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Poor Oral Health as a Chronic, Potentially Modifiable Dementia Risk Factor: Review of the Literature

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Abstract

Poor oral health, including caries, tooth loss, and periodontitis are ubiquitous worldwide, and are potentially treatable and preventable. Like adverse oral health conditions, Alzheimer disease and related disorders are also very common among aging populations. Established risk factors for Alzheimer disease include cerebrovascular disease and its vascular risk factors, many of which share associations with evidence of systemic inflammation also identified in periodontitis and other poor oral health states. In this review, we present epidemiologic evidence of links between poor oral health and both prevalent and incident cognitive impairment, as well as review plausible mechanisms linking these conditions including evidence from compelling animal models. Considering that a large etiologic fraction of dementia remains unexplained, these studies argue for further multidisciplinary research between oral health conditions including translational, epidemiologic, and possibly clinical treatment studies.

Keywords

Periodontitis; Periodontal disease; Tooth loss; Oral health; Caries; Dentures; Alzheimer disease; Cerebrovascular disease; Vascular dementia; Dementia; Epidemiology

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Compliance with Ethics Guidelines

Conflict of Interest

James M. Noble has received honoraria from Barclays for a single consulting event regarding IVIg as an AD therapeutic (trial has since been reported as failure).

Nikolaos Scarmeas declares that he has no conflict of interest.

Panos N. Papapanou declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

INTRODUCTION

Dementia is a common disorder among the elderly that becomes more prevalent with advancing age. It is typically medically refractory, reduces life expectancy, and diminishes quality of life for patients and their caregivers. Clinical Alzheimer Disease (AD) is the most common type of dementia, representing 60–70% of all cases. The prevalence increases with age from 5% in the seventh decade to 50% by the tenth decade of life[1, 2]. In the US alone, an estimated 5.1 million had AD in 2010 and this number is expected to increase to 13.2 million by 2050 [3]. Sporadic, late onset AD (LOAD) represents 98% of all AD cases and is likely due to a complex interaction of environmental, vascular, and genetic risk factors[4, 5]. However, the population attributable risk (PAR) associated with each of the vascular or environmental risk factors for AD does not exceed 15%, and approximately half of the risk for AD remains unexplained[6]. Thus, a search for additional, potentially causal risk factors is warranted.

Cognition and dental health may be related in several ways: A compelling and rather straight-forward argument can be made for cognitive impairment leading to poor dental health. That is, persons with impaired cognition may be expected to be inattentive to oral hygiene or may have restricted access to routine oral care as cognitive disease progresses,[7] and thus have worse dental health. Conversely, worth considering is whether poor oral health could instead be an antecedent condition, possibly contributing to subsequent cognitive impairment as a causal exposure, rather than as an outcome. Irrespective on the directionality of the association, here we briefly review the literature associating poor dental health and stroke, as it has been more fully reviewed elsewhere. Our focus is on the relationship between poor dental health and cognitive impairment, dementia, and Alzheimer disease, particularly emphasizing periodontal disease given its associations with systemic health.

EPIDEMIOLOGY OF POOR ORAL HEALTH AND PERIODONTAL DISEASE

Poor oral health, including periodontitis, caries, edentulism, and infrequent preventive care, become more prevalent among older people[8, 9].Edentulism is a global health problem in the elderly with prevalence as high as 78% in some European countries; persons with low socioeconomic status are disproportionately affected[10, 11]. Caries and periodontitis are thought to be two predominant causes of tooth loss, often co-occurring within individuals, and share several risk factors including poor oral hygiene, low socioeconomic status, and inattention to care. However, of these oral health states, periodontitis is more common among adults and progresses with age.[12, 13]

Worldwide estimates in the prevalence of periodontitis vary, partly because of substantial heterogeneity in definitions of the disease[14]. Clinical and serological markers of disease indicate that moderate to severe periodontitis may be prevalent in more than 50% of US adults.[15, 16] Exposure to established periodontal pathogens appears to begin as early as at 2 years of age, with a large proportion of the population exposed by adolescence[17], often by vertical and horizontal transmission patterns among family members.[18] While clinical

markers of periodontitis may vary with time or treatment, periodontal serum IgG levels typically remain stable.[19]

POOR DENTAL HEALTH AND CEREBROVASCULAR DISEASE

Prior to first explorations relating dental health to frank cognitive impairment, a number of studies explored the relationship between history of periodontal disease and incident stroke, [20, 21] with associations identified as ranging from no adverse risk to more than double. Epidemiological evidence supports an association between the level of serum antibodies to periodontal pathogens and stroke [22–24] and accelerated aortic atherogenesis,[25] while high levels of colonization by specific periodontal pathogens has been associated with increased carotid artery intimal-medial thickness.[26] To date, no treatment trials addressing mitigation of periodontal disease and incident stroke have been performed.

