www.idosr.org Omagor, 2025

©IDOSR PUBLICATIONS

ISSN: 2550-7931

International Digital Organization for Scientific Research IDOSRJAS1030000
IDOSR JOURNAL OF APPLIED SCIENCES 10(3):41-51, 2025.
https://doi.org/10.59298/IDOSRJAS/2025/103.4151

Microbiome Alterations in Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis represent a growing global health challenge, with complex etiologies that remain incompletely understood. Emerging evidence highlights the critical role of the gut microbiome in modulating neuroinflammation, immune responses, and neuronal function through the gut–brain axis. Alterations in microbial diversity and metabolite production have been linked to disease onset, progression, and symptom severity, suggesting that host–microbe interactions are integral to neurodegenerative pathology. Advances in sequencing technologies and multi-omics approaches are unraveling these mechanisms, while therapeutic strategies, including probiotics, prebiotics, synbiotics, dietary interventions, and fecal microbiota transplantation are being investigated for their potential to restore microbial balance and improve clinical outcomes. Despite these promising insights, major challenges remain, including disentangling causality from correlation, addressing methodological variability, and ensuring ethical and regulatory oversight in clinical applications. This review synthesizes current knowledge of gut microbiome–neurodegeneration interactions, evaluates therapeutic opportunities, and highlights future directions for research, precision medicine, and public health.

Keywords: Neurodegeneration, Gut microbiome, Gut–brain axis, Microbiome-targeted therapies and Host–microbe interactions.

INTRODUCTION

Neurodegenerative diseases (NDs) are among the major causes of disability and mortality, with patient numbers rising due to population ageing. Chronic neurodegeneration is linked to altered gut-microbial-host interactions. Accumulating evidence connects the gut microbiome and various neurodegenerative diseases, and microbiome alterations tend to occur years before the onset of neurodegeneration. Understanding these changes is crucial for early diagnosis and prevention strategies. Reliable experimental models that investigate microbiome alterations associated with neurodegeneration are still limited. Both clinical and experimental studies have noted microbiome alterations in neurological disorders. Recognising the link between neurodegeneration and microbiome dynamics could aid early clinical diagnosis before irreversible brain damage occurs, and microbiome-targeted therapeutics might mitigate the progression of these diseases [1].

Understanding the Microbiome

The microbiome describes the collection of microorganisms, including bacteria, archaea, fungi, algae, small protists, and viruses (mirobiota) and their genomes residing in a defined environment [1]. Newly hatched chickens harbor only endogenous microbes, after which intestinal microbial communities establish, culminating in a complex and diverse ecosystem dominated predominantly by bacteria. The intestinal microbiome exerts profound effects on the host, contributing to metabolic demands, supplying nutrients, providing vitamins and growth factors, influencing intestinal morphology and function, regulating the mucosal immune system, and conferring resistance against pathogenic microbes [1].

Definition and Composition

The human microbiome comprises trillions colonizing every part of the human body, with the gut microbiome being the most extensive, mainly composed of probiotic anaerobic bacteria. It plays a crucial role in regulating and

maintaining the host immune system and inflammatory response, and provides essential vitamins and nutrients for normal brain function [1]. Maintaining the homeostasis of the brain–gut axis is essential for mental health and behavior, as changes to the gut microbiota can influence the brain through neurological, hormonal, and immunological mechanisms. The gut microbiome maintains normal physiological brain functions through diverse metabolic mechanisms. Neurodegenerative diseases (NDs) represent a representative group of mental and neurological illnesses, and an imbalance in the gut microbiota is closely associated with NDs and their development [1]. The microbiota-gut-brain axis is a complex communication network involving various pathways such as the nervous system, immunity, and endocrine systems. Alterations in the microbiota-gut-brain axis can influence the progression of diseases affecting the central nervous system, including Alzheimer's disease (AD) and Parkinson's disease (PD). Given the influence of commensal bacteria on host regulatory systems, gut microbiota-targeted treatment strategies hold potential for treating CNS disorders [1, 2].

Functions of the Microbiome

The term microbiome is used to describe the collection of all the microorganisms, including bacteria, viruses, fungi, and other microbes, that naturally exist on and inside the human body surface [1]. These microorganisms significantly outnumber the cells in the human body and carry a wide range of genes, microbial genes outnumber host genes by approximately 100 times. Microbial cells are predominantly found in the gastrointestinal (GI) tract, with essential functions in the host's physiology ranging from nutritional homeostasis and metabolism to immune modulation. The microbiota plays a key role in maintaining gut immune homeostasis, partly by acting as a barrier against gut pathogens and influencing the adaptive immune system [1]. The synergistic action between the microbes and the host's immune system has a positive influence on host food processing and other metabolic functions, including nutrient acquisition, production of energy, and provision of vitamins and amino acids, which are critical for the growth of the host [1].

