Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's disease

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Abstract: Periodontal disease (PDD) is associated with increased risk of cardiovascular disease, cerebrovascular disease, and mortality in many studies, while other studies have begun to suggest an association of PDD with Alzheimer's disease (AD). This paper discusses how infectious pathogens and systemic infection may play a role in AD. The roles of infection and inflammation are addressed specifically with regard to known AD pathologic lesions including senile plaques, neuron death, neurofibrillary tangles, and cerebrovascular changes. A testable model of proposed pathways between periodontal infection and AD is presented including three possible mechanisms: a) direct effects of infectious pathogens, b) inflammatory response to pathogens, and c) the effects on vascular integrity. The role of gene polymorphisms is discussed, including apolipoprotein (APOE) ε4 as a pro-inflammatory and pro-infection genotype.
Keywords: periodontal disease, infection, inflammation, Alzheimer's disease

Periodontal disease (PDD) is associated with increased risk of vascular disease and mortality in more than 200 reports and reviews (eg, DeStefano et al 1993; Beck et al 1996; Garcia et al 1998; Loesche et al 1998a, 1998b; Arbes et al 1999; Wu et al 2000; Grau et al 2004). Far fewer studies have examined the relationship between oral health earlier in life and Alzheimer's disease (AD) in late life (Kondo et al 1994; Gatz et al 2006; Kim et al 2007; Stein et al 2007). Inflammation is recognized as a core process in atherosclerosis and cardiovascular disease (CVD), and may also have a major role in AD. Chronic inflammation, as measured by blood inflammatory markers (Table 1), is associated with increased risk for cognitive decline (Weaver et al 2002; Yaffe et al 2003; Alley et al 2008) and dementia (Schmidt et al 2002; Engelhart et al 2004; Tan et al 2007). PDD is a common source of chronic systemic infection. This review suggests mechanisms by which periodontal infection may promote AD. The proposed model gives a rationale for further experimental and clinical studies.

Research has documented declines in self-care and oral hygiene that occur in people with dementia (eg, Chalmers and Pearson 2005; Meurman and Hämäläinen 2006). Our focus, however, is periodontal disease in early and midlife when it is clear that oral disease is an antecedent to dementia and when there would be no reason to suspect that dementia could have led to the oral disease.

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Periodontal disease

PDD is a group of conditions that cause inflammation and destruction of the gums, alveolar bone, and other structures that support the teeth. The etiology is complex involving the presence of pathogenic bacteria found in dental plaque and individual variation in host immune response. PDD is a common source of chronic systemic

Table 1 Inflammatory markers associated with cognitive decline and dementia in epidemiological studies

Cytokines	Associated with
Interleukin 1 (IL-1)	Dementia (Framingham Study[1])
Interleukin 6 (IL-6)	Cognitive Decline (MacArthur Studies[2]; Health ABC Study[3])
	Dementia (Rotterdam Study[4])
Interleukin 10 (IL-10)	Cognitive Decline (Leiden 85 + Study[5])
Tumor necrosis factor alpha (TNF-α)	Cognitive Decline (Leiden 85 + Study[5]) Dementia (Framingham Study[1])
Acute Phase Proteins	
C-reactive protein (CRP)	Cognitive Decline (Health ABC Study[3]; Greek Community[6]) Dementia (Rotterdam Study[4]; Honolulu-Asia Aging Study[7])
α-1 antichymotrypsin (ACT)	Cognitive Decline (Longitudinal Aging Study Amsterdam[8])
	Dementia (Rotterdam Study[4])
Cell Adhesion Molecules	
Intercellular adhesion molecule (ICAM-1)	Cognitive Decline (Greek Community[6])
Vascular cell adhesion molecule (VCAM-1)	Cognitive Decline (Greek Community[6])

Notes: [1]Tan et al 2007; [2]Weaver et al 2002; [3]Yaffe et al 2003; [4]Engelhart et al 2004; [5]van Exel et al 2003; [6]Dimopoulos et al 2006; [7]Schmidt et al 2002; [8]Dik et al 2005.

infection in humans (Garcia et al 2000; Li et al 2000; Taylor et al 2006). The bacterial pathogens most strongly implicated in chronic periodontal disease are *Porphyromonas gingivalis*, *Tannerella forsythensis*, *Treponema denticola*, and *Actinobacillus actinomycetemcomitans*.

Elevated levels of interleukin 1 (IL-1) have been found in gingival crevicular fluid (GCF) of patients with experimentally induced gingivitis and active periodontal disease (Masada et al 1990; Kinane et al 1992). In patients with advanced periodontitis, substantial reduction of IL-1 levels occurred after treatment (Masada et al 1990). The simultaneous presence of *p. gingivalis* and *t. forsythensis* has been associated with increased GCF levels of inflammatory mediators and associated with more severe disease (Airila-Mansson et al 2006). In gingivitis, inflammatory mediators in the GCF do not penetrate deeply into tissues. Gingivitis advances to periodontitis when bacteria evade clearance by neutrophils and penetrate the deeper tissues (Offenbacher 1996).

