

The Role of Microbes for Triggering Neurological Diseases

Kainan Wang *

Radley College, Oxfordshire, England

* Corresponding Author Email: jerry.wang2019@radley.org.uk

Abstract. Neurological diseases have become a focus of study due to the aging of society. This research analysis different diseases including Parkinson's disease and Alzheimer's disease, where the microbes that cause or contribute to their development of symptoms. This includes what causes the diseases' symptoms and how microbes contribute to those symptoms. The symptoms of Alzheimer's disease are largely connected with neuroinflammation and amyloid build-up in the brain. *Spirochetes* are known to produce neuroinflammation. *Chlamydia pneumoniae* has been shown to increase in the patient's brain, but this is not supported by all research. *Porphyromonas gingivalis* infection is connected to neurodegeneration. Although exercise may aid in the slowing of the development of Alzheimer's disease, the underlying mechanisms are uncertain. Parkinson's disease is mostly caused by neuron death, which leads in decreased dopamine levels. This is due to DJ-1, which has been related to cell cycle checkpoint disruption. Repeated infections with *Citrobacter rodentium* cause Parkinson's-like motor symptoms as well as the mice lose their dopaminergic neuronal axonal varicosities. *Proteus mirabilis* causes neuronal loss. *Lactobacillus* and inflammation have been related in stroke. Other than the microorganisms discussed in this article, there are many more that influence the brain and contribute to diseases. More study could look into ways to reduce the presence of those microorganisms and reverse the damage they cause.

Keywords: Diseases, Microbes, Mechanism.

1. Introduction

As the prevalence of brain illnesses grows annually around the world, this topic has recently taken centre stage in research. Neurological diseases affected more than 280 million individuals worldwide in 2017. In America, 26% of those 18 and older, about one in every four people, are thought to experience a diagnosable neurological condition. Since 2001, an estimated 1.17 million persons in the United States who are 18 or older receive a diagnosis of a brain disease such as Parkinson's disease and Alzheimer's disease. This data represents roughly 0.45% of the adult population in the US. They are causing problems to the families and taking lives away at the same time [1]. The neurological illnesses remained the second-largest reason of mortality (about 9.4 million), under cardiovascular diseases such as coronary artery disease and arrhythmia, and the leading cause of disability-adjusted life years (around 273.1 million) [2]. Among those mortality, stroke which cuts the blood supply to brain instantly and dementia combined contributed to more than 87.2% [3].

Stress is the leading cause of neurological problems, while there are other various factors as well. Brain tumor risk may be increased by prolonged exposure to harmful substances like pesticides and radiation such as X-Ray from radioactive sources. Numerous brain illnesses can be caused by certain genes and genetic mutations, or they can be more likely to occur. Brain tumors, epilepsy, neurodegenerative disorders, neurodevelopmental problems, and mental illnesses have all been linked to particular genes or mutations, according to research. Genes that cause disease may run in families or develop randomly. A disorder of the central nervous system known as an autoimmune brain disease is brought on by immune cells or antibodies that attack the brain. Stroke and Alzheimer's disease or other brain diseases are normally associated with unhealthy lifestyle habits like smoking, drinking too much alcohol, not exercising, and eating poorly. Most traumatic brain injuries are caused by accidents and traumas. The chance of developing brain disorders like epilepsy and Alzheimer's disease can also be increased by a brain injury. Brain disorders can be brought on by infections brought on by bacteria, viruses, and other microorganisms. Microbes, which are responsible for the majority of illnesses, including brain problems, across the globe, hold enormous promise for the study

of neurological diseases since they are so closely related to people's daily lives [4]. The existing literature on various brain diseases will therefore be explored in this research to look for microbes linked to neurological problems. It will cover a portion of microorganisms affect the brain and how they influence the brain and contribute to certain diseases. By providing a direction of study, this paper should aid future research and experiments.

2. Alzheimer's Disease

2.1. Background

The most prevalent kind of dementia, named after the German psychiatrist Alois Alzheimer and originally reported in 1906, is Alzheimer's disease, which affects 95% of those over the age of 60. Amyloid-beta peptide ($A\beta$) that is often associated with neurofibrillary tangles and neurotic plaques continuously accumulate in the neocortical regions and medial temporal lobe of the brain, which are the most affected regions of the body. And the structure of the neurons and brain of patient is shown in Figure 1. Alois Alzheimer found the patient experienced a change in personality and memory loss before passing away. As a result, he defined this illness as a terrible disorder of the cerebral cortex [5].

