International Clinical and Medical Case Reports Journal
Review Article (ISSN: 2832-5788)

Impact of Gut-Brain Axis Dysfunction on Neurodegenerative Diseases

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Citation: *Sanat Malhotra, Shalini M. Impact of Gut-Brain Axis Dysfunction on Neurodegenerative Diseases. Int Clinc Med Case Rep Jour. 2026;5(3):1-6.*

Received Date: 26 February 2026; **Accepted Date:** 28 February 2026; **Published Date:** 01 March 2026

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INTRODUCTION

Gut bacteria, collectively called the gut microbiome, play a key role in overall human health. The human microbiota are a large and diverse microbial community that encompasses more than 100 trillion microorganisms, with the gut being one of the most fascinating ecosystems responsible for influencing several physiological functions in the host including host metabolism, vitamin production, immunomodulation, maintaining an essential gut mucosal barrier and even mental health [1].

Studies have focused on how the gut bacteria impact brain health, and research has thus established the “Gut Brain Axis”. The composition of the gut microbiome is dependent on both environmental and genetic factors and changes across the lifespan. This, along with genetic factors, could predispose to the development of degenerative diseases, particularly neurodegenerative diseases. In addition to senescence, environmental risk factors such as diet, chemical exposures and infection also shape the human gut microbiota. All these factors have been found in numerous studies to impact the gut-brain axis, thereby predisposing neurodegeneration and related diseases.

This article aims to review existing scientific evidence in order to enable better understanding of the gut brain axis, and how maintaining a good gut health can help prevent diseases like Alzheimer's disease, Parkinson’s disease, etc.

Gut-Brain Axis

The gut-brain axis refers to the bidirectional link between the Central Nervous System (CNS) and the gastrointestinal tract. While it is known that the Central Nervous System (CNS) regulates numerous physiological conditions in the body, pathological conditions of the body also have a direct relationship on the central nervous system function, primarily by their effect on the gut microbiota. There is crosstalk between the gut microbiota and the CNS, and this is what is referred to as the gut-brain axis.

Dysbiosis in the gut, defined as alteration in the composition of the gut microbiota, allows microbial metabolites to cause neuro-inflammation and other effects in the central nervous system [2], leading to the gradual onset of many neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) and Huntington's disease (HD) [3].

Gut Microbiome and its Impact on the Central Nervous System

The gut microbiome is constituted by a huge community of bacteria, archaea, fungi and viruses, with a great deal of variability between individuals [4]. Plant-based diets rich in prebiotics and fermented foods help maintain microbiome diversity and stability [5]. Cross-sectional studies have shown that gut microbiome composition in individuals with various neurological diseases is different when compared to healthy controls, suggesting a likely association [6].

The gut microbiota might influence the homeostasis of the CNS by modulating the immune system and, more directly, by producing metabolites, neuroactive molecules, and hormones that influence the functioning of the nervous and endocrine systems, making it a potential therapeutic target [6,7]. Some of the most beneficial gut bacteria include *Akkermansia muciniphila*, *Adlercreutzia equolifaciens* and *Christensenella minuta* which all contribute by producing bioactive metabolites like short-chain fatty acids (SCFAs) [8].

Anaerobic fermentation of indigestible polysaccharides such as dietary fibers and resistant starch by the microbiome in the large intestine leads to production of SCFAs, mainly acetate, propionate, and butyrate. The quantity in which they are produced depends on the type of diet and the composition of the gut microbiome. SCFAs help in mucus production, maintaining the intestinal barrier, and thus, immunoregulation. Apart from the local benefits to the gut, SCFAs can cross the Blood Brain Barrier (BBB), being responsible for the crosstalk between the gut and brain [9].

Gut Microbiome & Parkinson's Disease

Parkinson’s disease (PD) is a multi-factorial, progressive neurodegenerative disease believed to be caused by environmental and genetic factors. It is characterized by the loss of dopaminergic neurons in the substantia nigra and striatum, with abnormal accumulation of α-synuclein in the brain. The main symptoms of Parkinson’s Disease are resting tremors, stiffness, bradykinesia, and postural instability [10]. With disease progression, cognitive decline

might ensue. At times, non-motor symptoms such as behavioral changes, sleep disorders, and gastrointestinal and autonomic dysfunction may precede the motor symptoms [11].

