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Possible Link between *Porphyromonas gingivalis* and Amyloidosis in the Pathogenesis of Alzheimer's and Parkinson's disease

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1. Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurological conditions in man. Amyloidosis and neuro-inflammation are central to the pathology of both these diseases. The systemic inflammatory nature of both these conditions and particularly the origin of both the systemic inflammation and neuro-inflammation are becoming most relevant in pursuing effective treatment regimes. In this review, the link between periodontitis and AD and PD is discussed emphasizing the role of amyloidosis. Attention is also drawn to how the keystone bacterium in periodontitis, *Porphyromonas gingivalis* and its cellular inflammagens e.g. lipopolysaccharide (LPS) and proteases (gingipains), which may play a crucial role in driving systemic inflammation and neuroinflammation. Treatment and prophylaxis of AD and PD are also discussed.

2. Keywords: Periodontitis; Amyloidosis; Neurological diseases; Pathogenesis; Treatment; Prophylaxis

3. Introduction

Periodontitis, which is a common disease in the elderly population, has been associated with both AD [1-6] and PD [7-12]. It affects the supporting tissues of teeth and can lead to tooth loss if untreated. Several of the >1,000 bacteria identified in the oral cavity have been found in diseased periodontal pockets.

A keystone organism in this disease is the Gram-negative anaerobic rod *Porphyromonas gingivalis* [13-15]. According to the keystone-pathogen hypothesis, certain low-abundance microbial pathogens such as *P. gingivalis* can induce inflammatory disease by remodeling a normally benign microbiota into a dysbiotic one [14,15].A healthy periodontium is very important for the maintenance of an adequate quality of life. In Americans >65 years of age almost two-thirds (62.3%) had one or more periodontitis sites with ≥5 mm of clinical attachment loss and almost half had at least one site with a probing pocket depth of ≥4 mm [16].

The authors pointed out that the older adult population is growing rapidly in the USA and by 2040, the number of adult's ≥65 years of age will have increased by about 50%. It should be emphasized that periodontitis is not only related to local teeth problems. Bacteria from periodontitis sites can spread systemically through the blood stream (bacteremia), which is the common, but not the only way of systemic spread in periodontitis (for a review see [17]). Other routes of systemic spread could be by circumventricular organs, perivascular spaces, the olfactory tract and olfactory unsheathing

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cells. A bacteremia can occur several times each day from a patient with periodontitis and has been estimated to last for up to 3 hours [18]. It can be initiated by dental treatment, tooth brushing, flossing, chewing and use of toothpicks [19] and contains a wide spectrum of bacteria [20]. The aim of the present review is to discuss the possible link between periodontitis and AD and PD emphasizing the role of amyloidosis. Attention is also drawn to how the keystone bacterium in periodontitis, *P. gingivalis* and its cellular inflammagens, i.e., lipopolysaccharide (LPS) and proteases (gingipains), can play a crucial role in driving systemic inflammation and neuroinflammation. Treatment and prophylaxis of AD and PD will also be discussed. An outline of the review is presented in (Figure 1).

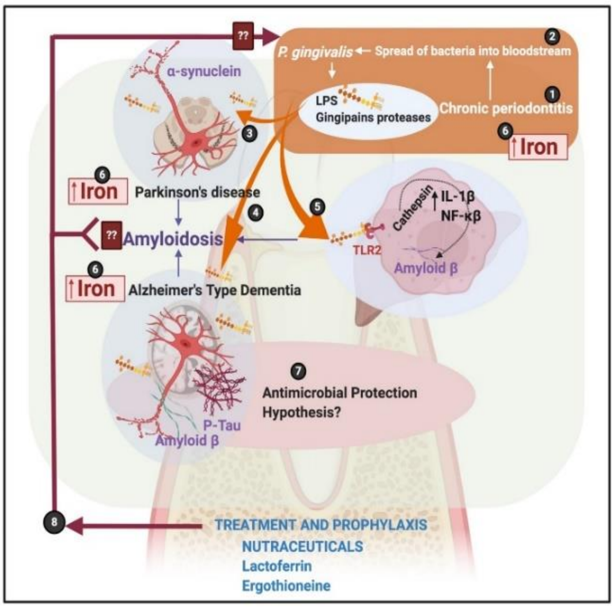

Figure 1: 1) Periodontitis and **2)** the spread of bacteria in the bloodstream; with specific focus on **3)** Parkinson's disease (PD), **4)** Alzheimer's disease (AD), **5)** liver disease and amyloidosis. **6)** Central to periodontitis and bacteria is also increased iron levels in AD, PD and amyloidosis. **7)** The Antimicrobial Protection Hypothesis is discussed together with **8)** treatment and prophylaxis focusing on amyloidosis OR increased iron levels OR bacteria in circulation, and the role of nutraceuticals.