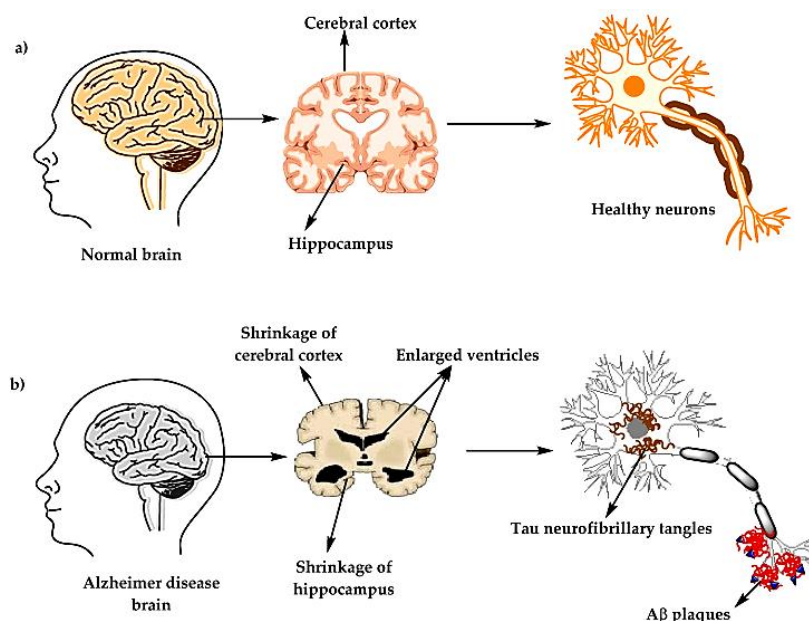


Figure 1. The structure of the neurons and brain [5]

Many bacterial infections contribute to amyloid build-up. This results to the accumulation of $A\beta$ plaques in the end of nerve cells. Neuroinflammation is another factor that has been strongly connected with the pathophysiology of Alzheimer's disease. It was once argued that hallmark AD traits such as $A\beta$ deposits and tau hyperphosphorylation can be exacerbated by neuroinflammation, causing tissue damage that is able to augment the response of inflammation, and eventually resulting in a vicious cycle of inflammation and tissue destruction. More than 20 microorganisms were discovered to be linked with Alzheimer's disease. Several microorganisms, including human herpes viruses and bacteria: *Borrelia burgdorferi* spirochetes, *Chlamydia pneumoniae*., and most recently, *Porphyromonas gingivalis*, have been postulated as Alzheimer's disease triggers. In principle, any viral agent capable of invading the brain may serve as the trigger [6].

2.2. Spirochetes

Spirochetes are host-associated helical or Gram-negative free-living bacteria with distinctive periplasmic fibrils. They are commonly the cause of Lyme disease, periodontitis, syphilis, leptospirosis, necrotizing ulcerative gingivitis, among other diseases. Bacteria like spirochetes are

powerful inflammatory stimulators. This is because of the presence of lipopolysaccharide (LPS), which is a bacterial endotoxin that is both amyloidogenic and inflammatory. Because bacterial cell wall peptidoglycan and lipopolysaccharide are resistant to breakdown by enzymes produced in mammals, they could produce a long-lasting inflammatory response. Research and study made by Ohnishi et al. [7] showed that *Borrelia burgdorferi*'s outer surface protein is amyloidogenic and creates amyloid fibrils in vitro, that are very similar to human amyloid deposits. Miklossy et al. [8] showed the exposure of cultured mammalian glial and neuronal cells to these *Borrelia* spirochetes resulted in the clinical characteristics of Alzheimer's disease, including elevated A β PP levels, A β deposition, and tau hyperphosphorylation. A β -immunoreactive "plaques" and thioflavin S positive, as well as granulovacuolar-like forms and tangle, were all shown in the cell cultures exposed to spirochetes.

