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ALZHEIMER'S DISEASE AND PERIODONTAL DISEASE: MECHANISMS UNDERLYING A POTENTIAL BI-DIRECTIONAL RELATIONSHIP

Pamela S. Stein, DMD†
Stephen Scheff, PhD‡
Dolph R. Dawson III, DMD, MS§

Abstract
Numerous studies support a link between oral and systemic disease. Recent data also suggest that periodontal disease is a significant risk factor for Alzheimer's disease. This paper provides an overview of Alzheimer's disease, discusses the etiology and epidemiology of periodontal disease, and outlines several plausible mechanisms accounting for a potential association between oral disease and neurodegeneration. These mechanisms include: 1) metastatic spread of gram-negative bacteria from the oral cavity to the brain via a transient bacteremia; 2) injury to brain tissue from systemic inflammatory mediators produced in response to periodontal pathogens; 3) cerebrovascular injury to brain; 4) genetic predisposition, particularly polymorphisms within the interleukin-1 gene family; and 5) malnutrition, weight loss, and wasting associated with periodontal disease. Understanding the role of oral disease in dementia is important: Given that there is currently no effective treatment for Alzheimer's disease, oral disease is a potential risk factor that could be prevented.

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Key Words: Periodontal disease, Alzheimer's disease, neurodegeneration, inflammation, dementia

Introduction

All countries are experiencing an increase in the number of people over the age of 65. In the US, changing demographics suggest a much higher number of elderly in the population.[1] Periodontal disease and Alzheimer's Disease (AD) are chronic conditions that commonly affect the elderly. Numerous cross sectional studies address the oral health status of individuals with AD and dementia.[2-13] Overall, evidence indicates that Alzheimer's patients exhibit poor oral health, including increased plaque, bleeding, and calculus than age- and gender-matched controls.[10] While it is true that Alzheimer's patients may be unable to adequately perform oral hygiene measures, thereby facilitating the development of periodontal disease,[14] a potential exists for a bi-directional relationship.[15-17] Researchers are now investigating the role of poor oral health and periodontal disease in development of AD. In this paper we provide an overview of AD, review the epidemiology of periodontal disease, and outline biologically plausible mechanisms underlying the relationship between periodontal disease and AD.

Alzheimer's Disease: An Overview

Alzheimer's disease is the leading cause of dementia in the US elderly population. Other dementias include vascular dementia, dementia accompanied by Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, and Parkinson's disease. AD is a progressive dementia characterized by early short-term memory impairment. The incidence of AD within the aging population is significant and disturbing: currently, an estimated 4.5 million Americans have AD, and it is estimated that 14 million will be afflicted by 2050. Approximately 1% of the population between 65 and 69 years of age has been diagnosed with AD, and the incidence increases loga-

† Assistant Professor, Anatomy and Neurobiology, University of Kentucky College of Medicine
‡ Associate Director, Sanders-Brown Center on Aging, University of Kentucky
§ Associate Director, Delta Dental of Kentucky Clinical Research Center, Center for Oral Health Research, University of Kentucky

rithmically with age, with 5% of individuals at 75 years of age and 22% of individuals at age 85. The clinical course of AD from the first identifiable symptoms averages 8-10 years but may continue as long as 20 years.[18] The annual cost in the US for care, lost productivity, and resource loss involving individuals with AD is approximately $100 billion.[19]

A clinical diagnosis of AD is based upon cognitive assessment tools, including the Mini Mental State Examination (MMSE)[20] and the Clinical Dementia Rating scale (CDR).[21,22] While the primary symptoms of AD are learning impairment and delayed recall, multiple aspects of cognitive deterioration often occur in the course of decline. These include inability to concentrate, confusion, decline in verbal skills, spatial disorientation, depression and other personality changes, limb rigidity and incontinence. As the disease progresses, every cognitive function becomes impaired and an individual scores zero on all tests.[23] A cognitively normal elderly individual can have a MMSE score of 26-30 while an individual with mild AD usually has a score < 23. The expected decline in individuals with AD is about 3 points per year. A CDR score of 1.0 or higher is an indication of AD.

