Periodontitis: a potential risk factor for Alzheimer's disease

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IN BRIEF

- Reviews available evidence of the potential association between periodontitis and Alzheimer's disease.
- Explains possible mechanisms for shared pathogenesis between periodontitis and Alzheimer's disease.
- Provides practical suggestions for future research to clarify the role of periodontitis as a risk factor for Alzheimer's disease.

GENERAL

The role of periodontitis as a risk factor for multiple systemic diseases is widely accepted and there is growing evidence of an association between periodontitis and sporadic late onset Alzheimer's disease (SLOAD). Recent epidemiologic, microbiologic and inflammatory findings strengthen this association, indicating that periodontal pathogens are possible contributors to neural inflammation and SLOAD. The aim of this article is to present contemporary evidence of this association.

INTRODUCTION

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ALZHEIMER'S DISEASE

Dementia describes a set of symptoms which includes memory loss, mood changes, problems communicating and difficulty reasoning.[1] Dementia is defined as a reduction in intellectual ability when compared to previous aptitude, which results in impaired function during ordinary daily activities despite unimpaired consciousness.[2]

Alzheimer's disease (AD) is an irreversible progressive neurodegenerative condition and the most common cause of dementia. It is difficult to assess the prevalence of AD due to differing diagnostic criteria, the absence of specific biological markers and the requirement for post-mortem autopsy to establish a definitive diagnosis.[2] However, in 2010 it was estimated that more than 35 million people worldwide were living with AD,[3] and in 2013 it was reported that around 496,000 people in the UK were affected.[1] AD is not necessarily an outcome of aging,[4] but its incidence approximately doubles every 5 years from the age of 65 years,[5] the odds of receiving a diagnosis of AD over 85 years of age exceed 1:3.[3] As the aging population increases the number of people living with AD is set to rise considerably.

Pathogenesis of Alzheimer's disease

AD is characterised by neuronal loss and the presence of senile plaques, which contain β-amyloid (Aβ) protein and neurofibrillary tangles of hyper-phosphorylated tau protein.[6] However, it has been shown that plaque accumulation does not correlate with loss of cognitive function,[7] by contrast soluble toxic forms of Aβ and tau are thought to contribute to the disruption of synaptic function and neurodegeneration.[8,9] Chronic inflammation is also characteristic of AD brains and inflammatory related proteins have been shown to be involved in the generation of Aβ and tangle formation.[10]

SLOAD is the most common form of AD, accounting for approximately 98% of all cases.[11] SLOAD has a complex multifactorial aetiology and a polymorphism of the apolipoprotein E4 allele (APOE-ε4) has been found to be a major risk factor,[12] this gene encourages Aβ to be deposited in the brain.[13] Although APOE-ε4 is thought to be the strongest genetic risk factor for SLOAD,[13] it is only one of 20 loci known to increase the hosts susceptibility to AD.[14] A number of polymorphisms in the genes associated with interleulin-1 (IL-1)[15–19] and tumour necrosis factor alpha (TNF-α) are believed to alter host susceptibility.[15,20–23]

A number of potentially modifiable risk factors are also thought to have a cumulative detrimental effect on the brain throughout life. These risk factors include infective agents, host immune response, cerebrovascular disease,[24] low cognitive reserve (that is, intelligence, occupation and education),[25] low physical activity levels,[26] alcohol intake,[27] early life deprivants, tooth loss,[24] age,[28] head injury,[29] and female gender.[30] Current evidence for individual modifiable risk factors for AD is at best moderate and at worst inconclusive and misleading.[31]

PERIODONTAL DISEASE

Periodontitis is a progressive destructive condition which affects the gingivae, periodontal ligament and alveolar bone due to chronic multifactorial inflammatory changes in the periodontal tissues as a result of the host response to periodontal pathogens.[32] More than 400 bacterial and viral species have been found to colonise the periodontal pocket.[33] The most virulent bacterial communities tend to contain Gram-negative bacteria capable of tissue invasion. They include *Aggregatibacter actinomycetemcomitans*, *Tanerella forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*.[34,35] Host response to periodontal pathogens can be affected by gene polymorphisms, particularly those that code for IL-1 and TNF-α.[23,36–38] Furthermore, the host response is known to be affected by many lifestyle factors, for example tobacco smoking and stress, which are similarly associated with increased risk of SLOAD.[39] Nutrition and other lifestyle factors are believed to affect gene expression.[23]

