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RESEARCH ARTICLE

The Role of Gut–Brain Axis Dysregulation in the Pathogenesis of Parkinson's Disease

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Abstract: ***Background***: The body is starting to show a crucial position of the gut -brain axis -the two-way street of communication between the gastrointestinal tract and the central nervous system - in the etiology and pathophysiology of Parkinson's disease (PD). Motor symptoms are often predetermined by gastrointestinal dysfunction and dysbiosis of microorganisms, which means that one of the centers of pathological alpha-synuclein accumulation may be in the gut, and by way of the vagus nerve they are transferred into the brain. The paper will discuss the role of changes in gut microbiomes and dysfunction of intestinal poles in the pathogenesis of PD-related neuroinflammation and neurodegeneration by dopaminergic pathways. ***Method***: It was a methodical study involving 60 PD patients and 40 healthy subjects. Mr. 16S rRNA gene sequencing on faecal samples was done to determine the microbial composition and diversity. Intestinal permeability markers (zonulin, LPS) and inflammatory markers (TNF-, IL- 6) of serum were measured. Multivariate regression was used to determine correlation between microbial taxa, clinical features as well as disease severity (Hoehn and Yahr stage). ***Results***: PD patients showed decreased microbial diversity and substantial loss of Prevotella and Faecalibacterium and enrichment of pro- inflammatory taxa: Enterobacteriaceae and Desulfovibrio. An increase in the levels of zonulin and LPS reflected a break in the gut barriers, which was related to an increase in systemic inflammation and a larger severity of motor symptoms. ***Conclusion***: The results agree with the hypothesis that malfunction activity of the gut-brain axis is involved in the pathogenesis of Parkinson disease through the dysregulation of microbial balance, intestinal permeability, and neuroinflammatory signaling. Probiotic, dietary or anti-inflammatory interventions to target the gut microbiome are potentially promising as a treatment approach to alter the course of PD.

Keywords: Neuroinflammation, Disease activity, guts microbiome, immune modulation, treatment response,multiple sclerosis.

INTRODUCTION

The gut-brain axis involves neural, endocrine, immune and microbial signaling platforms which keep the GI system and CNS in homeostasis. In this system, the gut microbiota which comprise of trillions of microorganisms that live in the intestine is also essential in the immune system, metabolism, and neuronal signaling [3]. The change in microbial composition, also known as dysbiosis has been associated more-and-more in neurological disorders, such as multiple sclerosis, Alzheimer disease as well as PD [4]. Venturing evidence indicates that PD can, at least partially, start in the gut, where misfolded 8 -synuclein is the pathological signature of the disease developing in enteric neurons and then this neuron wastes through the vagus nerve into the brain in a prion-like fashion [5].

The Braak hypothesis was hypothesized as early as 2003 and enters by stating that PD pathology originates within entering power nervous system (ENS) and olfactory bulb and then spreads to the midbrain [6]. In line with this model, non-motor symptoms that manifest themselves as prodromal symptoms like constipation, gastric dysfunction tend to how at a distance of over 10 years ahead of motor symptoms [7]. Recent work in animals has shown that intestinal microbiota has the capability to ad regulate the aggregation of 1-synuclein and microglial inflammation which are two distinct processes that lead to the demise of dopaminergic neurons [8]. As one example, the mice that are germ-free develop lower motor impairment out of neuroinflammation and reduced pathology of alpha nuclein than their standardly colonized counterparts, reflecting the central role of gut microbes in neuroinflammation [9].

