Porphyromonas gingivalis: A key role in Parkinson’s disease with cognitive impairment?

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Cognitive impairment (CI) is a common complication of Parkinson’s disease (PD). The major features of Parkinson’s disease with cognitive impairment (PD-CI) include convergence of \(\alpha\)-Synuclein (\(\alpha\)-Syn) and Alzheimer’s disease (AD)-like pathologies, neuroinflammation, and dysbiosis of gut microbiota. Porphyromonas gingivalis (P. gingivalis) is an important pathogen in periodontitis. Recent research has suggested a role of P. gingivalis and its virulence factor in the pathogenesis of PD and AD, in particular concerning neuroinflammation and deposition of \(\alpha\)-Synuclein (\(\alpha\)-Syn) and amyloid-\(\beta\) (A\(\beta\)). Furthermore, in animal models, oral P. gingivalis could cause neurodegeneration through regulating the gut-brain axis, suggesting an oral-gut-brain axis might exist. In this article, we discussed the pathological characteristics of PD-CI and the role of P. gingivalis in them.

KEYWORDS
Parkinson’s disease, cognitive impairment, Porphyromonas gingivalis, neuroinflammation, \(\alpha\)-Synuclein, amyloid-\(\beta\), gut microbiota

Introduction

Parkinson’s disease (PD) is a prevalent neurodegenerative disease caused by the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Cognitive impairment (CI) is a common complication of PD non-motor symptoms, including PD with mild cognitive impairment (PD-MCI) and PD dementia (PDD). PD-MCI, as an independent risk factor for PDD (1), is characterized by the transitional state that fails to meet the diagnostic criteria for PDD. A 5-year follow-up study of patients with PD showed that the cumulative incidence of PD-MCI in patients aged \(\geq\) 65 years is 41.3% after 5 years, and the conversion rate of patients with PD-MCI progressing to PDD within 5 years is about 39–50% (2).

The pathogenesis of PD-CI is unclear. Current studies have found that PD-CI-related pathologies include the deposition of \(\alpha\)-Synuclein (\(\alpha\)-Syn), Alzheimer’s disease-type pathologies (amyloid-\(\beta\), tau, and neurofibrillary tangles), and neuroinflammation (3–5). Recently, many studies have shown a correlation between Porphyromonas gingivalis (P. gingivalis) infection and PD (5–8). Interestingly, P. gingivalis has recently been shown to be associated with cognitive
impairment and a potential microbial driver in Alzheimer's disease (AD) (9–15). Therefore, this review summarizes the literature on the potential role of Porphyromonas gingivalis in PD-CI development and is aimed as a reference for further research and therapy.

Porphyromonas gingivalis

Porphyromonas gingivalis is a Gram-negative, anaerobic, and rod-shaped bacteria that colonizes the oral epithelium and is an important component of subgingival microbiomes. P. gingivalis is responsible for the chronic form of periodontitis through its capacity to remodel the commensal bacterial community, which promotes a state of dysbiosis (16). It can engineer its environment or modify the host’s immune response to modulate the entire ecosystem. It can also persist in host tissues through unique and intricate mechanisms, such as the alteration of inflammatory signaling pathways, the complement system, the cell cycle, apoptosis, and the interaction with various host receptors (17). During common activities, such as brushing, flossing, chewing, and dental procedures (18), P. gingivalis invades the vasculature from the infected periodontal pocket. Furthermore, a study using an animal model showed that it can also increase the permeability of the blood-brain barrier (BBB) and facilitate access of bacteria into the brain (19).

The strategies and pathogenicity of P. gingivalis largely rely on its various virulence factors. Among these, the secretory components and gingipains are major virulence factors, consist of lysine- and arginine-gingipain (Kgp and Rgp), which play essential roles in host colonization, host defense deactivation, tissue destruction, and nutrient acquisition (20). In addition, lipopolysaccharide (LPS), a structural component, is also a crucial pathogenic factor that can trigger the innate immune response via the activation of toll-like receptors (TLRs), leading to more lasting destruction of periodontal tissues (21). P. gingivalis LPS induces the expression of interleukin (IL)-6 and C-C motif chemokine ligand 2 (CCL2) in the brain microvascular endothelial cells, which may contribute to dysfunction of the BBB and subsequent neurological disorders (22, 23). Furthermore, P. gingivalis LPS can induce IL-8 elevation (24) and IL-10 decline (25) in the brain, which is consistent with cytokine changes in the cerebrospinal fluid (CSF) of patients with PD (26). Indeed, gingipains and LPS have attracted growing attention as virulence factors of P. gingivalis and recent studies have found that these two factors are present in the blood circulation and brain of PD and AD populations (5, 27). In addition to neurodegenerative diseases, studies have shown that P. gingivalis may be associated with other systemic inflammatory diseases, such as type 2 diabetes mellitus, rheumatoid arthritis, and cardiopulmonary disease (28).

