INTRODUCTION

Etymologically, the word is composed of two words “neuro” meaning nerve cells and degeneration meaning “change from a higher to a lower form, a worsening of mental, physical or moral qualities”. Degenerative means “involving degeneration”. Neurodegenerative disease is a pathological condition that affects neurons primarily. In practice, neurodegenerative diseases represents a broad group of neurological disorders with different clinical and pathological expressions affecting particular subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner. Among the hundreds of different neurodegenerative disorders, so far the lion’s share of attention has been given only to a handful, including Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS). The most consistent risk factor for developing a neurodegenerative disorder, especially AD or PD, is increasing age (Tanner, 1992). Over the past century, the growth rate of the population aged 65 and beyond in industrialized countries has far exceeded that of the population as a whole. Thus, it can be anticipated that, over the next generations, the proportion of elderly citizens will double and with this, possibly the proportion of persons suffering from some kind of neurodegenerative disorder.

HISTORY OF NEURODEGENERATIVE DISEASES

Neurodegeneration can cause a highly diverse group of neurological disorders. Neurological disorders have been described throughout human history and associated with gross abnormalities in brain appearance known for several hundred years (Berchtold and Cotman, 1998). However, in roughly the past 100 years, the link between neurodegeneration and neurological disorders has been identified and described extensively. As early as 1892, Bloq and Marinesco used the recently discovered carmine stain and found abnormal accumulation of an unknown substance into plaques in an elderly epileptic patient (Berchtold and Cotman, 1998). Two key findings were made in the early 1900s linking the loss of neuronal structure and function to neurological disorders. In 1907, Fischer extensively described plaque formation, finding neuropathological alterations in 12 of 16 cases of senile dementia, but not in 45 cases of progressive paralysis, 19 cases of functional psychosis, and 10 normal control subjects (Berchtold and Cotman, 1998). More famously, in the same year and in a single case, the German physician and pathologist, Alois Alzheimer, described in detail the presence of neurofibrillary tangles in neurons in the brain of a severely demented 51-year-old woman.

Alzheimer also noted the plaques that had been observed by Fischer (Alzheimer, 1907; Berchtold and Cotman, 1998). Roughly a decade later, specific regional neuronal cell loss was attributed to neurological sequelae. In Parkinson disease, tremor and rigidity in patients were found to be associated with cell loss in the substantia nigra (Tretiakoff, 1919).

MICROBIOME

The human microbiota is defined as a set of organisms inhabiting and interacting with the human body (Grice and Segre, 2011). The various interactions may be commensality, mutualistic, or pathogenic. The human microbiome is referred to as the genomic content of organisms (microbiota) inhabiting a particular site in the human body. Micro - organisms colonise various anatomical body sites such as the skin, the mucosa, gastrointestinal tract, respiratory tract, urogenital tract, and the mammary gland. They form a complex and discrete ecosystem that adapts to the environmental conditions of each niche (Whiteside *et al.*, 2015). From childbirth, a steady interaction (symbiosis) between the human body and its indigenous microbiota begins. These interactions play important roles in maintaining general health and wellbeing. Through coevolution, organisms make up the microbiota; they actively adjust to their specific habitats and reside in their respective niches within the human body (Yilmaz *et al*., 2014). As a result of their biological activities, these organisms are identified as part of the body, leading to various changes from conception until death. The human microbiome is constantly evolving in response to host factors. Factors such as age, nutrition, lifestyle, hormonal changes, inherited genes, and underlying disease are major determinants of the human microbiome at any given point in time. However, an alteration in the makeup of the human (dysbiosis) microbiota can lead to life-threatening illnesses (Whiteside *et al*, 2015). A balanced microbiota has shown to play an important role in health sustenance. The largest concentration of the human microbiome is found in the gut. These organisms are the major players in maintaining and sustaining the health of humans. Past studies on the human microbiome project have illustrated that changes in the immune environment may be directly linked to a dysbiotic flora of the gut. Also, life-threatening health conditions ranging from cancer, cardiovascular disease, bowel inflammatory disease and difficult-to-treat bacterial infections due to antibiotic resistance have also been linked with dysbiosis.

