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IP Journal of Nutrition, Metabolism and Health Science

Journal homepage: www.ipinnovative.com

Review Article

Interrelationship between Gut microbiota and Parkinson's disease

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ARTICLE INFO

Article history:
Received 10-09-2020
Accepted 19-09-2020
Available online 28-10-2020

Keywords:
Parkinson's disease (PD)
gut microbiota (GM)
gut microbiota-brain axis (GMBA)
cytokine response
toll-like receptors

ABSTRACT

Neurological outcomes like learning, memory and cognition are influenced by the gut microbiota (GM). These commensal GM modulates behavior and brain development and has implications in many neurological disorders like Alzheimer's disease, Parkinson's disease (PD), anxiety, stress, multiple sclerosis, etc. PD is a neurodegenerative disease which causes dysbiosis, α-synucleinopathy and affects the gut-brain axis which includes CNS (Central nervous system), ANS (Autonomic nervous system) and ENS (Enteric nervous system). There is a bidirectional communication between the brain and the gut called "gut microbiota-brain axis (GMBA)" and its dysfunction causes numerous diseases. This review focuses on the inter-relationship between the gut microbiome and the Parkinson's disease.

1. Introduction

Gut microbiota (GM) contains 100 trillion bacteria and some viruses, fungi, archaea. These microbes are 10 times greater than the number of cells present in the human body. GM contains 3 million genes which is 150 times more than the human genome. 1/3rd of the GM is similar in most people, while 2/3rd is specific for each individual. A study revealed that microbial fingerprint is unique for an individual and distinguishes him from others.[1] 50-60% of the GM cannot be cultured as they have host-to-host transmission.[2,3] Parkinson's disease (PD) is the most common second neurodegenerative disorder which affects 1-2 people per 1000 population in the world.[4] PD affects about 7-10 million people in the world,[5] this number may double by 2030 due to aging of the people.[6] A study says that Asians are less affected than the western people and their genetic causes of PD are distinct.[7] China is the leading country with a greater number of PD patients. In 2005, it is 48% which may reach 57% by 2030 [Figure 1].

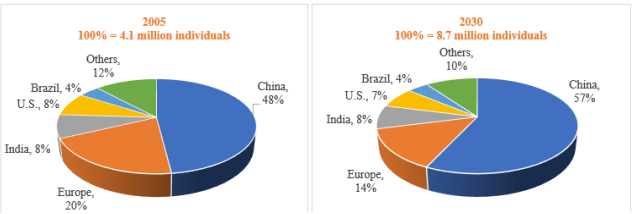

Fig. 1: Distribution of individuals with Parkinson's disease by country from 2005-2030.[8]

2. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder which causes muscular rigidity, akinesia, tremor, difficulty in walking and slowness of movement. Other symptoms include depression, dementia and dysfunction of ANS, CNS and ENS. There is a dopaminergic loss in substantia nigra pars compacta (SNpc) and it also causes α-synucleinopathy.[9,10] 80% of PD patients suffer from constipation.[11] The incidences of PD are probably higher in people between the ages 60-64 and lower at the age of

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https://doi.org/10.18231/j.ijnmhs.2020.015

35-39 [Figure 2]

2.1. *Gut microbiota and Parkinson's disease:*

GM contains one trillion microbes, among which bacteria is the dominant species in the GI tract. Bacteria contain mainly 4 phyla: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria.[12] Helicobacter pylori is the extensively studied microbe in association with PD. H. pylori inhibits the absorption of Levodopa (drug to manage PD) and causes motor impairments.[13] PD is also associated with SIBO (Small Intestinal Bacterial Growth), excessive bacterial growth in the small intestine and it causes motor impairments.[14,15] PD patients fecal sample analysis shows higher level of Enterobacteriaceae, which causes postural instability,[16] and lower levels of Prevotellaceae family of Bacteria, they are commensals which produce mucin and neuroactive SCFAs (propionate, acetate and butyrate). Decreased Prevotellaceae level in turn reduces the mucin synthesis, increases intestinal permeability and in the development of α-synucleinopathy. Lower prevotellaceae is also associated with increase in Lactobacillaceae, which in turn reduces the level of ghrelin (gut hormone), which is involved in nigrostriatal dopamine activity.[17] Another study reports that fecal sample of PD patient's showincreased levels of proteobacteria of the genus Ralstonia and reduced level of bacteria of genera Roseburia, Blautia and Copococcus. But no change in the Bifido bacteria level.[18]

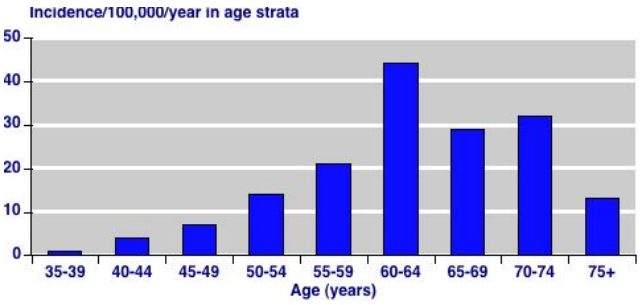

Fig. 2: Parkinson's disease incidence and age[19].