3.1. Alzheimer's disease and Parkinson's disease

AD and PD are the most common neurodegenerative diseases in man. They have a number of similarities [21], but also differences. Some of the similarities have been listed in Table 1.

Table 1: Major similarities between Alzheimer's and Parkinson's disease*.

Age-associated with a late debut.
Protein misfolding diseases.
Degenerative processes accompanied by neuroinflammation and systemic (inflammaging) inflammation.
Alterations in the peripheral immune system cytokine network (increased blood levels of IL-6, IL-1β and TFNα).
Several genes related to the immune system considered as risk factors.
The balance of antioxidant and oxidant system activity disturbed in different cells.

*Accumulated from Boyko et al. [21].

Both are progressive, age-related neurodegenerative diseases with a late debut. They are characterized by dementia with symptoms such as memory impairment, problems with orientation and task performance. The estimated prevalence of AD in the population >65 years of age is 10%-30% and the incidence 1%-3% [22]. Most patients with AD (>95%) have the sporadic form, which affects one in eight adults over 65 years of age [23].

A common feature of PD is the presence of intracytoplasmic inclusions that contain the protein, α-synuclein (AS). The presence of toxic aggregated forms of AS (e.g. amyloid structures) in PD is thought to signal the approach of subsequent pathology. At any time, PD affects 1%-2% per 1,000 in the population. Its prevalence increases with age and 1% of the population above 60 years is affected [24].

Male gender and advancing age are independent risk factors [25]. Traditionally, a higher male frequency has been reported in PD and a higher female frequency in AD [26]. Like AD, PD is mostly sporadic and familial forms of the disease constitute only a minor part <10%) of all cases [27].

3.2. Amyloidosis

Aggregation of proteins into amyloid fibrils and deposition of these fibrils into plaques and intracellular inclusions are hallmarks of amyloid diseases [28,29].

Accumulation and deposition of amyloid fibrils are collectively known as amyloidosis. At least 30 different proteins can be involved in amyloidosis of humans. Amyloidosis has been related to many pathological conditions that can be associated with ageing, e.g. AD, PD, type II diabetes and dialysis-related amyloidosis [29,30]. In amyloidosis normally soluble precursors undergo pathological conformational changes and polymerize as insoluble fibrils with the β-pleated sheet conformation [31], resulting in vital organ dysfunction, especially in heart, kidney and nerves and eventually death [28,32]. Genetic predisposition or dysfunctions of the immune system may favor amyloid fibril formation. Microbial amyloid has been claimed to have a role in neurodegeneration [33,34].