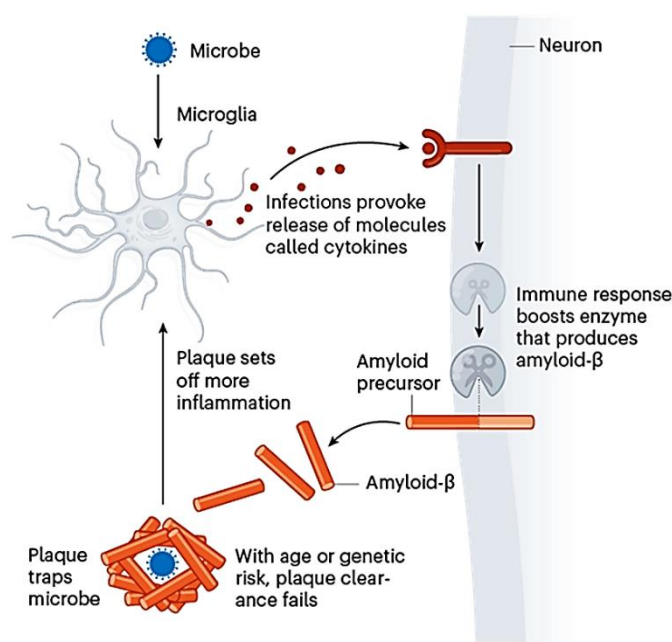


Figure 2. Cycle of infection and inflammation [9]

2.3. Chlamydia Pneumoniae

Chlamydia pneumoniae (*Cpn*) is a type of microorganism that causes respiratory tract infections, such as pneumonia or in other words lung infection. As shown in Figure 2, Balin et al. [9] presented the first evidence associating *Cpn* with late-onset Alzheimer's disease (LOAD) in 1998. The PCR tests for the *ompA* gene and chlamydial 16S rRNA were much more likely to be positive when autopsy brain tissue samples from a control group were compared to those from patients with AD. *Cpn* was directly discovered in Alzheimer's disease patients' brain specimens using immunoelectron microscopy and electron microscopy in the same investigation. Additionally, the immunohistochemical analyses revealed that in the perivascular regions of small to medium-sized blood vessels, the microglia, neuropil, and astroglial cells, all of which were tested positive for the presence of protein tau (monoclonal antibody against paired helical filaments, PHF-1) and demonstrated neurodegenerative pathology, *Cpn* infection occurred significantly more frequently. Chlamydial infectivity and viability in damaged brains were established using RTPCR and culture of chlamydial offspring. Infection of human astrocytoma cells with *Chlamydia pneumoniae* increased transcription of many genes involved in the host neuroinflammation process, microtubule function, APP processing, and lipid homeostasis. Nevertheless, it is worth mentioning that the findings arguing for a pathogenic role of *Chlamydia pneumoniae* infection in AD were only found in several studies, and now the results are being debated. It has been raised whether there are contamination issues with the PCR products and undefined immunohistochemistry staining techniques or false positive results were produced as a result of sequence homologies [10].

2.4. Porphyromonas Gingivalis

Porphyromonas gingivalis is a Gram-negative oral anaerobe that is involved in the aetiology of periodontal disease, which is a type of inflammatory disease which causes damage to the tissues that support the tooth and finally leads to the loss of the tooth. *P. gingivalis* generates significant virulence elements identified as gingipains, which are cysteine proteases composed of lysine-gingipain (Kgp), arginine-gingipain B (RgpB), and arginine-gingipain A. (RgpA). Gingipain immunoreactivity (IR) was substantially greater in the brains of AD patients than in the non-AD control people's brains. There are numerous routes for microbial entry to the brain [11], which include a permeable blood-brain barrier (BBB). *Porphyromonas gingivalis* is able to elicit both brain and peripheral immune responses. Periodontitis can have an indirect effect by causing peripheral inflammation. In this situation, combined with faulty susceptibility genes, which typically aid in waste elimination from the brain, can prime. This can prepare the microglial cells to adopt a phenotype that favors inflammation in combination with faulty susceptibility genes that typically aid in waste elimination from the brain [12]. *P. gingivalis* (ATCC 33277) has already been shown associated with the generation of neurodegeneration that is similar to the situation in AD in neurons obtained from iPSCs, which results in a quarter loss of neurons over only three days. Moreover, *P. gingivalis* has the ability to attack and live inside the neurons, producing proteolytically active intraneuronal gingipains, suggesting the possibility of direct neurodegeneration linked with NFT lesion formation in AD [11].

2.5. Effect of Exercise on Alzheimer's Disease

Recent research suggests that exercise may be helpful in decelerating or delaying the progression of AD. However, the fundamental mechanisms remained unknown. The current work looked at the influences of treadmill exercise on cognitive performance and amyloid- β (A β) deposition in amyloid precursor protein (APP)/PS1 mice in the early stages of AD progression, with a focus on microglia-mediated neuroinflammation. As shown in Figure 3, the findings showed that hippocampal cognitive function is protected and A β build-up 12 weeks of treadmill exercise protected and significantly reduced A β build-up. Treadmill exercise dramatically reduced neuroinflammation in the hippocampus, as shown by increased production of anti-inflammatory mediators and lower expression of pro-inflammatory factors [13].