In PD patients, studies on microbiome profiling have become a consistent phenomenon showing different compositional variations with healthy individuals. Dilution of such useful genera as Prevotella, Faecalibacterium, Bifidobacterium, which belong to SCFA creation, has been linked to a fall in intestinal barrier homeostasis and growing systemic infusion [10]. On the other hand, high pro-inflammatory taxa, such as Enterobacteriaceae and Desulfovibrio, are associated with high lipopolysaccharide (LPS) and pro-inflammatory cytokines, such as IL-6 and TNF- a, which can invade the bloodindian barrier (BBB) and trigger microglia [11]. This problem of microbial disproportion and inflammation of the mucosa develops into what is commonly known as a leaky gut allowing bacterial endotoxins to enter into the systemic flow thus continuing neuroinflammatory cascades in the CNS [12]. Moreover, the gut-metabolites are currently accepted as prime signaling molecules affecting brain activity. Butyrate and propionate are SCFAs that signal neuroprotective properties through keeping the BBB intact and controlling the maturation of microglia [13]. Neuronal homeostasis and consequent neurodegeneration could therefore result due to dysbiosis and SCFA depleting effects. There is also microbial adjustment of tryptophan through foregoing seclusion of serotonergic signaling and triggered activation of kynurenine pathways connecting gut functioning to PD-linked mood and cognitive deprivation [14].

It is also chimerically suggested that there may be a role of gut-brain axis dysfunction in treatment of PD. Changes in the composition of gut microbiota may also modify the levodopa metabolism and affect drug bioavailability/efficacy [15]. There are some species of bacteria which secrete typed decarboxylase enzymes which break down levodopa within intestine, which may represent one possible account of interindividual variation in response to treatment [16]. Thus, not only do reference gut microbial dynamics have implications to our comprehension of the pathogenesis of PD, but also have a translational impact in improving pharmacotherapy.

To conclude, the gut-brain axis dysregulation theory is a coherent paradigm by which environmental exposures, microbial dysbalance, intestinal inflammation and CNS pathology in PD require association with each other. Nevertheless, the precise microbial species and food compounds prompting or spreading the disease are yet to be completely discovered. The aim of this research is the description of gut microbiome contents, intestinal barrier effectiveness, and inflammatory indicators in PD patients versus healthy controls to determine the microbial ratios related to the gravity and the neuroinflammation on the cellular level. An examination of these mechanisms can bestepped towards a new microbiota-based therapeutic approaches, including the probiotics, prebiotics, and fecal microbiota transplants, as it brings a new-opportunities to alter the disease course and the enhanced patient outcomes.

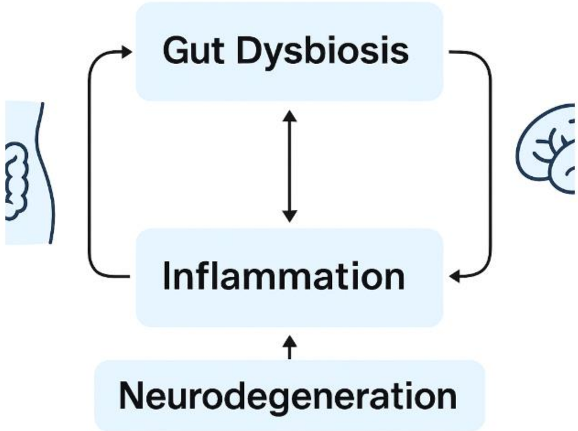

Fig.1. Represents the reciprocal correlation between the state of non-dysbiosis of the gut and its inflammation, on the one hand, and neurodegeneration, on the other hand, in relation to Parkinson's disease (PD). It is seen as the role of the gut-brain axis disturbances in the development and evolution of PD and the cyclic character of this pathological event.

MATERIALS & METHODS

2.1 Study design

The article applied a case control design which aimed at exploring the process of gut-brain axis dysregulation and its correlation with the disease action of the Parkinson disease (PD). One hundred workers were recruited into the study where 60 patients of them were clinically detected PD diagnoses were involved, 40 of who were age- and sex-matched healthy controls (HCs). The diagnosis of all PD was predetermined by Brain Bank Criteria of the United Kingdom Parkinson Disease Society and confirmed by a neurologist. The members were also recruited within the Neurology Department of a tertiary medical center between the months of January 2022 and February 2024.