Neurodegenerative Diseases Overview

Neurodegenerative diseases (NDs) are pathological conditions mainly affecting the central nervous system (CNS). They are characterized by progressive degenerative changes in neurons of specific areas of the brain, leading to a chronic decline in cognitive, emotional, and motor functions. Depending on the regions of the nervous system affected and the main clinical symptoms exhibited, NDs can be broadly classified into three categories: (i) cognitive dementias, (ii) autonomic ataxias, and (iii) motor neuron disorders. The most common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [1]. Despite different clinical presentations, all neurodegenerative diseases include neuroinflammatory processes that result in the impairment of cellular homeostasis. A substantial amount of new information has highlighted the importance that dysbiosis of the gut microflora may exert on the physiological state of the brain, as well as on the pathogenesis of neurological diseases. This has led to the concept of the gut–brain axis, a bidirectional communication system between the brain and the gut [1]. These new preclinical and clinical data confirm the importance of maintaining gut eubiosis for brain homeostasis and open new perspectives for interventions in brain diseases based on modulation of the gut microbiota. A mounting body of evidence points to the involvement of the gut microbiota in neurodegenerative diseases through abnormal gut–brain interactions. Moreover, the analysis of differences or changes in the gut microbiome may be useful as a non-invasive diagnostic or predictive/prognostic biomarker [1].

Types of Neurodegenerative Diseases

CNS disorders are common diseases with heavy burdens worldwide. Neurodegenerative diseases, including AD, PD, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), are all chronic, irreversibly progressive, and incurable [1]. The pathophysiological mechanisms of these diseases are complex and multifactorial. Though senile plaques and neurofibrillary tangles are the pathological hallmarks of AD, immune response disorders also contribute to this disease. Multiple sclerosis is an immune-mediated demyelinating central nervous system disorder [1]. ALS, characterized by the selective loss of motor neurons, is an adult-onset fatal neurodegenerative disorder. The main pathological process of PD involves the degeneration and necrosis of dopamine neurons in the substantia nigra pars compacta [1].

Pathophysiology of Neurodegeneration

Neurodegeneration is a pathological hallmark that defines several diseases, including AD, PD, MS, and ALS. The neurological alterations induced in such diseases are linked to the progressive functional loss of neurons and their subsequent death in the CNS and/or PNS. Despite the fact that the cause of neurodegeneration varies from one disease to another, some common features emerge across several conditions [1]. Oxidative stress, mitochondrial dysfunction, and primary inflammation are factors extensively explored for the potential roles that they play in neurodegeneration. Hyperactivation of microglia and astrogliosis accompany the neurodegenerative process and

are responsible for the proinflammatory alterations that are persistently present in the CNS [1, 2]. These phenomena include injured astrocytes and microglia actively engaged in the secretion of proinflammatory cytokines and chemokines involved in the destruction of the blood–brain barrier (BBB). Under such circumstances, prostaglandins and the complement system are subsequently activated in the CNS, leading to the recruitment of peripheral immune cells that may contribute to neuronal death. Disturbed homeostasis of Ca2+ ions and associated excitotoxicity is also a characteristic that appears in different neurodegenerative disorders. Inflammaging as the chronic low-grade inflammatory state observed with the natural aging process is an additional important factor that can trigger the onset or progression of neurodegenerative diseases [1]. Furthermore, alterations to the gut microbiota have a direct effect on all of the aforementioned features [1].

The Gut-Brain Axis

The gut-brain axis is a bidirectional communication system that links the gut and its microbiota with the brain and central nervous system. The axis encompasses various components, including the autonomic nervous system, neuroendocrine and neuroimmune pathways, the vagus nerve, the enteric nervous system, and the hypothalamic-pituitary-adrenal axis [1]. It facilitates bidirectional communications between the gut and brain via multiple pathways, including the vagus nerve, neurotransmitters, neuropeptides, the enteric nervous system, the central nervous system, the neuroimmune system, and the hypothalamic-pituitary-adrenal axis [2, 3]. Alterations in the gut–brain axis have been connected with neurodegenerative diseases, schizophrenia, depression, and other neurological disorders. Modulation of the microbiota can influence brain and nervous function in both animals and humans. Moreover, evidence links environmental toxins and infectious pathogens to neurodegenerative diseases. Dysbiosis or alterations of the performa in gut microbes can impede functions such as butyrate protection, leading to potential neuroinflammation in the brain and ultimately resulting in Parkinson's disease. Humans with Parkinson's disease often experience imbalances in their gut microbiota[2, 3].

Mechanisms of Communication

The concept of the gut–brain axis has been extended with the discovery of the bidirectional communication that occurs between gut microbes and the brain. Gut microorganisms influence brain function directly via the nervous system and neuroendocrine and neuroimmune systems and indirectly through the bacterial metabolites they produce [1]. Leukocytes and inflammatory mediators are able to cross the blood brain barrier (BBB) and act directly in the cerebral circulation. Pro-inflammatory and anti-inflammatory cytokines can induce inflammatory or anti-inflammatory responses in the microglia and in other antigen-presenting cells in the central nervous system (CNS) [1]. The communication between gut bacteria and the brain is also possible through the vagus nerve. Intestinal microorganisms modulate cerebral function by generating a variety of neuroactive metabolites (γ-aminobutyric acid, serotonin, dopamine, acetylcholine, and norepinephrine) that act by activating the vagus nerve. The vagus nerve carries ascending sensitive fibers from the stomach and intestines to the nucleus of the solitary tract in the brain stem [2]. There are inhibitory and stimulatory microbiota–vagus–nerve–mediated pathways conveyed in the CNS that are crucial to the regulation of emotions and thus to the establishment of a microbiota–brain–behavior axis [1, 2].