2.2. *Etiology of Parkinson's disease:*

The etiology of PD still remains unclear. It is mainly characterized by α-synucleinopathy (deposition of insoluble polymers of α-synuclein in the neuronal body and forms Lewy bodies). These Lewy bodies cause neurodegeneration and neuronal death.[20,21] PD is associated with depauperation of dopaminergic neurons in the substantia nigra pars compacta (SNc), which causes dopamine deficiency.[22–24] Decrease in the dopamine in the basal ganglia causes motor symptoms like bradykinesia, rigidity and tremor [.Figure 3]. The non-motor symptoms include gastrointestinal dysfunction, sleep disturbances, neuropsychiatric disorders (depression, apathy, cognitive impairment, and psychosis), sensory alterations (pain, olfactory impairment).[25] Dopamine modulators are administered to manage PD, even though it has serious side effects, limited benefit and may not be effective in the later stages of PD.[24–26] PD causes constipation which is associated with neurodegeneration of ENS,[27] α-synuclein accumulation with increased oxidative stress, local inflammation and intestinal permeability.[28,29]

Fig. 3: Etiology of Parkinson's disease.[30]

2.3. *Gastrointestinal dysfunction in Parkinson's disease:*

According to Edwards et al[31] PD patients have GI dysfunctions like abnormal salivation, constipation, dysphagia, nausea and defecatory dysfunction. Hypersalivation in PD patients is due to decreased swallowing frequency and it is symptomatic in 50% of PD patients.[32] Oropharyngeal dysfunction occurs in the oesophageal body or in the oesophageal sphincter among 60-70% of PD patients.[28–30] Aspiration pneumonia occurs due to dysphagia in 15-55% of PD patients.[32–34] Impaired gastric emptying is the important characteristic of PD patients with symptoms like early satiety, bloating, abdominal discomfort and nausea.[35] Amplitude of stomach contractions has also been reduced in PD patients.[36] Delayed gastric emptying causes impaired absorption of L-dopa and increases motor fluctuations.[37] Small bowel dysmotility may be due to SIBO (small Intestinal Bacterial Overgrowth), which is increased in PD patients.[38] Constipation may be an early manifestation for PD patients.[39–44] Colon transit time may be increased even in PD patients with asymptomatic constipation.[45] and its severity causes megacolon.[46] Incomplete evacuation and excessive straining are the symptoms of defecatory

dysfunction.[47,48]

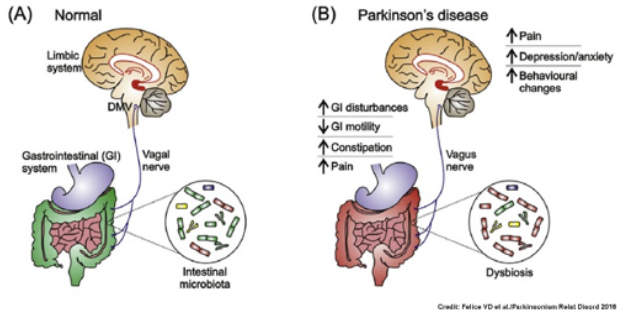

Fig. 4: Difference in the GI system in normal and Parkinson's disease.[49]

2.4. Microbiome-Gut-Brain Axis and Toll-Like Receptors in Parkinson's Disease

Toll-like-receptors (TLR) ligands are produced by the gut microbiota; under certain conditions it can exert pro-inflammatory effects.[50] Under physiological conditions, gut has a high tolerance to TLR ligands, where as in altered gut microbiota activate TLRs which trigger downstream signalling pathways creates inflammation and oxidative stress in gut and brain in the PD patients. TLR2 and TLR4 are two major TLRs evidenced in PD patients.[50] They can trigger neurotoxicity upon their activation; in contrast they can clear misfolded α-synuclein, being neuroprotective.[51]

2.5. Altered gut microbiota and inflammatory cytokine responses in patients with Parkinson's disease

Altered GM, induces abnormal production of inflammatory cytokines, which causes neuroinflammation in PD patients.[52] Inflammatory cytokines like IL-1β, IL-8 and TNF-α in the serum causes neurotoxicity, disruption of blood brain barrier and increases microglia-mediated inflammation.[53,54] IL-6 is the major cytokine elevated in PD patients compared to controls. SIL-2-R and TNF- α are also associated with severe symptoms of PD. It may be noted that non-motor symptoms like fatigue and depression are generated via inflammatory mechanisms.[55]

2.6. Structural changes of gut microbiota in Parkinson's disease

To analyse the structural changes, putative cellulose degrading bacteria like Ruminococcus, Blautia and Faecalibacterium and putative pathobionts like Proteus, Enterococcus, Escherichia-Shigella, Streptococcus were measured in healthy controls and PD patients.[56] The putative cellulose degraders were decreased, whereas putative pathobionts were increased, which in turn decreases the production of SCFAs (Short Chain Fatty Acids) and increase the production of neurotoxins and endotoxins. These changes in the gut microbiota are associated with PD pathology.[56]

2.7. Short chain fatty acids (SCFAs and gut microbiota in Parkinson's disease

SCFAs like butyrate, propionate and acetate are significantly lower in PD patients than the healthy controls of same age.[57] whereas valerate, isovalerate and iso-butyrate concentration remains same with control and the PD patients. These SCFAs can cross the brain and regulate the microglial activation.[58] SCFAs can cause motor dysfunctions in PD patients.[59]

3. Conclusion

GM is a potential modulator of brain and behaviour. It can directly or indirectly modify our brain neurochemistry. There is a variation in the GM in PD patients, which can be used as a biomarker to analyse PD pathogenesis. There is still a need to achieve the proper inter-relationship between GM and PD. There is no proper treatment to cure the PD patients, even though Levodopa is an anti-parkinsonian medicine, it has its own limitations. Further study is required to manage the gut microbiota and Parkinson's disease.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Cite this article: Manasa R, Prakruthi M, Naik R S, Shivananjappa M. **Interrelationship between Gut microbiota and Parkinson's disease**. *IP J Nutr Metab Health Sci* 2020;3(3):73-77.