Pathological characteristics of PD-CI

α-Syn and AD-type pathologies

Current neuropathological studies indicated that the convergence of α-Syn and AD-type pathologies is the major pathological features of PD-CI (4). The misfolding and aggregation of aberrant α-Syn in the patients' brain are the major characteristics of PD (29) that result in neuron loss and the clinical syndrome of idiopathic PD (30). Moreover, it was found that pathogenic α-Syn can transfer between cells leading to neurodegeneration (30–32). The importance of α-Syn is further emphasized in PD-CI studies which showed that α-Syn pathology is more extensive and severe in PDD than in PD without dementia. PDD cases are almost exclusively of the predominant stage of α-Syn pathology in the limbic system or neocortex and α-Syn pathology level can distinguish between PD and PDD (3, 33, 34). The progression of α-Syn pathology stage or cortical α-Syn pathology burden is highly correlated with the cognitive level decline (35–37). However, despite α-Syn pathology being the major driving force of the development in cognitive impairment in patients with PD, AD pathology was also found to play an important role in PD-CI (4). Many clinical studies revealed that the tau concentration in the CSF is associated with cognitive impairment in Parkinson's disease (38–41). In some studies, AD neuropathology seemed to be even more associated with PDD than with α-Syn pathology, but most of these patients with PD were assigned a diagnosis of PDD + AD (3, 4, 33). In fact, α-Syn pathological levels in the cortex and limbic system of patients with PDD + AD appeared to be higher than those of patients with PDD without AD comorbidities. An increased severity of cortical senile plaques (SPs) and burden of neurofibrillary tangles (NFTs) were also related to an increased cortical α-Syn pathological density (3, 33, 36, 42). Recently, Bassi et al. demonstrated that amyloid-β (Aβ) deposits dramatically accelerate α-Syn pathogenesis and spread throughout the brain after injecting α-Syn preformed fibrils into mice with abundant Aβ plaques. Recent pathological studies in vitro showed that AD-related pathologies could exacerbates α-Syn seeding activity and neurotoxicity (43, 44), suggesting an interaction between α-Syn pathology and AD-type pathologies in PD-CI.

Neuroinflammation

In addition to α-Syn and AD pathology, neuroinflammation is also a crucial factor in PD-CI. Although it is not clear how inflammation contributes to the pathogenesis of PD-CI, it is universally acknowledged that both central and peripheral inflammations contribute to the progression of neurodegeneration in PD-CI. A study by Lindqvist et al. (45) indicated that PD non-motor features were associated with
higher CSF levels of inflammatory markers. The C-reactive protein (CRP) level in the CSF of patients with PDD was significantly higher than that of patients with non-demented PD ($p = 0.032$) (45). In addition, a large cohort study of newly diagnosed patients with PD showed that higher levels of interferon gamma (IFN-γ), TNF-α, and CRP in blood are associated with a lower Mini-Mental State Examination (MMSE) score in patients with PD, and that IL-1β and IL-2 are related to a faster rate of cognitive decline (46). Recently, an animal study demonstrated that peripherally induced neuroinflammation potentiates the harmful effects of α-Syn. Furthermore, in genetic pathologic PD models, LPS-induced neuroinflammation aggravated cognitive deficits (47).

Neuroinflammation is mainly promoted by microglia and astrocytes. Under chronic peripheral inflammation, microglial and astroglial cells are overactivated by toll-like receptors (TLRs), resulting in the release of various inflammatory cytokines (e.g., TNF-α, IL-6, and CXCL1), leading to chronic neuroinflammation (48, 49). Neuroinflammation induces and exacerbates α-Syn and AD-type pathologies. Activated glial cells interact with α-Syn and AD-type pathologies (48, 50), and mediate their detrimental effects on both memory and neuroinflammation (47). These processes can promote a vicious circle and lead to PD-CI.

**Dysbiosis of gut microbiota**

Increasing evidence from studies of the gut–brain axis has suggested that the gut microbiome plays a critical role in neurodegenerative diseases, such as AD and PD (51). Previously, our research (52) has found that the gut microbiota of patients with PD-MCI was significantly altered compared with those healthy controls (HCs) and patients with PD with normal cognition (PD-NC). This is particularly manifesting in enriched genera from Porphyromonadaceae family, providing powerful evidence that the dysbiosis of gut microbiota may contribute to PD-CI (52).