The major pathological hallmarks of AD, first described by Alois Alzheimer in 1907,[24] are the presence of neurofibrillary tangles (NFT), neuropil threads (NT), and beta-amyloid plaques, often referred to as senile plaques (SP). While the presence or absence of these pathological structures does not necessarily indicate that an individual is inflicted with AD, a final diagnosis must include observation of some of these hallmarks. The abundance of NFT in the cerebral cortex is positively correlated with disease progression.[25,26] Although the severity of dementia also correlates with the cortical density and distribution of both NFT and SP, several studies have observed these lesions in cognitively intact elderly individuals,[27-31] suggesting they occur in the course of normal aging as well. More recent reports observe significant loss of synapses in the hippocampus and neocortex[32,33] coupled with significant neuronal loss.[34-37] It is still controversial which neuronal loss plays the most significant role in AD and whether or not the loss of larger neurons is more important than the site at which they are lost.

Currently there are no effective therapies for AD although numerous laboratories are working on preventive strategies. One of the problems associated with developing an effective therapy is that the etiologies of the disease are unknown. The greatest risk factor for AD is increasing age and a family history of the disease. But why these are significant risk factors and what happens to engage the neuropathological cascade of AD are unknown. Increasing evidence supports the involvement of oxidative stress, in which free radical levels exceed antioxidant defenses, as a major cause of AD.[38,39] Progressive oxidative modification of proteins is a normal consequence of aging and appears to underlie accumulation of amyloid-ß protein (Aß).[40-42] The amyloid hypothesis of AD states that the formation of Aß initially triggers AD.[43] Amyloid peptides are also potent activators of microglial cells in the brain.[44,45] Numerous studies have shown an inflammatory response associated with the presence of neuritic amyloid plaques involving microglia and astrocytes. Coupled with this activation is an upregulation of inflammatory cytokines and chemokines, which could potentially damage synapses and neurons leading to further microglial activation and astrogliosis.[46] While it is currently being actively debated whether inflammatory mechanisms cause CNS damage in AD, an inflammatory response certainly coincides with the neuropathology of the disease. Epidemiological studies provide intriguing evidence in support of use of nonsteroidal anti-inflammatory drugs (NSAIDs) for several chronic inflammatory diseases, including AD.[46-50] NSAIDs, such as aspirin, ibuprofen, naproxen, COX-2 inhibitors, and other medications, may lower the risk of AD.

Epidemiology of Periodontitis and Systemic Disease Association

The prevalence of a disease is defined as the proportion of cases in a specific population at a given point. The prevalence of severe, generalized periodontitis ranges from 5-15%.[51] Estimates are higher for mild periodontitis (21.8%) in the US.[52] Estimating periodontal disease trends is challenging and not without controversy. Borrell and colleagues have reported decreases in periodontitis prevalence from NHANES III to NHANES 1999-2000.[53] Others estimate that the number of adults over age 25 with some form of periodontitis will increase through 2010.[54]

Periodontal infections are the direct result of an interaction between a tooth-associated microbial biofilm and host defenses. A mature biofilm is comprised of large numbers of gram-negative anaerobes that stimulate a host response.[55] Neutrophils and other cells are recruited resulting from a host response and produce a variety of inflammatory mediators, including cytokines and prostaglandins.[56] The chronicity of the local lesion is important, as it is the continued generation of inflammatory mediators and subsequent interactions derived from the host response that leads to destruction of alveolar bone and connective tissue.[57,58] Research efforts have focused on this chronic inflammatory process and have defined mechanisms enabling specific bacterial cell invasion and the role of pathogens in the local destruction of oral tissues.[59] The impact of this process extends beyond the oral cavity, as is illustrated by examples of periodonto-

pathogenic processes believed to initiate or exacerbate systemic disease.