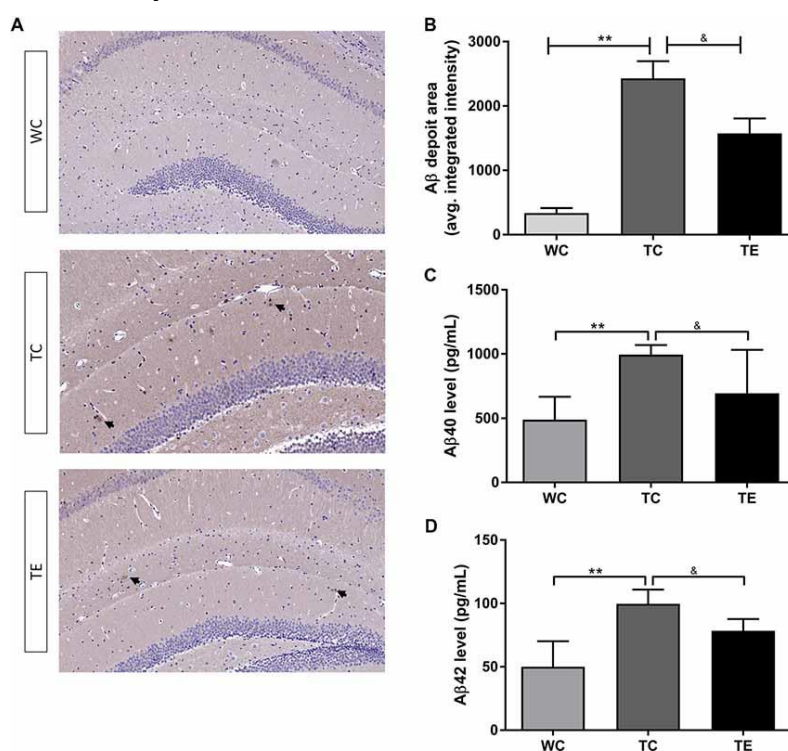


Figure 3. Treadmill exercise's effects on the amyloid- β (A β) levels of mice [13]

3. Parkinson's Disease

3.1. Background

Parkinson's disease belongs to neurological disorders that causes uncontrollable or unintentional actions such as stiffness, shaking in hands, and difficulties with coordination and balance. Those symptoms unremarkably seem bit by bit and progress over time. People could have trouble in talking and walking as the condition develops. They may also have depression, memory problems, sleep issues, weariness, and even behavioral and mental changes. In 2018, approximately 10 million people worldwide had the illness, accounting for less than 1% of the overall population. Most Parkinson's patients are over 60, although one in ten is under 50. Men have a slightly more possibility of diagnosing Parkinson's disease than women which is about 1.5 times more likely [14]. In the brain, there is a region called basal ganglia, which is in charge of the movement of body. When the nerve cells in this particular area of brain become either damaged or even die, the most noticeable signs symptoms and signs of Parkinson's disease will occur. Normally in human body, these neurons will release dopamine, which is an important brain neurotransmitter, as shown in Figure 4. When neurons become damaged or died, they produce less dopamine than normal level, which results into the movement impairments associated with the condition. People with Parkinson's disease also lose the ending part of nerves that normally produce norepinephrine, which is the sympathetic nervous system's principal chemical messenger, thereby regulating many functions in human body. However, the exact reason of the loss of neuron was not clear until a study recently.

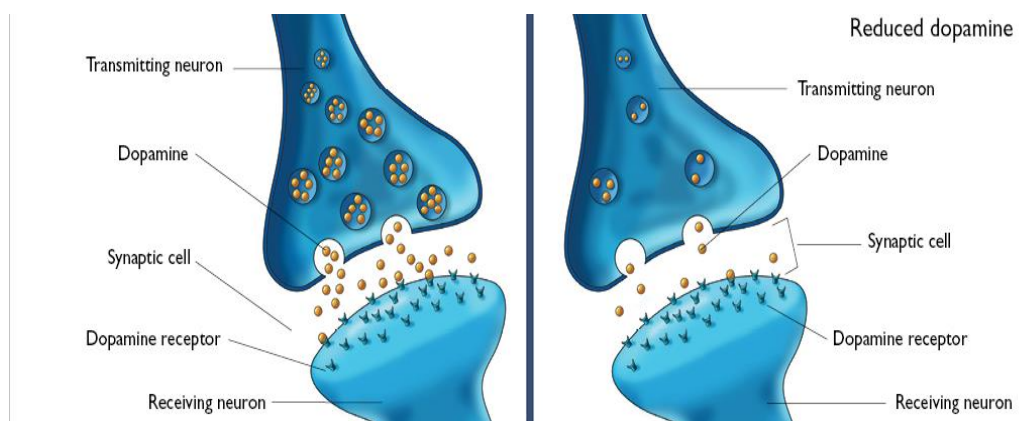


Figure 4. Dopamine level difference in Parkinson's disease [15]