Even low-grade infections in the oral cavity may be associated with moderate, sub-clinical systemic inflammatory response indicated by blood elevations of C-reactive protein (CRP) and interleukin 6 (IL-6) (D'Aiuto and Tonetti 2004; Taylor et al 2006). Severe PDD can induce chronic inflammation and immune reactions that result in loss of bone and soft tissue that supports teeth in the jaws. Systemic inflammatory markers are commonly elevated in individuals with PDD. In a recent review (Loos 2005), 8 studies showed that blood leukocytes and plasma levels of CRP were consistently higher in patients with periodontitis compared to healthy controls. In one study, carriers of common oral anaerobic bacteria had higher plasma levels of CRP (Bretz et al 2005). Furthermore, the severity of periodontal infection has been correlated with serum levels of inflammatory markers. For example, in the Atherosclerosis Risk in Communities study (ARIC), older adults with more extensive periodontal pockets had one-third higher plasma CRP than those with mild PDD (Slade et al 2003). Other inflammatory proteins such as IL-6 and tumor necrosis factor alpha (TNF-α) have been found to be elevated in advanced PDD. For example, individuals with extensive PDD had 2- to 4-fold higher mean plasma levels of IL-6 and TNF-α than those with mild or no disease (Bretz et al 2005).

The success of reducing CRP and other inflammatory markers with periodontal treatment has been mixed. Intervention studies of moderate to severe PDD use standard therapeutic scraping of dental calculus (scaling and root planing) alone or in combination with antiinflammatory or antiinfective drugs. Scaling and root planing alone reduced CRP levels in one study (D'Aiuto and Tonetti 2004) but did not reduce CRP, interleukins, or TNF-α in two other studies (Fokkema et al 2003; Ide et al 2003). Use of antiinflammatory drugs in combination with scaling and root planing reduced CRP and haptoglobin in one study (Ebersole et al 1997) and in another study antiinfective drugs in combination with scaling and root planing reduced CRP, especially among those with elevated baseline CRP (Mattila et al 2002). Extraction of all teeth in advanced PDD patients caused a reduction in blood CRP, fibrinogen, white cells, platelets, and plasminogen activator inhibitor-1 in another study (Taylor et al 2006). Though the most effective treatment for reduction of inflammation in PDD remains unclear, treatment of periodontal infection may help to reduce systemic inflammation.

PDD has been associated with increased risk of mortality, cardiovascular disease, and stroke in a large number of studies. For example, in the National Health and Nutrition Examination Study (NHANES), a large US national sample, adults with periodontitis had a 46% increased risk of independent all-cause mortality and a 25% increased risk of coronary heart disease (DeStefano et al 1993). Other studies have shown that individuals with markers of poor oral health

are at 2 to 4 times greater risk for stroke (Beck et al 1996; Loesche et al 1998b; Wu et al 2000; Grau et al 2004).

Severity of PDD has shown a dose-response relationship with disease outcomes and mortality (Loesche et al 1998a; Arbes et al 1999). A longitudinal dental study of veterans found that individuals with the deepest probing pocket depths and the greatest degree of alveolar bone loss had the highest independent mortality risk (Garcia et al 1998). Though not all studies have supported PDD as a risk for CVD and cerebrovascular disease, most reports support a modest relationship (see Scannapieco et al 2003 for a systematic review).

PDD may also be associated with increased risk for AD. In Swedish twins, Gatz and colleagues (2006) found that those who had lost half or more of their teeth before age 35 had a 1.7-fold greater risk for AD, after controlling for other factors. Within a twin pair, the demented twin was four times more likely to have had worse oral health before age 35. Similarly, a case control study of AD in Japan found that loss of more than half of adult teeth by age 50–60 increased AD risk by 2.6-fold (Kondo et al 1994). In this study, PDD occurring 20–30 years prior to dementia onset was the most frequent cause of tooth loss. In a study of 144 nuns, having few or no teeth predicted a 4.3-fold higher risk of dementia, but only among those who did not carry the apolipoprotein (APOE) ε4 allele (Stein et al 2007). The study included dental records that indicated whether teeth were lost due to PDD or other causes. In a Korean community population, persons with fewer teeth were at 1.6-fold greater risk of dementia in subsequent years if they did not have their missing teeth replaced by dentures (Kim et al 2007). Teeth are commonly lost as a result of periodontal infection and dental caries, both of which are caused by exposure to bacteria. Less commonly, teeth are lost due to trauma. Studies that measure markers of periodontal infection, not just tooth loss, will be important to establishing whether oral health may be related to AD.

Systemic infection: From mouth to bloodstream

The mouth is a primary channel by which external organisms enter the body. Transient bacteremia occurs after tooth brushing and flossing as well as after normal dental procedures (Loos 2005; Forner et al 2006). In individuals with good oral and immune health, the transient bacteremia has few consequences. It is suspected that individuals with periodontal infection have higher levels of pathogenic accumulation and may experience transient bacteremia multiple times per day (Li et al 2000; Loos 2005; Forner et al 2006). Gram-positive and Gram-negative oral bacteria contain several components within their membranes that can induce pro-inflammatory cytokines including IL-1, IL-6, and TNF-α. Lipopolysaccharide (LPS) endotoxin is the most often studied of these bacterial components (Beck et al 1996; Wilson et al 1996).