Genco and colleagues reviewed the epidemiology and possible mechanisms involved in periodontal and cardiovascular disease (CVD).[60] They reported that some investigators find a direct effect of oral bacteria such as *Porphyromonas gingivalis* and *Streptococcus sanguis* on induction of platelet activation and aggregation, which may contribute to atheroma formation and thrombosis. In their review they describe human studies identifying oral periodontopathogens in atherosclerotic plaque, along with animal studies implicating *P. gingivalis* in activating the acute-phase response.[60] It is believed that acute-phase activation promotes lipemia and formation of atheromas. Mechanistic models for *P. gingivalis*-accelerated atherosclerosis, including microbial invasion, immunological sounding, pathogen trafficking and autoimmunity, have been proposed by Gibson and colleagues.[61] Genco and colleagues also reported several case-control and cross-sectional studies evaluating coronary heart disease and poor oral health.[60] One study evaluated NHANES III data and found that the odds of having a heart attack increased with the severity of periodontitis, while another supported the association of specific periodontal pathogens and myocardial infarction. Most longitudinal studies reporting such an association found that the level or burden of periodontal disease was important.

Investigations of linkages of preterm birth and diabetes to periodontal disease have increased because of the enormous economical and social burden caused by these health problems. Offenbacher and colleagues report that mothers with significant periodontal disease had a 7.5 fold increase in the risk of having a preterm, low birth weight baby.[62] A recent study by Pitiphat and colleagues report 65% higher levels of C-reactive protein (CRP) among pregnant women with periodontitis compared with periodontally healthy women.[63] Clinical intervention trials are being conducted to investigate if non-surgical periodontal intervention therapy reduces the incidence of preterm birth and low birth weight babies. In addition, there appears to be a bi-directional relationship between periodontal disease and diabetes, with improved metabolic control seen in poorly controlled diabetics following periodontal therapy.[64-66]

P. gingivalis has also been linked pathogenetically to rheumatoid arthritis (RA) through the enzyme peptidylarginine deiminase (PAD). Rosenstein and colleagues hypothesize that individuals predisposed to periodontal disease exhibit autoimmune responses, such as production of rheumatoid factor.[67] PAD enzyme breaks down fibrin in the periodontal pocket and parallels intra-articular breakdown of fibrin and other proteins. The authors note that several RA treatments, such as treatment with nonsteroidal anti-inflammatory drugs, ameliorate periodontal disease. Golub and colleagues propose a "two-hit" model of chronic destructive periodontitis.[68] They cite several animal and human studies supporting their model that a subgingival biofilm (the first hit) is followed by a disease (the second hit, such as rheumatoid arthritis), which in turn increases levels of circulating inflammatory biomarkers. The second hit also results in increased alveolar bone loss. Therefore, defining mechanisms mediating systemic induction of periodontal disease may provide improved treatment strategies for chronic local and systemic diseases.

When evaluating epidemiological studies of periodontal disease it is important to consider differences in the definition of case severity, populations sampled, sites selected and sampling procedures used in a particular study.[69] Dietrich and Garcia note that randomized control trials are needed to assess periodontal treatment efficacy in reducing CVD and stroke, but that such an approach may not be sufficient to determine the etiology of periodontal disease in these conditions.[70] Therefore they stress the need for further well-designed observational studies to facilitate understanding of disease relationships.

Plausible Links Between Periodontal Disease and AD

It is clear that periodontal disease is associated with numerous systemic diseases, although it is too soon to tell if we can add AD to the list. Investigators are currently asking whether poor oral health promotes development of AD and dementia. Thus we outline below *plausible* biological mechanisms linking periodontitis and AD.

Metastatic Spread of Gram-negative Bacteria from the Oral Cavity to the Brain via Transient Bacteremia or Neuronal Pathways

For years it has been known that oral bacteria can disseminate to distant sites within the body.[72-75] Elderly [76] and immunocompromised patients, such as those suffering from cancer, diabetes, or rheumatoid arthritis, may be especially vulnerable to systemic oral pathogens.[77] Any dental procedure that causes bleeding can produce transient bacteremia.[78] It is well documented that certain dental procedures, such as extractions, periodontal surgery, periodontal scaling and root planing, induce hematogenous seeding.[79-84] The American Heart Association provides guidelines to prevent infections of the joints, cardiac valves, and endocardium caused by oral bacteria.[78] Could oral pathogens also infect the brain with subsequent neuropathological consequences? Additionally, could the bacteremia responsible for this neuropathology be the result of chronic periodontal disease?

