A Literature Review: The Possible Role of Periodontal Diseases in Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are characterized by neuronal death and subsequent degeneration in the central nervous system (CNS). The immune system and inflammatory processes are vital in the progression of these diseases. Growing evidence has linked various peripheral diseases, including cardiovascular disease, diabetes, and respiratory disorders, to the CNS through systemic inflammation. Inflammation in the oral cavity, particularly from periodontal diseases like gingivitis and periodontitis— which involve chronic inflammation of the gingiva, bone, and ligaments—also impacts the CNS. Inflammation in the oral cavity may reach the brain if associated cytokines, bacterial products, toxins, and bacteria spread to the CNS, which occurs via two main mechanisms: blood circulation and neural pathways. Neuroinflammation affects the initiation and progression of neurodegeneration and, therefore, neurodegenerative diseases. This paper presents the unified hypothesis that chronic periodontal inflammation can act as a systemic trigger, accelerating neurodegeneration across AD, PD, and HD through shared cytokine cascades. This review aims to expand upon AD - periodontal disease linkage, while also establishing a theoretical connection between PD, HD, and periodontal diseases, demonstrating the need for further research.

Introduction

Oral health, traditionally disconnected from neurology, may offer valuable insights into preventing brain disorders due to systemic inflammation. Neurodegenerative diseases are commonly characterized by neuronal death and progressive degeneration in the central nervous system (CNS) in a progressive manner. These diseases cause a decline in

cognitive function, movement, and other neurological functions and pose a significant global health concern. Unfortunately, no therapeutic methods have shown a considerable effect on the progression of the diseases (Agnello et al., 2022).

Neurodegenerative diseases encompass Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). These diseases are commonly caused by accumulating aggregated and misfolded proteins, leading to neurodegeneration (Ruffini et al., 2020).

Genetic, epigenetic, and environmental factors are critical in the progression of these diseases (Agnello et al., 2022). Neurodegeneration, as a multifactorial phenomenon, is commonly reported to be caused by the interplay of four main mechanisms: (a) genetic predisposition and environmental factors (Armstrong, 2020); (b) blood-brain barrier (BBB) disruption (Huang X et al., 2021); (c) pathogenic protein aggregation and dysregulation; and (d) neuroinflammation and inflammatory factors (Zhang et al., 2023).

The immune system and inflammatory processes have a role in various mental and physical health issues. Inflammation is a mechanism that protects the host against bacteria, viruses, toxins, and infections by the activation of immune and non-immune cells (Furman et al., 2019). The inflammatory response causes changes in the body. Despite being a protection mechanism, peripheral inflammation may induce interorgan communication pathways such as the lung-brain axis, resulting in various diseases, from cardiovascular diseases to lung diseases, type 2 diabetes, and cancer, as well as several neurodegenerative diseases (Furman et al., 2019). Therefore, neuroinflammation is classified as autotoxicity rather than autoimmunity, as neurons are self-destructed mainly through the innate immune system rather than the adaptive immune system (McGeer et al., 2001). The innate immune system plays a role in earlier stages, while adaptive immune systems get activated when inflammation is chronic (Çekici et al., 2014). The gut-brain axis is a commonly discussed communication pathway. Inflammation in the oral cavity can cause systemic inflammation leading to the said consequences. Periodontal disease can accelerate the progression of cardiovascular disease, diabetes, and respiratory disorders (Jepsen et al., 2018).

Several publications discuss the connection between AD and periodontal diseases (Sochocka et al., 2017; Kantarci et al., 2020; Bouziane et al., 2023). However, a gap in the literature exists to demonstrate a connection between PD’s and periodontal diseases. Furthermore, limited research addresses the connection between other neurodegenerative diseases, such as HD, and periodontal diseases. This review highlights current insights into the oral cavity-brain axis, focusing on how periodontal inflammation can lead to neurodegenerative diseases, including AD, PD, and HD.

Methods

A literature review was selected to examine periodontal diseases' role in neurodegenerative diseases. Using periodontal diseases, neurodegenerative diseases, Alzheimer's disease, Parkison's disease, Huntington's disease, gut-brain axis, periodontitis, gingivitis, inflammation, and neuroinflammation as keywords, research papers were searched on PubMed. They were further filtered for relevant information based on their abstracts. This paper made use of 50 papers.