Although the role of intestinal flora alteration in PD-CI is not completely known, we can still deduce hints from the results of recent studies. First, according to Braak’s hypothesis (53), the accumulation of aberrant α-Syn is initiated in the gut and propagates via the vagus nerve to the brain. Furthermore, growing evidence showed that α-Syn may be transmitted in a prion-like manner (54–57). Recent studies also supported Braak’s hypothesis in the etiology of PD and the prion-like theory (58), and indicated that the prion-like seeding activity of aberrant α-Syn may be related with its post-translational modifications (such as, carboxy-truncation) or oligomerization (59, 60). Several factors, such as antibiotics, diet, birth mode, or stress may trigger or promote the translocation of intestinal microorganisms and microbial products (such as, LPS), which would cause oxidative stress and mucosal inflammation, and promote the accumulation of α-Syn in the enteric nervous system (ENS) (61–63). Indeed, recent experiments have shown that the LPS of intestinal microorganisms can regulate the aggregation and toxicity of α-Syn and lead to cognitive decline (47, 64). Second, LPS from gut microbiota can disrupt the integrity of the BBB (62, 65, 66), which may promote neuroinflammation and SNpc damage. Finally, an experiment using a mouse model showed that microbiome disturbances have influences on microglia-mediated brain Aβ deposition (67). Collectively, these results suggest that alterations in the intestinal flora may facilitate the deposition of α-Syn and Aβ, and neuroinflammation, resulting in the induction induce PD-CI.

**P. gingivalis and PD**

In earlier studies, the view was that motor and cognitive disturbances that are caused by PD, could contribute to the progression of periodontal disease (68, 69). However, as periodontal disease is gradually found to be related to the onset and progression of AD (10), a reverse correlation between periodontal disease and PD is increasingly attracting attention (68, 70). The studies by Chen et al. (6, 71) showed that the risk of developing PD in patients with periodontitis is significantly higher than that in controls [adjusted hazard ratio (HR) = 1.431, $p = 0.002$] and patients without periodontitis who had a significantly lower risk of developing PD after dental scaling over 5 consecutive years [adjusted odds ratio (OR) = 0.204, $p = 0.0399$]. Another similar study by Jeong et al. (7) suggested a weak association between periodontitis and PD (log rank $p < 0.001$).

Recently, a study by Adams et al. (5) showed that gingipain R1 (RgpA), produced by *P. gingivalis*, is present in the blood circulation, highlighting the potential involvement of *P. gingivalis* in Parkinson’s disease. In addition, Adams et al. found that the whole blood of patients with PD is hypercoagulable, due to the presence of hyperactivated platelets and fibrin(ogen) amyloid features. These results are consistent with previous finding (72) that clots are denser and hyperclottable in patients with PD. Moreover, preliminary data suggested a role of *P. gingivalis* LPS and gingipain in the systemic inflammatory and hypercoagulable pathology of PD.

The R1441G mutation in the leucine-rich repeat kinase 2 (LRRK2) gene results in late-onset PD (73). A recent animal study by Feng et al. found that (8), orally administrating live *P. gingivalis* to LRRK2 R1441G mice three times a week for 1 month, can induce a mutant LRRK2-dependent reduction of dopaminergic neurons in the substantia nigra, an increase in mutant LRRK2 expression, and the activation of microglia, leading to peripheral IL-17A secretion and IL-17 receptor A (IL-17RA) upregulation. These results provide further evidence on the correlation between *P. gingivalis* and PD.
**P. gingivalis** and cognitive impairment

Alzheimer’s disease is the most common neurodegenerative disorder that causes cognitive impairment (49). Many studies have revealed that periodontitis increases the risk of AD (9–11). **P. gingivalis**, the main pathogen in periodontitis, was shown to play an important role in AD. In a cross-sectional study, patients with high **P. gingivalis** IgG had worse delayed verbal memory and impaired subtraction in a dose-response relationship (12). The study by Stein et al. indicated that after adjusting for confounders, such as age and smoking, serum antibody levels of **P. gingivalis** were higher in AD patients with cognitive impairment and positively correlated with the stage of AD development (13). Furthermore, **P. gingivalis** DNA, LPS (14), and gingipains (15) have been recently detected in the brains of patients with AD.

Amyloid-β plaques, neurofibrillary tangles, and neuroinflammation are the major hallmarks of AD. **P. gingivalis** may promote the progression of AD by contributing to these pathologies. The study by Wu et al. (74) showed that chronic exposure to **P. gingivalis** LPS for 5 consecutive weeks causes AD-like phenotypes, such as learning and memory deficits, microglia-mediated neuroinflammation and Aβ accumulation in neurons of middle-aged wild-type mice. In addition, cathepsin B (CatB) may be crucial for this process, as **P. gingivalis** LPS-induced AD-like phenotypes were found to be CatB-dependent. Interestingly, CatB plays a critical role in peripheral Aβ generation, as **P. gingivalis** infection induces the production of Aβ in inflammatory macrophages via activating the CatB/NF-κB signaling (75). Subsequently, a study by Zeng et al. (76) indicated that **P. gingivalis** infection can promote the CatB/NF-κB-dependent receptor for advanced glycation end (RAGE) expression in cerebral endothelial cells, which mediates the influx of peripheral Aβ into the brain across the BBB. These results revealed a potential pathogenesis of AD, associated with **P. gingivalis** induction of induced peripheral Aβ production and influx, resulting in AD-type pathologies in the brain, and in which CatB plays an important role.