The role of the GI tract in the pathogenesis of Parkinson's Disease has been hypothesized since the 1980s. In the past decade, it became clear that alterations in the gut microbiota can be either a potential disease biomarker and/or disease modifier. More than 80% of patients with Parkinson's Disease experience gastrointestinal symptoms [12]. Clinical studies profiling the microbiota of Parkinson's Disease patients reported several alterations relative to healthy controls. As in other neurodegenerative diseases, Parkinson's Disease has been associated with inflammation, specifically inflammaging, defined as the senescence of the immune system [13]. Dysbiosis and gut inflammation are now considered important contributors to the disease pathogenesis.

Gut Microbiome & Alzheimer's Disease

Alzheimer's disease is the most common cause of cognitive decline worldwide. It is characterized by the deposition of Amyloid plaques, leading to neuroinflammation, synaptic dysfunction and ultimately, neuronal loss and brain atrophy. Alzheimer's Disease is a neurodegenerative disorder that causes progressive loss of cognition, memory, and motor ability. Patients with Alzheimer's Disease have been shown to have an imbalance of gut bacteria - exhibiting reduced gut microbial diversity and higher levels of inflammation-promoting bacteria. Resulting gut-brain axis dysfunction leads to intestinal inflammation [14]. Some studies have even reported altered gut microbiome composition in people with Alzheimer's Disease compared to healthy controls [15]. This negatively impacts the production of SCFAs including butyrate, propionate, and acetate, in patients with Alzheimer's Disease [16]. This decrease in SCFAs leads to increased epithelial leakage and bacterial translocation, with a consequent increase in circulating Gram-negative bacteria and Lipopolysaccharides, microglia activation, and amyloid deposition in the CNS [17].

Ageing itself impacts the gut microbiome composition and diversity, favoring a shift to more proinflammatory bacteria, such as *Bacillus fragilis, Bacteroides fragilis*, and *Faecalibacterium prausnitzii*, as against the more immune-regulatory bacteria. This, when compounded by other causative factors, leads to significant gut dysbiosis and a marked increase in the resulting risk of Alzheimer's Disease.

Role of Probiotics

Probiotics are defined as non-viable food components that confer health benefits to the host and are associated with modulating the microbiome. Studies have shown that probiotics can help maintain intestinal homeostasis by stabilizing the epithelial barrier, increasing the production of SCFAs, modulating the mucosal immune system towards a more immunoregulatory response, and inhibiting the production of proinflammatory cytokines.

The administration of a probiotic mixture of Lactobacillus and Bifidobacterium has been proven in studies to be directly capable of influencing the concentration of neurotransmitters such as GABA and glutamate in the CNS [18].

In a recent randomized trial on people with Alzheimer's Disease, the daily administration of a probiotic mixture of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* for 12 weeks was found to show a statistically significant improvement in the mini-mental state exam (MMSE) score compared to controls [19].

Probiotics also showed promising results in people with Parkinson's Disease. Recent studies have confirmed a possible positive role of the probiotic mixture in relieving constipation and motor symptoms [20]. In addition, even though the exact mechanism of action is unknown, probiotic treatment has been shown to modulate intestinal permeability, mucosal inflammation, and stimulate the production of SCFAs [21].

Diet & its Role

Diet, medication, and lifestyle directly impact gut health and consequently, the progression of Alzheimer's disease. With diet alteration, the gut microbiome composition and the abundance of SCFAs and gut metabolites can change drastically, thereby influencing inflammation inside the CNS through the Gut-Brain Axis [22].

Various types of diets have been proposed as beneficial in preventing or ameliorating neurodegenerative diseases. One such diet, the Mediterranean diet, is rich in vegetables, whole grains and low in dairy, with the main source of fat being olive oil. Recent studies reported an improvement in motor and cognitive symptoms in Parkinson's Disease following adherence to a Mediterranean diet, in addition to a reduced risk of developing the disease [23].

Another diet, the ketogenic diet, is a nutritional program rich in fats and low in carbohydrates. It has been investigated for its role in neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease and has shown promising results [22].

CONCLUSION

Research is ongoing and facts are ever evolving in understanding the causative and contributory factors of neurodegenerative diseases. It is proven that processes throughout the whole body, not just in the brain, contribute to their gradual development. These processes often involve and impact the gut microbiome, a unique ecosystem. The resulting shift to a pro-inflammatory environment in the gut through the gut-brain axis directly affects brain function. It is thus imperative to focus on modulating the human gut microbiome through dietary recommendations, healthy lifestyle modifications, and probiotics in order to prevent or slow the onset of neurodegenerative diseases. Further studies are recommended on interventions to help prevent disease state and optimize good health before ageing and related changes set in.

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