Neuroinflammation and Systemic Inflammation

Inflammation occurs when cardinal signs caused by a subsequent reaction of vessels allow serum fluid to reach the site of inflammation, and local proteins are produced in response to the starting stimulus (McGeer et al., 2001). A prominent factor in the initiation and progression of neurodegenerative diseases, typically originating within the CNS, is inflammation. Nevertheless, peripheral infection and the subsequent peripheral inflammation can similarly alter the inflammatory processes in the CNS (Kamer et al., 2008). The inflammatory hypothesis is one prominent hypothesis connecting inflammation to neurodegeneration, especially causing AD pathogenesis (Kamer et al., 2008).

The inflammation in the brain is primarily initiated by amyloid beta (Aß) protein accumulation in senile plaques, hyperphosphorylated tau protein, and neurofibrillary tangles. These products are causative of neurodegenerative disease and continue accumulating as the disease progresses (McGeer et al., 2001; Kamer et al., 2008). This pathology stimulates the glial cells in the brain. As a result, cytokines and proteins such as tumor necrosis factor (TNF)-α, interleukin (IL)-1ß, IL-6, IL-8, and C-reactive proteins (CRP) are produced, elevating the proinflammatory agent levels (Kamer et al., 2008; Wang et al., 2019). The elevated levels further stimulate the glial cells, this time positively reinforcing the production of the proteins accumulating within the brain. This creates a positive feedback loop, which leads to neurodegeneration as seen in Figure 1 (Kamer et al., 2008; Wang et al., 2019).

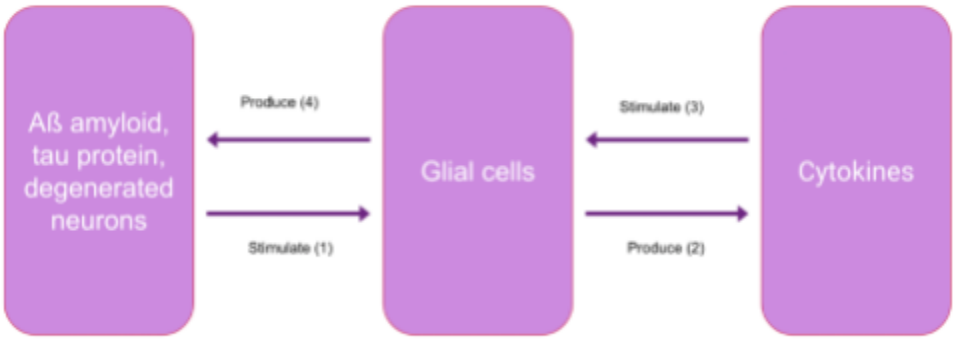

FIGURE 1. Positive Feedback Loop of Neurodegeneration. The figure shows the positive feedback mechanism involved in neurodegeneration. Aβ, tau, and damaged neurons activate glial cells (1), which produce cytokines (2). These cytokines further stimulate glial cells (3), leading to more production of neurodegenerative molecules (4).

Therefore, TNF-α inhibitors (TNFIs), both BBB-penetrating and non-BBB-penetrating, have shown therapeutic effects for neuroinflammation in the PS19 transgenic mouse model of tauopathy (Ou et al., 2021). The study suggests that reducing peripheral cytokine surges could slow down CNS pathology, which shows the therapeutic value of targeting oral-origin inflammation. Zhu et al. 's (2017) cross-sectional case-control study including 96 AD, 140 cognitively impaired without dementia, and 79 cognitively healthy participants demonstrated that IL-8 is associated with both cognitive impairment and AD. Elevated IL-8 here supports the broader pattern of chemokine overlap between gum disease and AD, reinforcing a systemic link. In another study, Lyra e Silva et al. (2021) showed that IL-6 is elevated in AD patients' brains and plasma, and it correlates favorably with brain inflammation and negatively with mini-mental state examination scores.

When the target of the inflammatory response is not eliminated, the inflammation becomes systemic (McGeer et al., 2001). For instance, a study has shown that local inflammatory bowel disease can lead to neuroinflammation becoming systematic (Do et al., 2018). Spielman et al. (2018) suggested that managing and maintaining a healthy gut microbiota might reduce the prevalence of neurodegenerative disorders. In a similar study, Albaret et al. (2020) found that Helicobacter pylori-induced gastritis may be correlated with neuroinflammation.