To the best of our knowledge, no study has directly demonstrated the correlation between **P. gingivalis** and PD-CI. However, in a report by La Vitola et al. (47), it was shown that *Escherichia coli* (E. coli) LPS-induced neuroinflammation can aggravate the toxic effects of α-Syn and cognitive deficits. However, in the study by Zhang et al., although either **P. gingivalis** LPS or *E. coli* LPS was shown to impair spatial learning and memory in the MWM test, no significant differences were observed between the effects of the two LPS species (24). These results suggest that, despite their structural differences, **P. gingivalis** LPS may have similar mechanisms to those of *E. coli* LPS in exacerbating the α- Syn detrimental effects and cognitive impairment.

**P. gingivalis** and gut microbiota

According to previous reports, the density of **P. gingivalis** in saliva of patients with severe periodontitis can reach to 10^6/ml (77–79). Since humans produce 1–1.5 L of saliva a day, about 10^{12–10^{13}} **P. gingivalis** bacteria might be daily swallowed by patients with severe periodontitis (80). Animal studies showed that the oral administration of **P. gingivalis** at simulated doses causes gut microbiota dysbiosis and gut permeability impairment, resulting in systemic inflammation in mice (80, 81). It was reported that **P. gingivalis**-induced dysbiosis is related to arthritis (65, 82), type 2 diabetes (83), and non-alcoholic fatty liver disease (NAFLD) (84).

As gut microbiota plays an important role in the gut-brain axis, whether **P. gingivalis** promotes neurodegenerative diseases through regulating the gut-brain axis, is still under research. Feng et al. (8) have found that the oral administration of **P. gingivalis** can lead to gut permeability impairment and an increase in the accumulation of α-Syn in the colon neurons of LRRK2 R1441G mice. Although the authors did not detect α-Syn in the brain or small intestine, this finding supports the previous point that the accumulation of aberrant α-Syn is initiated in the gut (53, 58). In addition, emerging evidence by Chi et al. (85) shows that oral **P. gingivalis** induces gut microbiota dysbiosis, exacerbates neuroinflammation, and ultimately lead to a decline in cognitive function. Furthermore, the number of neurons in the hippocampal and cortical regions was significantly decreased, and amyloid plaques appeared in brain. The results from these two studies are consistent with the characteristics of PD-CI mentioned above, indicating an oral-gut-brain axis may exist and contribute to PD-CI, which is worthy of further confirmation in future studies.

**How is P. gingivalis involved in PD-CI?**

Based on the evidence mentioned above, we hypothesize that **P. gingivalis** may be involved in PD-CI through two pathways (Figure 1).

On the one hand, daily activities, such as tooth brushing and chewing, as well as dental procedures in patients with severe periodontitis can promote the entry of **P. gingivalis** into the vasculature from the periodontal pocket through ulcerated epithelium and lymphatic vessels (18, 28, 86). Additionally, **P. gingivalis** can destroy oral tissues to enter the bloodstream by gingipain (20). The entry of **P. gingivalis** into the bloodstream leads to bacteremia and the activation of the
The potential pathways of *P. gingivalis* involvement in Parkinson’s disease with cognitive impairment (PD-CI). (A) *P. gingivalis* enters the vasculature from the periodontal pocket, leading to bacteremia and systemic inflammation. (B) Gingipain and lipopolysaccharide (LPS) produced by *P. gingivalis* are present in the blood. (C) *P. gingivalis* infection induces the production of peripheral amyloid-β (Aβ) in inflammatory macrophages. (D) *P. gingivalis* impairs the function of the blood-brain barrier (BBB) by facilitating LPS, gingipain, and peripheral Aβ entry to the brain more easily, which causes neuroinflammation and Alzheimer’s disease (AD)-type pathologies. (E) *P. gingivalis* is swallowed and enters the intestine. (F) *P. gingivalis* induces dysbiosis of the gut microbiota and intestinal inflammation, contributing to the accumulation of aberrant α-Synuclein (α-Syn) in the gut. (G) Aberrant α-Syn propagates from the gut to the brain via the vagus nerve. (H) Neuroinflammation, AD-type pathologies, and α-Syn promote each other effect in the brain, leading to a vicious cycle and resulting in PD-CI.
host immune response. Peripheral cytokines are subsequently increased (e.g., IL-1β, IL-2, IL-17A, and TNF-α), and systemic inflammation is induced, which facilitates the generation of peripheral Aβ. As P. gingivalis would impair the function of BBB, virulence factors, such as LPS, gingipain, and peripheral Aβ can easily enter the brain, resulting in the activation of microglia and astrocytes, causing neuroinflammation through TLRs. Ultimately neuroinflammation promotes aberrant α-Syn aggregation and AD-type pathologies in brain.

On the other hand, the oral-gut-brain axis may be another crucial mechanism. Patients with severe periodontitis can swallow large amounts of P. gingivalis each day. When entering the intestine, P. gingivalis may induce dysbiosis of gut microbiota, which simultaneously activate TLRs in the intestine, leading to intestinal inflammation and increased intestinal permeability. In addition to exacerbating systemic inflammation, the gut dysbiosis also contribute to the accumulation of aberrant α-Syn in the gut. Subsequently, α-Syn could propagate from the gut to the brain via the vagus nerve in a prion-like manner, aggravating α-Syn deposition and misfolding in the brain.

