16,17</sup> Because levodopa is predominantly absorbed in the small intestine but is metabolised and inactivated in the stomach, the delayed gastric emptying may result in reduced levodopa bioavailability and medication effect.<sup>3</sup>

### Constipation

Constipation is one of the most troublesome manifestations of gastrointestinal dysfunction in PD.<sup>18</sup> Constipation has been reported in up to 90% of patients with PD,<sup>16</sup> with an estimated 50% having less than 3 bowel movements per week.<sup>10</sup> Constipation is caused by delayed colonic transit and/or paradoxical contractions of the anal sphincter during defecation (known as defaecatory dyssynergia).<sup>10</sup> Other factors reported to affect colonic movement include drugs (including medications for PD, particularly drugs with anticholinergic properties), intestinal inflammation, gut microbiota, and neuro-humoral factors.<sup>16,19</sup>

Symptoms of constipation include reduced frequency of defaecation, unsuccessful defecation, and a sensation of incomplete emptying.<sup>5,16</sup> Constipation can also lead to systemic effects that may include decreased appetite, impaired absorption (which may lead to the delay or failure of the absorption of levodopa), dysbiosis, and possibly, reabsorption of intestinal toxins.<sup>3</sup>

*“Constipation is one of the earliest prodromal symptoms of PD”*



Constipation is a commonly-noted prodromal symptom of PD<sup>13,20,21</sup> and has been included as a risk factor for future development of the disease in the International Parkinson and Movement Disorder Society (MDS) criteria for prodromal PD.<sup>22</sup> Clinical reports show that patients with PD may develop constipation 20 years before motor symptoms appear, making it one of the earliest recognisable prodromal features.<sup>23,24</sup>

Constipation in early PD may also serve as a biomarker for identification of patients at risk for cognitive impairment and dementia. In a recent longitudinal study in patients with PD, constipation and its severity at the time of PD diagnosis were significantly associated with the subsequent development of dementia.<sup>25</sup> In another recent longitudinal analysis of patients newly-diagnosed with PD, patients with constipation had significantly faster conversion to cognitive impairment and were more than twice as likely to develop dementia compared to patients without constipation.<sup>26</sup>

## ***H. pylori* infection and small intestine dysfunction**

Evidence for upper gut dysbiosis in PD is mainly limited to small intestinal bacterial overgrowth (SIBO) and *Helicobacter pylori* infection.

*H. pylori* infection has been reported in approximately 25–70% of PD patients.<sup>3,27</sup> Infection with *H. pylori* has been associated with more severe PD.<sup>28</sup> It has been proposed that *H. pylori* could be involved in the pathogenesis of PD due to the chronic inflammatory response triggered by the infection.<sup>16</sup> The adverse effect of *H. pylori* infection, however, may be at least partly due to reduced absorption of levodopa in infected patients.<sup>29</sup>

Small intestinal bacterial overgrowth is a gut dysbiosis in which the small intestine is excessively colonised by bacteria that are typically found in the large intestine. A meta-analysis of 11 studies reported a SIBO prevalence of 46% in PD patients.<sup>30</sup>

Evidence for an association between SIBO and *H. pylori* infection with more severe PD are inconsistent and eradication of these conditions has been shown to improve motor symptoms in some studies but not others.<sup>31-33</sup>

## **Alpha-synuclein aggregates – do they arise in the gut and travel to the brain?**

Lewy body pathology (of which alpha-synuclein is the major constituent) in the brain is a well-characterised, defining neuropathological feature of PD.<sup>34</sup> In 2006, Braak and colleagues reported their findings that alpha-synuclein aggregations could also be found in the gastrointestinal tract of patients with PD who had not yet developed motor symptoms. Braak and his team postulated that the ENS might be affected before the CNS in the disease course of PD, and that the vagal nerve could be the route by which the neuropathology of PD spreads from the gut to the brain.<sup>35</sup>

Evidence from animal studies showed that alpha-synuclein can indeed spread from the gastrointestinal tract to the brain via the vagal nerve, and this can lead to death of brain dopaminergic neurons.<sup>36</sup> This hypothesis gained support from several studies including epidemiological data from a Danish registry of patients who underwent vagotomy with a follow-up of more than 20 years, which showed that full truncal vagotomy was associated with a decreased risk of PD over the subsequent 20 years compared to people in



the general population.<sup>37</sup> The hypothesis that PD starts in the gut has gained support over the years<sup>13,38</sup> but evidence against the idea also exists<sup>39-41</sup> and the area remains under active investigation.