Many of the risk factors associated with cerebrovascular disease are also associated with dementia. For example, vascular risk factors[27, 28] including diabetes mellitus,[28–33] dyslipidemia,[34] hypertension,[35] atrial fibrillation,[36] smoking,[28, 37–39] hyperhomocysteinemia,[40] and obesity[41–45] have been associated with the development of dementia, including AD. Up to 33% of dementia patients with AD pathology have concomitant stroke[46] and patients may be more likely to become demented when both AD pathology and cerebrovascular disease are present[47, 48].

POOR DENTAL HEALTH AND COGNITIVE IMPAIRMENT

Poor oral hygiene

Inattention to oral health care may be a precursor to many oral health diseases and could be a longstanding habituation among individuals, or alternatively could change in advancing age for various reasons including impaired physical movements, with or without cognitive impairment being implicated. In a subgroup of the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (Gems), drawn from a population of those aged 75 years and above in eastern Finland, AD was associated with both poor oral hygiene (OR=12.2 [1.9–77.0]) and poor denture hygiene (OR=2.9 [1.1–7.8]).[49] In the Aichi Gerontological Evaluation Study (AGES) Project, among older Japanese aged 65 years and above, those without regular dental visits were more likely to have incident dementia (HR=1.44 [1.04–2.01]).[50] Exploratory analyses within a small clinical trial examining the effect of dental care on incident pneumonia in a group of elderly nursing home residents demonstrated a 1.5 point significantly slower decline in Folstein Mini Mental Status Exam score after 2 years in oral care recipients[51]. However, from this study one cannot determine whether the effect specifically related to the dental hygiene intervention, or was instead simply related to greater frequency of attention to general health needs in the intervention subjects.

Caries

Caries is the most common cause of tooth loss in younger patients and thought to be caused by acid-producing oral microbiota, in individuals with poor oral hygiene and frequent intake sugar-rich diet the context of chronic poor attention to dental hygiene.[52, 53] In contrast to periodontitis, however, caries is not typically thought to cause a systemic host inflammatory

response. Several case-control studies have identified caries in older adults and cross-sectional associations with impaired cognition; [54, 55] these findings have been corroborated in larger community based cohorts. In the Gems cohort, caries was associated with Alzheimer disease (RR=2.8 [1.8–4.5] as well as non-AD dementia (RR=3.4 [1.9–6.4]);[49] another Finnish cohort of older adults identified similar patterns of increased caries rates being associated with cognitive impairment.[56] A case-control study of elderly Australians found that dementia patients were more likely to have declining oral health including worsening caries when followed longitudinally.[57]

Tooth loss

Tooth loss reflects the end stage of a several oral diseases, alone or in combination, including caries, periodontal disease, and endodontic infections. Thus, tooth loss is a marker of cumulative morbidity of pathologic oral inflammatory conditions including periodontitis, and has been associated with prevalent cognitive impairment in several cross-sectional studies. In the Health Survey for England 2000, an association between edentulism and cognitive impairment among population aged 65 years and older was strong (OR=2.61 [1.49–4.28]), although it was primarily driven by community based subjects, as no relationship was identified among those residing in nursing homes.[58] The Study of Health in Pomerania in northeast Germany suggested that women may be at greater risk for having tooth loss associated with prevalent cognitive impairment.[59] Several studies drawn from Asian populations have found similar associations between tooth loss and prevalent cognitive impairment, including a small Japanese case-control study of late-life tooth loss.[60] In the Fujiwara-kyo study, a large community-based study of persons aged 65 years and older, those with the fewest teeth had the highest risk of cognitive impairment (OR=1.71 [1.05–2.78]); in addition, there was a significant trend for fewer teeth predicting cognitive impairment.[61] However, other cross-sectional studies exploring dental health and cognition have either failed to identify edentulism as a risk for dementia[49] or found only a weak association with cognitive impairment.[62]