In individuals with good oral hygiene the number of oral pathogenic bacteria reaching the systemic circulation is small. However, this number increases twofold to tenfold in persons with periodontal disease.[85] High levels of pathogenic bacteria, coupled with the edematous state of the infected periodontal pocket, leads to ongoing, chronic dissemination of periodontal bacteria into the bloodstream. One study demonstrated positive cultures of oral bacteria in arterial blood in 55% of patients with severe periodontal disease.[86]

As early as 1891, it was suggested that oral bacteria could "lodge in some weak point in the brain" and result in brain infection and abscess.[75] Indeed, there are numerous reports of brain infection testing positive for oral bacteria, with most cases specifically linked to periodontal pathogens.[87-98] Brain infection by one such bacteria, *Actinobacillus actinomycetemcomitans*, is associated with coagulative necrosis of cortical cells and white matter.[95]

The flora of periodontal disease consists largely of gram-negative bacteria. Current research has identified brain receptors specific for gram-negative bacteria.[99] Brain infections by gram-negative bacteria have been linked to Alzheimer's etiology, specifically late-onset sporadic AD.[100] A recent histologic study demonstrated the presence of gram-negative *Chlamydia pneumonia* in cells of affected brain regions in 17 of 19 post mortem Alzheimer's brains, while brains of controls were not infected.[101] In another post mortem study, oral *Treponema* was found in the cortex of 14 of 16 Alzheimer's brains compared with only 4 of 18 control brains. *Treponema* was detected in cells of the trigeminal ganglion, suggesting that bacteria may reach the brain through branches of the trigeminal nerve.[102]

Overall these studies indicate that it is biologically feasible for pathogenic oral bacteria to disseminate through the bloodstream, reach the brain and either initiate or exacerbate existing lesions.

Injury to Brain Tissue from Systemic Inflammatory Mediators Produced in Response to Periodontal Pathogens

It is also possible that pathogenic periodontal bacteria do not "infect" the brain but rather induce a systemic inflammatory response leading to injury of brain tissue. Since host responses to periodontal disease, such as upregulation of proinflammatory mediators, show significant positive correlation with coronary artery disease and premature birth, neuropathological responses may also be induced.

Inflammation is a recurrent theme among investigations of oral and systemic diseases.[103-105] The cascade of inflammatory events associated with periodontal disease begins with endotoxin, a high molecular weight lipopolysaccharide found in the cell wall of gram-negative periodontal bacteria.[106-108] Endotoxin initiates inflammation locally in the periodontal pocket by stimulating inflammatory cells such as monocytes, macrophages, fibroblasts and T cells to produce cytokines and prostaglandins (PGE2).[105,109-111] Cytokines transmit information from cell to cell at very low levels, in the nanomolar to picomolar range.[108] Some of the most important inflammatory cytokines associated with periodontal disease are interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tissue necrotizing factor-alpha (TNF-α). IL-1 and TNF-α signal hepatic cells to produce several Type 1 acute phase proteins, among them CRP.[112]

Studies have shown increased levels of proinflammatory cytokines in inflamed gingival tissues compared with healthy tissue[113] and in the gingival crevicular fluid in patients with active periodontal disease.[114,115] Elevated levels of acute phase proteins, including CRP, have also been demonstrated in the gingival crevicular fluid.[116-118] It is suggested that inflammatory mediators produced locally may "spill over" into the systemic circulation, producing increased serum levels of cytokines and acute phase reactants.[103,108,110] In addition, daily bacteremias, or chronic "trickling" of pathogenic periodontal bacteria into the circulation, could initiate a systemic cascade of inflammatory events resulting in a sustained elevation of inflammatory products.[119]

Indeed investigators have found markers of systemic inflammation when analyzing the serum of individuals with periodontal infections. A study by Ebersole and colleagues showed that levels of endotoxin detectable in the blood increase with the level of oral disease.[112] Periodontal pathogens have been shown to elicit a circulating antibody response.[120-122] Abnormally elevated serum levels of PGE2[123] and CRP[124-129] have been found in people with periodontitis. In one study of an elderly population, Bretz and colleagues found significantly higher levels of IL-6 in the blood of those with extensive periodontal disease compared with controls.[130] This finding is noteworthy because IL-6 is associated with local production of amyloid proteins,[112] and in the Alzheimer's brain it may regulate production of amyloid proteins found in neuritic plaques, which are shown in Figure 1.[131]

Cytokines have been implicated in the pathophysiology of several psychiatric disorders, including AD, because of their ability to stimulate neurochemical, neuroendocrine, and neuroimmune changes in the brain.[132] As noted, inflammatory mediators can damage synapses and neurons and activate microglia and the inflammatory cascade.