Impact on Neurological Function

The bidirectional communication between the gut microbiota and the brain, known as the gut-brain axis, operates through neural, endocrine, neuroendocrine, and immunological pathways. Alterations in the diversity and composition of the gut microbiota influence neurological function. The gut microbiome participates in nutrient metabolism and affects the immune, endocrine, and nervous systems, as well as the blood-brain barrier, through the production of neurotransmitters, short-chain fatty acids, and lipopolysaccharides. As a result, dysbiosis has been implicated not only in psychiatric disorders but also in neurodegenerative diseases [1]. Dysregulation of the gut and oral microbiota leads to increased inflammation and oxidative stress in neurodegenerative and cerebrovascular diseases, indicating a potential role in disease pathogenesis [1, 2, 3]. Patients with Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) exhibit alterations in their microbiomes that, in combination with other factors, may worsen symptoms. Consequently, a growing number of researchers and clinicians advocate for maintaining eubiosis and employing microbiome-modulating interventions, such as probiotics, prebiotics, synbiotics, postbiotics, and fecal microbial transplantation, as adjunctive treatments for these neurodegenerative disorders [1, 2].

Microbiome and Alzheimer's Disease

Alzheimer's disease (AD) is characterized by neuronal death in the hippocampus and cerebral cortex, extracellular amyloid-β (Aβ) plaques, and intracellular neurofibrillary tangles of hyperphosphorylated tau protein. These pathological features are accompanied by neuroinflammation and synapse loss. Although the pathology of AD begins early in life, it is accompanied by mild cognitive impairment and memory loss in the elderly [1]. The gut

microbiota appears to play a pivotal role along the gut–brain axis and in brain health, with dysbiosis observed in AD patients. In these individuals, the abundance of various microbial taxa is altered; intriguingly, certain microbes correlate with the cerebrospinal fluid levels of t-tau and Aβ42, clinical indicators of AD. This finding supports the hypothesis that AD pathology may initiate in the gut and spread through the vagus nerve to the brain. The importance of the gut microbiota was further demonstrated in the 5xFAD mice model, where exposure to a probiotic strain mitigated memory impairment and Aβ accumulation in the brain through modulation of the Th17/Treg balance [2]. In AD patients, probiotic supplementation has yielded positive effects on the Mini Mental State Examination (MMSE) score. Probiotics and prebiotics enhance cognition by fostering the growth of beneficial butyrate-producing bacteria, whereas a reduction of the butyrate-producing genera Agathobacter and Lachnospira has been reported in AD. Additionally, fecal microbiota transplantation (FMT) has emerged as a promising novel treatment, with evidence that FMT can restore gut dysbiosis and reduce Aβ accumulation in rodent AD models [1, 3].

Alterations in Gut Microbiota

The gut microbiota regulates several physiological functions and the communication between the gut and the brain, providing the basis for gut-brain-microbiota communication [1]. Nearly 500 species of bacteria inhabit the intestine, and the maintenance of their homeostasis is vital to the health of the host. Alterations in gut microbiota are linked to several pathological conditions, including neurodegenerative diseases [2]. The study of ageing and microbiota, especially the effects that changes on microbiota composition can have on the brain during ageing, is a topic with clear implications for age-related neurodegenerative disorders. The gut microbiome of patients with dementia differs significantly from that of healthy subjects. A higher abundance of Escherichia, Lactobacillus and Oscillospira has been found in patients with dementia; Bacteroides are more abundant in the early stages and Proteobacteria during the late stages of dementia [3]. Symptomatic patients show reduced contents of Acinetobacter, Bifidobacterium, Blautia and Lactobacillus compared with asymptomatic patients. Several bacteria secrete amyloid peptides that can interfere with the folding of neural proteins, and both Parkinson's and Alzheimer's diseases are also linked to a wide range of metabolites (excreted by gut bacteria) as well as alterations of the microbiome in the progression of the diseases. Therapeutic approaches that could potentially slow disease progression include the use of microbiota-based probiotics [1, 2, 3].

Clinical Implications

Several distinct neurodegenerative diseases exhibit related patterns of gut microbial alteration, indicating common underlying processes that may reflect disease progression and present targets for personalized therapeutic intervention through microbiome modulation [1]. In Alzheimer's disease (AD), gut microbial communities shift from predominantly anti-inflammatory and probiotic species towards taxa with pro-inflammatory and pro-fibrotic tendencies. Parkinson's disease (PD) gut dysbiosis predicts more severe symptomology; conversely, deliberate modulation of the microbiome and gut–brain axis through dietary supplementation and exposure to selected bacteria offers promising strategies to mitigate disease progression. Multiple sclerosis (MS) pathology correlates with gut microbiome composition, with targeted microbial members influencing immune responsiveness. Therapeutic approaches exploiting these microbial interactions show potential to control aberrant inflammation and reduce morbidity [1]. Amyotrophic lateral sclerosis (ALS) patients demonstrate decreased microbial diversity, evenness, and richness, and distinct taxonomic differences relative to healthy controls; a consistent relationship between microbiome characteristics and disease progression further implicates the microbiota as a candidate for disease modification and personalized treatment [1, 2]. Although the role of the gut and associated microbiota in neurodegenerative disease pathology is well-established, the precise pathways and mechanisms linking microbial alterations to the central nervous system remain incompletely understood. Research to elucidate these connections promises to define novel targets for therapeutic intervention and clarify the broader impact of environmental, social, and genetic factors on disease initiation and progression [1]. Furthermore, the potential of the microbiome itself as a therapeutic agent warrants exploration to complement intervention strategies.