In the UK the prevalence of severe periodontitis appears to have increased between 1998 and 2009.[40] UK and US epidemiologic

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studies indicate that periodontitis affects large numbers of the population and, similar to AD prevalence increases as the population ages.[40,41] Over 38% of US adults aged 30 and over had either moderate or severe periodontitis, however, for adults aged 65 and over this figure increased to 64%.[41]

Periodontitis is a common source of chronic systemic infection.[42–44] The non-keratinised periodontal pocket and junctional epithelium, particularly when ulcerated, can act as an entry portal for bacteria and their endotoxins to enter the systemic circulation.[43,45–47] Presence of such bacteria in the circulatory system causes systemic immunomodulatory effects, which form part of the host response to periodontal pathogens.[41,48,49] In addition to local intraoral effects periodontal disease has a potentially negative impact on general health due to associations with other chronic inflammatory diseases, such as atherosclerotic cardiovascular disease (AVCD),[50–54] diabetes[55] and cognitive decline.[56] Periodontal disease is recognised as a significant public health concern.[57]

The pathogenesis of periodontitis, ACVD, diabetes and cognitive decline is not fully understood. However, there is an emerging awareness of co-dependant risk and pathogenesis for these diseases and positive correlation between attaining periodontal stability and diabetic control has recently been recognised.[55] Inflammatory and immune responses to infection are thought to provide a connection between these diseases at a fundamental level,[58] indeed, ACVD and diabetes as well as periodontitis are recognised risk factors for SLOAD.[59]

EPIDEMIOLOGICAL EVIDENCE OF AN ASSOCIATION BETWEEN ALZHEIMER'S DISEASE AND PERIODONTAL DISEASE

Oral hygiene is significantly compromised in patients affected by AD because the cognitive processes of learning, attention and memory are progressively damaged. As the neurologic degeneration of AD progresses, daily activities are disrupted by temporal and spatial disorientation and reduced motor skills.[2] Poor oral hygiene and dental morbidity have been correlated with the presence and increased severity of AD.[60–64] The resultant halitosis, discomfort and bleeding when brushing can hinder carer assistance with oral hygiene and result in lower self-esteem and quality of life in those affected.[60] This negative cycle leads to increased periodontal destruction; which has in the past been attributed to poor plaque control. It is also possible that the long-term inflammatory burden on the systemic circulation causes neural degeneration.[65]

The possibility of periodontitis in early and mid-life acting as a precursor to dementia in later life is increasingly being recognised.[51] In such cases the symptoms of dementia were not present in early and mid-life, so dementia impaired oral hygiene would be an unlikely causative factor for the periodontitis observed. Longitudinal data measuring periodontal status, inflammatory markers and cognitive status would be useful,[51] however, such data are in short supply. Many previous studies that have associated periodontitis with AD have not measured periodontal indices or used clinical diagnoses as a measure of the presence and severity of periodontitis as one might expect, instead many relate AD to tooth loss.[24,66–71] While it is likely that some tooth loss is due to periodontitis there are numerous other potential causes of tooth loss, thus an association between periodontitis and AD cannot be reasonably concluded from such studies. For example, patients who have fewer educational experiences and lower cognitive levels are more likely to have extractions[66,72] and also more likely to develop the signs and symptoms of AD.[73] Nevertheless, periodontitis is a potential cause of tooth loss and many studies have associated AD in late-life with tooth loss in early and mid-life.[24,66–71]