THE ROLE OF MICROBIOME IN NEURODEGENERATIVE DISEASES

Microbes can enter the brain through hematogeneous spread, which is one of the most common pathways observed in neurological infections. In this process, the organisms

infiltrate the bloodstream, and from there, they traverse the blood–brain–barrier (BBB) to reach the brain (Espinal *et al*., 2022). Then, they directly invade the brain by exploiting an impaired BBB via extracellular DNA and lipopolysaccharides (LPS). If the integrity of the BBB is compromised, either due to injury, inflammation, or other underlying conditions, bacteria and fungi can penetrate the barrier and gain access to the brain. Additionally, bacterial extracellular DNA and LPS, which are released by bacteria during infection, can directly disrupt the BBB and facilitate bacterial entry into the brain (Tetz, 2022). This theory underscores the significance of a robust BBB in preventing microbial invasion and highlights the critical role of its compromise in facilitating brain infections.

Another mode of bacterial entry involves the invasion of brain microvascular endothelial cells (BMECs). These cells line the blood vessels within the brain and form a crucial component of the BBB. Research has demonstrated that certain bacteria can induce a process called macropinocytosis in BMECs. Macropinocytosis involves the non-specific uptake of extracellular fluid and solutes, and when activated by bacteria, it enables their internalization into the endothelial cells (Espinal *et al*., 2022). This mechanism could provide a direct route for bacteria to breach the BBB and enter the brain parenchyma.

Remarkably, in certain cases, bacteria can also invade the fetal brain following maternal hypoxia. Maternal hypoxia refers to a condition characterized by a decreased oxygen supply to the mother, which can impact the developing fetus. Studies have shown that certain bacteria can cross the placenta and infiltrate the fetal brain during maternal hypoxia, leading to adverse neurological outcomes (Zarate *et al*., 2017). This pathway highlights the vulnerability of the developing brain and emphasizes the potential consequences of bacterial infections during pregnancy.

Another proposed theory is the invasion of the central nervous system via the olfactory bulb (Pisa *et al*., 2020). The olfactory bulb is the most external part of the central nervous system and directly connects the external environment with the brain. One of the earliest signs of PD is anosmia as a result of degeneration of the olfactory bulb due to α-synuclein-related pathology and neurotransmitter alterations (Doty, 2012). This theory provides an explanation for the presence of C. acnes, a major constituent of the skin flora, in both AD and PD brains (Pisa *et al*., 2020). However, further studies are needed to confirm this theory, and evidence directly supporting it are not yet available.

Furthermore, bacterial peptidoglycan, a component of bacterial cell walls, has been found to mediate gut-brain communication through the Nod2 receptor. The Nod2 receptor is present in both the gut and the brain and plays a role in immune regulation. Activation of the Nod2 receptor by bacterial peptidoglycan can initiate signaling pathways that affect brain function and communication (Gabanyi *et al*., 2022). This highlights the intricate relationship between the gut microbiota and the brain and suggests a potential pathway through which bacteria can indirectly influence brain health and function.

Lastly, the modulation of the microbiota-gut-associated lymphoid tissue (GALT)-brain axis by prebiotics has been shown to indirectly impact the brain. Prebiotics are dietary fibres that promote the growth and activity of beneficial gut bacteria. By positively influencing the gut microbiota composition, prebiotics can have downstream effects on the GALT and subsequently affect brain function and behaviour (Elena *et al*., 2019). This theory highlights the potential of modulating the gut microbiota as a strategy to indirectly mitigate the risk of bacterial invasion and associated neurological complications.

In summary, possible theories for microbial invasion include haematogenous spread, invasion of BMECs, impairment of the BBB, maternal hypoxia, and gut-brain communication pathways (Figure 1). Understanding these mechanisms is crucial in comprehending how they contribute to the development of neurodegenerative diseases. This knowledge provides valuable insights into the tactics used by bacteria to breach the brain's defenses and initiate neurological damage associated with neurodegenerative diseases.

