

Alzheimer's disease, Down Syndrome and Periodontitis: What is the Connection?

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Abstract

Alzheimer's disease diagnoses are increasing due to patients longer life span. Inflammation plays a strong role and this and other factors link Down Syndrome and periodontal disease to Alzheimer's disease. This article aims to review numerous similarities and conditions that link Alzheimer's disease, Down Syndrome, and periodontal disease.

Keywords: Alzheimer's disease; Apolipoprotein E; Brain metabolism; Chromosome 21

Background

Alzheimer's disease continues to grow as a national health priority. Recent estimates suggest that Alzheimer's disease affects more than 6 million Americans and about 11% are living with Alzheimer's disease. By 2050 the number is projected to be more than 13 million [1]. Alzheimer's disease is the 6th leading cause of death and is the leading cause of dementia and is characterized by a progressive and irreversible deterioration of cognition, function, and behavior [2]. The pathogenesis of Alzheimer's consists of an accumulation of β -amyloid peptide ($A\beta$) and the deposition of neurofibrillary tangles of tau protein, culminating in neuronal synaptic dysfunction and loss [3]. Apolipoprotein E (ApoE) may also influence the development of Alzheimer's by participating in the synthesis, lipidation state, complex formation, and other mechanisms [4].

Overview and Considerations

Thus, a dramatic rise in life span over the last century has forced us to face this devastating disease, which was not such a serious problem 100 years ago [5]. The pathological hallmarks of Alzheimer's Disease brains include cortical atrophy, most predominant in the medial temporal lobe and, microscopically, extensive neuronal loss and intracellular and extracellular abnormal fibrillar deposits [5].

One of the first advancements was made through painstaking protein chemical characterization of senile plaques and neurofibrillary tangles. Whether have shown that individuals carrying APOE4, whether heterozygous or homozygous, experience damage to the blood-brain barrier. This damage increases as cognitive impairment worsens [6] and may, indirectly,

interfere with β -amyloid peptide clearance, thereby favoring its aggregation [7].

APOE4 may contribute to neuronal degeneration through direct neurotoxicity or by amplifying the harmful effects of other aggressors [8]. Moreover, APOE4 has been found to be capable of hyper-phosphorylating the tau protein, generating chronic neuroinflammation by compromising its anti-inflammatory function and may also reduce brain metabolism [4].

Early findings noted that although these lesions are highly resistant to various kinds of detergents or denaturants, Glenner successfully purified cerebrovascular amyloid from AD brains in 1984 and determined the first 24 amino acids [9]. This small protein was designated as β -amyloid protein ($A\beta$), after the β -pleated sheet structure. Beyreuther and Masters [10] extended this work and showed that the same protein ($A\beta$) is also the major constituent of amyloid cores in the parenchyma of Alzheimer's diseased brains. In 1987, cDNA encoding β -amyloid precursor protein (APP) was cloned. Subsequent intensive molecular and cell biological studies of Alzheimer's Disease continued [9,10].

At first, $A\beta$ was thought to be a pathological molecule generated by abnormal cleavage of APP, which was observed only in AD brains. It was noted that APP must be cleaved in the middle of the membrane to generate $A\beta$. However, in 1992 $A\beta$ was found to be secreted constitutively from various types of cells [11].

Several observations revealed that Alzheimer's disease is a multifaceted disorder in which protein misfolding, neuronal degeneration, and inflammation intersect. Understanding the origins of the neuroinflammatory signals that sustain this process is essential. Comorbidities such as Down Syndrome and periodontal disease all signal Alzheimer's disease related changes with beta-amyloid protein influence, central neurodegenerative and peripheral inflammatory changes Kendall [12,13].

(Thus, the β -amyloid precursor protein (APP) gene was one of the first identified causative genes for familial Alzheimer's Disease (FAD). In individuals with Down syndrome, the presence of an extra copy of the APP gene accelerates $A\beta$ accumulation and resulted in earlier plaque formation. Systemic inflammatory conditions influence amyloid biology through the upregulation of interferon-induced transmembrane protein 3 (IFITM3), a protein known to enhance secretase activity. When IFITM3 levels rise during inflammation, the production of $A\beta_{42}$ likewise increases, demonstrating that peripheral inflammation can directly modulate central amyloidogenic pathways [12,13] Taken together, these processes may progress to lead to Alzheimer's disease (AD) as a multifaceted result of protein misfolding, neuronal degeneration, genetic susceptibility, and chronic inflammation. Patients with Down's syndrome (trisomy 21) were also known to invariably develop Alzheimer's disease neuropathology in earlier life, in their 20s to 40s. [14] (2020).

Greater production of $A\beta_{42}$ contributes to the development of early onset Alzheimer's disease. B -amyloid is the bridge

between these disorders. Chromosome 21 is the gene involved in the production of β -amyloid. β -amyloid fragments can become plaques in the brain. Individuals with AD have a high accumulation of B-Amyloid. Individuals with Down Syndrome have an overproduction of β -Amyloid [5].

This established a view that AD is not a single-gene disease but rather a genetically heterogeneous disorder exhibiting similar clinical and pathological phenotypes (in other words, AD syndrome [15].