The oral cavity has several barriers, physical, electrical, and chemical, that inhibit penetration by pathogens. First, the surface epithelium tissue layer provides a physical barrier composed of tight junctions and a chemical barrier containing peptide antibiotics called defensins. An electrical barrier affects the flow of electrons between the oral cavity and microbes that are introduced. The high reduction potential in the oral cavity increases oxidation of local bacteria. Another layer of protection is an immunological layer of antibody-forming cells. Finally, the reticuloendothelial system protects through phagocytosis to engulf and destroy bacteria upon entry into the blood (Weinberg et al 1998; Loesche and Lopatin 2000). If these barriers are compromised by PDD, trauma, or immune suppression, microbes can disseminate to cause acute or chronic infection (Li et al 2000). Once in the bloodstream, these bacteria can induce acute phase response characterized by increased white blood cell counts and the release of inflammatory cytokines.

Supragingival plaque, above the gums, contains dense layers of Gram-positive bacteria (see Figure 1). If these bacteria penetrate the epithelium, they may survive the oral cavity barriers and enter the bloodstream (Loesche and Lopatin 2000). Though not specifically associated with PDD, the number of these bacteria increase in conditions of poor oral hygiene and may leak into the blood and result in the inflammation of distant systems.

Subgingival plaque, below the gums, contains primarily Gram-negative organisms in individuals with disease (Loesche and Lopatin 2000). These get trapped in the space between the tooth and the gum tissue and provoke local inflammatory responses giving rise to PDD. PDD is characterized by chronic Gram-negative infection in which bacteria may enter the bloodstream via the epithelium. Ulcerations in the gingival epithelium allow bacteria to spread from the pocket between the tooth and gum into the capillaries of the epithelium and thus into systemic circulation. Bacterial endotoxin (LPS contained in bacterial cell membranes) may enter the bloodstream. In PDD, the large surface area of the pockets allows a larger degree of LPS endotoxin to enter compared to the intact endothelial lining and more limited pockets in individuals without disease. LPS induces cytokine production and its entry may alter blood coagulation and promote atherosclerosis and thrombogenesis (Valtonen 1991; Stoll et al 2004). Cytokines produced locally, for

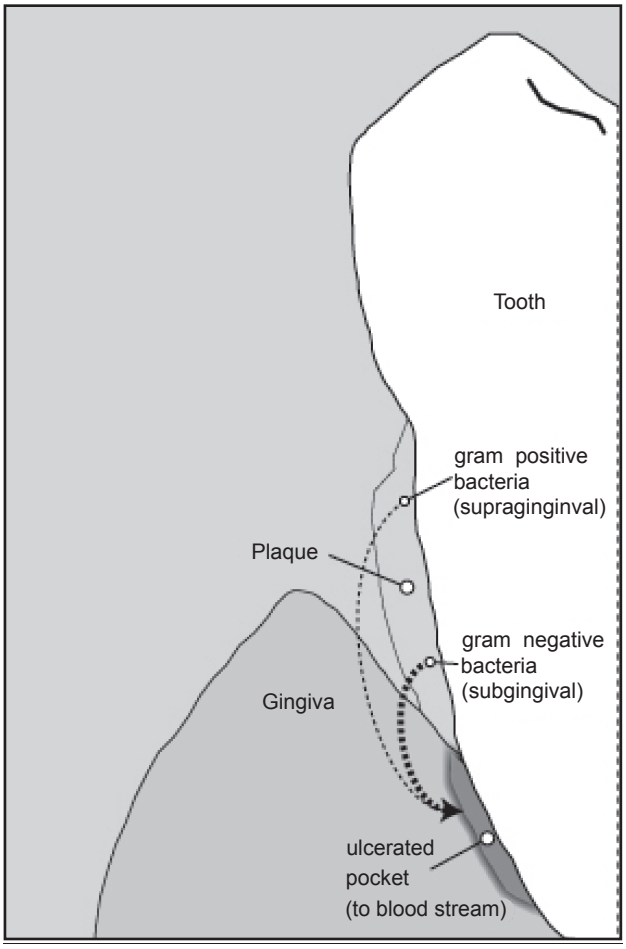

Figure 1 In periodontal disease, the gingiva recedes from the tooth forming pockets through which bacteria may more easily enter the bloodstream.

example in the periodontium, are generally degraded locally. However, under conditions of repeated challenge, cytokine receptors may become saturated and less able to eliminate cytokines, thus allowing them to "spill over" into systemic circulation affecting serum levels of cytokines and acute phase reactants (Offenbacher 1996). Chronic periodontal infection continuously attracts circulating leukocytes to inflamed periodontal tissues keeping immune cells activated (Fokkema et al 2003).