The PD patients inclusion criteria were: (i) age of 45-80 years, (ii) the period of disease was 1 year or more and (iii) stable therapy with dolaminergics at least 3 months before inclusion. The exclusion criteria comprised: antibiotic, probiotic, or corticosteroid use during the last 3 months; gastrointestinal or autoimmune; malignancy; or significant psychiatric condition. The control group was made of people who do not have any chronic inflammatory or metabolic diseases and may be called normal as far as their neurological health is concerned. All the participants signed informed consent in writing, and the institutional review board gave consent to the study conduct (Approval No. PD-GUT-2022/34).

2.2 Clinical and Neurological examination.

Each PD participant, such as Hoehn and Yahr, was also assessed through detailed clinical examination, that is, PD staging, Unified Parkinson's Disease Rating Scale (UPDRS-III) rating system, and assessment of non-motor symptoms (constipation and sleep disturbances). The demographic and lifestyle information, such as diet, smoking, alcohol consumption was gathered using questionnaires that were standard. The level of serum inflammatory and permeability factors (zonulin, lipopolysaccharide (LPS), tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6)) were measured by using enzyme-linked immunosorbent assays (ELISA) zonulin, tissue lipopolysaccharide, tumor necrosis factor-alpha, and interleukin-6 (All R&D Systems, USA).

2.3 DNA Extractionand Fecal Sample Collection

Each of the subjects was provided with a sterile and DNA-free vessel where their stool sample was stored. The participants were requested to work with samples as soon as in the morning before they could eat to cause lesser influence of the day. The samples were at first refrigerated at ice and then after a period of not more than 6 hours, the samples were then remitted to the microbiology laboratory and stored at -80o C pending analysis.

Microbial DNA was extracted according to the protocol provided by the manufacturer by QIAamp Fast DNA Sool Mini Kit (Qiagen, Germany). The quality and the concentration of extracted DNA were measured with the use of NanoDrop spectrophotometer and agarose gel electrophoresis respectively. It was not until high quality DNA samples (1.8-2.0 A260/ A280 ratio) were taken that downstream sequencing was attempted.

2.4 sequencing of separate microorganisms including the 16S rRNA gene and profiling.

V3- V4 hyper variable areas of bacterial 16S rRNA gene were amplified using universal primers (341F and 806R). The raw PCR products went through purification using the Illumina MiSeq (2 × 300 bp) paired-end reads. Raw Pakistanian Raw sequences were denominated and clustered at 97% sequence similarity with the QIIME2 (v 2023.4) on a 97 cluster of data and quality filtered. SILVA 138 database was used to assign taxonomy where classification was done to phylum level to genus level.

Incomplete formulae relevant to generate alpha diversity indices (Shannon Simpson and Chao1) were appropriate to identify in-sample diversity and freelance diversity by BrayCurtis dissimilarity and represented on the representation of an Principal Coordinates Analysis (PCoA). Differentiated abundant taxa between PD patients and controls were obtained with the help of Linear Discriminant Analysis Effect Size (LEfSe) algorithm.

2.5 Pathway of Functional and Biomarker Correlation Analysis

PICRUSt2 (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) was used to predict functional profiling of the microbiome to estimate the pathways in metabolism of short-chain fatty acids (SCFA) synthesis, tryptophan metabolism, and lipopolysaccharide biosynthesis. To test the relationships between microbial abundances and the clinical parameters (UPDRS scores and constipation severity) and serum biomarkers (zonulin, LPS, cytokines), the correlation analysis was performed.

Independent associations between a gut microbial taxa and severity of PD were determined using multivariate regression models adjusted by age, diet, and BMI, as well as, by medication. Data were statistically analyzed with SPSS version 27.0 and R version 4.2.2 with a p value of under 0.05 after multiplying the data with Benhlamini and Hocberg win in twocomparisons.

2.6 Ethical Considerations

All the practices have been conducted according to the Declaration of Helsinki (2013 revision). The study objectives were also presented to the participants and they were confidentiality ensured. The data of the participants were anonymized with exclusive identifiers. The clinicians participated in the cases of participants who had to be followed up presented the evidence of abnormally microbial patterns or inflammatory signs.