Co-occurring conditions such as Alzheimer's and Down Syndrome can result as patients with Down Syndrome begin the aging process. Many individuals with DS develop AD neuropathology. The prevalence of clinical dementia in Down Syndrome doubles approximately every 5 years, from about 9% of individuals in their 40's to about 80% in those over the age of 54 and about 95% in those who live to the age of 68 [14]. Dementia, cardiovascular, and lung pneumonia infections make up the most common causes of death in people with DS over the age of 36 years old [14].

In persons with Down Syndrome, dementia is also associated with a five-fold increase in mortality rate compared to individual without dementia. In individuals with DS it's unclear if apolipoprotein E (ApoE) impacts AD and mortality risk. Seizures may eventually occur in > 70% of individuals with DS-AD, which are associated with accelerated cognitive decline and increased mortality. Rates of cerebrovascular disease (CVD) including microbleeds are seen, suggesting vascular contributions to DS-AD are serious risk factors [16].

Chronic inflammation and microbial infections are other factors associated with Alzheimer's disease (AD). Recent research highlights a potential link between AD and periodontal disease - a chronic inflammatory condition caused by dysbiotic oral bacteria such as *Porphyromonas gingivalis* (*P. gingivalis*). These pathogens may reach the brain via the bloodstream or trigeminal nerve, triggering neuroinflammation through microglial activation and promoting pathological changes, including amyloid- β accumulation and Tau hyperphosphorylation. *Porphyromonas gingivalis* secretes virulence factors like gingipains and lipopolysaccharides (LPS), which disrupt immune responses and contribute to neuronal damage. Genetic predispositions, such as mutations in microglia-regulating genes (e.g., TREM2, CD33, CLU), further impair immune function and exacerbate Alzheimer's disease pathology. chronic inflammatory periodontal disease is also driven by other bacteria such as, *Tannerella forsythia*, and *Treponema denticola*. The bacterial toxins (e.g., gingipains) can enter systemic circulation and reach the brain, triggering an innate immune response. This activates microglia and astrocytes, leading to chronic neuroinflammation. There is also an association between periodontitis and higher amyloid load [16,17].

Oral tissue alterations occur especially along the oral mucosal areas. Zhang et al. showed that inflammatory responses and

osteoclastogenesis are commonly involved in the development of periodontitis [18]. Animal studies revealed that the periodontium is aggravated, causing ischemia and inflammation and is associated with inflammatory mediators which aggravate oral mucosal tissues [18]. The association of periodontitis was found to be statistically significant. Higher age predicted greater incidence of periodontal disease. The most common risk factors attributed to periodontal disease are pathogenic bacteria and tooth deposits [18]. *Porphyromonas gingivalis* (*P. gingivalis*) is a major etiological that contributes to the prognosis of periodontal disease and is involved in the process to modulate the pathogenesis of bacteria-mediated bone loss [17,19].

ApoE was quantified in levels in the crevicular fluid of individuals with β -amyloid and without Alzheimer's disease (AD), discovering that in patients with periodontitis, regardless of the presence of AD, there was an increase in ApoE secretion compared to controls without periodontal disease [8].

Aging, a common risk factor for both diseases, weakens immune defenses and the blood-brain barrier, facilitating bacterial entry into the brain. As no cure currently exists for Alzheimer's, preventing and managing periodontal disease could be a promising strategy to reduce the risk and progression of AD. This review underscores the need for interdisciplinary approaches and further research into the oral-systemic connection to better understand, prevent, and treat neurodegenerative diseases like Alzheimer's [19].

Sleep is another factor that may play a bi-directional role in the development of AD. Sleep disorders are not only prevalent in AD but also may predict future development of AD. Sleep is thought to increase the clearance of toxins such as amyloid. Adults with DS frequently experience sleep disruption [20], which could have multiple causes and also have a high prevalence of obstructive sleep apnea, which is a risk factor for AD. Obstructive sleep apnea has been hypothesized to be associated with cognitive decline in Down Syndrome. This high prevalence of sleep disruption in DS suggests that this population may provide a window into understanding the link between sleep amyloid and dementia [21].

Alzheimer's disease, Down Syndrome and periodontal disease all have a strong association with β -amyloid protein and chronic inflammation. β -Amyloid is central to Alzheimer's Disease and overexpressed in Down syndrome. There is an association between periodontal disease, Alzheimer's disease and Down Syndrome in that all three have a higher β -amyloid load. This higher load of β -amyloid may disrupt synaptic function in the brain, may cause cognitive decline and contribute to neurodegeneration.

Conclusion

Understanding autosomal inflammatory disorders, Down Syndrome, periodontitis and its relationship to Alzheimer's disease is important for scientific advancement. Continued efforts

are needed to assess public health impact and dangers associated neurodegenerative and pro-inflammatory conditions. The story of B-amyloid begins at birth in Down Syndrome and ends with Dementia in Alzheimer's disease. B-amyloid is the bridge between these two devastating disorders. Chromosome 21 is the gene involved in the production of β -amyloid.

There is a continued need to evaluate cytological and morphologic alterations of brain in patients with Alzheimer's disease. Numerous neurodegenerative cells and microglia must be studied. Additionally, there are significant inflammatory processes that lead to the breakdown of many cellular systems. These associations cause pathological declines and may disrupt synaptic function in the brain, may cause cognitive decline and contribute to neurodegeneration. This complex process of diminishing systemic conditions are most likely inflammatory, genetic, environmental and clinical. Further research in these diseases will allow us to better understand and treat these rapidly progressive diseases.

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