Bacteria are not the only pathogens that are likely to enter the system when defenses are vulnerable. Viruses are frequently detected in periodontal pockets (Kubar et al 2005). In one study of 30 patients with advanced periodontitis, 78% had at least one of five viruses and 40% were co-infected with two to five viruses (Parra and Slots 1996), particularly herpes viruses including cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV) found in 60%, 30%, and 20% of patients, respectively. Herpes viruses also infect inflammatory cells in periodontitis (Contreras et al 1999). The potential role of bacterial and viral pathogens in AD pathogenesis is discussed in more detail below.

Transmigration from bloodstream to brain

Though the blood–brain barrier (BBB) generally prevents entry of substances into the brain, there is evidence that inflammatory cytokines can enter or influence the brain under certain circumstances. For example, IL-6 and certain other blood cytokines elevated during the acute phase response enter the brain to initiate sickness behaviors including fever, malaise, reduced appetite, and decreased social contact (Perry 2004). These behaviors are a normal response that is adaptive to conserve energy stores when fighting infection and possibly protect others from the spread of disease. IL-6 and other cytokines may be transported across the intact BBB through specific transport processes (Pan and Kastin 1999; Banks et al 2002). IL-6 and other cytokines may also enter through fenestrated capillaries in circumventricular organs (including the pineal gland, vascular organ of the lamina terminalis, area postrem, and subfornical organ) near the base of the brain that are outside the BBB and are more easily penetrated (Banks et al 2002; Perry 2004).

Infectious pathogens and AD

Exposure to infectious pathogens of various types is a possible risk factor for AD, although mixed results allow only tentative conclusions (Balin and Appelt 2001; Holmes et al 2003; Itzhaki et al 2004; Kinoshita 2004; Little et al 2004; Mattson 2004; Ringheim and Conant 2004; Robinson et al 2004; Wozniak et al 2005). Research has focused primarily on the bacterium *Chlamydia pneumoniae*, and herpes viruses including HSV and CMV. Very few studies have reported investigating the presence oral disease-related bacteria in AD (eg, Riviere et al 2002).

C. pneumoniae infection is characterized by chronic inflammation and is generally acquired orally or nasally. Although some studies found *C. pneumoniae* in post-mortem AD brains (Balin and Appelt 2001), other labs failed to replicate these results (Nochlin et al 1999; Gieffers et al 2000; Ring and Lyons 2000; Wozniak et al 2003). *C. pneumoniae* antigens have been located in microglia and astroglia cells in brain regions with AD neuropathology (Itzhaki et al 2004). An *in vitro* cell model of the BBB showed the possibility that *C. pneumoniae* could enter the brain (MacIntyre et al 2003). In other studies that have not been replicated, infective *C. pneumoniae* was obtained postmortem from an

AD brain and induced amyloid plaques in a mouse model (Little et al 2004).

Treponema bacteria, a family of Gram-negative spirochetes commonly associated with PDD, was found in the brains of AD patients with greater frequency than in non-AD controls (Riviere et al 2002). The AD patients also had a greater variety of treponema species. The levels of bacteria measured in the blood did not differ between the AD patients and controls suggesting that AD subjects may be more susceptible to infection in the central nervous system (CNS) than controls. Antigens for two types of treponema were found in the trigeminal ganglia, pons, and hippocampus possibly indicating that the bacteria reached the brain via the trigeminal nerve. Other spirochetes have been found in the brain tissue, blood, and cerebrospinal fluid of AD patients (Miklossy 1993), however the finding was not confirmed in another study (McLaughlin et al 1999) and the link of spirochete presence to AD has been treated with skepticism (Hammond et al 1993).

Viral infection may also be a risk factor for AD, particularly herpes viruses. Nondemented older adults with high serum levels of antibodies for CMV had faster rates of cognitive decline over a four year period than those with low levels of CMV antibodies (Aiello et al 2006). HSV-1 is found in a high proportion of non-AD elderly brains (Jamieson et al 1992) and is most often not found to be associated with dementia. This does not preclude the role of HSV in AD, because presence of a virus is not sufficient to result in disease. Individual factors such as immune function, pathogen virulence, and genetic factors determine the outcome of exposure to a virus. Latent viruses may be reactivated by immunosuppression, stress, or inflammation in the brain (Itzhaki and Wozniak 2007). In AD brains, HSV-1 is present in areas of AD neuropathology. Remarkably, APOE ε4 allele carriers showed more than 15-fold risk of AD in the presence of HSV-1 in this sample. The APOE alleles may affect the degree or recurrence of viral damage, rather than susceptibility to infection with the virus (Itzhaki et al 1997; Itzhaki and Wozniak 2006). HSV-1 may contribute to the formation of amyloid plaques and abnormally phosphorylated tau protein, possibly by attenuating the processing of amyloid precursor protein (APP) into the toxic Aβ-peptide (Shipley et al 2005; Itzhaki and Wozniak 2007).