There are two main pathways for peripheral inflammation to reach the CNS through cytokines: (a) blood circulation and (b) neural pathways. Using blood circulation, cytokines might enter the CNS from the brain areas without the BBB. However, it is still possible for them to reach the CNS in the areas protected by the BBB using various methods. This includes directly transporting the cytokines into the brain by inducing BBB to increase permeability using fenestrated capillaries and transporters. Alternatively, the mere presence of these cytokines in the bloodstream may stimulate the brain endothelial cells to produce cytokine-inducing signaling molecules, which amplify the mentioned cytokines within the brain (Kamer et al., 2008).

Craig et al. (2022) found that *in vivo* models of colitis demonstrate increased BBB permeability and greater CNS immunological activation, demonstrating that pro-inflammatory cytokines reach the brain from peripheral organs and induce neuroinflammation. However, Obermeier et al. (2013) posited that in the absence of certain components of the BBB, the BBBB could collapse, making it possible for various molecules to

travel through the bloodstream to reach the brain causing inflammation (Obermeier et al., 2013).

Cytokines might also use the neuronal pathway to reach the CNS. There are three main ways in which this can happen: (a) cytokines might stimulate afferent fibers of peripheral neurons, (b) they may use channels or compartments associated with peripheral nerves, or (c) activate peripheral inflammatory cells, which provides access to the brain for cells like T cells and macrophages (Kamer et al., 2008).

Alternatively, bacterial products such as lipopolysaccharide (LPS), outer membrane proteins, and lipoteichoic acids might trigger an immune response activating the CD14 receptor. As a result, further brain cytokines are produced, contributing to the neuroinflammation pathology mentioned above (Kamer et al., 2008; Wang et al., 2019).

Bacteria can also reach the brain using blood circulation and neural pathways. In this case, the bacteria driving peripheral inflammation directly invade the brain (Kamer et al., 2008). Oral bacteria such as *Chlamydia pneumoniae* and spirochetes like *Treponema denticola, and Borrelia burgdorferi* have been detected in the CNS within the blood, cerebrospinal fluid, and brain tissue, supporting the presence of both mechanisms (Balin et al., 1998; Miklossy et al., 2006; Foschi et al., 2006). In their research, Gotow et al., 1982 emphasize leaky regions, often associated with fenestrated capillaries. According to the study, these leaky zones allow for the selective flow of chemicals into the brain, which can affect both physiological functioning and pathological states (Gotow et al., 1982). Banks, 2005 suggest that various transport mechanisms, including facilitated diffusion and active transport, are critical for the effective delivery of cytokines across the blood-brain barrier (BBB) and within the central nervous system (CNS), emphasizing the link between inflammation and Alzheimer's disease pathogenesis, implying that dysregulation of cytokine transport may contribute to neuroinflammation and neuronal damage (Banks, 2005).

Periodontal Diseases: Inflammation in the Oral cavity

Periodontal diseases include a wide variety of conditions that cause chronic inflammation of the gingiva, bone, and ligament, which are the supporting tissues of the dentition (Kinane et al., 2017). It has been reported that approximately 20-50% of the population has been affected by a type of periodontal disease. Hence, signifying a global problem with increasing prevalence (Wang et al., 2019). The dental plaque contains hundreds of different species (Kinane et al., 2017). Indeed, over 700 species of bacteria and other microorganisms make up dental plaque. These microorganisms physically and chemically interact with each other, maintaining a balance (Sedghi et al., 2021).

In a healthy person, the balance between the number of each organism prevents the initiation of any destructive activity, while these

microorganisms, including gram-negative bacteria, spirochetes, and viruses, accumulate and initiate chronic gingivitis and chronic periodontitis in people with poor oral health because of the imbalance in their microfilm called dysbiosis (Kinane et al., 2017). This invasive activity and inflammatory response is fairly rare when good oral health is maintained (Loesche et al., 2001).

The first periodontal disease that appears is gingivitis. The local bacteria in the dental plaque initiate a localized inflammation (Kinane et al., 2017). Gingivitis brings about a progressive loss of collagen attachment to the alveolar bone. Mostly, gingivitis is not painful. The gingival bleeding and loss of attachment do not cause irritation. Therefore, the problem is usually identified during a dental check, often after the initial stage of periodontal diseases where the damage is reversible (Loesche et al., 2001). When gingivitis is not treated on time, gingivitis progresses to chronic periodontitis, causing gingiva, bone, and ligament loss. As a result, deep periodontal pockets are created, increasing the risk of tooth loss (Kinane et al., 2017).