Some studies that provide more robust evidence for a causal link between periodontitis and AD have been published. In a longitudinal cohort study, which followed 152 subjects for 20 years, from 50 to 70 years of age, it was found that, for those subjects with less than 10 missing teeth, greater levels of periodontal inflammation correlated with lower cognitive levels.[60] In another longitudinal aging cohort study of 144 nuns in Milwaukee it was demonstrated that over time those with APOE-ε4 and fewer teeth had more rapid rates of cognitive decline than those with neither or either of these risk factors.[71] Moreover, the Veterans Affairs longitudinal cohort study, which followed 597 community dwelling men for 32 years, found that tooth loss, periodontal pockets and progression of alveolar bone loss were associated with impaired cognition particularly in those over 45 years.[74] Further analyses of the third US national health and nutrition survey which included 2,355 people aged 60 years and over, showed associations between periodontitis and cognitive impairment, and between measures of immunoglobulin to the common periodontal pathogen *Porphyromonas gingivalis* and cognitive test performance.[75] Another epidemiologic study, which included a cohort of 5,138 people aged between 20 and 59 years, revealed that after education and adjustment for other confounding variables, gingival bleeding and loss of periodontal attachment were significantly associated with cognitive impairment.[76]

While epidemiologic evidence suggests periodontal disease may be a risk factor for SLOAD, both chronic periodontitis and SLOAD are multifactorial conditions which share many of the same lifestyle risk factors for example, tobacco smoking and previous education.[40,41,59] Thus, an epidemiologic association between tooth loss/periodontal disease and cognitive impairment does not indicate causation.

PLAUSIBILITY OF A POTENTIAL CAUSAL RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND ALZHEIMER'S DISEASE: MICROBIAL FACTORS

Bacteraemia of oral origin has been recognised since the 1970s.[46,47] It has been speculated that the proliferation and dilation of the periodontal vasculature and ulceration of the periodontal epithelium, seen in chronic periodontitis, provide a larger surface area for the entry of microorganisms into the blood stream compared to healthy gingival tissue.[45] Although this has not been proven beyond doubt, a recent systematic review and meta-analysis determined that plaque accumulation and gingival inflammation significantly increase the prevalence of bacteraemia following tooth brushing.[43] Gingival inflammation has also been significantly associated with the incidence of bacteraemia following scaling and root planning.[44] Thus patients with periodontitis may have a higher risk of developing systemic diseases of oral origin.[77]

The viability of a number of periodontal pathogens in atherosclerotic plaques has recently been recognised,[78,79] and adds credence to the possibility that oral bacteria can reach the brain via the systemic circulation. *Porphyromonas gingivalis*[79,80] and *Treponema denticola*[79,81] have both been implicated in aortic inflammation and atherosclerotic plaque formation with viable bacteria being isolated from both oral and atherosclerotic plaques in animal models. Thus, such pathogens have the potential to linger in the systemic circulation and prolong what was previously thought to be a transient bacteraemia.

It has been speculated that the permeability of the blood-brain barrier increases with age and precedes the development of AD. This has been demonstrated in animal models, where mice that were genetically modified with a mutation in the amyloid precursor protein gene, associated with early onset Alzheimer's disease (EOAD) in humans, were shown to have increased permeability

of the blood-brain barrier and increased formation of senile plaques when compared to control mice.[82] The effects became more apparent as the mice aged.

It has also been hypothesised that periodontal pathogens may enter the brain via the peripheral nerve pathways,[83] this being a potential route for the transfer of viruses, particularly herpes viruses. The identification of oral *Treponema* in the trigeminal ganglia also supports the neural route.[84] In addition it has been reported by a number of authors that peripheral infections and inflammatory markers can access the brain.[85–87] Furthermore, the circum-ventricular organs are not protected by the blood-brain barrier,[88] and thus could potentially act as an entry portal for bacteria to reach other parts of the brain.[65]

Microorganisms have been isolated more frequently from the brains of AD specimens than age-matched non-AD specimen's post-mortem. *Chlamydophila pneumoniae*[89,90] and the spirochetes *Treponema denticola*[84] and *Borrelia burgdorferi*[91] have all been isolated from AD brain specimens post-mortem, but not always from areas of AD neurodegeneration. Furthermore, *Chlamydia pneumonia* has been shown to cross the blood-brain barrier in an *in vitro* model[92] and to be capable of inducing amyloid plaque formation in an animal model.[93] More recently, lipopolysaccharide from *Porphyromonas gingivalis* has been shown capable of crossing the blood-brain-barrier in AD brain samples but not in non-AD control brain samples post-mortem.[94] A seminal article which assessed the available evidence for an association between spirochetes in the brain and Alzheimer's disease against Koch's and Hill's postulates found a causal relationship was probable.[73] Some of the spirochetes involved were known periodontal pathogens, such as *Treponema denticola*, *Treponema socranskii*, *Treponema pectinovorum* and other oral *Treponema*.