Infection with viruses early in life may put individuals at risk of becoming re-infected throughout life, even chronically (Robinson et al 2004). Since AD develops later in life, it is hypothesized that pathogens acquired early in life are not expressed until decades later. Age-related decline in immunity against pathogens or a long period of pathogen latency may offer explanations for the effects of pathogens found in older adulthood and rarely found in younger people (Itzhaki et al 2004; Robinson et al 2004). Systemic infection may result in the entry of cytokines into the brain and inflammation that reactivates latent HSV, further enhancing damage (Itzhaki and Wozniak 2006).

Viruses may infect multiple sites throughout the body including the periodontium and the brain without requiring a direct relationship between the different sites. It remains possible that PDD and AD are both partially, but independently, influenced by viruses.

Inflammation and AD

Inflammatory markers appear to be higher in persons with AD than normal age-matched controls. Blood IL-6 (Singh and Guthikonda 1997) and α1-antichymotrypsin (ACT) levels (Licastro et al 1995) are elevated in some AD patients compared to controls. In the brain, acute phase proteins IL-1, IL-6, S-100, CRP, and α2-macroglobulin are elevated in the temporal cortex of AD patients compared to controls (Griffin et al 1989; Wood et al 1993; McGeer et al 1994). CRP and serum amyloid P are localized to the characteristic AD extracellular amyloid deposits and neuronal tau protein aggregates post-mortem (Kalaria 1992; Duong et al 1997). Microvessels from AD brains release 60% to 88% more IL-1β, IL-6, and TNF-α than non-AD controls (Grammas and Ovase 2001). Though some AD patients have elevated systemic inflammatory markers, it is not clear whether systemic inflammation precedes dementia or if neuroinflammation itself might result in systemic inflammation. Longitudinal studies, discussed below, suggest that elevated systemic inflammation predicts dementia months to years later; however, neurological changes can precede clinical signs of dementia by more than a decade.

In community based samples, elevated blood inflammatory markers predict risk for dementia and incidence of cognitive impairment (Schmidt et al 2002; Engelhart et al 2004; Tan et al 2007; Alley et al 2008). In the Rotterdam Study, elevated blood IL-6, CRP, and ACT predicted increased risk of dementia onset over a year later (Engelhart et al 2004). Over a follow-up period of 25 years, men in the Honolulu-Asia Aging Study had a 3-fold increased risk for dementia in the top quartiles of inflammatory markers versus the lowest quartile at midlife (Schmidt et al 2002). In individuals with AD, elevated IL-1β predicted rates of cognitive decline (Holmes et al 2003). Patients with elevated markers preceding a baseline exam showed a greater rate of cognitive

decline over a two-month follow-up period than those who did not have elevated levels prior to baseline. Though high levels of inflammatory markers predict dementia risk and cognitive decline in the demented, they may not be associated with decline in those with higher levels of normal cognitive function (Dik et al 2005; Alley et al 2008). For example, Dik and colleagues (2005) found that ACT was associated with declines in mental status, but not with measures of memory, fluid intelligence, or information processing speed.

Model of proposed mechanisms for an association between periodontal infection and AD

This model proposes possible links between oral infection and the pathology of AD. We do not claim that oral infection or inflammation are the causes of AD, rather we propose that they may contribute to, exacerbate, and share risk factors with AD. Pathogenic bacteria in the oral cavity can lead to periodontal infection. Individuals vary in susceptibility to infection, partly due to the state of their oral hygiene and possibly due to particular genotypes that are more vulnerable to infection and have elevated inflammatory responses (discussed in more detail below). Once bacteria and/or viruses enter the blood stream, the infection may become systemic. From systemic circulation, pathogens and their products may cross the BBB and enter the brain. This may contribute to the development of AD pathology through three interrelated processes (see Figure 2). They are the direct effects of pathogenic products, the inflammatory response to these pathogens, and the effect on vascular integrity. These processes have been demonstrated to impact microglial activation, the production and formation of amyloid beta (Aβ) and tau protein, and cerebrovascular pathology. Microglial activation is associated with neuron death in AD though the causal direction remains undetermined. Aβ and tau proteins are central contributors to inter-related AD pathologies, plaques and neurofibrillary tangles.

Pathogen products

The cell walls of Gram-negative bacteria contain LPS that induces a number of host defenses. LPS stimulates certain inflammatory cytokines that are associated with microglial activation and altered processing of APP (Brugg et al 1995; Mattson 2004). Animal studies show that chronic infusion of LPS into rat brains may result in long lasting inflammatory reaction with pathological changes. These changes include an increased number of activated astrocytes, increased number and density of reactive microglia, increase in IL-1β, TNF-α, and beta amyloid precursor protein (βAPP), the degeneration of hippocampal pyramidal neurons, impairment in spatial working memory, and decreased size of hippocampus and temporal lobe associated with increased lateral ventricles (Hauss-Wegrzyniak et al 2000).