Microbiome and Parkinson's Disease

Emerging evidence implicates gut microbiota dysbiosis as a key factor in the development of Parkinson's disease. Dysbiosis disrupts gastrointestinal homeostasis and promotes inflammation, possibly initiating the disease in the enteric nervous system and enabling transmission of α-synuclein pathology to the brain [4]. These observations suggest that the gut microbiota constitutes a promising therapeutic target to prevent or slow Parkinson's progression [4].

Gut Dysbiosis in Parkinson's

Alterations in gut microbiota composition (gut dysbiosis) have been reported in Parkinson's disease (PD) patients [4]. In several PD cohorts, a decline of short-chain fatty acid (SCFA)-producing bacteria has been observed. Such

variations correlate with inflammatory cytokine levels and progression of motor symptoms. Similar patterns have been reported by Zhang et al., who highlight the involvement of SCFA-producing microbes and the correlation between microbiome shifts and severity of gastrointestinal and non-motor symptoms. The group also considers microbial profiles across PD clinical subtypes, the progression of gut microbiota alterations over time, and the predictive value of prodromal gastrointestinal complaints for later cognitive decline in de novo patients. They further discuss the influence of gut dysbiosis on PD animal models and its potential impact on dopaminergic therapies [4].

Potential Therapeutic Targets

Multiple studies have indicated that microbiome alterations can be important potential therapeutic targets in neurodegenerative diseases [4]. Probiotic and prebiotic supplementation may alleviate symptoms and decelerate the progression of several neurodegenerative disorders. For example, in certain illnesses, probiotics alone might be insufficient, and their combination with prebiotics has proven more effective. In pivotal gut dysbiosis conditions, such as Clostridium difficile infection, clinical evidence supports Fecal Microbiota Transplantation (FMT) from healthy donors as a beneficial intervention, suggesting its applicability in neurodegenerative diseases characterized by gut dysbiosis. Several clinical trials are examining the effects of FMT in Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis. Moreover, other strategies currently utilized for modulating the microbiome include dietary adjustments and the administration of antibiotics [2, 3, 4].

Microbiome and Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, characterized by demyelination and neurodegeneration. Although the exact cause of MS remains unclear, it is believed to result from an aberrant immune response triggered in genetically predisposed individuals by environmental factors [1]. Relative changes in the richness of Bacteroidetes, Firmicutes, Streptococcus, and Anaerostipes have been associated with MS [2]. The alteration of the gastrointestinal tract microbiome influences the immune response and disease progression in MS. Modulation of the gut microbiome composition through probiotics, prebiotics, fecal microbiota transplantation, and dietary modification is suggested as a potential therapeutic strategy for MS. Comprehending the pathways linking the microbiome with neurodegenerative diseases presents an opportunity to develop new therapeutic pathways for these challenging conditions, including MS. A wide range of public data, especially from genome-wide association studies in AD, PD, MS, and ALS, are now available. However, in the context of microbiome research in neurodegenerative diseases, several challenges persist [3].

Influence on Immune Response

Intrinsic factors that regulate the immune response are crucial for modifying susceptibility to multiple sclerosis (MS). The gut microbiota influences immune modulation and may thereby contribute to MS pathogenesis. Changes in microbiome composition can disrupt the balance between pro-inflammatory and anti-inflammatory responses, promoting neuroinflammation. Given recent evidence linking microbiota involvement to neurological disorders, modulating alterations in the microbiome during MS progression emerges as a promising therapeutic strategy [2]. The human microbiome comprises the total genetic material of all commensal microorganisms residing in the body, including bacteria, viruses, fungi, yeasts, and protozoa. These microbes constitute diverse ecosystems that play essential roles in various physiological processes [3]. The microbiome contributes to immunological, digestive, and metabolic functions and can influence an individual's susceptibility to certain pathologies. Changes in the microbiome affect the gut-brain axis a mutual communication pathway between the brain and the gut highlighting the interplay between microbiome alterations during neurodegenerative diseases and the consequent neurological manifestations [1, 4].

Microbiota Modulation Strategies

Various approaches for altering the gut microbiota composition are currently investigated in both experimental and clinical settings to prevent, delay, or treat neurodegenerative diseases. Antibiotic exposure modifies the composition of the gut microbiota and has been tested in different models of neurodegenerative diseases [5]. Oral antibiotics depleted the intestinal flora in the MPTP mouse model of Parkinson's disease, leading to a reduction in MPTP toxicity; however, the same treatment had no effect on the development and progression of ALS in the SOD1 mouse model. Prebiotics, foods or substances that promote the growth or activity of microorganisms, have a well-recognized protective role in several neurological disorders [1]. A 6-month intervention with a prebiotic fiber mix (Bimuno, carbohydrate mixture) induced cognitive improvement in human subjects aged 60 years and older, whereas fructooligosaccharides or fructans decreased inflammation and decreased the expression of Aβ-protein in models of Alzheimer's disease. The administration of B-GOS or xylooligosaccharide (XOS) and DHA improved cognitive functions and diet-induced changes in gut microbiota composition in an Alzheimer's disease rat model. Symbiotics, which combine prebiotics with probiotics, enhance the survival of the ferments