In Parkinson's disease (PD), DJ-1 is an important multifunctional protein that functions as a molecular chaperone, antioxidant, glyoxalase, protease and transcriptional regulator. It was proven by many historical resources that it associates with PD. Yet, the precise method by which DJ-1 failure adds to Parkinson's disease progress remained unknown. María José et al. performed a comparative proteomic study between neurons lacking DJ-1 and wild-type cortical neurons to reveal that DJ-1 is implicated in the disruption of the checkpoints of the cell cycle. What they found was that more p-tau and -synuclein proteins, altered mitogen-activated protein kinase (MAPK) signaling pathways and phosphoinositide-3-kinase/protein kinase B (PI3K/AKT), and cyclin-dependent kinase 5 dysregulation (Cdk5) were present. Cdk5 is generally implicated in synaptic formation, axon formation, and dendritic growth, but under pathological situations, it can additionally promote cell cycle advancement. Furthermore, they discovered a decrease in proteasomal activity, which was most likely caused by tau phosphorylation, which can also result in the initiation of mitogenic signaling pathways. In conclusion, their data suggest that DJ-1-associated PD may be caused by aborted cell cycle re-entry for the first time [16].

Several microorganisms, including viruses, bacteria, and fungus, have been associated to a higher risk of triggering or developing Parkinson's disease in people. These microorganisms including but not limited to: *Citrobacter rodentium* and *Proteus mirabilis*. Microbial infections can trigger

comparable common PD mechanisms, including as systemic inflammatory responses, α -synuclein misfolding, and mitochondrial disruption.

3.2. *Citrobacter Rodentium*

Citrobacter rodentium is a mouse mucosal bacterium which have numerous pathogenic pathways in common with the clinically significant human gastrointestinal illnesses enterohaemorrhagic *E. coli* (EHEC) and enteropathogenic *Escherichia coli* (EPEC). As a result, *C. rodentium* has already being used for a long time as a model to study the molecular basis part of EHEC and EPEC infection in humans. The discovery that bacterial LPS may increase mitochondrial antigen presentation without Parkin or PINK1 was leading to the hypothesis that even familial types of Parkinson's disease could be impacted by host-microbe interactions [17]. Furthermore, emerging data implicating the gut-brain axis in Parkinson's disease revealed that the disease start may begin in the stomach. *C. rodentium*, a Gram-negative intestinal pathogen utilized to imitate pathogenic *E. coli* infections in mice, was recently reported to stimulate the production of antimitochondrial CD8⁺ T cells and mitochondrial antigen presentation in Pink1^{-/-} mice [18]. Pink1^{-/-} mice lost dopaminergic neuronal axonal varicosities and developed PD-like motor symptoms after being infected with *C. rodentium* repetitively in intestine. Although antimitochondrial CD8⁺ T cells might penetrate the CNS, CD8⁺ T cells caused direct killing of dopaminergic neurons was still only demonstrated in vivo neuronal preparations [18]. This data suggests a two-hit model for disease progress: an environmental shock, for example an intestinal infection, and a genetic predisposition, that includes a mutation in a familial Parkinson's disease gene. Though several other familial Parkinson's disease-related genes are implicated in lysosomal degradation pathways and/or mitochondrial dynamics, it is still unknown whether they are also engaged in the mitochondrial antigen-presentation route [19]. It is also unknown if other Gram-negative infections are able to elicit a similar reaction in Pink1^{-/-} mice. However, it is confirmed that all Gram-negative bacteria studied in vitro could trigger the appearance of mitochondrial antigens [18].