Several studies have identified tooth loss as a risk for incident cognitive impairment. In the VA Dental Longitudinal Study, community-dwelling men with tooth loss were more likely to have impaired cognitive test performance, with those over the age of 45 being more significantly affected.[63] In the HARMONY Swedish twin registry, dementia was associated with mid-life tooth loss (OR=1.49 [1.14–1.95]).[64] In the United States, in the Religious Orders Study, fewer teeth in adulthood were significantly associated with incident dementia (HR 2.2 (1.1–4.5).[65] APOE-£4 appeared to be a significant effect modifier in this relationship, with impaired memory developing at a younger age among APOE-ε4 carriers, particularly those with fewer teeth in adulthood.[66]

Impaired chewing ability and dentures

Patients with tooth loss, even when given dentures, have inadequate chewing capacity (low masticatory efficiency); a reported maximum load on natural teeth during chewing is 8 to 15 kilograms [67] while a typical load by sustained dentures is less than 2 kilograms.[68] In the Swedish Panel Study of Living Conditions of the Oldest Old people (SWEOLD), a national sample of elders aged 77 and above, those with impaired chewing ability were more likely to

be cognitively impaired (OR=1.72 [1.05–2.80]).[69] In a prospective study of community dwelling elderly residents in Kwangju, South Korea, those persons with tooth loss and no dentures were most likely to develop dementia (OR=1.61, [1.02–2.49])[70] and this was additionally corroborated in AGES (HR=1.85, [1.04–3.31]).[50]

Persons with low masticatory efficiency may have to adapt to eat diets low in fiber and essential micronutrients,[71] and high in saturated fats and cholesterol, possibly due to ease of chewing these foods relative to fiber-rich foods.[72] Such dietary changes, adaptive to low masticatory efficiency, could potentially increase the risk for stroke and dementia by making difficult adherence to diets thought to be protective against AD such as the "Mediterranean diet" [73, 74]. However, dietary habits may instead be confounded by lifelong influences of taste, economics, social norms, or unhealthy lifestyle decisions associated with tooth loss. [75, 76] Micronutrient deficiencies, such as vitamin B12 and thiamine deficiency, may also develop as a result of edentulism [77] and may contribute to cognitive impairment (Fig 1).

Periodontitis

Periodontitis is a chronic oral biofilm-mediated infection[78, 79] that is strongly associated with tooth loss in adults. Several studies have associated periodontitis with prevalent and incident cognitive impairment. In the VA Dental Longitudinal Study, for each tooth lost, pocket depth progression and alveolar bone loss progression were additionally associated with impaired cognitive test performance, with the strongest associations observed in individuals over 45 years of age.[63] We identified a cross-sectional association between a serological marker of a common periodontitis pathogen *(Porphyromonas gingivalis)* and poor cognitive test performance among patients aged >60 years in NHANES-III.[80] Our group additionally identified serum antibodies to several periodontal pathogens were associated with incident AD in a complex relationship including adverse or protective risk, depending upon the pathogen studied.[81] Serum antibodies to several other periodontal organisms have been identified as potential risk markers for AD and mild cognitive impairment.[82] In an age-matched case-control study of AD patients and healthy elders, serum levels of TNF-alpha and IgG antibodies to periodontal bacteria discriminated between the two groups at the time of cognitive diagnosis.[83]

Pathophysiologic links between periodontitis and cognitive impairment—From a neuropathological standpoint, AD is a progressive neurodegenerative process initially related to accumulation of excess brain amyloid-beta (Aβ) protein and subsequent tau deposition[84]. Amyloid metabolism is complex and is influenced by local and systemic host inflammatory mediators. These include interactions between advanced glycation end products (AGEs) and their receptor RAGE that affect transduction of extra-cellular Aβ and influx of vascular Aβ, leading to increased intracellular Aβ[84].