Herpes simplex virus and cytomegalovirus have been isolated from periodontal pockets[95,96] and have also been detected in the brain tissue of older adults with and without AD.[97,98] It has been suggested that latent viruses may be reactivated by immunosuppression, stress or inflammation in the brain and that the APOE-ε4 allele may also affect the reactivation and/or degree of damage caused by viruses within the brain.[99] Indeed the APOE-ε4 allele is likely to make the host more susceptible to a number of environmental risk factors for AD.

INFLAMMATORY MECHANISMS LINKING PERIODONTAL DISEASE AND ALZHEIMER'S DISEASE

Fundamental to the inflammatory hypothesis of AD is inflammation in the brain, which once begun continues and causes neurodegeneration.[100] This is believed to occur due to microbial stimulation of the immune response, which causes glial cells to release the Aβ and hyperphosphorylated tau proteins, found in senile plaques and neurofibrillary tangles, in a positively perpetuating cycle.[83] Chronic inflammation is not thought to be the primary cause of AD, rather a secondary phenomenon. However, reducing cerebral inflammation may slow the progress and delay the onset of AD.[101] Chronic periodontitis has been shown to result in sustained and increased levels of inflammatory products in the circulation.[102] Individuals vary in their susceptibility to infection, partly due to the components within the biofilm and partly due to their particular genotype.[51] A hyper-inflammatory phenotype has been associated with periodontitis,[103,104] that causes some individuals to have exaggerated inflammatory responses to pathogens.

Inflammatory biomarkers include cytokines (intercellular signalling molecules that have an immuno-modulatory effect) such as IL-1, interleukin 6 and TNF-α, as well as acute phase proteins including C-reactive protein. Inflammatory cytokines produced by the periodontal tissues during periodontitis can enter into the blood stream,[105–107] and have been implicated both in periodontitis[23,51,102,108–111] and in the neurological changes of AD.[23,51,112–122] It could be that AD and periodontitis share the same or similar hyper-inflammatory phenotypes, that when activated by certain environmental factors have a detrimental effect on host periodontal and neural tissue.

It remains uncertain whether systemic inflammation precedes AD, so it is also possible that the peripheral inflammatory response, mounted against periodontal pathogens or the pathogens themselves could induce or increase neural inflammation and thus contribute to AD onset and progression. Regardless of the cause, systemic inflammation has been shown to predict dementia.[51,116,118]

Aβ aggregation, central to the amyloid cascade hypothesis of AD, has been shown to be modulated in response to a number of environmental stressors, to act as ligand for a number of receptors and molecules which have been transported across the blood-brain barrier and to induce a number of pro-inflammatory activities. Aβ has been shown to be active against eight clinically relevant microorganisms *in vitro*.[123] It was proposed, therefore, that Aβ is an antimicrobial peptide acting as an effector molecule of innate immunity. The same study found that temporal lobe samples from the AD brains contained significantly higher antimicrobial activity than the brains of age-matched, non-AD subjects.

Stimulation of the innate immune system by persistent sub-acute infection of the brain with bacteria or viruses may trigger an amyloid cascade leading to Aβ generation and deposition.[123] Genetic factors could also influence Aβ production and clearance. While the genes associated with EOAD are believed to cause Aβ accumulation without a trigger from the innate immune system,[124] individuals with APOE-ε4 gene associated with SLOAD may be more susceptible to cerebral infection.[125] Transient cerebral infection or non-infective insult to the brain may lead to a persistent self-perpetuating innate immune response; this could be the result of traumatic brain injury,[126] stroke,[127] or gaseous anaesthetic agents.[128]