Chronic periodontitis has predominantly affected adults, in which epithelial tissue bone, and ligament are lost irreversibly due to chronic inflammation. Cigarette smoking and diabetes mellitus are two of many risk factors. These periodontal diseases are also often associated with the federal poverty line, Mexican American ethnicity, and African American ethnicity (Kinane et al., 2017). Nevertheless, aggressive periodontitis, which is very similar to chronic periodontitis aetiologically and histopathologically but relies more on an established heritable component, also occurs in children (Kinane et al., 2017).

There are six main mechanisms by which periodontal bacteria attack the periodontal pockets: (i) create contiguity-purulent lesions, (ii) cause aspiratory-respiratory diseases, (iii) get into the bloodstream creating metastatic infection and/or systematic diseases, (iv) release their endotoxins, specifically lipopolysaccharides (LPS), into the bloodstream acute systematic response and/or systematic disorders, (v) releasing other virulence factors in the bloodstream such as peptidyl arginine deiminases causing diseases like rheumatoid arthritis, (vi) inducing host response system causing systematic disorders (Kamer et al., 2008).

Periodontitis pathogenesis starts with the presence of bacteria, which induces an innate immune response that is critical in the early stages; toll-like receptors (TLRs) are active in the innate response to pathogens, which can contribute to bacterial persistence (Çekici et al., 2014). If acute inflammation fails to resolve, adaptive immunity gets activated as inflammation becomes chronic. Cytokine pathways activate T cells and other immune cells, thereby, regulating adaptive immunity. Cytokines, including IFN-γ and IL-17, have been linked to progressive periodontal diseases (Çekici et al., 2014).

Human epithelial cells in the gingiva protect the body from pathogens working as a physical barrier. However, when dendritic

Langerhans cells of the epithelium bring the alien material to immune cells, neutrophils engulf to kill the bacteria, creating a severe chronic inflammatory response affecting the overall oral health negatively by alveolar bone resorption and degradation of ligament fibers, as well as the formation of granulation tissues (Kinane et al., 2017).

As a result of the host defense mechanisms, various cytokines, and several proteins are released in the presence of periodontal diseases and inflammation. Furutama et al.'s (2020) study, periodontal disease was induced in wild-type C57BL/6j mice. Using quantitative PCR and enzyme-linked immunosorbent assay, it was revealed that IL-6 produced by periodontal inflammation promotes neuroinflammation and disrupts the BBB in the hippocampus, potentially resulting in cognitive decline (Furutama et al., 2020). Their mouse data directly connects gingival IL-6 to hippocampal damage, bridging oral and neural inflammation. Furthermore, in a meta-analysis, researchers found that IL-8 gene expression and IL-8 protein levels, commonly associated with systematic inflammation and cognitive decline, were more significant in gingival tissues of chronic periodontitis patients than in healthy people (Finoti et al., 2017). The evidence suggests that IL-8 could be a potential biomarker that links local and systemic diseases. In their study, Kibune et al. (2022) including 28 adults, approximately 67 years old with mild to moderate chronic periodontitis reported that TNF-α plays a role in the onset and progression of periodontal inflammation. Their findings further revealed that salivary levels of TNF-α and sTNF-R1 were significantly correlated with the severity of periodontal inflammation, with sTNF-R2 being particularly associated with the level of inflammation (Kibune et al., 2022). Routine oral sampling could identify patients at neuro-risk early due to the mirroring effect of salivary TNF-α on tissue status. A study of 100 systemically healthy people, aged 30-55 years, discovered that serum CRP, a protein related to inflammation and cognitive impairment, levels were considerably higher in the chronic periodontitis groups compared to the healthy control group (Shankar et al., 2023). Raised CRP further illustrates how periodontal inflammation amplifies whole-body inflammatory tone.Furthermore, IL-1α, and IL-1β, have been reported to have a vital role in the initial and ongoing inflammatory response in periodontitis (Brodzikowska et al., 2019). IL-12 is another pro-inflammatory cytokine produced by macrophages and dendritic cells in the oral cavity in response to periodontal diseases. Still, it can cause tissue damage if the inflammatory response is excessive or prolonged (Issaranggun Na Ayuthaya et al., 2018). In a study using C57BL/6 mice with periodontal disease, Almarhoumi et al. (2023) found a 36% increase in activated microglia in their brains after 30 days compared to controls. This increase was accompanied by elevated expression of TNF-α, IL-1β, IL-6, TLR2, and TLR9 leading to an enhanced inflammatory response. These findings reaffirmed peripheral inflammation in the oral cavity may indeed reach the brain (Almarhoumi et al., 2023).