Periodontitis is currently considered to impact overall health via complex mechanisms mediated through a state of enhanced systemic inflammation[21]. Periodontitis is associated with both a local[85] and a systemic inflammatory response characterized by elevation in multiple serum cytokines including interleukin-1 (IL-1),[86] IL-6,[87, 88] C-reactive protein (CRP),[87, 89] and TNF-alpha[90–92] and generation of serum antibodies to common periodontal

organisms[15, 93]. Several hundred periodontal pathogens have been implicated in causing periodontal disease,[94] although only a small fraction of these hundreds of pathogens are cultivable and have been demonstrably associated with establishing a progressively pathogenic milieu at the biofilm interface.[78] Gingival tissues of patients with periodontitis express high levels of AGEs and RAGE[95], and AGE-RAGE interactions are one of the key mechanisms underlying the observed accelerated periodontal tissue breakdown in patients with diabetes[96]. Importantly, treatment of periodontitis has been associated with significant reduction in serum levels of IL-6[87], IL-6 soluble receptor[97] and CRP[98], and a substantial improvement in vascular endothelial function[97, 99–101]. Thus, although several specific periodontal pathogens have been specifically studied in the relationship between periodontitis and stroke or cognitive impairment, it is more likely that downstream systemic inflammatory responses affect this relationship, rather than individual pathogens.

In addition to stroke, periodontitis has been associated with risk factors for cardiovascular disease[25, 102–105] and diabetes.[106–108] Risk factors for stroke and dementia, including diabetes,[109, 110] obesity,[111] and smoking[112] have a similar systemic inflammatory profile to periodontitis,[112, 113] suggesting that inflammatory markers may contribute to a final common pathway of impaired cognition, perhaps mediated through a cascade of atherogenesis[114, 115] related to systemic inflammation.[113] Interestingly, high levels of CRP have also been reported to act as an effect modifier of the association between carriage of the APOE e4 allele and memory impairment in patients without dementia.[116]

ANIMAL MODELS RELATING POOR ORAL HEALTH AND COGNITIVE IMPAIRMENT

As detailed above, numerous human epidemiologic studies have identified both cross sectional and longitudinal relationships between poor oral health and cognitive impairment. Although these reports can perhaps validate hypotheses of associations, one must turn to other studies, such as animal, biochemical, and pathologic models to begin to understand possible causal links. Moreover, given overlapping adverse oral health conditions, animal models may provide an opportunity to determine which adverse oral health condition may be most specifically associated with cognitive impairment, as well as identify possible treatment paradigms.

To date, several animal models have started to explore these associations in both experimental tooth loss and periodontitis. Young rats made surgically edentulous and fed nutritionally identical powder, rather than pelletized foods, were significantly more likely than dentate rats to have poor spatial memory and decreased stimulated acetylcholine release in the parietal cortex,[117] the mechanisms for this relationship were unclear but proposed to relate to decreased mastication-induced sensory stimulation leading to degeneration of secondary neurons in the spatial pathway of the alveolar and trigeminal nerves,[118, 119] and through downstream cortical-brainstem circuits, contribute to diminished cortical cholinergic function. A subsequent rat model which found similar clinical findings validated some elements of this earlier model, through identification of hippocampal neuronal loss and

decreased trkB-mRNA expression suggesting decreased hippocampal synaptic transmission.[120]

Subsequent amyloidogenic mouse models have suggested experimental edentulism induces hippocampal neural cell loss,[121, 122] alters astroglial behavior in the hippocampus, [121, 123] and changes hippocampal gene expression.[124] Experimental tooth loss in another mouse model over-expressing amyloid precursor protein has been associated with decreased numbers of pyramidal cells in CA1 and CA3 hippocampal subregions, but without significant associated changes in histopathologic or soluble amyloid.[125] More recently, an amyloidogenic mouse model with experimental *P. gingivalis* periodontitis (non-edentulous mice) developed impaired memory and significantly increased hippocampus and whole brain amyloid plaque loads, as well as elevated brain IL-1β and TNF-α;[126] peripheral measures of systemic inflammation or periodontal antibodies were not measured. Taken together, these models shed light on plausible causal links between poor oral health dementia, including the possibility of different causal pathways between tooth loss and periodontitis and cognitive impairment.