**Discussion**

Collectively, the pathology of PD-CI has three major characteristics: convergence of α-Syn and Aβ pathologies, neuroinflammation, and dysbiosis of the gut microbiota. The currently available studies showed that P. gingivalis infection correlates with these features of PD-CI, underlining the association between P. gingivalis and PD, and between P. gingivalis and cognitive impairment, respectively. However, these studies have indirectly shown that P. gingivalis is associated with PD-CI, while no study has provided direct evidence of the association between P. gingivalis and PD-CI. Thus, the correlation between P. gingivalis and PD-CI needs further confirmation in subsequent studies.

**Author contributions**

XZ conceived the concept of the review. DL did initial systemic search to find articles and drafted the manuscript with TR. XZ, HL, and GL modified the article. All authors contributed to the final manuscript and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**References**

1. Hoogland J, Boel JA, de Bie RMA, Geskus RB, Schmand BA, Dalrymple-Alford JC, et al. Mild cognitive impairment as a risk factor for Parkinson’s disease dementia. *Movement Disord.* (2017) 32:1056–65. doi: 10.1002/mds.27002

2. Pedersen KE, Larsen JP, Tysnes O, Alves G. Natural course of mild cognitive impairment in Parkinson disease. *Neurology.* (2017) 88:767–74. doi: 10.1212/wnl.0000000000003634

3. Compta Y, Parkkinnen L, O’Sullivan SS, Vandrovcova J, Holton JL, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson’s disease dementia: which is more important? *Brain.* (2011) 134:1493–505. doi: 10.1093/brain awt031

4. Irwin DJ, Lee VMY, Trøjanoński DQ. Parkinson’s disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies. *Nat Rev Neurosci.* (2013) 14:626–36. doi: 10.1038/nrn3549

5. Adams B, Nunes JM, Page MJ, Roberts T, Carr J, Nell TA, et al. Parkinson's disease: a systemic inflammatory disease accompanied by bacterial inflammagens. *Front Aging Neurosci.* (2019) 11:210. doi: 10.3389/fnagi.2019.00210

6. Chen C, Wu Y, Chang Y. Periodontal inflammatory disease is associated with the risk of Parkinson’s disease: a population-based retrospective matched-cohort study. *PeerJ.* (2017) 5:e3647. doi: 10.7717/peerj.3647

7. Jeong E, Park J, Park Y. Evaluation of the association between periodontitis and risk of Parkinson’s disease: a nationwide retrospective cohort study. *Sci Rep.* (2021) 11:16594. doi: 10.1038/s41598-021-96147-4

8. Feng Y, Wu Q, Peng Y, Liang F, You H, Feng Y, et al. Oral P. gingivalis impairs gut permeability and mediates immune responses associated with neurodegeneration in lrrk2 r1441g mice. *J Neuroinflamm.* (2020) 17:347. doi: 10.1186/s12974-020-02027-5

9. Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Calliford D, et al. Periodontitis and cognitive decline in Alzheimer’s disease. *PLoS One.* (2016) 11:e0151081. doi: 10.1371/journal.pone.0151081

10. Kamer AR, Craig RG, Dasanayake AP, Brys M, Gledzik Sobanska L, Leon MJ. Inflammation and Alzheimer’s disease: possible role of periodontal diseases. *Alzheimer’s Dement.* (2008) 4:242–50. doi: 10.1016/j.jalz.2007.08.004

11. Chen C, Wu Y, Chang Y. Association between chronic periodontitis and the risk of Alzheimer’s disease: a retrospective, population-based, matched-cohort study. *Alzheimer’s Res Ther.* (2017) 9:56. doi: 10.1186/s13195-017-0282-6

12. Noble JM, Borrell LN, Papapanou PN, Elkind MSV, Scarpace N, Wright CB. Periodontitis is associated with cognitive impairment among older
Intracerebral inoculation of pathological Porphyromonas gingivalis and its systemic impact: current status.

J Clin Periodontol. (2003) 10:803–11. doi: 10.1080/03002297.2003.1080550

16. Olsen I, Lambris JD, Hauhenggilla G. Porphyromonas gingivalis disturbs host-commensal homeostasis by changing complement function. J Oral Microbiol. (2017) 9:1340011–85. doi: 10.1080/20002297.2017.1340085

17. Chopra A, Bhat SG, Sivaraman K. Porphyromonas gingivalis adopts intricate and unique molecular mechanisms to survive and persist within the host: a critical update. J Oral Microbiol. (2020) 12:1801090. doi: 10.1080/20002297.2020.1801090

18. Forner L, Larsen T, Kliian M, Holmstrup P. Incidence of bacteremia after tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol. (2006) 33:401–7. doi: 10.1111/j.1600-051x.2006.00924.x