Viruses could also contribute directly to AD pathology. HSV has glycoproteins that are very similar in amino acid sequences to Aβ and tau protein and may aggregate like

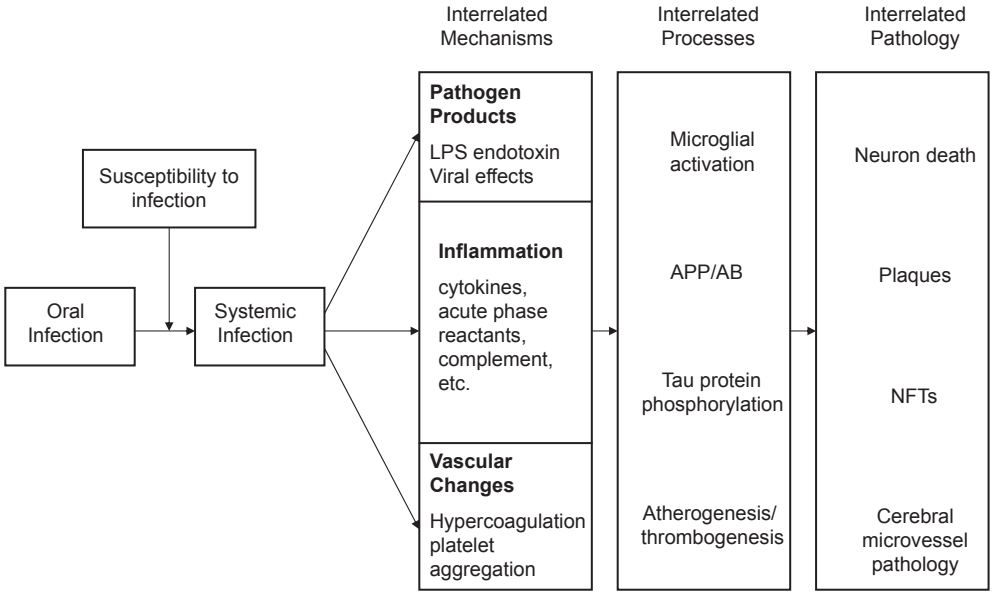

Figure 2 Proposed pathways between periodontal infection and Alzheimer's disease pathology.
Abbreviations: LPS, lipopolysaccharide; APP, amyloid precursor protein; AB, amyloid beta; NFTs, neurofibrillary tangles.

Aβ (Cribbs et al 2000; Takakuwa et al 2001). HSV may also impact the processing of APP (Benboudjema et al 2003). For example, Shipley and colleagues (2005) reported that HSV-1 and HSV-2 infection of neuronal cells in vitro caused rapid decreases in cell levels of full length APP. The production of Aβ may be increased as a result of altered APP processing or may also result directly from HSV infection (Satpute-Krishnan et al 2003; Itzhaki and Wozniak 2006).

Inflammation

It is clear that inflammation is involved in AD. However, it is not yet clear if inflammatory processes initiate pathological processes or merely contribute to disease progression. There are several mechanisms through which systemic inflammation might contribute to pathogenesis in AD. These include the priming of microglia, dysregulation of APP and Aβ processing and metabolism, the activation of microglia in response to Aβ, and a neurotoxic loop or vicious cycle in which immune response intended to be neuroprotective leads to exacerbation of the process.

The presence of primed microglia may influence the response of the brain to systemic infection. In aging individuals, changes in glia can cause exaggerated inflammatory responses (Licastro et al 2005). It is hypothesized that in AD and other neurodegenerative diseases, microglia become activated, leading to higher production of inflammatory mediators and chronic overreaction to subsequent stimuli (Marx et al 1998; Perry 2004). Microglia release many inflammatory mediators in the brain including acute phase proteins, complement factors, prostaglandins, free radicals, and cytokines (Perry 2004). Aβ peptides in the brain may also potentiate monocyte transmigration from blood to brain (Brod 2000).

The processing and metabolism of APP and Aβ is critical in AD pathogenesis (Blasko and Grubeck-Loebenstein 2003; von Bernhardi et al 2007). In AD, this balance is dysregulated. Aβ is aggregated as oligomers and fibrils which have varying neurotoxicity (Klein et al 2001). Systemic inflammation and cytokine production can augment the regulation of APP and Aβ, though the effects are complex and may depend on which combination of mediators is present (Marx et al 1998; Blasko and Grubeck-Loebenstein 2003; Dziedzic 2006; Heneka and O'Banion 2007).

Griffin and colleagues (1998) proposed that IL-1 is critical to the processing of βAPP, favoring continued Aβ deposition and the cyclical continuation of inflammatory response and cytokine overexpression. TNF-α and interferon gamma in combination also alter the metabolism of βAPP, trigger Aβ peptide production, and inhibit soluble APP secretion (Blasko et al 1999). IL-1 stimulates APP synthesis and factors that lead to its amyloidogenic properties (Schmitt et al 1996), contributes to the phosphorylation of tau protein favoring tangle formation, increases production of nitric oxide synthase fatal to cells, and increases the production of acetylcholinesterase responsible for the breakdown of acetylcholine which is important in learning and memory function (Mrak and Griffin 2005). Beta secretase, a protease that cleaves APP and results in toxic Aβ peptides, may also be upregulated by inflammatory mediators (Heneka and O'Banion 2007). In mice with APP gene mutations, systemic administration of LPS resulted in altered expression and processing of APP and increased production of Aβ (Sheng et al 2003). Mice with this gene mutation generate high levels of amyloidogenic Aβ.