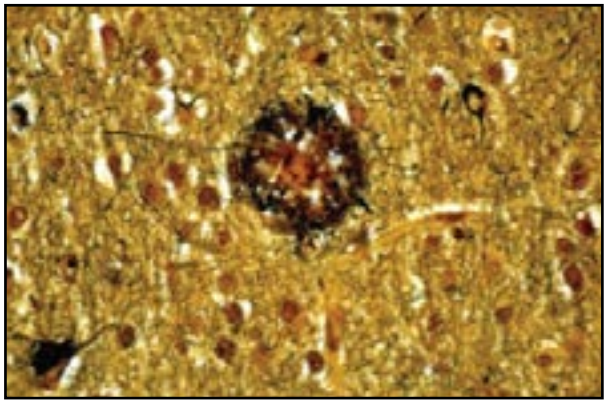


Fig. 1

Bielschowsky stained neuritic plaque from an individual with AD. Specimen provided by Dr. Stephen Scheff, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY.

IL-1 is particularly relevant to the pathogenesis of AD since it is overexpressed in neuritic plaques.[133] In addition, IL-1 increases synthesis of beta–amyloid precursor protein and activates astrocytes.[134]

Given the evidence for the role of chronic inflammation in AD,[133] it is reasonable to suggest that long-term systemic exposure to periodontal pathogens and their subsequent chronic production of inflammatory mediators may precipitate neuropathological changes.

Periodontal Disease Increases the Risk of Cerebrovascular Injury to Brain

Stroke, or cerebrovascular accident, affects the blood supply to the brain. There are two types of stroke: hemorrhagic, in which an artery supplying oxygen-rich blood to the brain ruptures, and ischemic, when a blood vessel supplying the brain is blocked by a local thrombus or an aggregation of bacteria and fibrin from a distant source.[77] Although stroke is not considered a major risk factor for AD,[135] stroke has been related to the severity of clinical symptoms in Alzheimer's patients,[136] and individuals with a history of stroke demonstrate more rapid decline in memory performance than do healthy individuals.[137] Stroke is a significant risk factor for dementia.[135] In fact, the risk of dementia increases ninefold in subjects experiencing ischemic stroke.[139] The relationship between stroke and periodontal disease thus merits discussion.

Recent findings suggest that periodontal disease is an important risk factor for stroke.[140] Beck and colleagues found that persons with severe periodontal bone loss at baseline had nearly 3 times the chance of experiencing a cerebrovascular accident (CVA) compared with those with minimal bone loss or no periodontal disease.[140] Elter and colleagues examined 9,415 dentate and 1,491 edentulous adults and found stroke associated with both edentulism and clinical attachment loss of 3 millimeters or greater.[141] Findings from similar studies by Grau and colleagues indicate that subjects with severe periodontal disease, as defined by clinical attachment loss of 6 mm or greater, had from 4.3[142] to 7.4[143] times greater risk of cerebral ischemia than control subjects or subjects with mild periodontal disease. In an investigation of plaque index scores and oral hygiene practices of 401 US veterans, it was shown to have a significant association with stroke.[144] Examining subjects under the age of 50, Syrjänen and colleagues found a greater risk of ischemic cerebrovascular disease in males with severe dental infections combined with other bacterial infections.[145] In a case control study, patients with acute cerebrovascular ischemia were found to have more severe periodontal disease when compared with age and sex-matched nonstroke patient controls.[143] In addition, men who have 24 or fewer teeth have been shown to have a greater risk of stroke.[146]