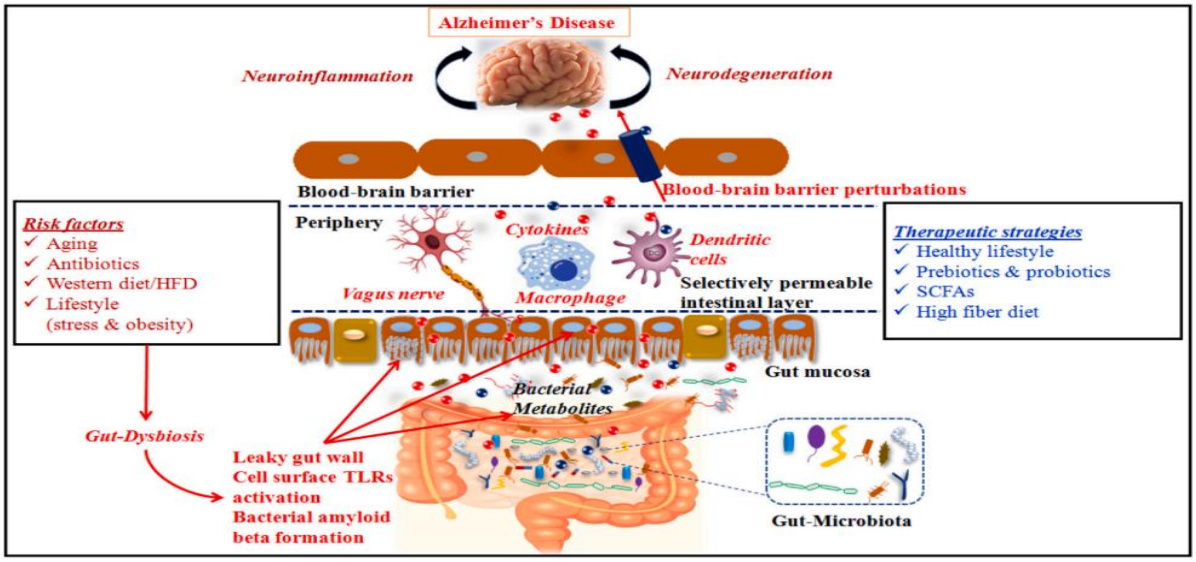

Fig. 1: The MGB axis and its role in Alzheimer's disease.

The gut dysbiosis may contribute to initiate the pathogenesis through modulation of enteric nervous system as well as formation of bacterial metabolites and amyloid formation in gut. These pathological features induce local and systemic inflammation through activation of immune cells and TLRs. These inflammatory features cause increased permeability of intestinal as well as blood-brain barrier permeability and ultimately contribute to develop the pathogenesis of Alzheimer's disease. (Abbreviation used: HFD – high fat diet, TLRs – Tool-like receptors, SCFA – short chain fatty acids).

LINK BETWEEN MICROBIOME AND NEURODEGENERATIVE DISEASES

Recent advances in scientific understanding have shed light on the bidirectional communication network known as the gut-brain axis, which serves as a critical link between the gut microbiome and the central nervous system. This axis facilitates constant communication between the gut and the brain through various signalling pathways, including neural, immune, and hormonal pathways.

Through this communication network, the gut microbiome exerts significant influence on brain function and behaviour, impacting processes such as cognition, mood regulation, and even neuron inflammation. Conversely, changes in brain function and neurologic conditions can, inturn, influence the composition and function of the gut microbiome, creating a dynamic interplay between the two.