REQUIREMENT FOR FUTURE CLINICAL INTERVENTION STUDIES

Predictions of a global AD epidemic estimate that the prevalence is set to quadruple from 2006 to 2050.[129] Without a cure for AD and in the face of an epidemic the cost of dementia to the global economy is set to rise significantly from the 2010 estimate of £604 billion.[130] It has been estimated that the annual cost for institutionalised dementia care in the UK will rise from £5.1 million in 2002 to £16.7 million in 2031.[131] According to expert consensus opinion the disabling effects of dementia are surpassed only by terminal cancer and spinal cord injury,[132] and place a vast physical, psychological and economic strain on those affected and their carers, friends and family.[133]

While available drug treatments for AD, that is cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, can provide symptomatic benefits they do not alter the progressive neuro-degeneration or end-stage outcome of AD.[134,135] In 2010 an independent expert consensus report concluded that recommendations for the prevention of AD and cognitive decline could not be made due to a lack of robust evidence.[31] This highlights the need for further research into potential modifiable risk factors for AD including periodontitis.

Periodontal therapy has been shown to reduce peripheral infection and the systemic inflammatory biomarkers for periodontitis and AD.[136,137] Further research is required to determine whether reducing the systemic bacterial and inflammatory load through effective periodontal therapy may delay the onset and progression of Alzheimer's disease.

If effective periodontal therapy could delay the onset and progression of AD by one year it has been predicted that there could be almost