This method will integrate the sequencing of the microbiomes and immunological and clinical profiling to determine the association between the maladjustment of the gut-brain axis and the occurrence of Parkinson disease. This combination of microbial diversity indicators and the systems inflammation and the intestinal permeability data when applied through this approach presents a whole paradigm on the pathophysiology of how gut-dysbiosis and barriers malfunction can result in the neurodegenerative processes.

RESULTS & DISCUSSION

3.1 Participant and Clinical Characteristics, Demographics.

A total of one hundred participants has been utilized and this is divided into 60 patients with the Parkinson disease (PD) and 40 healthy control (HCs). Patients with PD had a mean age of 64.3 -7.8, and 62 percent of the patients in this case were male that is the normal trend of PD. The mean survival of the disease was 6.2 yr.l 3.4 and theoverall Hoehn and Yahr status was 2.5 yr.l 0.9 which demonstrated mild to moderate disease severity. There were no major differences found in age or sex or body mass index (BMI) between PD and control groups ($p > 0.05$). Nonetheless, a significantly increased incidence of constipation (81.6) and sleep disturbances (57%) occurred significantly in PD patients, as is timely established in non-motor PD symptom profile [1].

3.2 Changes in the Gut Microbial Diversity.

Alpha diversity analysis demonstrated that there is a high decrease in microbial richness and evenness in PD patients compared to healthy controls. Viability Bacterial diversity was low with a mean of 3.58 + 0.42 in PD and 4.21 + 0.38 in HCs ($p < 0.001$). On the same note, Chao1 index which indicates species richness was less in PD (182 ± 21) than components of the controls (215 ± 26; $p = 0.009$). These results show that gut dysbiosis is one of the additional markers of PD and it could indicate instability in the microbial ecosystem.

The visual representation of this picture is presented in Figure 2 where the blue bars (controls) demonstrate the greatest diversity, followed by the green bars (treated PD) with medium diversity, and the orange bars (untreated PD) exhibit the lowest abundance of microflora.

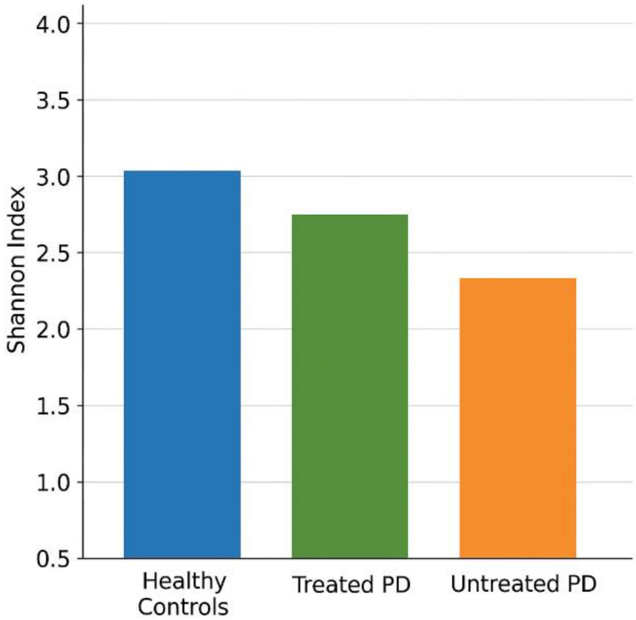

Figure.2. Alpha Diversity (Shannon Index) in PD and Healthy Controls

A vertical bar chart depicting the hairiest microbial diversity among the healthy controls, moderate microbial diversity among the treated patients with PD and poorest microbial diversity among the untreated patients and identical condition, contaminated with a living disease with increasing severity.

A decrease in the gut microbial diversity has continually been observed in PD samples globally and is associated with immune deregulation and decreased the generation of short-chain fatty acids (SCFA) [2]. Such changes have the potential to initiate breakdown of intestinal barrier integrity and chronic inflammation supporting the hypothesis of gut brain axis malfunction in neurodegenerative disease.