3.3. Relationship between *Porphyromonas gingivalis* and amyloidosis

Lipopolysaccharide-initiated coagulation is accompanied by a proteolysis of fibrinogen implying that the generated fibrin is both inflammatory and resistant to fibrinolysis. Interestingly, the form of fibrin produced is amyloid in nature because much of its normal α-helical content is transformed to β-sheets, as occurs with other proteins in established amyloidogenic and prion diseases [34]. A recent study by Nie et al. [35] found that chronic systemic *P. gingivalis* infection in mice increased inflammatory responses and Aβ-producing molecules, i.e., host Aβ precursor protein- AβPP cleaving secretase enzymes in the liver. Peripheral clearance of Aβ is known to occur primarily in the liver and is undertaken by monocytes/macrophages through phagocytosis [36,37]. In liver macrophages *P. gingivalis* has been shown to induce a rapid production of interleukin 1-beta (IL-1 β) followed by intracellular accumulation of Aβ through activation of Toll-like receptor 2/nuclear factor kappa B (TLR2/NF-κB) signaling [35]. In order to induce accumulation of Aβ, NF-κB-dependent cathepsin (Cat) B was needed for cleaving pro-IL-1 β and processing AβPP [35]. Another focus of the Nie et al. [35] study was Aβ1-42, which is the toxic form of Aβ in AD, together with Aβ3-42. The latter occurs earlier in AD than Aβ1-42. CatB was shown to stimulate intracellular production of Aβ including Aβ3-42 which produces IL-1 β promoting brain inflammation. CatB increased the levels of Aβ3-42 in the liver macrophages of *P. gingivalis*-infected mice in vivo and *P. gingivalis*-infected macrophages in vitro. Aβ3-42 levels were two-fold higher than Aβ1-42 levels. Aβ3-42, which is detected exclusively in the AD brain, also caused significant death of macrophages and reduced their phagocytic capacity compared to that of Aβ1-42. This study was significant because it confirmed that *P. gingivalis* could have systemic effects related to AD. There is reason to believe that blood-derived Aβ can enter the brain and cause Aβ-related pathologies and functional deficits in neurons of the hippocampus thereby contributing to the pathogenesis of AD [38]. Local production of Aβ in the brain induced by *P. gingivalis* has been detected in AD brains from in vivo experimental animal models [39,40] and possibly also in humans [41]. Thus, Ilievski et al. [39] found that chronic oral application of *P. gingivalis* to wild type mice caused deposition of extracellular Aβ1-42 in the parenchyma of hippocampi accompanied by neurodegeneration and local inflammation, similar to what was reported previously [42].

Furthermore, Leira et al. [40] found that experimental periodontitis in mice was associated with long-term increase of Aβ1-42. *P. gingivalis* may also initiate amyloid production in PD patients. A recent study reported major virulence factors of *P. gingivalis* such as gingipain R1 (RgpA) and LPS in the circulation of such patients [11].

This probably caused presence of amyloid (fibrin (ogen) in the blood plasma of these patients, which may have affected the development of PD [11,43].

In support of this, LPS-binding protein (LBP) has been found to reverse the amyloid state of fibrin seen in type 2 diabetes with cardiovascular co-morbidities [30,44].

3.4. Possible role of *Porphyromonas gingivalis* in

Alzheimer's disease and Parkinson's disease

Several recent papers have implicated an association between *P. gingivalis* and AD [4,35,38,39,45-49]. In addition, studies have reported an association between periodontitis and PD. Thus, Chen et al. [3] found in a nation-wide population-based case control study that patients with periodontitis (n=5,396) had a significantly higher risk of developing PD than controls (n=10,792) matching in sex, age, index of year (occurrence of periodontitis) and comorbidity. Chen et al. [10] also reported that patients with periodontitis (n=4,765) who had been subjected to dental scaling over five consecutive years, had a significantly lower risk of developing PD than controls without periodontitis (n=10,060). Other reports supporting an association between periodontitis and PD have also been published [7-9,12,38].

A recent study reported major virulence factors of *P. gingivalis* such as gingipain R1 (RgpA) and LPS in the circulation of PD patients [11]. This may have induced systemic inflammation, hyper coagulation, presence of amyloid (fibrin (ogen) in plasma and ultrastructural changes in the blood platelets of these patients [11,43].

3.5. Possible role of amyloidosis in Alzheimer's disease

In AD, accumulation of amyloid beta (Aβ) and neurofibrillary tangles are major characteristics in the brain. Aβ is considered as a neurotoxic peptide [50]. This toxicity may be exerted in a number of ways such as through pore formation causing leakage of ions, disruption of cellular calcium balance and loss of membrane potential. Aβ can also promote apoptosis, cause synaptic loss and disrupt the cytoskeleton [51]. Although the Aβ plaques are generally thought to be harmful, Aβ oligomers, which can be produced both extracellularly and intracellularly, have been suggested to be the primary noxious form [51]. The Amyloid Cascade Hypothesis maintains that the neurodegeneration in AD is due to abnormal accumulation of Aβ plaques in various areas of the brain [52]. This hypothesis has continued to gain support over the last two decades, particularly from genetic studies. Thus, inter-species comparative gene expression profiling between AD patients' brains and two mouse models were performed to determine the relative importance of these factors [53]. Gene expression commonly changed in AppNL-G-F/NL-G-F mice and gene expression in the human AD cortices correlated with the inflammatory response or immunological disease. Among the expressed AD-related genes C4a/C4b, Cd74, Ctss, Gfap, Nfe212, Phyhd1, S100b, Tf, Tgfbr2 and Vim were increased in the AppNL-G-F/NL-G-F cortex as amylogenesis proceeded with increased gliosis. Genes commonly changed in the 3xTg-AD-H and human AD cortices correlated with neurological disease. The AppNL-G-F/NL-G-F cortex showed altered expression of genes defined as risk factors for AD by genome-wide association study or identified as genetic nodes in late-onset AD. These results indicated a strong correlation between cortical Aβ and the neuroinflammatory response.