Alzheimer's Disease and Periodontal Diseases

AD is a neurodegenerative disease that progresses slowly with onset usually during late adulthood, over the age of 65, caused by neuritic plaques and neurofibrillary tangles. It is the most common type of dementia. In 2020, there were about 50 million AD patients worldwide (Breijyeh et al., 2020). AD is caused by various factors such as age, genetics, head injuries, vascular diseases, infections, and environmental influences. (Breijyeh et al., 2020) The cause behind neuritic plaques, and neurofibrillary tangles leading to mitochondrial damage, activation of microglia, synaptic loss, and neuron death is still not clear; yet, there are two prominent hypotheses: The cholinergic hypothesis and the Amyloid Hypothesis (Wang et al., 2015; Breijyeh et al., 2020) The cholinergic hypothesis of Alzheimer's disease (AD) suggests that a dysfunction of acetylcholine-containing neurons in the brain contributes considerably to cognitive impairment in AD patients (Terry et al., 2003). The amyloid hypothesis suggests that AD is caused by the accumulation of Aβ-containing senile plaques in the brain and hippocampus, leading to neurotoxicity, tau protein abnormalities, neuroinflammation, and neurodegeneration (Breijyeh et al., 2020). Neither of the hypotheses alone explains the complex pathogenesis of AD (Terry et al., 2003; Breijyeh et al., 2020).

It has also been widely suggested that, in addition to these two mechanisms, neuroinflammation pathways through the activation of microglia cells may contribute to AD development. Various proinflammatory cytokines including TNF-α, IFN-γ, IL-1β, IL-6, and IL-18 have been shown to be increasingly synthesized in the AD brain (Wang et al., 2015).

Wang et al. (2017) emphasize that in Alzheimer's disease, Aβ peptide accumulation activates microglia. This results in elevated levels of IL-1β. The production of IL-1β causes tau hyperphosphorylation. A subsequent neuronal death and neurodegeneration occurs. Furthermore, IL-1β has a role in the inflammatory response. This leads to further Aβ deposition. This creates a positive feedback loop between inflammation and neurodegeneration. Likewise, TNF-α contributes to the inflammatory response in AD as its levels are elevated due to Aβ accumulation. It causes neuroinflammation, which is linked to loss of synaptic function and neuronal death. It also collaborates with Aβ to enhance the production of reactive nitrogen species that damage neurons. Wang et al. stated that other cytokines such as IL-6, IL-12, and IL-18 are also associated with the neuroinflammatory process.

On the other hand, there is still some controversy regarding some of these cytokines. Jabbari Azad et al.'s (2014) case-control study found that IL-6 in AD patients increases, which is correlated with age rather than AD severity, and that other cytokines, such as IL-1 and IL-4 were not found to

be associated with Alzheimer's severity. These mixed IL-6 results highlight the need for longitudinal designs to clarify causality.

In a study involving people with periodontal issues and cognitive assessments, Sochocka et al. (2017) suggested that as periodontal health decreases, cognitive abilities decrease, leading to AD pathogenesis, and this is possibly due to heightened systemic inflammation and raised levels of cytokines including TNF-α and IL-6. Meanwhile, Kantarci et al.'s (2020) study explored the effects of experimental periodontitis in a mouse model of AD revealing that AD may also be a risk factor for tooth loss and periodontal disorders, indicating a bi-directional relationship between AD and periodontal diseases. Notably, IL-6 and TNF-α, are continuously up-regulated in AD, which are also raised in periodontitis, suggesting a common peripheral trigger. PD also has similar cytokine patterns.

Parkinson's Disease and Periodontal Diseases

In 2016, about 6.1 million people were affected by PD, making it a common and increasingly prevalent global condition. Like AD, PD progresses very slowly, sometimes over a decade, making the early stages difficult to recognize. The disease involves gradual progression and an increase in disabilities over time. Known risk factors include a family history of PD, tremors, constipation, and even being an on-smoker are associated with PD. PD is generally characterized by bradykinesia in combination with rest tremor and/or rigidity. Non-motor features, including cognitive decline, depression, and pain, also significantly affect PD patients (Bloem et al., 2021).