19. Poole S, Singhrao SK, Kesavalu L, et al. Active invasion of Porphyromonas gingivalis and infection-induced complement activation in apo-e− mice brains. J Alzheimer’s Dis. (2014) 43:67–80. doi: 10.3233/JAD-140315

20. Guo Y, Nguyen KA, Potempa J. Dichotomy of gingipains action as virulence factors: from cleaving substrates with the precision of a surgeon’s knife to a meat chopper-like brutal degradation of proteins. Periodontal 2000. (2010) 54:15–44. doi: 10.1002/peri.2010.001077.x

21. Jia L, Han N, Du J, Guo L, Luo Z, Liu Y. Pathogenesis of important virulence factors of Porphyromonas gingivalis via toll-like receptors. Front Cell Infect Microbiol. (2019) 9:262. doi: 10.3389/fcimb.2019.00262

22. Sato N, Matsuomoto T, Kagawauchi S, Seya K, Matsumiya T, Ding J, et al. Porphyromonas gingivalis lipopolysaccharide induces interleukin-6 and c-c motif chemokine ligand 2 expression in cultured hcmc3/human brain microvascular endothelial cells. Gerodontontology. (2020). 39:199–47. doi: 10.1111/1600-051x.12545

23. Kimura A, Yoshukura N, Hayashi Y, Inuzuka T. Cerebrospinal fluid c-c motif chemokine ligand 2 correlates with brain atrophy and cognitive impairment in Alzheimer’s disease. J Alzheimer’s Dis. (2018). 61:581–8. doi: 10.3233/JAD-170519

24. Zhang J, Yu C, Zhang X, Chen H, Dong J, Lu W, et al. Porphyromonas gingivalis lipopolysaccharide induces cognitive dysfunction, mediated by neuronal inflammation via activation of the th1 signaling pathway in c57bl/6 mice. J Neuroflamm. (2018). 15:3347. doi: 10.1186/s12974-017-1023-x

25. Zhang X, Zhang X, Qiu C, Shen H, Zhang H, He Z, et al. The imbalance of th17/treg via stat3 activation modulates cognitive impairment in rodents. J Neuroinflamm. (2021). 18:110–31. doi: 10.1186/s12974-021-02438-4

26. Wijeyekoon RS, Moore SE, Farrell K, Breen DP, Barker RA, Williams Gray CH. Cerebrospinal fluid cytokines and neurodegeneration-associated proteins in Parkinson’s disease. Movement Disorder. (2020). 35:1062–6. doi: 10.1002/mds.29015

27. Dioguardi M, Crincoli V, Laino L, Alovisi M, Sovereto D, Masangelo F, et al. The role of periodontitis and periodontal bacteria in the central nervous system and the gut microbiome. Neuroinflamm. (2014) 6:53. doi: 10.3389/fnagi.2014.00053

28. Fereshtehnejad S, Zeggahi Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson’s disease: biomarkers and longitudinal progression. Brain. (2017) 140:1959–76. doi: 10.1093/brain/awx118

29. Liu C, Cholerton B, Shi M, Ginghina C, Kin KC, Auinger P, et al. CSF tau and a42 predict cognitive decline in Parkinson’s disease. Parkinsonism Relat D. (2015) 21:271–6. doi: 10.1016/j.parkreldis.2014.12.027

30. Parnetti L, Farotti L, Eusebi P, Chiasseri D, De Carlo C, Giannadrea D, et al. Differential role of csf alpha-synuclein species, tau, and a42 in Parkinson’s disease. Front Aging Neurosci. (2014) 6:63. doi: 10.3389/fnagi.2014.00053

31. Li J, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, et al. Lewy bodies in Parkinson’s disease with lewy body pathology. Ann Neurol. (2012) 8:196–203. doi: 10.1002/ana.23659

32. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The gut microbiota: a neglected player in neurodevelopmental disorders? Lancet. (2017) 16:135–6. doi: 10.1016/S1474-4422(16)30328-3

33. Harding AJ, Halliday GM. Cortical lewy body pathology in the diagnosis of dementia. Acta Neuropathol. (2001) 102:355–63. doi: 10.1007/s004010100390

34. Pan L, Li C, Meng L, Tian Y, He M, Yuan X, et al. Tau accelerates alpha-synuclein aggregation and spreading in Parkinson’s disease. Brain. (2022). doi: 10.1093/brain/awac171

35. Liu C, Cholerton B, Shi M, Ginghina C, Kin KC, Auinger P, et al. apoE exacerbates a-synuclein seeding activity and contributes to neurotoxicity in Alzheimer’s disease with lewy body pathology. Acta Neuropathol. (2022) 143:641–62. doi: 10.1007/s00401-022-02421-8

36. Lindeqvist D, Hall S, Suruya Y, Nielsen HM, Janelidze S, Brandlin L, et al. Cerebrospinal fluid inflammatory markers in Parkinson’s disease – associations with depression, fatigue, and cognitive impairment. Brain Behav Immun. (2013) 33:183–9. doi: 10.1016/j.bbi.2013.07.007