during the transit through the intestinal flora. Probiotic treatment has been tested intensively in the prevention and control of neurodegenerative disorders; some current clinical trials are recruiting for studying their effects [1, 3]. The administration of probiotics or a combination of probiotics and selenium in Alzheimer's disease patients improved cognitive performance and metabolic status in a series of clinical trials. In clinical studies on Parkinson's disease and multiple sclerosis patients, the administration of probiotics was related to a better disease outcome achieved through immune system regulation. Fecal microbiota transplantation (FMT) consists of the transfer of functional microbiota of healthy donors into patients by infusion of fecal material. The biological rationale for this approach is the fact that the gut microbiota plays a tremendous role as immune-modulator and regulator of the gut-brain axis. Treatment based on the transplantation of fecal microbiota from healthy donors has been employed starting from animals and, as case reports, also in Parkinson's disease patients, demonstrating the feasibility of the approach [1]. The potential beneficial role of FMT is determined by the reconstruction of the microbial community in recipients and the inhibition of neuroinflammation, thus the therapy could be proposed to affect the progression or the severity of the neurological disorder. Larger, randomized placebo-controlled clinical trials could offer the opportunity to define the role of FMT procedure in neurodegenerative diseases [1, 2, 3].

Microbiome and Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the loss of motor neurons, resulting in muscle weakness and death within 3 to 5 years. The disease is genetically and clinically heterogeneous, with environmental factors also influencing susceptibility [5]. Alterations in the gut microbiota have been observed in ALS patients at all disease stages, including decreased abundance of butyrate-producing bacteria such as Roseburia intestinalis and Eubacterium rectale. The gut microbiota–gut–brain axis is closely implicated in neurodegenerative diseases and may influence ALS initiation and progression [6]. Microglia, the resident immune cells of the central nervous system (CNS), become dysregulated in ALS and contributes to motor neuron damage. The gut microbiome influences immune defense and metabolic regulation both locally and in distant organs. Emerging evidence supports a role for gut microbiome and its metabolites in ALS pathogenesis by affecting the CNS through the blood–brain barrier. Impairments of the intestinal epithelium and tight junctions may also contribute to disease progression, and probiotic supplementation has improved motor ability in animal models [6]. While alterations in gut microbiota have been detected prior to the onset of motor neuron dysfunction, some studies report inconsistent differences in microbiota composition between ALS patients and healthy controls. Initial investigations found dysbiosis characterized by overgrowth of harmful bacteria and reduced diversity of beneficial bacteria, suggestive of a mechanistic link to ALS pathogenesis [7]. Patients with higher microbiome richness, diversity, and a greater Firmicutes to Bacteroidetes ratio face increased risk of early mortality. Significant differences in gut microbiome profiles evolve during disease progression, marked by decreased protective bacteria and increased neurotoxic species [7]. Levels of butyrate-producing bacteria decline as the disease advances, suggesting that microbiome alterations influence clinical course rather than risk of onset. Animal studies demonstrate pre-symptomatic dysbiosis with decreased beneficial bacteria such as Akkermansia muciniphila and elevated potentially harmful species including Ruminococcus torques and Parabacteroides distasonis, which may exacerbate ALS symptoms [7].

Microbial Diversity Changes

The gut microbiome plays an essential role in maintaining host homeostasis by influencing the immune system and metabolic functions. Alteration of the gut microbiome composition or function (dysbiosis) is associated with impaired neurophysiological activities. Microbiome analysis, proteomic studies of biomarker validation, and disease modeling have provided mechanistic insights into dysbiosis-mediated neurodegeneration. Microbial ecosystems are driven by the composition of distinct groups and subgroups of bacterial taxa cohabitating and interacting in a preferred community [1]. Using fecal metagenomic sequencing and 16S ribosomal RNA gene profiling, the human gut microbiome was stratified into three clusters or enterotypes, each classified by a dominant genus: Bacteroides, Prevotella, and Ruminococcus. Along with dominant genera, a shared network of co-occurring genera was detected [1]. These microbes share functional properties like saccharolytic and proteolytic pathways, deriving energy from specific diets. Dominant genera influence macromolecular functions such as energy production, with less abundant microbes supporting these functions through specialized roles. A balance among high- and low-abundant species is crucial for gut health, and environmental factors like diet and antibiotics can induce dysbiosis, altering microbial compositions and potentially deteriorating gut health. Mapping microbial networks can generate profiles to understand microbe–microbe and microbe–host interactions, aiding in disease stratification, clinical subtyping, and biomarker identification for neurodegenerative diseases. Meta-analyses of clinical data, combined with mechanistic studies in animal models, can help unravel microbe-mediated pathophysiological changes [1].

Link to Disease Progression

The association of microbiome alterations in neurodegeneration has been demonstrated, but the link to disease progression remains unclear [1]. Parkinson's disease patients with rapid disease progression showed lower abundances of Akkermansia, Pseudomonas, and Christensenellaceae compared to those with slower progression; high Pseudomonas abundance is associated with longer survival in Amyotrophic Lateral Sclerosis. At the phylum level, Proteobacteria, Actinobacteria, and Verrucomicrobia were increased in the rapid progression group, while Firmicutes abundance was higher in the slow progression group. Taxa with antimicrobial and anti-inflammatory effects exhibited a positive correlation with the pro-inflammatory genus Proteus in Multiple Sclerosis patients, complicating their role in disease progression; Corynebacterium [1] and Granulicatella increases in Multiple Sclerosis could also correlate with disease advancement. In Amyotrophic Lateral Sclerosis, dysbiosis with an elevated pro-inflammatory ratio of Escherichia coli and Enterobacteria counts to beneficial taxa is linked to disease onset and progression. Further investigation is required to elucidate how distinct alterations of the intestinal microbiome influence the progression of different neurodegenerative disorders and to enable targeted therapeutic development [1, 2].