CONCLUSIONS

Poor oral health, including tooth loss, caries, and periodontal disease, may be an unrecognized risk factor contributing to the development of cognitive impairment through dietary changes, malnutrition, and a systemic inflammatory response associated with increased risk of stroke and AD. This growing body of evidence justifies further, multimodal exploration including periodontal disease burden, clinical oral health markers, and systemic host response to better understand the possible contribution of clinical, microbiologic and serologic markers of periodontal infection to a potential causal pathway for cognitive impairment among the elderly.

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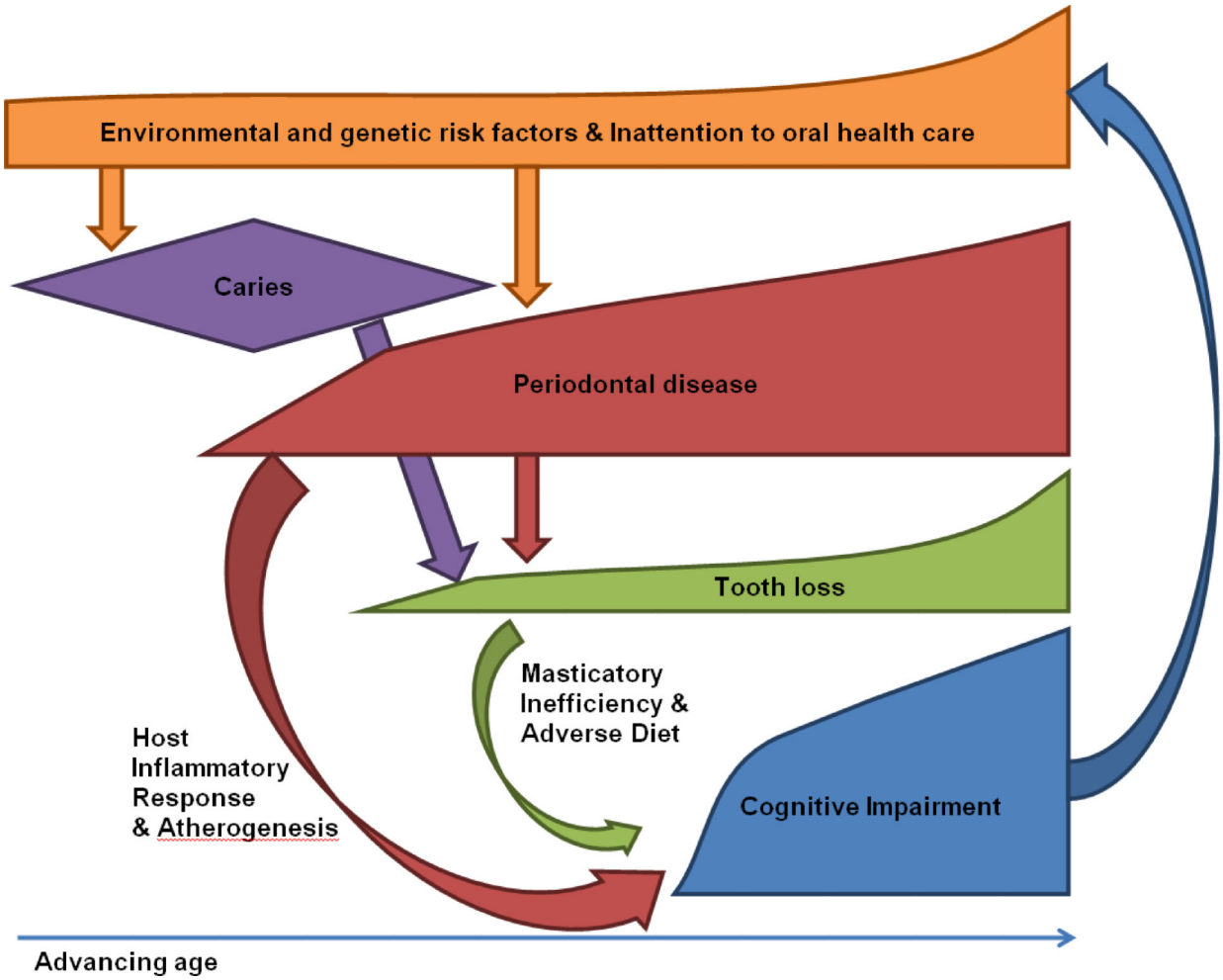

Figure 1.
Proposed pathway associating poor oral health and cognitive impairment.