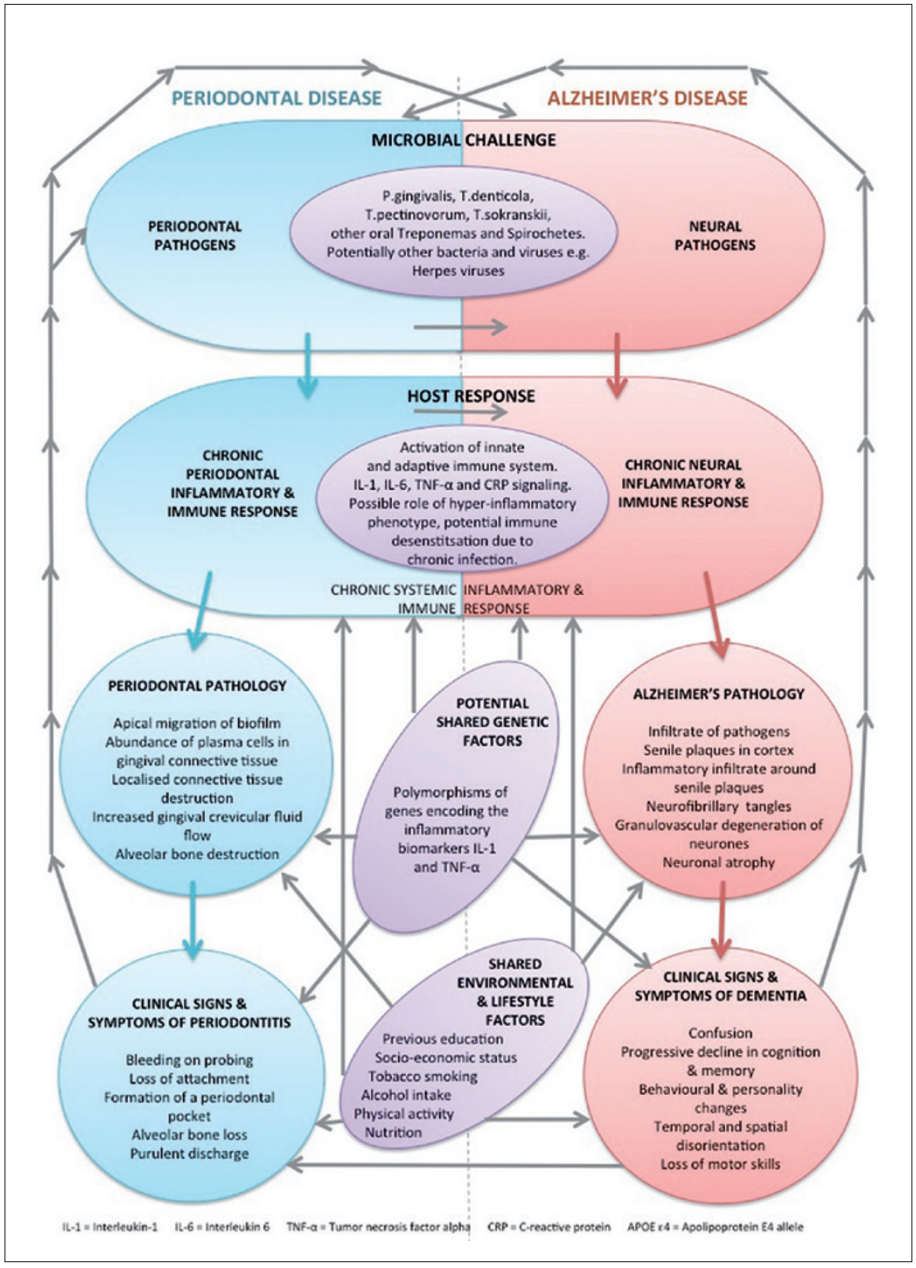

Fig. 1 Shared features for periodontitis and Alzheimer's disease pathogenesis

9.2 million fewer cases of AD by 2050, with much of the decline ascribed to those who require the most costly care.[129] Such an effect would also be likely to improve patients and their carers' quality of life.

POTENTIAL FURTHER RESEARCH

As it remains to be determined whether periodontitis is a risk factor for Alzheimer's disease and whether effective treatment of periodontitis will delay the onset and progression of SLOAD further research studies are indicated, these include:

- Longitudinal epidemiologic cohort studies that follow a population and measure their periodontal and cognitive status from middle to old age to confirm a correlation
- Post-mortem analysis to compare levels of periodontal pathogens in brain tissue from patients with AD and healthy controls. Identification of new periodontal pathogens not yet associated with Alzheimer's disease and determination of their micro-anatomical association to the histopathological hallmarks of AD
- *In vitro* or mammalian model studies to determine how periodontal pathogens enter the brain, their ability to form biofilms in the brain once there and the mechanisms by which they and the immune & inflammatory response could induce the pathological changes associated with AD
- Studies to determine whether the genetic polymorphisms associated with SLOAD are associated with periodontitis and vice versa
- Pilot clinical and quality of life studies to determine whether it is feasible to effectively treat periodontal disease in those who suffer from AD
- Clinical trials to measure the impact of periodontal treatment on inflammatory biomarkers, presentation, progression and quality of life of those who suffer from AD.

Such research will be particularly challenging due to the multifactorial aetiology and chronic nature of periodontitis and AD. The specific needs and disabilities of those who suffer from AD will also pose unique challenges. To validate findings research will require collaboration between experts from scientific, medical and dental disciplines, independent and multi-centre investigations, adequate funding support and large sample sizes for clinical intervention trials with careful statistical analysis to determine the effects of potential confounding variables. It is therefore likely that progress in this field will be gradual.

CONCLUSION

Current literature suggests an association and shared pathogenesis between periodontitis and AD, which has been summarised in Figure 1. The mechanisms of this association are not fully understood. Therefore, further research is required to prove and determine the raison d'être for this association. Several potentially coexistent theories are proposed:

- The direct invasion of periodontal pathogens and/or their virulence factors into brain tissue is implicated in the pathogenesis of AD
- Chronic exposure to periodontal pathogens and their endotoxins result in modification of the systemic inflammatory mediators, which are implicated in the pathogenesis of AD
- Periodontitis and AD may share a common underling cause due to expression of underlying hyper-inflammatory phenotypes
- The effects of periodontal pathogens on the systemic circulation are implicated in the formation of atherosclerotic plaques and therefore, AD is an outcome of inflammatory changes to vessel walls and reduced blood flow to the brain
- AD and periodontitis share risk factors and similar, but non-contributory, inflammatory pathogeneses
- The effects of AD have a negative effect on plaque control, which has a detrimental effect on periodontal heath.

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