



IBS a Risk Factor or Just Overlaps with Constipation of Prodromal Parkinson's Disease?

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Abstract

Constipation is considered as a most predominant gastrointestinal non motor symptom of Parkinson's disease (PD) which occurs one or two decades before the diagnosis of PD. The cause of constipation may be gut microbiota dysbiosis, neurodegeneration of enteric nervous system causing dysmotility or sometimes no reason found. Irritable bowel syndrome (IBS) on the other hand can cause constipation, diarrhoea or both. Researchers think most common cause of IBS is related to stress. However recently, in addition to constipation, a diagnosis of irritable bowel syndrome (IBS) was also found to be associated with increased PD risk. Gut microbiota alterations is seen in both cases. It is also interesting to note whether IBS like bowel symptoms comes with other non-motor symptoms together or is a single identity. We are not sure whether IBS is a risk factor for developing PD in future or IBS-C is just a non-motor symptom of PD. The pathophysiological connection between these disorders are not known till date because of unavailability of studies.

Keywords

Constipation, Non motor symptom, Parkinson's disease, Irritable Bowel Syndrome, Microbiota

Abbreviations

IBS-C: Irritable bowel syndrome-constipation

IBS-D: Irritable bowel syndrome-diarrhea

IBS-M: Irritable bowel syndrome-mixed

IBS-U: Irritable bowel syndrome-unclassified

PIGD: postural instability and gait difficulty

TD: Tremor dominant

IND: Indeterminate

FC: Functional constipation

FGID: Functional Gastrointestinal Disorders

FBDSI: Functional Bowel Disorder Severity Index

IBS-SSI: Irritable bowel syndrome Symptom Severity Index

KP: Kynurenine pathway

NAE: N-acylethanolamine

SCFA: Short chain fatty acid

Introduction

Parkinson's disease is a neurodegenerative disease presents clinically with motor and non-motor symptoms [1]. The motor features mainly comprise of rigidity, bradykinesia, postural instability and resting tremor. The non-motor features include a variety of symptoms such as psychiatric abnormalities, executive dysfunction, autonomic dysfunction, sleep disturbance, sensory complaints, anosmia and gastrointestinal symptoms [2]. In clinical practice three motor phenotypes have been described in (PD): postural instability and gait difficulty (PIGD) dominant, tremor-dominant (TD), and indeterminate (IND) subtype [3]. Gastrointestinal symptoms are one of the most common non motor symptoms substantially hampering quality of life [4].

A lot of research has been done to understand the progression and pathophysiology of gastrointestinal dysfunction in Parkinson's disease [5,6]. Important causes may include motor dysfunctions, autonomic dysfunctions, adverse effect of antiparkinsonian medications, microbiota dysbiosis, and enteric neurodegeneration to name a few [2,7,8]. Constipation can affect up to 70% of patients with PD [2]. It is also a frequent non motor symptom and is considered one of the strongest risk factors for PD [9,10]. Constipation is also emerging as one of the earliest features of autonomic dysfunction in Parkinson's disease, developing as early as 15-3 years before motor features [11]. One study defined constipation as when patients had bowel movement less often than three times per week [12], whereas other researchers relied on a description from clinical records based on

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patients' documentation [13]. A population-based study reported that risk of development of Parkinson's disease increases with constipation severity (hazard ratios ranged from 3.3-4.2) [14]. The pathophysiological mechanisms behind constipation in PD include prolonged intestinal transit and pelvic floor dyssynergia [15,16]. Despite its high prevalence, no specific constipation questionnaire has been validated in PD patients [17].

The Rome III criteria is a standard method for assessing functional gastrointestinal disorders such as functional constipation (FC) and irritable bowel syndrome (IBS), since no biomarkers have been identified till date [18]. In the recently published updated Rome IV criteria, functional gastrointestinal disorders are defined as disorders of gut-brain axis interaction. Douglas A. Drossman has stated about Functional Gastrointestinal Disorders (FGID) as a group of disorders classified by gastrointestinal symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, altered central nervous system processing [19]. Irritable bowel syndrome (IBS) on the other hand has subtypes like IBS constipation (IBS-C), IBS-diarrhoea (IBS-D), IBS-mixed (IBS-M), IBS-unclassified (IBS-U) [20]. Drossman and colleagues also used FBDSI (Functional Bowel Disorder Severity Index), IBS-SSI (IBS Symptom Severity Index) to grade it into mild, moderate severe [21]. IBS is associated with an increased risk of developing PD in the Taiwanese population [22].

Dysregulation of the gut brain axis and alterations in the composition of intestinal microbiota have been previously linked to IBS pathogenesis and symptoms [23]. Several studies have reported a higher relative abundance of Firmicutes and reduction in the relative abundance of Bacteroidetes and Bifidobacteria in IBS patients [24,25]. The results for the abundance of Prevotella have not been consistent [24,26]. Filip Scheperjans et al has reported previously persons with a high abundance of Prevotellaceae was very unlikely to have PD however low Prevotellaceae levels do not seem to be specific for PD, because they have been reported in patients with autism and type 1 diabetes [27-29]. Changes in the gut microbiota might lead to low grade inflammation and increased permeability of the gut mucosa previously linked to IBS [30,31]. Gut mucosal changes have also been reported in PD and it has been speculated whether this could initiate alpha-synuclein associated neurodegeneration in the enteric nervous system that subsequently spreads to the central nervous system as initially proposed by Braak [32,33]. Study by T. H. Mertsalmi et al has suggested Prevotellaceae emerged as a key species related to PD, and now also to PD-associated IBS-like symptoms in their cohort [34].

Discussion

In PD patients, IBS+ was associated with more reported non-motor symptoms [34]. The prevalence of IBS in Japanese general population using ROME III criteria was (13.1–14.0%) [35], however Mishima et al has reported a prevalence of IBS in PD cohort was 17% [36]. Stool consistency and bowel affects can vary according to coffee intake, smoking, water intake, probiotics, insoluble fiber, beta blockers and other constipating agents taken over the counter. No study till date has considered these factors in a large group of study to draw a definite conclusion.

Rome IV criteria should be used to assess for more understanding of gastrointestinal dysfunction in PD. Procedures like colonoscopy has to be added to rule out any inflammatory, metabolic, anatomical or obstructive causes. A colon transit time can be useful test to rule out any another disease or explanation [37]. Gilles J Guillemain et al recently reported large kynurenine-to-tryptophan ratio due to the overexpression of kynurenine pathway (KP) enzymes is observed in different human health complications, including irritable bowel syndrome, inflammatory diseases, cancer, and neurodegenerative disorders. Gut microbiota can consume tryptophan and subsequently decrease its availability for the human body as this amino acid can be received from diet only [38]. Roberto Russo et al recently reported about lipids like N-acyl ethanolamine (NAE) and short chain fatty

acids (SCFAs), such as butyrate can interact with gut-brain axis and can cause dysbiosis of microbiota which is involved in process of inflammation (IBS) and neurodegeneration like PD [39,40].

Conclusion

In summary we reviewed a common pathoclinical mechanism of a subtype of IBS with constipation as a preclinical non motor symptom of PD. Evidence definitely suggests a complex interaction with gut-brain axis, inflammation and gastrointestinal microbiota dysbiosis. Use of newest Rome IV questionnaire could provide a basis for better understanding of the gastrointestinal dysfunction in PD. We are not sure now whether IBS is a risk factor of PD because of lack of studies till date. If the connection between IBS, PD, microbiota and inflammation is confirmed by further studies, future research and management in PD could profit from the accumulating evidence on the pathophysiology and treatment of IBS.

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