Given the heterogeneity of PD, with some arguing that it is a syndrome of different diseases (and causes), it seems likely that a gut-first origin for PD applies to a subset, but not all, PD patients.<sup>3,42,43</sup>

Our understanding of the role of the gastrointestinal system in PD has evolved considerably over the past decade. Regardless of where the pathology begins, we now know that the gastrointestinal system is not simply impaired in PD but may well play an active role in the pathogenesis of the disease.<sup>2</sup>

*“Alpha-synuclein aggregates may arise in the gut and travel to the brain”*

## The role of inflammation in PD

Chronic inflammation has become increasingly recognised to play a crucial part in the onset and progression of PD.<sup>4,45</sup> The complex role of inflammation and immune dysfunction in PD has been reviewed in detail by Tansey and colleagues.<sup>4,46</sup> The precise trigger(s) for inflammatory dysfunction are still not clear, but multiple studies have demonstrated that patients with PD exhibit changes in their gut microflora that are not seen in healthy individuals.<sup>47-49</sup>

Gut microflora and their intriguing potential role in the development of PD are discussed in more detail in companion articles.

## References

1. World Health Organization. Parkinson's disease. Available at <https://www.who.int/news-room/fact-sheets/detail/parkinson-disease>. Accessed July 2022.
2. Fasano A, Visanji NP, Liu LW, et al. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol*. 2015;14:625-39.
3. Tan AH, Lim SY, Lang AE. The microbiome-gut-brain axis in Parkinson disease – from basic research to the clinic. *Nat Rev Neurol*. 2022;18:476-495.
4. Tansey MG, Wallings RL, Houser MC, et al. Inflammation and immune dysfunction in Parkinson disease. *Nature Reviews Immunology*. 2022;1-17.
5. Warnecke T, Schäfer KH, Claus I, et al. Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. *npj Parkinson's Disease*. 2022;8:31.
6. Annahazi A, Schemann M. The enteric nervous system: “A little brain in the gut”. *Neuroforum*. 2020;26:31-42.
7. Santos SF, de Oliveira HL, Yamada ES, et al. The Gut and Parkinson's Disease—A Bidirectional Pathway [Mini Review]. *Frontiers in Neurology*. 2019;10.
8. Rao M, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. *Nat Rev Gastroenterol Hepatol*. 2016;13:517-28.
9. Derkinderen P, Rolli-Derkinderen M, Chapelet G, et al. Tau in the gut, does it really matter? *J Neurochem*. 2021;158:94-104.
10. Han MN, Finkelstein DI, McQuade RM, et al. Gastrointestinal Dysfunction in Parkinson's Disease: Current and Potential Therapeutics. *J Pers Med*. 2022;12.
11. Yong VW, Tan YJ, Ng YD, et al. Progressive and accelerated weight and body fat loss in Parkinson's disease: A three-year prospective longitudinal study. *Parkinsonism Relat Disord*. 2020;77:28-35.
12. Soliman H, Coffin B, Gourcerol G. Gastroparesis in Parkinson Disease: Pathophysiology, and Clinical Management. *Brain Sci*. 2021;11.
13. Scott GD, Lim MM, Drake MG, et al. Onset of Skin, Gut, and Genitourinary Prodromal Parkinson's Disease: A Study of 1.5 Million Veterans. *Mov Disord*. 2021;36:2094-2103.
14. Ivan IF, Irincu VL, Diaconu Ş, et al. Gastro-intestinal dysfunctions in Parkinson's disease (Review). *Exp Ther Med*. 2021;22:1083.
15. Suntrup S, Teismann I, Bejer J, et al. Evidence for adaptive cortical changes in swallowing in Parkinson's disease. *Brain*. 2013;136:726-38.
16. Knudsen K, Szwebs M, Hansen AK, et al. Gastric emptying in Parkinson's disease – A mini-review. *Parkinsonism Relat Disord*. 2018;55:18-25.
17. Bestetti A, Capozza A, Lacerenza M, et al. Delayed Gastric Emptying in Advanced Parkinson Disease: Correlation With Therapeutic Doses. *Clin Nucl Med*. 2017;42:83-87.
18. Stirpe P, Hoffman M, Badiali D, et al. Constipation: an