37. Williams Gray CH, Wijeyekoon R, Yarnall AJ, Lawson RA, Breen DP, Evans JR, et al. Serum immune markers and disease progression in an incident-Parkinson’s disease cohort (scicle-pd). Movement Disorder. (2016) 31:995–1003. doi: 10.1002/mds.26563

38. La Vitola P, Balducci C, Baroni M, Artioli L, Santamaria G, Castiglioni M, et al. Peripheral inflammation exacerbates a-synuclein toxicity and neuropathology in Parkinson’s models. Neuroph Appl Neuro. (2021) 47:41–60. doi: 10.1111/nan.12645

39. Fellner L, Stefanova N. The role of glia in alpha-synucleinopathies. Mol Neurobiol. (2018) 55:475–86. doi: 10.1007/s12035-018-9500-3

40. Fellner L, Irschick R, Schanda K, Reindl M, Klimaschewski L, Poewe W, et al. Tolllike receptor 4 is required for a-synuclein dependent activation of microglia and astroglia. Glia. (2013) 61:349–60. doi: 10.1002/glia.22437

41. Navarro V, Sanchez-Mejias E, Jimenez S, Munoz-Castro C, Sanchez-Yare R, Davila JC, et al. Microglia in Alzheimer’s disease: activated, dysfunctional or degenerative. Front Aging Neurosci. (2018) 10:140. doi: 10.3389/fnagi.2018.00140

42. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. Cell. (2016) 167:915–32. doi: 10.1016/j.cell.2016.10.027

43. Chen T, Gao Y, Qiu Y, Jiang S, Zhang Q, Zhang J, et al. Gut microbiota altered in mild cognitive impairment compared with normal cognition in sporadic Parkinson’s disease. Front Neurol. (2020) 11:137. doi: 10.3389/fneur.2020.00137

44. Braak H, Bohl JRE, de Vos RA, Del Tredici K. Parkinson’s disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic embryonic nigral transplants in Parkinson’s disease. Acta Neuropathol. (2007) 113:421–9. doi: 10.1007/s00401-007-0193-x
54. Volpicielli-Daley LA, Luk KC, Patel TP, Tanik SA, Ruddle DM, Sieber A, et al. Exogenous α-synuclein fibrils induce lewy body pathology leading to synaptic dysfunction and neuron death. Neuron. (2011) 72:57–71. doi: 10.1016/j.neuron.2011.08.033

55. Pan-Montoto F, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, et al. Environmental toxins trigger pd-like progression via increased alpha-synuclein release from enteric neurons in mice. Sci Rep. (2012) 2:898. doi: 10.1038/srep00898

56. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowska JQ, et al. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science. (2013). 338:949–53. doi: 10.1126/science.1227157

57. Lee SJ, Desplats P, Sigurdson C, Tsigelny I, Madliah E. Cell-to-cell transmission of non-prion protein aggregates. J Neurochem. (2011) 6:702–6. doi: 10.1038/jn.2010.143

58. Kim S, Kwon S, Kim T, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal propagation of pathological α-synuclein from the gut to the brain models Parkinson's disease. Neuron. (2019) 103:627–41. doi: 10.1016/j.neuron.2019.05.035

59. Sorrentino ZA, Xia Y, Gordon KM, Hasi E, Gliasson BI. Carboxy-terminal truncations of mouse alpha-synuclein after aggregation and prion-like seeding. FEBS Lett. (2020) 594:1271–83. doi: 10.1002/1873-3468.13728

60. Du X, Xie X, Liu R. The role of α-synuclein oligomers in Parkinson's disease. Int J Mol Sci. (2020) 21:8645. doi: 10.3390/ijms21228645

61. Sampson TR, Debelius JW, Thron T, Janssen S, Shahtii GG, Ilhan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. (2016) 167:1469–80. doi: 10.1016/j.cell.2016.11.018

62. Bhattacharya Y. Microbiota-gut-brain axis: interaction of gut microbes and their metabolites with host epithelial barriers. Neurogastroenterol Motil. (2018) 30:e13366. doi: 10.1111/nmo.13366

63. Forsyth CR, Shannon KM, Kordower JH, Voigt RM, Shaikh M, Jaglin JA, et al. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease. PLoS One. (2011) 6:28032. doi: 10.1371/journal.pone.0028032

64. Bhattacharyya D, Mohite GM, Krishnamoorthy J, Gayen N, Mehra S, Navalkar A, et al. Lipopolysaccharide-induced modulation α-synuclein aggregation and alters its biological function. ACS Chem Neurosci. (2019) 10:2229–36. doi: 10.1021/acschemneuro.8b00773

65. Banks WA, Gray AM, Erickson MA, Salameh TS, Damodarasamy M, Sheibani N, et al. Oral administration of Porphyromonas gingivalis induces dysbiosis of gut microbiota and mediates cerebrovascular-related amyloid β accumulation after Porphyromonas gingivalis infection. J Neurochem. (2021) 158:724–36. doi: 10.1111/jnc.15096