Neuroinflammation is one of the hallmarks of PD as it is activated by microglia in the brain releasing various cytokines. PD induces a low-grade inflammatory state, marked by an imbalance between pro-inflammatory and anti-inflammatory cytokines. This imbalance is a central factor in the disease's progression. IL-6 levels are consistently elevated in PD patients, correlating with disease severity. IL-6 can have both neuroprotective and neurodegenerative effects, depending on its context and concentration. Additionally, patients exhibit elevated levels of IL-1ß, which contributes to inflammation and neuronal damage, further exacerbating PD (Dzamko, 2023).

Reale et al.'s (2009) study including 40 patients diagnosed with PD and 40 healthy persons as the control group, baseline and LPS-induced levels of IL-8, IL-1ß, and TNF-α were considerably greater in PD patients. We speculate that PD patients may be more prone to secondary cytokine production when exposed to an antigen than compared to the normal population. Sawada et al.'s (2006) study found that TNF-α and IL-6 are produced from activated microglia in PD and that the overactivated microglia show a toxic change contributing to neurodegeneration. According to Yılmaz et al.'s (2023) study, there is no substantial link between chronic periodontitis and the development of Parkinson's disease. Yet, the fact that persons with various health issues are more likely to acquire PD shows that having multiple ailments may

increase the chance of PD in some chronic periodontitis patients (Lee et al., 2024). Similar to AD, PD has also interestingly been shown to cause periodontal tissue inflammation, promoting a more significant systemic inflammatory burden

posing as a risk factor for periodontal diseases. This cytokine environment, like those found in AD suggests a systemic inflammatory origin. Similar cytokine patterns are seen in HD as well.

Huntington's Disease and Periodontal Diseases

HD is a rare neurodegenerative disease with a prevalence of only % 0.005 - 0.01% in the Caucasian population. HD is characterized by motor, cognitive, and psychiatric disturbances combined with unintended weight loss, sleep and circadian rhythm disturbances, and autonomic nervous system dysfunction, a chorea that gradually spreads to all muscles. The disease typically begins between the ages of 30 and 50. Unlike AD and PD, HD is an autosomal dominant inherited disease caused by an elongated CAG repeat of 36 or more on the short arm of chromosome 4p16.4 of the Huntington gene. As the disease progresses, patients with HD become completely dependent on full-time care for daily activities. Most HD patients ultimately die from pneumonia, followed by suicide (Roos, 2010).

Like other neurodegenerative diseases, immune activation is involved in HD. HD is also correlated with several pro-inflammatory cytokines that cause neuroinflammation. IL-1β, IL-6, IL-8, IL-10, and TNF-α are increased in peripheral blood in HD patients. However, in Rodrigues et al.'s (2016) study of 3 mutation carriers and 14 healthy controls, only IL-6 from those cytokines showed higher levels in mutation carriers. Even these results were not statistically significant enough to obscure whether IL-6, and other cytokines, influence the severity of the diseases (Rodrigues et al., 2016). According to Jia et al.'s review (2022), based on the evidence of increased levels of TNF-α in HD, one study demonstrated the therapeutic potential of DN-TNF-α, a TNF-α inhibitor. If TNF-α blockade proves beneficial, periodontal control might serve as a non-pharmacological complement.

Discussion

Inflammatory marker	Periodontitis	AD	PD	HD
IL-6	elevated in salivary and gingival levels	elevated in the brain and plasma	elevated in serum	limited data, some elevation
TNF-α	elevated in salivary and gingival levels	elevated in microglia expression	elevated in serum	elevated in peripheral blood
IL-1β	elevated in the gingival levels	elevated after Aβ stimulation	elevated in serum	reported but sparse
IL-8	elevated in gene and protein levels	elevated linked to white-matter lesions	data lacking	data lacking

FIGURE 2. Shared Pro-Inflammatory Cytokine Elevations Across Periodontitis, Alzheimer's, Parkinson's, and Huntington's Disease. This table shows the overlapping cytokine elevations in periodontitis, AD, PD, and HD. IL-6, TNF-α, and IL-1β rise across all conditions.