Alzheimer's Disease (AD): AD, generally known as dementia or cognitive impairment, is a typical degenerative disease of the central nervous system in the elderly, accounting for 60 %-80 % of all dementias (Hu *et al*., 2016). Its feature is a progressive decline in cognitive function (Kowalski and Mulak, 2019). The neuropathology of AD is characterized by the deposition of amyloid b (Ab), followed by the formation of hyper phosphorylated tau protein, which compose plaques and neurofibrillary tangles (Jouanne *et al*., 2017). These deposits can trigger neuroinflammation, giving rise to synapse loss and neuronal death (kohler *et al*., 2016). A clinical trial conducted on patients with AD found that amyloid-positive patients demonstrated a lower abundance of Eubacterium rectale and *Bacillus subtilis* and a higher abundance of *Escherichia/Shigella* in their stools compared to other groups, indicating the role of both amyloid and relevant bacterial accumulation in cognitive impairment (Cattaneo *et al*., 2017). It has been hypothesized that some components of the intestinal microbiota, such as *B. subtilis* and *E. coli,* secrete large amounts of lipopolysaccharides and amyloid

proteins (Mancuso and Santangelo, 2018), which may directly traverse the intestinal barrier or blood brain barrier damaged by aging or disease, and/or exert an indirect effect to pass through these protective physiological barriers by lipopolysaccharide/amyloid-induced cytokines or other small pro-inflammatory molecules, leading to the development of AD (Jiang *et al.,* 2017). The microbiome of the elderly with AD shows a lower proportion of bacteria synthesizing butyrate that contributes to anti-inflammatory activity and immunity regulation, as well as greater abundance of taxa that are known to cause pro inflammatory states. Therefore, a potential therapy of AD is to modulate intestinal homeostasis by decreasing inflammatory, and increasing anti-inflammatory, microbial metabolism. New research has found that fecal microbiota transfer therapy can ameliorate amyloidosis, tau pathology, reactive gliosis, and cognitive impairment in AD mice, which might be associated with a reversal of abnormalities in circulating blood inflammatory monocytes and in the colonic expression of genes associated with macrophage activity (Kim *et al*., 2020).

Parkinson's Disease (PD):

PD is recognized as the second most common neurodegenerative disease, a movement disorder that is estimated to affect 1-2 out of every 1,000 people worldwide (Caputi and Garon, 2018). PD patients also often suffer from non-motor symptoms, the most common of which is gastrointestinal dysfunction. PD is characterized histopathologically by a remarkable depletion of dopaminergic neurons in the substantia nigra pars compacta, resulting in dopamine deficiency in the striatum, while intracellular eosinophilic inclusions (socalled Lewy neurites and Lewy bodies) are visible in the remaining neurons (Caputi and Garon, 2018). Alpha-synuclein (a-syn) aggregates, the main neuropathological markers of PD, are present in the submucosal and myenteric plexus of the enteric nervous system before being detected in the brain, which may indicate a spread of the disease from gut to brain (Felice *et al*., 2016). The pathogenesis of PD may also relate to intestinal inflammation. Metabolites of the intestinal microbiota may trigger an immune response that induces intestinal inflammation and even the development of PD (Campos-acuna *et al.,* 2019). Sequencing of intestinal microbiota has revealed that the relative abundance of Enterobacteriaceae in the feces of PD patients is strongly correlated with the severity of postural instability and gait difficulties compared to controls. In addition, lower levels of the intestinal hormone ghrelin, which is involved in regulating the activity of nigrostriatal dopamine, are associated with increased abundance of Lactobacillaceae and decreased abundance of Prevotellaceae in the

gut microbiome (Caputi and Garon, 2018). The Gram-negative Prevotellaceae are involved in increasing mucin synthesis in the intestinal mucosal layer. Therefore, a decreased abundance of Prevotellaceae may lead to decreased mucin synthesis and increased intestinal permeability, resulting in more exposure to bacterial antigens and endotoxins, which may trigger excessive asyn expression in the colon and even in the brain. Also, the microbiome of PD patients is characterized by a decreased abundance of butyrate-producing bacteria with an increased abundance of pro-inflammatory Proteobacteria, which may trigger inflammation-induced misfolding of a-syn. Osteocalcin ameliorates the motor deficits and dopaminergic neuronal loss in PD mice through increasing the potential of microbial propionate production and activating free fatty-acid receptor 3 in enteric neurons (Hou *et al*., 2021).