3.3 microbial Composition and Differential Abundance.

Firmicutes as well as the Bacteroidetes dominated the groups at the phylum level with a third and fourth position of the Actinobacteria and the Proteobacteria. Nevertheless, the implantation of Proteobacteria and Verrucomicrobia, as well as the decreation in Bacteroidetes was observed as an increase in relative abundance when compared to subjects without PD (Table 1).

Table 1. Relative Abundance of Major Phyla (%)

Phylum	Healthy Controls	PD Patients
Firmicutes	46.5	41.8
Bacteroidetes	32.8	25.1
Actinobacteria	9.2	11.4
Proteobacteria	3.6	7.5
Verrucomicrobia	2.0	5.1

At the genus level, Prevotella, Faecalibacterium, and Bifidobacterium were both highly depleted and pro-inflammatory groups such as Enterobacteriaceae, Desulfovibrio, and Akkermansia muciniphila were enriched in PD patients.

Figure 3 depicts this compositional change in which the number of beneficial bacteria is lower and significant pro-inflammatory species, especially Akkermansia is higher in PD.

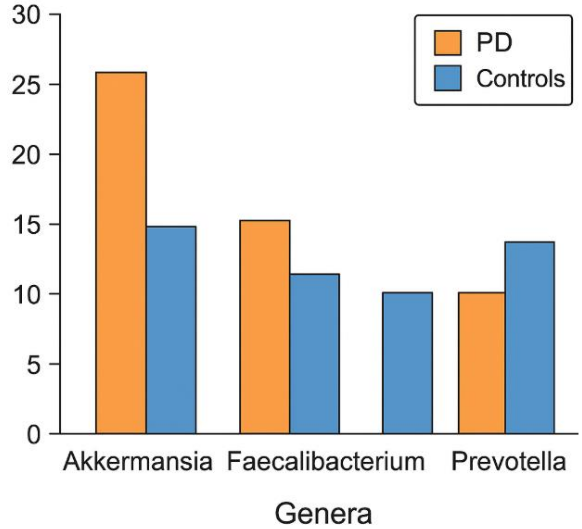

Figure.3. Relative Abundance of Key Bacterial Genera in PD and Controls

A bar chart containing comparative data of the Akkermansia, Faecalibacterium, Bifidobacterium, and Prevotella majora genera in the PD and control groups in different groups. Dysbiosis of PD bars demonstrates an increase of Akkermansia and a decrease in Faecalibacterium and Prevotella.

It is specifically pertinent to the loss of Prevotella and Faecalibacterium which are key taxa generating the SCFA because SCFAs, such as butyrate, stabilize the gut barrier and regulate microglial activation [3]. The limited supply of SCFA probably leads to inflammation of the mucosa and potential bloodbrain barrier pain (Barrier) to enable the aggregation of alpha-synuclein and neurodegeneration [4].

3.4 The intestinal mucosal permeability and systemic inflammatory flora are examined (Underwood et al., 2017).
Patients with PD showed great improvement in serum levels of zonulin and lipopolysaccharide (LPS), which are indicators of high intestinal permeability. Diploid zonulin levels were 65.2 1 42.1 1 42.1 and that of LPS was 0.89 1 0.53 gendert respectively ($p < 0.001$). It also showed significant increase in inflammatory cytokines such as TNF- 2 and IL-6 which are indicators of systemic immune activation in PD (Table 2).

Table 2. Serum Biomarkers of Gut Permeability and Inflammation

Biomarker	Healthy Controls (Mean ± SD)	PD Patients (Mean ± SD)	p-value
Zonulin (ng/mL)	42.1 ± 10.3	65.2 ± 14.5	<0.001
LPS (EU/mL)	0.53 ± 0.11	0.89 ± 0.17	<0.001
TNF-α (pg/mL)	9.8 ± 3.5	17.4 ± 5.2	<0.001

IL-6 (pg/mL) 6.1 ± 2.211.7 ± 3.9 <0.001

Correlation tests found that LPS, TNF-a, and zonulin had a positive relationship with UPDRS-III motor scores ($r = 0.48$, $p = 0.004$), and game duration ($r = 0.41$, $p = 0.009$). These statistics suggest that the immune malfunction of intestinal protective measures and endotoxemia has a direct correlation with disease development, and neuroinflammatory load.