3.6. Possible role of amyloidosis in Parkinson's disease

In PD, the progressive impaired motor function is a result of dopaminergic neuronal loss, particularly in the substantia nigra [54]. A common finding from degenerating dopaminergic cells is intracellular inclusions of particles, known as Lewy bodies (LBs) [55,56]. The major component of LBs is the fibrillary form of AS. This reflects the role of protein misfolding in PD pathology [57,58], which is believed to cause protein deposition and trigger degenerative signals in the neurons. Protein misfolding reduces the ability of AS to interact with vesicular trafficking and modulate neurotransmission. Conformational changes and co-aggregation of AS also initiate autophagy, which is one of the main pathways of AS degradation (for a review see [59]). The amyloid aggregation of AS is pathognomonic of PD and other neurodegenerative disorders [60]. AS can be found in a number of toxic aggregates that range from soluble oligomers to insoluble amyloid fibrils. Prefibrillar oligomers are considered the most neurotoxic species. Gallea et al. [60] reported that AS oligomerization, by altering binding affinity and/or curvature sensitivity depending on membrane composition, had a great impact on protein-lipid interaction. This study brought new insights into how the formation of prefibrillar intermediate species may contribute to neurodegeneration due to a loss-of-function mechanism.

3.7. *P. gingivalis*, iron and amyloidosis

It is well established that bacterial growth and subsequent colonization are dependent on the ability of bacteria to acquire and use iron as an essential nutrient. Iron and serum ferritin also play an important pathological role in inflammatory and neurodegenerative diseases [61,62]. Both AD and PD are characterized by having increased iron levels that drives systemic inflammation as well as neuro-inflammation [62-66]. It is also known that proteins transport iron across the brain microvascular endothelial cells prior to dementia and the onset of AD and that this process causes aggregation of amyloid-β peptides [67]. This aggregation is a key in cerebral amyloid angiopathy. In PD, AS pathology and dysfunction of iron homeostasis are also well-known [68].

Iron is of particular importance to the virulence of *P. gingivalis*, as the bacterium uses TonB-dependent outer-membrane receptors (HmuR, HusB, IhtA), gingipains proteases (Kgp, RgpA, RgpB) and lipoproteins and hemophore-like proteins (HmuY, HusA) to acquire iron and heme [69,70]. *P. gingivalis* has also the ability to cleave transferrin and this process is a significant mechanism for the acquisition of iron during periodontitis. The increased presence of iron, periodontitis and *P. gingivalis* might be central in the development of amyloidosis in AD and PD.

3.8. Possible antimicrobial protection provided by amyloid

Recently, a hypothesis - The Antimicrobial Protection Hypothesis - was formulated for AD suggesting that amyloid may provide possible antimicrobial protection. [71]. According to this hypothesis, Aβ deposition is an early immune response to a genuine or mistakenly perceived immune challenge. Aβ first entraps and neutralizes pathogens. Then Aβ fibrillization initiates neuroinflammatory pathways. These help fighting the infection and clear Aβ-/pathogen deposits. Accordingly, the Antimicrobial Protection Hypothesis tries to explain how an increased brain microbial burden can directly exacerbate Aβ deposition, inflammation and progression of AD. By doing so, this model extends but remains fairly consistent with the Amyloid Cascade Hypothesis.

3.9. Treatment and prophylaxis of AD and PD

Despite long-lasting attempts, researchers and medical professionals are still not able to provide an effective treatment for AD [72]. The problem may be related to failure in fully understanding the molecular mechanisms of AD, development of adequate drugs and early diagnostic approaches. As already indicated from the above, one possible therapeutic strategy might be elimination of Aβ and possibly phosphorylated tau (P-tau) proteins and inhibition of their aggregation [73].