What mechanism underlies the association between periodontal disease and stroke? Li suggests that in individuals with periodontal disease bacteria and cytokines disseminating into the systemic circulation contribute to stroke by altering platelet function and promoting atherosclerosis and blood coagulation, a hypothesis supported in the literature.[77] Proinflammatory mediators (IL-1, TNF-α, PGE2, and IL-6) produced in response to the bacterial challenge of periodontal disease induce the release of platelet activating factor (PAF).[108] Platelet aggregation-associated protein expressed on the periodontal pathogen *P. gingivalis* has been found to induce platelet aggregation, potentially increasing the chance of acute thromboembolic events.[147-149] In addition, *P. gingivalis* can activate endothelial cells.[150] Individuals with periodontitis have been found to have significantly higher levels of serum fibrinogen.[151] As noted, periodontal pathogens have been found in human artheromas. Haraszthy and colleagues found that 44% of human atheromas removed during carotid endarterectomies tested positive for at least one of the following periodontal pathogens: *A. actinomycetemcomitans*, *Bacteroides forsythus*, *P. gingivalis*, or *Prevotella intermedia*.[152] In a similar study by Zambon and colleagues, periodontal pathogens were found in over half of the atheromas examined.[153]

Data from recent studies thus indicates that periodontal disease affects platelets and blood coagulation, influences thrombus formation, and activates endothelial cells, all of which contribute to the onset of stroke and could potentially result in the types of neuropathology associated with cognitive impairment.

Genetics: Polymorphisms in the Interleukin 1 Gene Family

Inflammation is a lifesaving defense mechanism against bacterial and viral pathogens. However, if unchecked, it can become chronic and play a role in numerous pathologic processes, including periodontal disease and AD.[108,133] Genetic factors may predispose one to a high risk phenotype favoring chronic inflammation because of a hyper-responsive immune system.[154]

Investigations of the genetics of both AD and periodontal disease show polymorphisms (variations) in the interleukin 1 gene family associated with the disease. Human chromosome 2 (2q13) contains 3 IL-1 genes in a cluster.[155] Two encode the proteins IL-1A and IL-1B, which produce the proinflammatory mediators IL-1α and IL-1ß, respectively. The third gene encodes a protein that binds IL-1 receptor sites functioning as a receptor antagonist.[156]

Periodontal research suggests that specific polymorphisms in the IL-1 gene cluster constitute a risk factor for chronic periodontitis.[157] The risk appears to increase when a particular polymorphism is combined with smoking.[158-162] Studies show a significant association between the severity of adult periodontitis and specific IL-1 polymorphisms.[156,159] Individuals with this "periodontitis-associated genotype" exhibit significantly elevated levels of IL-IB in gingival crevicular fluid that remain high even after treatment.[163] In a related study by Poicut, an IL-1 polymorphism related to periodontal disease was found to correlate with a twofold to fourfold increase in IL-1ß production.[164] These studies offer explanations for individual differences in susceptibility to and variations in clinical expression of periodontitis demonstrated in previous studies.[165-167]

Genetic studies in AD have also identified risk alleles in the coding regions of IL-1α (IL-1α-889)[168-170] and IL-1ß (IL-1B-511) genes.[171] These genotypes are associated with overexpression of IL-1 in brain tissue, plaque formation, overgrowth of dystrophic neuritis, and elevated neuronal acetylcholinesterase.[172] Yucsoy and colleagues found a significant association between genetic variations in the IL-1 gene family and AD and suggested that such variations increased the risk for AD.[171] Other investigators studying Italian and American subjects demonstrated the IL-1α-889 allele may be a risk factor for sporadic AD.[173] Bosco and colleagues also showed that individuals with particular variations in the IL-1 gene cluster were at increased risk of developing AD (odds ratio 4.8).[174] The results of a meta analysis of all studies investigating potential association of IL-1 genes and AD showed a strong association in persons with early onset AD.[175] A related study by Grimaldi found a significant association between specific polymorphisms in the cluster, primarily in the gene encoding IL-1A, and AD onset before 65 years of age.[169] Nicol found that of 232 confirmed Alzheimer's cases, 12.9% possessed the IL-1A 2,2 genotype, while only 6.6% of the controls showed this variation.[175] A similar study demonstrated an IL-1A polymorphism known as allele 2 in 46% of individuals clinically diagnosed with AD compared with 34% in the control population.[168]

Genetic studies of both AD and periodontal disease therefore indicate a common theme of variants in the IL-1 gene family. Individuals with particular polymorphisms produce significantly elevated IL-1, which could promote increased inflammatory responses and a predisposition to diseases related to chronic inflammation. Further investigation of genetic factors underlying both AD and periodontal disease should provide insights into the pathogenesis of both processes.