Research Methodologies

Metagenomics, the study of microbial genomes in their natural environment, enables identification and quantification of microbial communities without the need for culturing. Clinically relevant metabolites and metaproteomics complement metagenomic findings by elucidating microbial function [1]. These integrated approaches have elucidated microbiome alterations in neurodegenerative diseases. In Alzheimer's disease (AD), for example, microbiome profiles from the ADNI cohort inform longitudinal clinical studies, while fecal microbiota transplantation (FMT) and germ-free animal models offer mechanistic insights. Similar strategies apply to Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [1, 2, 7].

Microbiome Analysis Techniques

The availability of microbiome analysis techniques has rapidly increased in recent years. Microbiome analysis of the gut microbiome is based on stool or mucosal biopsies. Larger clinical trials usually include analysis of the stool microbiome because of the easy application and tolerability compared to gut mucosal biopsies (Rajilić-Stojanović et al. 2013) [2, 7]. Nonetheless, the analysis of mucosal biopsies might be more suitable in selected cases because it reflects the microbiota in closest proximity to the intestinal epithelium. Additionally, the analysis of mucosal biopsies has been shown to be less influenced by lifestyle factors such as diet. Sample processing involves several incubation steps using specialized kits to increase bacterial DNA concentrations. In the next step, the bacterial 16S ribosomal RNA (rRNA) gene, present in all bacteria but highly variable among species, is amplified using PCR. Sequencing is most often done by using the Illumina sequencing machine in 2×300 bp paired-end analysis (Caporaso et al. 2012). Microbiome analyses are usually performed in relatively small clinical and/or experimental studies. Population analyses and comparisons were performed using the web-based Microbiome Analyst Tool (Dhariwal et al. 2017) in previous analyses on Parkinson's disease (PD) and multiple sclerosis (MS) cohorts (Hill-Burns et al. 2017; Dicks et al. 2022) [7].

Clinical and Experimental Studies

Neurodegenerative diseases are the result of complex interactions between environmental and genetic factors. Nevertheless, the precise etiology of most neurodegenerative diseases remains unknown [2]. However, there is growing evidence, from both clinical and experimental studies, that the microbiome contributes to the development of neurodegenerative diseases 8. Therefore, modulating the microbiome might delay or prevent the development of neurodegenerative diseases and offer a novel therapeutic option for patients with neurodegenerative diseases [2].

Current Therapeutic Approaches

Therapeutic strategies for neurodegenerative diseases currently emphasize symptomatic control due to the absence of curative or disease-modifying treatments [2]. Emerging evidence underscores the gut microbiome as a promising therapeutic target, given the established association of neurodegeneration with microbial alterations. Interventions that modulate microbiota composition such as probiotic administration, prebiotic supplementation, and fecal microbiota transplantation, offer prospective means to restore a healthy microbial milieu. Probiotics can enhance beneficial bacterial populations and influence immune regulation, prebiotics provide substrates that promote the growth of favorable microbes, and fecal transplantation aims to reestablish a balanced microbial ecosystem [9]. These approaches have demonstrated potential to attenuate disease-related pathologies and clinical manifestations across various neurodegenerative conditions. Further investigation is necessary to elucidate precise mechanisms and optimize therapeutic protocols [9].

Probiotics and Prebiotics

Probiotics and prebiotics represent complementary strategies for modulating the gut microbiota and promoting host health [10]. Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host". Conversely, prebiotics are non-digestible food components that facilitate growth and activity of beneficial indigenous microorganisms in the gastrointestinal tract. Thus prebiotics encourage the selective growth and activity of beneficial microbes, while probiotics directly supply beneficial microbes to the gut. Probiotic strains with clinical impact on human illness include members of the genera Lactobacillus and Bifidobacterium [10].

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a procedure used to alter the composition of gut microbiota by transplanting feces from a healthy donor to a patient [10]. The alterations could be natural or induced by administration of agents, such as antibiotics or probiotics, to the patient, which indirectly alter the microbiome composition through the FMT. FMT was first used in 1958 for the treatment of pseudomembranous colitis. Since then, its application has expanded to other gastrointestinal conditions, including inflammatory bowel disease, irritable bowel syndrome, and hepatic encephalopathy, as well as neurological disorders, particularly Parkinson's disease [10].The application of FMT to neurodegenerative diseases arises from observations of alterations of the microbiome composition in patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis. These propositions have been supported by experimental animal studies on autism, depression, anxiety, and several other psychiatric disorders. In Parkinson's disease, where the evidence is strongest, the clinical and experimental studies suggest that gut dysbiosis plays a modulatory role on brain function via the gut–brain axis, making it a candidate both for disease-modifying therapy and for alleviation of treatment-unrelated symptoms [10].