Since AD can start many years before the clinical symptoms appear, it is important to find drugs that can be given at an early stage where the cognitive impairment is mild (MCI). This will require facilities to screen, diagnose and deliver a therapy to people at risk. According to the RAND report [74], there is hope that recent clinical trials may lead to disease-modifying therapy in the near future. The therapy is expected to treat early-stage AD to prevent or delay the progression to dementia.

As far as PD is concerned, most treatment is anchored in pharmacological substitution of striatal dopamine, in addition to non-dopaminergic approaches to motor and non-motor symptoms and deep brain stimulation for intractable L-DOPA-related motor complications [75]. Restoration of striatal dopamine by gene-based and cell-based approaches have been tried and aggregation and cellular transport of AS have become therapeutic targets. One of the greatest challenges in PD therapy is probably to identify markers for prodromal disease stages, which could allow disease-modifying therapies to start earlier.

In this connection Ingar Olsen would like to repeat that Chen et al. [10] found that dental scaling, which is the commonest approach for treatment and prophylaxis of periodontal disease, significantly decreased the risk of PD. This approach seeks to eliminate subgingival plaque with *P. gingivalis* as a keystone bacterium in periodontitis. It cannot be excluded that poor oral health has neurological consequences by enabling *P. gingivalis* to deteriorate cognitive function [38]. It should also be mentioned that Dominy et al. [4] found *P. gingivalis* located in AD brains and that AD could be treated with small-molecule inhibitors of *P. gingivalis* gingipains. Thus, Kgp inhibitor COR271 and RgpB inhibitor COR286 provided a dose-dependent protection against *P. gingivalis* in SH-SY5Y neuroblastoma cells. This indicated that a cheap and feasible prophylaxis in AD and PD could simply be by preventing accumulation of dental plaque. This prophylaxis should start early as it may take 10 years or so for periodontitis to develop neurological disease. Similarly, deposits of Aβ in the brain can start 10 to 20 years before the clinical symptoms of cognitive decline and the diagnosis of AD is established [6].

New research on therapeutic drugs for neurodegenerative diseases have led to the development of multi target drugs, that possess selective brain monoamine oxidase (MAO) A and B inhibitory moiety, iron chelating and antioxidant activities, capacity to augment brain levels of endogenous neurotrophin (BDNF, GDNF VEGF and erythropoietin) and induce mitochondrial biogenesis [76,77]. Another therapeutic approach might be to directly address the increased levels of iron in AD and PD. Such an approach might limit iron for usage by bacteria like *P. gingivalis* and directly impact on its virulence. Molecules of interest might be lactoferrin (LF) and ergothioneine [78]. Both are nutraceuticals that can act as iron-mopping agents. In PD, iron chelation [79] with LF has been suggested to be an effective therapy for prevention and treatment. Furthermore, LF might protect vulnerable dopamine neurons from degeneration by preserving mitochondrial calcium homeostasis [80]. LF was also found to be important in AD, as iron chelator, where it may prevent iron deposition and has the ability to block Aβ-aggregation, tauopathy and neuronal damage [81]. It also has the ability to inhibit *P. gingivalis* and its resulting biofilm [82,83].

3.10. Concluding remarks

AD and PD are multifactorial diseases. The amyloid hypothesis and the assumption that in AD, Aβ toxicity is the primary cause of neuronal and synaptic loss, is being replaced by a more holistic and systemic disease paradigm [84]. The same is true for PD and AD. However, it seems clear that deposition of amyloid is related to the pathogenesis of both and that the keystone pathogen in periodontitis, *P. gingivalis*, can initiate such deposits. Therefore, a link between *P. gingivalis* and amyloidosis in the pathogenesis of AD and PD may exist. *P. gingivalis* and its cellular inflammagens, e.g. LPS and proteases (gingipains), may play a crucial role in driving systemic inflammation and neuroinflammation. The systemic inflammatory nature of both AD and PD and particularly the origin of both the systemic inflammation and neuro-inflammation, are becoming most relevant in pursuing effective treatment regimes. Treatment and prophylaxis may focus on amyloidosis or increased iron levels or bacteria in circulation and the role of nutraceuticals. We should continue practicing meticulous dental hygiene by removing dental plaque before it extends subgingivally and initiate periodontitis through its major pathogen, *P. gingivalis*.

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