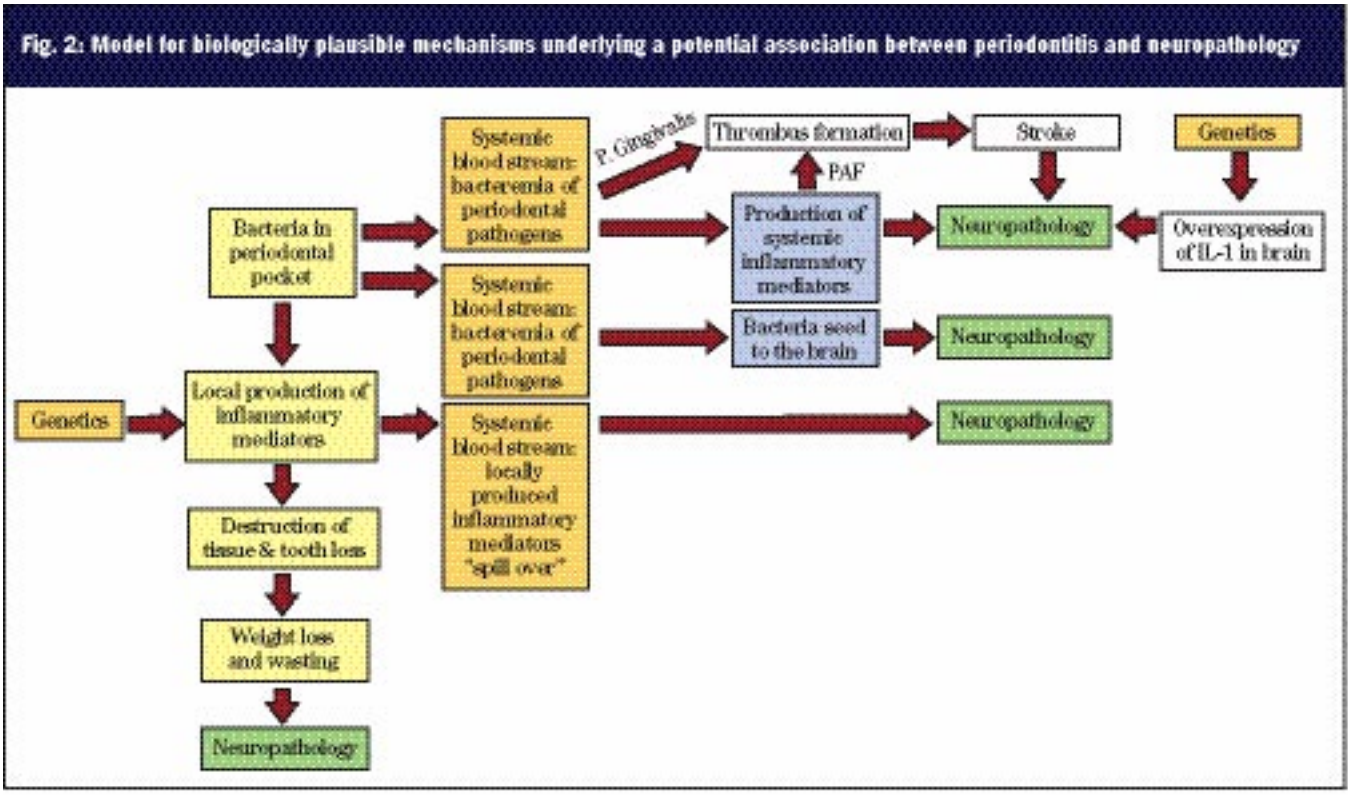
Weight Loss and Wasting Associated with Periodontal Disease May Contribute to Cognitive Decline

Periodontal disease contributes to general wasting of body tissues in two ways. First, it often results in tooth loss, which often leads to problems with chewing, swallowing and food selection.[10] Individuals also poorly absorb nutrients from food when it is not well masticated.[77] Evidence from several studies indicates a deterioration in nutritional status in individuals missing teeth.[177-179]