Amyotrophic Lateral Sclerosis (ALS):

ALS is a progressive neurodegenerative disease that is associated with the death of brain and spinal motor neurons (Roy and Banerjee, 2019). The prominent features of ALS are microglial activation and chronic neuroinflammation (Spielman *et al*., 2018). The symptoms of ALS include muscle weakness, muscle stiffness, muscle spasms, muscle twitching, cramps, and coordination problems, which lead to speech, swallowing, and breathing difficulties (Roy and Banerjee, 2019). A clinical study of ALS patients found that gastrointestinal symptoms precede neurological symptoms, and examination of feces demonstrated that the diversity of intestinal microbiota is lower in ALS patients than in healthy controls (Spielman *et al*., 2018). Another clinical study reported changes in the composition of gut microbiome in ALS patients, including a significant decrease in the Firmicutes/Bacteroidetes ratio along with a decrease in the relative abundance of Anaerostipes, Oscillibacter, and Lachnospiraceae. This suggests that a pro-inflammatory gut microbiome disorder may disrupt the intestinal epithelial barrier, promote an immune/inflammatory response, and alter bowel motility. Some researchers have hypothesized that intestinal barrier dysfunction facilitates the entry of toxins from the intestinal lumen to the blood, causing an increase in circulating lipopolysaccharides and an innate immune response, which plays a vital role in the pathogenesis of ALS (Fang, 2016). A metabolite of the gut microbiome, nicotinamide, improves the motor symptoms and gene expression patterns in ALS mice and nicotinamide is reduced systemically and in the cerebrospinal fluid in ALS patients (Blacher *et al*., 2019).

Huntington's Disease (HD):

HD is a progressive brain disease caused by amplification of the trinucleotide cytosine-adenine-guanine repeat sequence in the Huntington gene (Bianchi *et al.,* 2019). This mutation produces polyglutamine-expanded huntingtin protein, causing neuropsychiatric symptoms, cognitive impairment, and involuntary choreiform movements. HD is one of the most fatal inherited neurodegenerative diseases without effective drug treatment (Sharma and Taliyan, 2015). Clinical studies have reported that a distinct serum metabolic profile, thought to originate from gut microbe-derived metabolites, is present in pre-symptomatic HD subjects and early symptomatic HD subjects, compared to controls, pointing to a potential role for the microbiome in the progression of HD (Tremlett *et al*., 2017). Multi-omics integration analysis of HD mice suggests that the gut microbiome modulates the pathogenesis of HD by altering plasma metabolites (Kong *et al*., 2021). These findings may provide clinically useful biomarkers for the onset, progression, and phenotypic variability of HD.

TREATMENT OF NEURODEGENERATIVE DISEASES

Acute and chronic neurodegenerative diseases, including prion disease, frontotemporal dementia, Pick's disease, progressive supranuclear palsy, spinocerebellar ataxias, brain trauma, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, and Parkinson's disease (PD), are illnesses associated with high morbidity and mortality rates (Prusiner,2001; Friedlander, 2003). A characteristic of many neurodegenerative diseases is progressive neuronal cell death (Yuan and Yankner, 2000). During the past decade, considerable progress has been made in understanding the process of cell death (Hengartner, 2000). The symptoms and the exacerbations of these diseases are much different according to their specific pathways of cell death, and having their own mechanisms of cell death leads to novel therapeutic strategies.

Today, there is no treatment that can cure degenerative diseases, but we have many symptomatic treatments. There are some advantages of Western medicines for these diseases, such as:

- Dopaminergic treatments for PD and movement disorders (Mizuno, 2004),
- Cholinesterase inhibitors for cognitive disorders
- Antipsychotic drugs for behavioral and psychological symptoms of dementia
- Analgesic drugs for pain
- Anti-inflammatories for infections
- The use of deep brain stimulation to stop tremor and refractory movement disorders (Okun 2014; (Chaudhari and Schapira, 2009),).