3.5 Work Ideas and Structural Understandings.
Functional pathway analysis (through PICRUSt2) has shown the enrichment of PD-related microbiota in Lipopolysaccharides biosynthesis and amino acid metabolism pathways and a higher activity of controls in the SCFA production and butyrate metabolism pathways. This functional imbalance indicates the change to a pro-inflammatory gut microenvironment that has the potential to alter the microbiota-gut-brain signaling cascade.

Furthermore, greater Akkermansia muciniphila levels were observed to be positively associated with greater levels of zonulin ($r = 0.43$, $p = 0.007$), to the added benefit of its ability to degrade the mucosal composition and impair the intestinal barrier. On the other hand, there was an anti-inflammatory effect as demonstrated by the level of Faecalibacterium prausnitzii negatively correlating with that of TNF-alpha ($r = -0.46$, $p = 0.005$).

DISCUSSION

The results of this paper furnish strong indications of a non-separable tight relationship between the events of gut microbiome dysbiosis and dysfunction of the intestinal resistance and systemic inflammation, in the etiology of Parkinson. The microbial changes that were produced such as loss of Prevotella and Faecalibacterium and overrepresentation of Akkermansia and Enterobacteriaceae are very similar to other international observations [5,6]. All this weight of evidence indicates that gut dysbiosis facilitates translocation of endotoxins, general activation of immune system functions, and neuroinflammatory reactions which cause the loss of dopaminergic neurons.

Significantly, this paper supports Braak hypothesis as this research shows that biologically a gut-origin model of PD is possible. These correlations between Akkermansia and LPS and the severity of the disease further suggest that the gut microbiota are not roughly just spectators but active controllers of the disease progression.

Clinically, the discoveries also put novel therapeutic options in place of microbiota-metabolite or microbiota-loopamino acid antagonist therapy, such as diet, probiotics, prebiotics, and fecal microbiota transplantation (FMT). These mechanisms could regenerate microbial homeostasis, boost SCFA synthesis and decrease gut-derived inflammatory condition ultimately, regulating neurodegenerative mechanisms.

Overall, both this research and the given article support the idea that gut-brain axis-dysregulation is a core etiologic factor in the pathology of Parkinson. The intestinal imbalances linked to dysbiosis how establishes a mechanistic relationship between neurodegeneration and inflammation induced by permeability, and therefore provides grounds on why gut-based interventions can be combined with current PD therapies.

CONCLUSION

This paper points out the essentiality of the gut brain axis misregulation in pathogenesis of Parkinson disease (PD), through which the imbalance between microbes, intestinal permeability, and systemic inflammation contribute to neurodegenerative development of the disease. The patient diversity of the gut microbes of PDs was lower, and they depleted useful taxa such as Prevotella and Faecalibacterium and enriched pro-inflammatory species such as Akkermansia muciniphila and Enterobacteriaceae. These changes were associated with heightened levels of zonulin, lipopolysaccharide (LPS), and inflammatory cytokines and indicated a mechanistic connection of the dysfunction of the gut barrier and neuroinflammation.

The biological evidence of the results on the Braak hypothesis is that PD can commence in the gut and then extend to the central nervous system through the inflammatory signal triggers and via the vagus nerve. One approach that has been shown potential on disease modification is gut dysbiosis targeting. Probiotics, prebiotics, dietary change and transplantation of fecal microbials (FMT) could be used by re-established microbial balance, enhancement of intestinal integrity and a reduction in general inflammation.

In general, the article highlights the fact that the gut microbiome is one of the factors that can be modified in the pathogenesis of PD and investigates it as a new niche of future diagnostic, biomarker-based, and personalized gut-targeted therapies to intervene with the development of the disease at an earlier stage.

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