Current research suggests a connection between tooth loss and AD. In a recent twin study examining several potentially modifiable risk factors for dementia, tooth loss before the age of 35 was shown to be strongly associated with AD.[15] Data from a study by Kondo and colleagues also suggest tooth loss is an AD risk factor.[16] A six year prospective cohort study found subjects with fewer teeth at baseline showed a greater probability of developing mental impairment.[17]

To interpret these findings, it must be acknowledged that tooth loss could mark prior inflammation and that chronic exposure to inflammatory products may mediate an increased AD risk. However, in an animal study of the effect of extracted molar teeth, defects in cholinergic neurotransmission and impaired spatial memory were observed.[180] These observations suggest that something more than inflammation plays a role in this outcome, and a logical choice would be impaired chewing and the nutritional deficiencies that follow.

Periodontal disease also contributes to weight loss and wasting through the effects of bacterial products and proinflammatory mediators. Lipopolysaccharide found in the cell wall of gram-negative periodontal pathogens has



been shown to induce metabolic wasting.[108] Inflammatory cytokines associated with periodontal disease including IL-1 and TNF-α are implicated in weight loss and wasting in the elderly. TNF-α regulates cachectin, a cytokine responsible for inducing cachexia, a syndrome which includes anorexia, weight loss and protein wasting.[181] IL-1 has also been shown to induce significant anorexia.[182,183] In addition, IL-1 and TNF-α contribute to sarcopenia, or loss of muscle mass in the elderly,[183,184] and individuals with higher serum levels of TNF-α exhibit lower body cell mass and less appendicular skeletal muscle mass.[185] These findings are significant because declining body mass index is associated with cognitive decline and increased risk of AD.[186]

In summary, both tooth loss and inflammation related to periodontal disease may accelerate unintentional weight loss and muscle wasting, which in turn may accelerate neurodegeneration.

Conclusion

Recently much research has examined potential associations between oral and systemic diseases, but few studies have investigated a potential link between oral disease and AD or dementia. AD is a significant health problem that will likely become even greater as the population ages. It is established that AD contributes to deterioration in oral health.[10] Some studies suggest that oral disease contributes to AD or cognitive impairment.[15-17,71] However, data supporting a bi-directional association is limited, and it is currently unclear which occurs first, oral disease or AD. It is possible that the lines are blurred and that each disease contributes to the pathogenesis of the other.

Several biologically plausible mechanisms are proposed for a potential association between the two diseases and summarized in Figure 2. It should be noted, however, that because the etiology of AD is complex and multi-factorial, it is unlikely that any one mechanism is purely causal but instead may "tip the balance" in favor of dementia in an individual otherwise at risk.

It is important that research continue to investigate more fully what role oral disease plays in the pathogenesis of AD. Though costly and time consuming, large prospective randomized clinical studies and interventional studies are needed to clarify the interrelationship of these two diseases and should encourage design of more effective intervention strategies.[103] Although some risk factors are immutable for AD (family history and age), oral disease is one that can be prevented.

Whether poor oral health contributes to or is the product of dementia, the clinical implications are similar. Early preventive care must be established and a program put into place to maintain oral health.[187] For individuals with

AD, as cognitive and physical abilities decline, oral hygiene measures will likely suffer and dental visits become less frequent. This lack of care may result in a vicious cycle producing increased inflammation, exacerbating both periodontal disease and AD, and resulting in further decline of oral health measures.

We cannot tolerate that poor oral health is often accepted as a normal part of aging. There is adequate data to indicate that untreated oral disease leads to significant morbidity, mortality, and avoidable healthcare costs.[76] It is critical that relationships between elderly patients and their caregivers be established with dentists, dental hygienists, physicians, nursing staff and other care providers.[10] When everyone participating in the health care of a patient is convinced of the importance of maintaining oral health, more positive overall health outcomes will be achieved. Furthermore, those in charge of distribution of healthcare resources must be educated about the role oral disease plays in systemic diseases, in the hope that they will realize that the increased expense of oral health care is far less than the cost of ignoring it.

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