66. Li et al. Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. Neuron. (2020) 594:1271–83. doi: 10.1002/1873-3468.13728

67. Chen C, Huang J, Wu Y, Chang Y. Dental scaling decreases the risk of Parkinson's disease: a nationwide population-based nested case-control study. Int J Environ Res Public Health. (2018) 15:15875. doi: 10.3390/ijerph15081587

68. Pretorius E, Bester J, Page MJ, Kell DB. The potential of LPS-binding protein to reverse amyloid formation in plasma fibrin of individuals with Alzheimer-type dementia. Front Aging Neurosci. (2018) 10:257. doi: 10.3389/fnagi.2018.00257

69. Gaig C, Exquerra M, Martí MJ, Munoz E, Valdecasas F, Tolosa E. Ltrk2 mutations in spanish patients with Parkinson disease frequency, clinical features, and incomplete penetrance. Arch Neurol. (2006) 63:377–82. doi: 10.1001/archneur.63.3.377

70. Wu Z, Ni J, Liu Y, Yeeling H, Takayama F, Collicutt A, et al. Catepsin B plays a critical role in inducing Alzheimer's disease-like phenotypes following chronic systemic exposure to lipopolysaccharide from Porphyromonas gingivalis in mice. Brain Behav Immun. (2017) 65:350–60. doi: 10.1016/j.bbi.2017.06.002

71. Nie R, Wu Z, Ni J, Zeng F, Yu W, Zhang Y, et al. Porphyromonas gingivalis infection induces amyloid-β accumulation in monocyes/macrophages. J Alzheimer's Dis. (2019) 72:479–94. doi: 10.3233/JAD-190298

72. Zeng F, Liu Y, Huang W, Qing H, Kadwado T, Kashiwazaki H, et al. Receptor for advanced glycation end products up-regulation in cerebral endothelial cells mediates cerebrovascular-related amyloid β accumulation after Porphyromonas gingivalis infection. J Neurochem. (2021) 158:724–36. doi: 10.1111/jnc.15096

73. van-Troll-Lindén B, Toerkko H, Alaluusua S, Jousimies-Somer H, Askainen S. Salivary levels of suspected periodontal pathogens in relation to periodontal status and treatment. J Dent Res. (1995) 74:1789–95. doi: 10.1177/0022034597074041201

74. Saygun I, Nizam N, Keskiner I, Bal V, Kubar A, Aciel C, et al. Salivary infectious agents and periodontal disease status. J Periodontal Res. (2011) 46:235–8. doi: 10.1111/j.1600-0765.2010.00313.x

75. Boutagga K, Savellhoff PHM, Winkel EG, van Winkelhoff AJ. Comparison of subgingival bacterial sampling with oral lavage for detection and quantification of periodontal pathogens by real-time polymerase chain reaction. J Periodontol. (2007) 78:79–86. doi: 10.1902/jop.2007.060078

76. Nakajima M, Arimatsu K, Kato T, Matsuda Y, Minagawa T, Takahashi N, et al. Oral administration of P. gingivalis induces dysbiosis of gut microbiota and impaired barrier function leading to dissemination of enterobacteria to the liver. PLoS ONE. (2015) 10:e134234. doi: 10.1371/journal.pone.0134234

77. Arimatsu K, Yamada H, Miyazawa H, Minagawa T, Nakajima M, Ryder MJ, et al. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. Sci Rep. (2015) 5:77618. doi: 10.1038/srep04828

78. Sato K, Takahashi N, Kato T, Matsuda Y, Yokoi M, Yamada M, et al. Aggregation of collagen-induced arthritis by orally administered Porphyromonas gingivalis through modulation of the gut microbiota and gut immune system. Sci Rep. (2017) 7:6955. doi: 10.1038/s41598-017-07916-7

79. Kashiwagi Y, Abaraya S, Sugiyma N, Narukawa Y, Sakamoto Y, Takahashi M, et al. Porphyromonas gingivalis induces entero-hepatic metabolic derangements with alteration of gut microbiota in a type 2 diabetes mouse model. Sci Rep. (2021) 11:18398. doi: 10.1038/s41598-021-97968-2

80. Wang T, Ishikawa T, Sasaki M, Chiba T. Oral and gut microbial dysbiosis and non-alcoholic fatty liver disease: the central role of Porphyromonas gingivalis. Front Med. (2022). doi: 10.3389/fmed.2022.82190

81. Chi L, Cheng X, Lin L, Yang T, Sun J, Feng Y, et al. Porphyromonas gingivalis-induced cognitive impairment is associated with gut dysbiosis, neuroinflammation, and glycemic dysfunction. Front Cell Infect Microbiol. (2021) 11:755925. doi: 10.3389/fcimb.2021.755925

82. Berggreen E, Wiig H. Lymphangiogenesis and lymphatic function in periodontal disease. J Dent Res. (2013) 92:1074–80. doi: 10.1177/0022034513504589