Researchers have also aimed to produce medicines to slow the development of diseases, such as Riluzole for ALS, Cerebellar ataxia and Huntington's disease (Traynor *et al*, 2006), NSAIDs (non-steroidal anti-inflammatory drugs) for Alzheimer's disease (Stewart *et al.*, 1997) and caffein A2A receptor antagonists and CERE-120 (adeno-associated virus serotype 2-neurturin) for the neuroprotection of PD (Schwarzschild *et al.*, 2003). However, we have not yet progressed very well; there still remain too many problems to administrate the progressive and serious symptoms of these diseases (Mizuno, 2004).

AFRICAN TREATMENT OF NEURODEGENERATIVE DISEASES

Plant-based remedies are potent nutritional diets to combat PD and other NDDs (Sarrafchi *et al*., 2016; Saurabh, *et al.*, 2017). Medicinal plants used among traditional practitioners in West Africa to treat NDDs are readily available, cultivated, easily sourced, and consumed even as vegetables. Medicinal plants used in managing neurological diseases were documented. Some of these medicinal plants are reported as memory enhancers, possibly boosting cognitive performance impaired by AD and PD. Medicinal plants such as *Bacopa floribunda, Spondiamombin, Allium sativum, Aframomummelegueta. Cordia millenii, Paraquentianigrescen, Scoparia dulcis, Celeomegynandra, Dalbergia lacteal, Cola acuminata, Musa sapientum, Senecio abysinicus, and Angraecumeichlerianum* have been utilised (Shonibare and Ayoola, 2016). The main benefits of using these medicinal plants are safe utilisation with little or no side effects, affordable and accessible for local residents.

ECONOMIC IMPACT OF NEURODEGENERATIVE DISEASES

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), have significant economic implications.

1). Direct healthcare costs:

The cost of medical care, medications, and hospitalization for individuals with neurodegenerative diseases is substantial. Alzheimer's disease, in particular, has been associated with high healthcare costs. A study published in the journal Alzheimer's and Dementia estimated that the global cost of dementia-related care was around $1 trillion in 2018 .

2).Caregiver burden:

Family members and friends often take on the role of caregivers for individuals with neurodegenerative diseases. The economic impact of caregiving includes lost productivity, missed workdays, and the emotional toll on caregivers. A report by the Alzheimer's Association indicated that in the United States, unpaid caregivers provided an estimated 18.6 billion hours of care in 2019, valued at over $244 billion (Alzheimer's Association, 2020).

3). Lost productivity:

Neurodegenerative diseases can lead to disability and a decrease in workforce productivity. A study published in JAMA Neurology found that the economic burden of Parkinson's disease in the United States was approximately $52 billion in 2017, including both direct and indirect costs (Dorsey *et al.,* 2018).

4). Research and development costs:

The search for effective treatments and cures for neurodegenerative diseases requires substantial research and development investments. The cost of developing new drugs and therapies can be high. A report by the Pharmaceutical Research and Manufacturers of America (PhRMA) highlighted the challenges and costs associated with developing new medicines for neurological disorders (PhRMA, 2019).

5). Long term care facilities:

Individuals with advanced stages of neurodegenerative diseases may require long-term care in facilities, contributing to the overall economic burden. A study in the journal Health Affairs estimated that the cost of care for individuals with Alzheimer's disease in the United States in 2010 was between $159 billion and $215 billion (Hurd *et al.,* 2013).

CONCLUSION

The importance of the microbiota in neurodegenerative illnesses is becoming more widely acknowledged. The gut microbiome interacts with the central nervous system bi directionally through the gut-brain axis, influencing behaviour and brain function. Dysbiosis, or an imbalance in the gut microbiome, has been associated with neurotoxicity and inflammation in neurodegenerative illnesses such as Parkinson's and Alzheimer's. Certain microbial species and their by-products can affect mechanisms linked to dementia, such as oxidative stress, mis folding of proteins, and neurotransmitter modulation. Probiotics and dietary modifications are two examples of therapeutic approaches that target the gut microbiome and have the potential to slow the progression of disease by re-establishing microbial balance and lowering neuroinflammation. Comprehending these intricate interplays presents prospects for inventive

diagnostic and therapeutic methodologies in the management of neurodegenerative illnesses. To fully realize the potential of microbiome-based therapies in the fight against neurodegeneration, more research is necessary.

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