Future Directions in Research

Recent discoveries regarding the microbiome's influence on health and disease provide new opportunities to clarify the etiology and pathogenesis of neurodegeneration, as well as to develop improved diagnostic and therapeutic tools tailored to each individual [11]. . In combination with systematic characterization of the microbiome and metabolome, parallel research efforts utilizing advanced experimental models will continue to drive conceptual, mechanistic, and translational breakthroughs [11]. Despite substantial progress, neurodegenerative diseases continue to impose a growing health and economic burden worldwide. The rapid expansion of large epidemiological, clinical, and multi-centre research studies will allow for longitudinal monitoring, which can assist in stratifying affected individuals for combination therapies. Continued investment into pioneering experimental, computational, and clinical approaches aimed at enhancing the beneficial microbiota or their molecular components will generate new insights into disease mechanisms and open avenues for novel therapeutic interventions [1].

Emerging Technologies

Microbial communities in the environment and in the animal body have great effects on evolution and on the health of their multicellular hosts. The abundance of microbes associated with living bodies reflects the skill of micro-organisms to invade, multiply, etc. as well as the skill of living entities to use and control microbes. Humans are no exception [9]. In the course of evolution an elaborate system has been developed, the microbiota inside the gastrointestinal tract. This can be seen as a miniature organ system with specific functions. These are related on the one hand to immunity, e.g. mucosal defence, and on the other hand to estimations of costs and benefits in a very complex environment. Methods in metagenomics, culture analysis, and rapidly growing information on the human genome reveal novel functions of the microbiota and new insights into the principles of the microbe–host interaction [9]. The approach is from macro- to microbiology but at the same time also from microbiology to macrobiology. Other microbial communities include the oral cavity and the skin. Neurological conditions such as ALS, Parkinson's and Alzheimer's disease are associated with the broad presence of neurotoxic metal exposure. The development of clusters of ALS (p-BMA) in the south of Italy has been linked to the environmental presence of β-N-methylamino-L-alanine (BMAA) produced by cyanobacteria. Cyanobacteria have been found worldwide in desert crusts with ticks as vectors to large wild animals and grazing cattle. The incidence of multiple sclerosis (MS) is not uniform throughout the world. Judicious investigations into the role of the microbiota are expected to bring enormous advances to human health [9]. Emerging technologies continue to integrate multiple mechanistic omics platforms to push microbiome research beyond correlational studies to provide fundamental insight into the role of microbiomes, their functions, and molecular level interactions with the host. Longitudinal multi-omics, ranging from metagenomics through meta-metabolomics and the host transcriptome, provides a wide-angle lens for investigating the microbiome in health and disease. Incorporating emerging culturomics approaches, disease

progression can be investigated down to individual microbial species and related to changes in both the local microbial environment and host molecular profiles [12].

Longitudinal Studies

Longitudinal studies constitute an essential research strategy for understanding the spatiotemporal influences of the microbiome on the host [1]. The human gut harbors approximately 1013∼1014 microbial cells representing ∼1,000 diverse bacterial species, outnumbering the total human cells by almost one order of magnitude. The Bidirectional communication between the gut microbiota and the brain occurs primarily through neural, endocrine, and immune pathways. Alterations in the gut microbiome are correlated with the diagnosis and severity of Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis. Parts of this chapter draw on insights from "Microbiome Alterations in Neurodegenerative Diseases" (sections 11.1–11.3) and "Microbiome and Neurodegenerative Diseases" (sections 1–2).

Ethical Considerations

Observations about the microbiome have ethical repercussions that the scientific community must urgently address. Alterations in immunity, nutrition and metabolism or environmental toxicological exposure must be considered, in view of the putative use of brain microbiota replacement therapies. Further, given the effects of gut microbiota on the brain of individuals with neurodegenerative disease, researchers should carefully consider the challenge of obtaining informed consent for future longitudinal microbiome-brain projects. It is unclear whether microbiota obtained from patients with phylogenetically and enterotypically similar microbiomes but from different habitats will similarly shape the brain. One must be cautious in the collection of samples from healthy donors [11]. Moreover, microbiomes represent uncharacterized biological entities that have the potential to serve as reservoirs for opportunistic pathogens or are capable of transferring antibiotic resistance and virulence genes. Microbiomes undergo rapid ecological and evolutionary change in response to a variety of human or environmental fluctuations [9]. In practice, patient microbiome data are not protected in the same way as one's genetic profile, but microbiome data can still be used to identify individuals and delineate populations. Current regulations for human DNA should also be extended to microbiome data, a point especially relevant for collaborations with pharmaceutical companies, with the risk of patients being exploited. Lastly, the absence of a regulatory framework and standardized experimental or computational procedures is a challenge with respect to the preservation, analysis and sharing of samples [11]. Technological advances should coincide with ethical guidelines to ensure the responsible use of patient microbiome data [9].