Aβ and its aggregation trigger the activation of microglial cells which respond by producing acute-phase proteins, complement components, prostaglandins, and cytokines some of which are neurotoxic or contribute to aggregation by stimulating Aβ production. This response may be more injurious than the plaques and tangles to which inflammatory processes are responding, resulting in neural damage and death (McGeer and McGeer 1995; Marx et al 1998; Neuroinflammation Working Group 2000; Wilson et al 2002; Blakso and Grubeck-Loebenstein 2003; Bate and Williams 2004; D'Andrea et al 2004; Nagele et al 2004; Dziedzic 2006; von Bernhardi et al 2007).

Nonspecific responses of phagocytic cells can remove Aβ deposits, as well as recruit more microglia which produce more immune mediators. Cell attempts to dissolve plaques and tangles may cause toxicity via the release of neurotoxic substances including nitric oxide and other reactive oxygen species (Marx et al 1998; Heneka and O'Banion 2007). Proinflammatory cytokines including IL-6 and TNF-α can be directly toxic in high concentrations or can stimulate further Aβ production, aggregation, and toxicity (Marx et al 1998; Brod 2000; Blakso and Grubeck-Loebenstein 2003; Perry 2004; Heneka and O'Banion 2007). Chronic inflammation may result in chronic acute-phase protein secretion which favors the formation of Aβ fibrils. This fibrillar conformation of Aβ may be important in its ability to induce inflammation (Blasko and Grubeck-Loebenstein 2003). Over sustained periods of time, these products may contribute to neurodegeneration via injury of surrounding noninfected cells resulting in neuron loss (Rogers et al 2002).

Vascular changes

Oral bacteria including *Streptococcus sanguis* and *P. gingivalis* have been shown to result in the expression

of platelet aggregation proteins that may play a role in the formation of atheromas and thrombi possibly contributing to vascular disease (Herzberg and Meyer 1996, 1998; Sharma et al 2000; Pham et al 2002). High levels of atherosclerosis have been found to increase the risk of cognitive decline independent of other factors (Haan et al 1999). Furthermore, the presence of inflammatory cytokines in the blood increases platelet aggregation in cerebral blood vessels which can lead to atherogenesis and thrombus formation associated with strokes and hypoperfusion.

Vascular changes in the brain may also contribute to the formation of AD pathology. Platelets are a primary source of APP (Bush et al 1990; Chen et al 1995; Zandi and Breitner 2001) and platelet aggregation associated with cerebrovascular pathology may increase the production of Aβ in the brain. In endothelial cells, Aβ causes the secretion of inflammatory proteins which upregulate the production of APP (Grammas and Ovase 2001).

Possible role of genes in infection and inflammation

Acquisition of infectious disease requires the presence of both a pathogen and a susceptible host. The expression of disease depends on virulence of the pathogen and immune response of the host to the pathogen (Beck et al 2000). Periodontal researchers (Beck et al 1996) hypothesize a hyperinflammatory phenotype that causes some individuals to have exaggerated inflammatory reactions in response to pathogens. Particular alleles in the HLA-DR3/4 or -DQ system are suspected to produce exaggerated inflammatory responses to infection. Carriers have peripheral blood monocytes that secrete 3- to 10-fold greater amounts of inflammatory mediators in response to LPS. For example, patients with refractory periodontitis, a condition in which oral health does not improve despite treatment and proper hygiene, release higher levels of IL-1β and prostaglandin-E2 than patients with non-refractory periodontitis (Hernichel-Gorbach et al 1994).

Polymorphisms for genes involved in inflammatory process are a logical target for exploration in understanding a possible common cause or link between periodontal disease and Alzheimer's disease. Several candidate genes have been proposed that may potentially link PDD and CVD (Kornman et al 1999; Kornman and Duff 2001; Goteiner et al 2008). While no publications have directly considered gene polymorphisms common to PDD and AD, IL-1 and TNF-α polymorphisms have been associated with both diseases (Diehl et al 1999; Galbraith et al 1999; Grimaldi et al 2000; Nicoll et al 2000; McCusker et al 2001; Raneiro et al 2004). Not all studies have confirmed these associations (Craandijk et al 2002; Folwaczny et al 2004; Donati et al 2005) and more research on genetic polymorphisms is needed to explain discrepant findings (Loos et al 2005).

The APOE ε4 allele is implicated in susceptibility to infection or the degree of resulting damage from viruses (Itzhaki et al 1997; Lin et al 1998, 2001; Wozniak et al 2005). AD brains positive for HSV were 17 times more likely to carry the APOE ε4 allele compared to HSV-negative non-AD brains suggesting that the combination of an APOE ε4 allele and HSV may confer higher risk for AD than either alone (Itzhaki et al 1997).