3.3. *Proteus Mirabilis*

Proteus mirabilis is a Gram-negative bacterium, which is able to migrate across surfaces in a distinctive bulls'-eye shape. In clinical research, this bacterium is mostly a urinary tract infection, especially in those patients who are experiencing long-term catheterization. A recent faecal microbiota research investigating multiple animal models that are chemically induced for Parkinson's disease revealed that Gram-negative bacteria including *Proteus mirabilis* that is significantly abundant from the Enterobacteriaceae family were considerably enhanced in the chemically treated mice in comparison to the other controlled mice [20]. Comparing to mice given MPTP alone, greater dopaminergic neuron degeneration, microglial activation, and PD-like motor symptoms, can all be caused by administration of *P. mirabilis* with MPTP treatment. Despite the fact that *Proteus mirabilis* can encode curli fimbriae and possesses an LPS-containing cell wall, the particular methods of how *P. mirabilis* cause neurodegeneration have not been examined. The injection of *P. mirabilis* compromised the blood-brain barrier and increased serum LPS levels, and the researchers did notice a rise in aSyn fibrils in both the brain and the colon. Still, it is unknown whether the fibrils were directly neurotoxic and where they originated. Although this was not tested, the reported rise in LPS level could help to stimulate mitochondrial antigen presentation. In humans, an experimental study of a German group discovered a greater richness of *Proteus* species in patients who are diagnosed with Parkinson's disease [21], while this has not been reported in another research [22].

4. Stroke

4.1. Background

A stroke is a well-known lethal medical illness that usually appears when the blood flow to a part of the brain is cut off. Strokes have two primary triggers: hemorrhagic and ischemic, which contribute

to about 85% of all the stroke instances [23]. The prevalence of stroke has already reached pandemic proportions. Worldwide, about a quarter of people over the age of 25 will be diagnosed with a stroke during their lives. Over 110 million people worldwide have had a stroke. Every year, nearly 12.2 million new strokes occur [24]. Strokes induced by microbial infections are responsible for a modest percentage of all cases. It is widely acknowledged that a variety of illnesses, including parasitic (most commonly neurocysticercosis), fungal (*cryptococcus*, *aspergillus*, mucormycosis), bacterial (*syphilis* and *tuberculosis* are classic examples), and various viruses, can directly cause stroke. Certain pathogens have long been known to induce stroke by causing parenchymal or meningeal brain vasculitis and inflammation. Other pathogens can increase the risk of stroke by causing inflammation, hastening atherosclerosis, or activating coagulation pathways. *Lactobacillus* is one of the most recently discovered bacteria linked to an elevated risk of ischemic stroke.

4.2. *Lactobacillus*

Despite not performing a full genomic shotgun study, Manoj P. et al. detected an increase in gram-positive gut bacteria *Lactobacillus spp.* following stroke [25]. Following an ischemic stroke, proinflammatory cytokines are produced by *Lactobacillus ruminis*. Thus, an increase in the *Lactobacillus* subgroup could explain the increased inflammation in stroke. After being treated with multi-species neuroactive probiotics that contain *Lactobacillus spp.* for eight-weeks, the depressive-like behaviour in rats reduced significantly. Based on these findings, the levels of *Lactobacillus* found in their study following xenon administration were associated with antianxiety and antidepressant benefits in these animals. Furthermore, *Lactobacillus spp.* controls the expression of a number of neurotransmitters via the vagus nerve, including dopamine, gamma-aminobutyric acid, glutamate, and 5-HT and thus it is almost certain that a link exists between the degree of anxiety and depression and lower levels of *Lactobacillus* bacteria in the gut [25].

5. Conclusions

In Alzheimer's disease, both *spirochetes* and *Porphyromonas gingivalis* are known to initiate and develop neuroinflammation, while *Porphyromonas gingivalis* infection is also connected to neurodegeneration. *Chlamydia pneumoniae* has been shown to increase in the patient's brain and therefore might be associated with Alzheimer's disease, however not all research is supporting this observation and further research will be needed to give a conclusion. Parkinson's disease is mostly caused by neuron damage or death, which leads in a decreased dopamine level in brain. This can be caused by DJ-1, which has been related to cell cycle checkpoint disruption, or *Proteus mirabilis* that causes neuronal loss. Repeated infections with *Citrobacter rodentium* could cause Parkinson's-like motor symptoms as well as the mice in experiments lose their dopaminergic neuronal axonal varicosities. *Lactobacillus* that is present in the brain of stroke patients and inflammation have been related in the risk of stroke. Those are only a small portion of neurological disease and a small portion of microbes that contribute to those diseases. Further research could focus on determining the exact mechanisms of some microbes and target on the potential way of reversing or lessen the impact that they already brought. Ways to prevent those infections from microbes could also be a focus of study in the future.

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