Periodontal diseases have been shown to activate the immune system through the stimulation of epithelial cells, which release various cytokines, such as IL-6, IL-8, TNF-α, CRP, IL-1 and IL-12 (Finoti et al., 2017; Issaranggun Na Ayuthaya et al., 2018; Brodzikowska et al., 2019; Furutama et al., 2020; Kibune et al., 2022; Shankar et al., 2023). This review highlighted the two mechanisms – blood circulation and neural pathways– and 3 types of molecules – cytokines, bacterial products and toxins, and bacteria– that play a crucial role in inflammation reaching the CNS (Kamer et al., 2008). Although these cytokines are linked to neurodegeneration, their individual roles remain unclear. Figure 2 is included to clarify the current evidence. Notably, IL-6 and TNF-α rise in all three diseases and in periodontitis, implying that a single peripheral signal set may prime distinct neurodegenerative phenotypes.

The connection between AD and periodontal diseases has already been discussed and supported by multiple studies (Sochocka et al., 2017). This review focused on providing examples of how cytokines and inflammation may alter the neurons and create or further AD pathogenesis when they reach the brain.

The literature lacks studies discussing the connection between PD and periodontal diseases. The current papers mainly discuss how PD may lead to periodontitis (Yılmaz et al., 2023). There was one available study suggesting no substantial link between chronic periodontitis and the

development of PD (Lee et al., 2024). The study suggests that combining large cohorts with oral-health metrics could help determine if periodontitis is truly independent of PD risk. However, the presence of proinflammatory cytokines such as IL-6, IL-1ß, IL-8, and TNF-α leads to further neurodegeneration and worsening of PD presentation (Swada et al., 2006; Reale et al., 2009; Dzamko, 2023). Considering that these cytokines may reach the brain due to periodontal diseases, theoretically, periodontal diseases may play an essential role in the initiation and progression of PD. Therefore, conducting further primary research on the topic is necessary and may lead to the development of novel therapeutic methods that combat oral inflammation as a preventative care for individuals at risk of developing PD, especially for those who have a family history of PD.

Furthermore, the literature also lacks information about periodontal diseases' potential role in HD. As a genetic disorder, HD cannot be caused by periodontal diseases. Yet, theoretical evidence points out that periodontal diseases might hasten the onset and progression of HD. For instance, TNF-α has proven to be one of many proinflammatory cytokines involved in HD pathogenesis, worsening the progression of the disease, which is why there have been efforts to test TNF-α inhibitors as therapeutic methods (Jia et al., 2022). TNF-α is one of the many cytokines produced in the oral cavity in response to inflammation. Using the various mechanisms explained previously, these cytokines may reach the CNS, possibly worsening the state of HD. Unfortunately, the studies regarding HD and even proinflammatory cytokines in HD pathogenesis, such as IL-1β, IL-6, IL-8, IL-10, and TNF-α, are limited. AD, HD, and PD support a unified pathogenic framework in which chronic periodontal inflammation serves as a systemic trigger. This propagates neuroinflammatory cascades that accelerate otherwise distinct neurodegenerative processes. Further research into how each cytokine affects the HD brain may lead to the development of novel therapeutic methods. Additionally, if applicable, animal model studies could help clarify the role of periodontal diseases in the progression of HD. Understanding this relationship may support the development of therapeutic methods or strategies to prevent oral inflammation in HD patients, potentially improving their overall quality of life and reducing suicidal rates. Case studies on this topic might also reveal whether the age of HD onset is influenced by patients' oral health. It is important to highlight that most studies are cross-sectional, suggesting periodontal disease may be an early marker, necessitating longitudinal cohorts tracking baseline oral health and neuroimaging outcomes for causal inferences.

A possible research study may be a five-year prospective cohort study to investigate whether baseline periodontitis severity predicts longitudinal changes in white-matter integrity on MRI. Furthermore, a clinical study that combines saliva-and-plasma cytokine panels with

standardized cognitive tests may demonstrate whether peripheral inflammatory signatures correlate with measurable neurocognitive decline. Finally, a mouse study can be used to test whether ligature-induced gum disease worsens α–synuclein–driven Parkinsonian pathology.

Conclusion

Genetic and environmental factors play a role in the formation of neurodegenerative diseases. Any inflammatory process in any area of the body can cause cytokine production and the formation of neurodegenerative diseases such as AD, PD, HD, or the progression of the disease. In this sense, the oral cavity and its diseases can cause cytokine production and neurodegenerative diseases due to chronic inflammatory infections. We believe that it is beneficial for brain health to closely monitor the oral health of society and to treat chronic inflammatory processes without producing cytokines.

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