APOE ε4 alleles may also play a role in inflammatory response to infection. For example, mice with APOE ε4 genotypes have greater elevations of inflammatory cytokines in systemic circulation and in the brain in response to LPS than those with APOE ε3 (Lynch et al 2003). The ability of astroglial cells to phagocytize Aβ may also depend on APOE type (Heneka and O'Banion 2007). ApoE and other genetic markers of hyperinflammatory response could be used to identify individuals at risk for targeted prevention and treatment.

Establishing a relationship

Many more studies are needed to validate an association between periodontal disease and dementia, including prospective studies that directly measure oral microbiology. Several requirements must be met before a causal relationship between PDD and AD can be established. First, PDD must precede dementia. Among the few longitudinal or archival studies that have reported tooth loss as a risk factor for dementia, two have measured periodontal disease as a possible cause for the tooth loss (Shimazaki et al 2001; Stein et al 2007), although none has established periodontal disease per se as the risk factor for dementia. Next, PDD must be correlated with AD. A few studies have suggested this is to be the case (eg, Kondo et al 1994; Gatz et al 2006; Stein et al 2007) although tooth loss was used as the index of PDD in these studies. Finally, all other possible contributors must be controlled for. While this is not entirely possible, steps have been and could be taken to account for some potential contributing factors. This includes external factors that might contribute to both tooth loss and dementia separately such as viral infection in different body systems, head injury, low socioeconomic status, malnutrition, or an exaggerated inflammatory profile. Eventually, randomized-controlled intervention trials with a long follow-up period would be needed to establish

whether preventive oral health measures could reduce the risk of AD.

For inflammation to be clearly established as a mediator for the relationship between PDD and dementia, it should be present in both oral disease and dementia as has been demonstrated through several studies (Licastro et al 1995; Singh and Guthikonda 1997; Loos 2005). Treating PDD should reduce inflammation (Ebersole et al 1997; Mattila et al 2002; D'Aiuto et al 2004; Taylor et al 2006) and reducing inflammation should lead to reduced incidence of dementia. Epidemiological studies suggest that nonsteroidal antiinflammatory drugs (NSAIDs) may protect against the development of AD if taken in midlife, many years prior to the diagnosis of dementia (eg, Hayden et al 2007). However, evidence from epidemiological studies, fundamental pathology, and clinical trials suggest that COX-2 inhibitors fail to reduce AD pathology and have not been shown to be effective in individuals who have already developed dementia (Townsend and Pratico 2005; McGeer and McGeer 2007).

No published studies have measured inflammation concurrently with PDD and dementia to allow a determination of its role in the relationship. It is necessary to determine whether inflammatory processes in the brain are initiated or exacerbated by systemic infection and inflammation resulting from PDD, or whether they reflect completely independent sources (eg, immune response to AD pathology).

Conclusion

This review and synthesis of the association between PDD and AD integrates research from disparate fields. Despite evidence that oral disease may be a risk factor for dementia, little attention has been devoted to explaining the potential mechanisms for this association (see Stein et al 2006). We propose that bacterial and viral infections commonly found in PDD may impact the brain, either directly or via systemic signals to the brain, and contribute to the development of AD. Periodontal infections may result in harmful pathogenic products leading to systemic inflammatory responses. Elevated systemic inflammatory response may contribute to the exacerbation of existing brain pathologies. Infections may also contribute to vascular pathology with the potential to impact brain function. PDD and AD may also share common risk factors such as genetic polymorphisms related to production of inflammatory mediators.

Though there are theoretical reasons for suspecting that pathogens may play a role in AD, controversy remains given the mixed results of post-mortem brain studies (Kinoshita 2004). Further evidence is needed to determine whether pathogens contribute uniquely to AD or are involved in a common cause. For example, perhaps those carrying the APOE ε4 allele may have a hyperinflammatory response to challenges from pathogen products or be highly vulnerable to infection.

Few studies have attempted to link oral health with AD diagnosis or disease pathology and none have investigated the role of inflammation as a potential mediator. Information about history of chronic infection among AD patient populations would help to investigate this hypothesis. Longitudinal data measuring periodontal status, levels of inflammatory markers, and cognitive status would be ideal.

If systemic infection and inflammation prove to be contributors to AD, several preventive measures and treatment strategies would be implied. Such developments may be particularly significant given the paucity of promising preventative strategies for AD at the present time. Focus on the prevention of oral and other sources of systemic infection would be warranted. Timely treatment of periodontal infection might be indicated to reduce risk of systemic infection and inflammation. Though successful treatment of PDD has shown reductions in inflammation (eg, Taylor et al 2006), it remains to be determined whether this would reduce risk of CVD or dementia. Identification of individuals susceptible to infection and hyperinflammation would allow for targeted prevention to reduce contact with pathogens and treatment strategies to reduce harm from hyperinflammatory incidents.

The model presented here should enable researchers to test specific hypotheses regarding the multiple inter-related mechanisms that may be responsible for an association between oral infection, inflammation, and the development of Alzheimer pathology. In particular, research should examine whether pathogen products and inflammation resulting from periodontal infection are related to these same processes suspected to contribute to pathology in AD or whether the two diseases merely share common risk factors.

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