Patient Consent and Privacy

The progression of neurodegenerative diseases traverses multiple stages, with early intervention offering the greatest hope for successful treatment. Consequently, patient enrollment in experimental protocols and clinical trials frequently occurs before a definitive diagnosis can be established. In this context, securing informed consent presents significant challenges. Any discussion of psychoactive experimental substances must begin by clarifying that informed consent is both a legal and ethical cornerstone of medical practice, prohibiting unauthorized interventions on conscious individuals [13]. Ethical practice dictates that individuals entering research protocols do so fully aware of their rights, including the freedom to withdraw consent at any time without jeopardizing access to standard care or provoking punitive action from caregivers or investigators. Informed consent is particularly fraught when patients lack full consciousness or the faculties necessary to make uncoerced decisions. Ongoing efforts to refine the mechanisms for obtaining valid consent from vulnerable individuals remain crucial for the advancement and credibility of neurodegenerative disease research. Protecting patient privacy constitutes an additional ethical imperative. Sensitive data such as age, anatomical imaging, and biomarker profiles4994can enable cross-referencing with existing studies and, when combined with legal records, may unmask the identity of subjects and the locations where samples were collected [13]. Navigating governmental regulations across diverse jurisdictions further complicates data management and patient protection. These often ambiguous or contradictory legal frameworks governing data collection and distribution may impede the dissemination of findings, discoveries, or therapeutic innovations, thereby potentially delaying medical progress. Addressing these ethical and regulatory complexities is essential for maintaining the integrity of research platforms and for fostering the continued development of effective interventions [13].

Regulatory Challenges

Similar to other therapies, microbiome-centered treatments face regulatory challenges. Qualified professionals should initially treat patients, but individuals may seek treatments independently [1]. Relevant questions arise in informed consent and recruitment, ranging from privacy issues to the possibility of inadvertently enrolling a trial participant who has an adverse reaction. Also, because the microbiome is involved in nearly all biological processes, it is complicating many aspects of human health beyond infectious disease, including chemical

exposures, nutrition, behavior, and neurodegeneration [1]. The intricacy of the microbiome and its virtually ubiquitous involvement in human health, external exposures, and behavior will make safeguarding and managing treatments and data exceedingly difficult as microbiome-centered therapies become more common [1].

Public Health Implications

Neurodegenerative diseases exact significant health and economic tolls at population and individual scales. Microbiome alterations emerge as critical drivers of these conditions, warranting dedicated attention. Healthcare professionals must acknowledge the potential of gut microbial modulation as a preventive and therapeutic strategy for neurodegenerative disorders [14]. Awareness initiatives and educational programs targeting those affected are imperative to foster understanding of microbial hygiene and prophylaxis. Policy development is essential to facilitate personalized microbial manipulation interventions, thereby enhancing strategies aimed at mitigating the impact of neurodegeneration on public health [14, 1].

Public Health Implications: Awareness and Education

Awareness of the impact of microbiome alterations on the initiation and progression of neurodegeneration is still limited among the general population and clinicians, despite an increasing research emphasis on this topic [8]. Education is advancing rapidly, but it is necessary to establish mechanisms for disseminating the latest knowledge about the microbiome–neurodegeneration axis to the public and the medical community whenever important discoveries are made. Efforts by international organizations, such as the World Health Organization (WHO), alongside relevant government agencies have begun to raise awareness about this concern in the scientific and general communities [8]. Nevertheless, many governments still lack sufficiently informed public health policies, and funding remains inadequate to support a comprehensive research agenda in this domain. Such policies are urgently required to facilitate the transition of promising but complex and heterogeneous research findings into alternative clinical treatments and preventive strategies with broad impact. Both the benefits of awareness and education and the challenges associated with their implementation underscore the titled formulation of this section [1, 8].

Policy Recommendations

Targeted modulation of gut microbiota community members currently represents an important angle to counteract the progression of neurodegenerative diseases. Identification of disease-relevant taxa and generation of an etiological framework will ultimately form the basis for novel microbially based therapeutic strategies [11]. Successful implementation of these approaches could also lower the burden on health-care systems. Preventive public health measures should highlight the importance of proper microbial colonization for neurological well-being, and research into early developmental microbiota formation may reveal new targets for intervention.

Existing policy measures are regrettably limited, despite the substantial and growing burden of neurodegenerative diseases. Given the potential of microbiome-based therapeutics, extensive policy interventions constitute an urgent priority. Current policy should focus on surveillance to improve epidemiological quantification of neurological disorders [11]. Long-term frameworks to map the spread of potentiating risk factors are essential. New schemes for the collection and protection of neurological data constitute urgent priorities, enhancing the capacity to track disease prevalence. Crucially, political programs fostering and regulating investment in microbiome-based research and treatment should be developed. Innovative regulatory frameworks that can cope with the unique challenges of microbiome-based medical applications represent a critical need [11, 14].

CONCLUSION

The interplay between the gut microbiome and neurodegenerative diseases underscores a paradigm shift in understanding brain health. Evidence increasingly supports that dysbiosis and altered microbial metabolites influence neuroinflammation, protein aggregation, and immune dysregulation, thereby contributing to the pathophysiology of Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis. While microbiome-targeted interventions hold therapeutic promise, significant gaps persist in establishing causality, standardizing methodologies, and translating findings into clinical practice. Ethical and regulatory considerations further highlight the need for cautious but innovative approaches. Future research should prioritize longitudinal and mechanistic studies, integrate multi-omics and computational models, and advance personalized strategies to harness the microbiome for prevention and treatment. Ultimately, clarifying host–microbe dynamics may unlock novel avenues for mitigating the global burden of neurodegeneration and improving quality of life for affected populations.

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CITE AS: Omagor Jacob (2025). Microbiome Alterations in Neurodegenerative Diseases. IDOSR JOURNAL OF APPLIED SCIENCES 10(3):41-51.
https://doi.org/10.59298/IDOSRJAS/2025/103.4151