- emerging risk factor for Parkinson's disease? *Eur J Neurol.* 2016;23:1606-1613.
19. Xu J, Wang L, Chen X, et al. New Understanding on the Pathophysiology and Treatment of Constipation in Parkinson's Disease. *Front Aging Neurosci.* 2022;14:917499.
  20. Abbott RD, Petrovitch H, White LR, et al. Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology.* 2001;57:456-62.
  21. Schrag A, Horsfall L, Walters K, et al. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol.* 2015;14:57-64.
  22. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord.* 2015;30:1600-11.
  23. Yang R, Gao G, Yang H. The Pathological Mechanism Between the Intestine and Brain in the Early Stage of Parkinson's Disease. *Front Aging Neurosci.* 2022;14:861035.
  24. Savica R, Carlin JM, Grossardt BR, Bower JH, et al. Medical records documentation of constipation preceding Parkinson disease: A case-control study. *Mov Disord.* 2009;24(11):1752-8.
  25. Camacho M, Macleod AD, Maple-Grødem J, et al. Early constipation predicts faster dementia onset in Parkinson's disease. *NPJ Parkinsons Dis.* 2021;7:45.
  26. Leta V, Urso D, Batzu L, et al. Constipation is Associated with Development of Cognitive Impairment in de novo Parkinson's Disease: A Longitudinal Analysis of Two International Cohorts. *J Parkinsons Dis.* 2021;11:1209-1219.
  27. Çamcı G, Oğuz S. Association between Parkinson's Disease and Helicobacter Pylori. *J Clin Neurol.* 2016;12:147-50.
  28. Tan AH, Mahadeva S, Marras C, et al. Helicobacter pylori infection is associated with worse severity of Parkinson's disease. *Parkinsonism Relat Disord.* 2015;21:221-5.
  29. Nyholm D, Hellström PM. Effects of Helicobacter pylori on Levodopa Pharmacokinetics. *J Parkinsons Dis.* 2021;11:61-69.
  30. Li X, Feng X, Jiang Z, et al. Association of small intestinal bacterial overgrowth with Parkinson's disease: a systematic review and meta-analysis. *Gut Pathogens.* 2021;13:25.
  31. Lolekha P, Sriphanom T, Vilaichone RK. Helicobacter pylori eradication improves motor fluctuations in advanced Parkinson's disease patients: A prospective cohort study (HP-PD trial). *PLoS One.* 2021;16:e0251042.
  32. Fasano A, Bove F, Gabrielli M, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord.* 2013;28:1241-9.
  33. Tan AH, Lim SY, Mahadeva S, et al. Helicobacter pylori Eradication in Parkinson's Disease: A Randomized Placebo-Controlled Trial. *Mov Disord.* 2020;35:2250-2260.
  34. Goedert M, Spillantini MG, Del Tredici K, et al. 100 years of Lewy pathology. *Nat Rev Neurol.* 2013;9:13-24.
  35. Braak H, de Vos RA, Bohl J, et al. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett.* 2006;396:67-72.
  36. Holmqvist S, Chutna O, Bousset L, et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. *Acta Neuropathol.* 2014;128:805-20.
  37. Svensson E, Horváth-Puhó E, Thomsen RW, et al. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol.* 2015;78:522-9.
  38. Gries M, Christmann A, Schulte S, et al. Parkinson mice show functional and molecular changes in the gut long before motoric disease onset. *Mol Neurodegener.* 2021;16:34.
  39. Tsukita K, Sakamaki-Tsukita H, Tanaka K, et al. Value of in vivo  $\alpha$ -synuclein deposits in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord.* 2019;34:1452-1463.
  40. Engelender S, Isacson O. The Threshold Theory for Parkinson's Disease. *Trends Neurosci.* 2017;40:4-14.
  41. Beach TG, Adler CH, Sue LI, et al. Vagus Nerve and Stomach Synucleinopathy in Parkinson's Disease, Incidental Lewy Body Disease, and Normal Elderly Subjects: Evidence Against the "Body-First" Hypothesis. *J Parkinsons Dis.* 2021;11:1833-1843.
  42. Lionnet A, Leclair-Visonneau L, Neunlist M, et al. Does Parkinson's disease start in the gut? *Acta Neuropathol.* 2018;135:1-12.
  43. Leclair-Visonneau L, Neunlist M, Derkinderen P, et al. The gut in Parkinson's disease: Bottom-up, top-down, or neither? *Neurogastroenterol Motil.* 2020;32:e13777.
  44. Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease—the gut-brain axis and environmental factors. *Nat Rev Neurol.* 2015;11:625-36.
  45. Pajares M, A IR, Manda G, et al. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. *Cells.* 2020;9.
  46. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? *NPJ Parkinsons Dis.* 2017;3:3.
  47. Romano S, Savva GM, Bedarf JR, et al. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. *npj Parkinson's Disease.* 2021;7:27.
  48. Nishiwaki H, Ito M, Ishida T, et al. Meta-Analysis of Gut Dysbiosis in Parkinson's Disease. *Mov Disord.* 2020;35:1626-1635.
  49. Toh TS, Chong CW, Lim SY, et al. Gut microbiome in Parkinson's disease: New insights from meta-analysis. *Parkinsonism Relat Disord.* 2022;94:1-9.