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CASE REPORT

Periodontal Disease and Alzheimer's Disease -A New Link

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ABSTRACT:

The molecular and cellular mechanisms responsible for the etiology and pathogenesis of Alzheimer's disease have not been defined; however, inflammation within the brain is thought to play a pivotal role. Studies suggest that peripheral infection/ inflammation might affect the inflammatory state of the central nervous system. Chronic periodontitis is a prevalent peripheral infection that is associated with gram-negative anaerobic bacteria and the elevation of serum inflammatory markers including C-reactive protein. Recently, chronic periodontitis has been associated with several systemic diseases including Alzheimer's Disease. In this article we review the several potential mechanisms through which chronic periodontitis can possibly contribute to the clinical onset and progression of Alzheimer's Disease.

Key words: ***Periodontitis, Alzheimer's disease, Dementia***

Introduction

Alzheimer's disease is the most common form of dementia. It is a brain disorder which gradually destroys the ability to reason, remember, imagine and learn. Over the course of the disease, people with Alzheimer disease no longer recognizes themselves or much about the world around them. Depression, anxiety and paranoia often accompany these symptoms. This disease was first described by German Psychiatrist Aloris Alzheimer in 1906. In 1996, Alzheimer's Disease was clinically diagnosed in approximately 4 million people in the United States; this figure is expected to triple in the next 50 years. Women are more affected than men at a ratio of almost 2:1. Age is an important risk factor. At the age of 60 years, the risk of developing Alzheimer's Disease is estimated to be 1%, doubling every 5 years to reach 30% to 50% by the age of 85. Other reported risk factors include lower levels of intelligence and education, small head size, and a family history of the disease.

Periodontitis is the inflammation of the periodontium that extends beyond the gingiva and produces destruction of connective tissue attachment of the teeth.

The etiology is complex involving the presence of pathogenic bacteria found in dental plaque and individual variation in host immune response. The severity of periodontal infection has been correlated with serum levels inflammatory markers.[1]

Pathophysiology

The classic neuropathologic findings in Alzheimer's Disease include amyloid plaques,

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neurofibrillary tangles, and synaptic and neuronal cell death.

Amyloid Plaques

The amyloid plaques or senile plaques contain forms of β-amyloid protein. β-amyloid protein is a 39- to 42-amino acid peptide that is formed by the proteolytic cleavage of β-amyloid precursor protein and is found in extracellular deposits throughout the central nervous system. β-amyloid protein is believed to interfere with neuronal activity because of its stimulatory effect on production of free radicals, resulting in oxidative stress and neuronal cell death.

Neurofibrillary Tangles

Neurofibrillary tangles are paired helical filaments composed of tau protein, which in normal cells is essential for axonal growth and development. However, when hyperphosphorylated, the tau protein forms tangles that are deposited within neurons located in the hippocampus and medial temporal lobe, the parietotemporal region, and the frontal association cortices, leading to cell death.

Neuron and Synapse Loss

Areas of neuronal cell death and synapse loss greatly affect neurotransmitter pathways. The death of cholinergic neurons in the basalis nucleus of Meynert leads to a deficit in acetylcholine, a major transmitter believed to be involved with memory. In addition, loss of serotoninergic neurons in the median raphe and adrenergic neurons in the locus ceruleus lead to deficits in serotonin and norepinephrine, respectively.

Role of Microglia in the Pathogenesis of Alzheimer's Disease

Microglia are small giant cells of mesodermal origin that are distributed throughout the gray and white matter of the nervous system. They are specialized immune cells, related to macrophages which can take on attack and phagocytic roles when activated. Activated microglia secrete a wide range of inflammatory mediators, are capable of migrating to sites of inflammatory activity and exhibit scavenger responses to damaged tissue and accumulations of abnormal proteins. Because of these properties activated microglia are widely considered to play a pivotal role in Alzheimer's Disease inflammation.

Association Between Alzheimer's And Periodontal Disease

Inflammation is thought to play a significant role in the etiology and pathogenesis of Alzheimer's Disease. Increased brain inflammatory molecules such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-β (TNF-β) participate in activating and perpetuating molecular pathways that may contribute to neurodegeneration. The significance of this "inflammatory hypothesis" is that factors capable of altering the levels of inflammatory molecules may alter the expression and progression of Alzheimer's Disease.[2]

Periodontitis is a peripheral, chronic, infectious disease. The interaction between periodontopathic bacteria and the host response in periodontitis may result in significant systemic inflammation characterized by production of inflammatory molecules including IL-1β, IL-6, and TNF-α. Therefore, periodontal bacteria and systemic inflammatory molecules may contribute to brain inflammation that characterizes Alzheimer's Disease.[3] Clinical studies have reported tooth loss to be a significant risk factor for Alzheimer's Disease and/or dementia with odds ratios of 5.5 and 6.4, respectively.[4] The Third National Health and Nutrition Examination Survey (NHANES III) showed that gingival bleeding, loss of periodontal attachment and serum *P. gingivalis* IgG were significantly associated with lower cognitive function even after extensive adjustments for confounders.[5]

Periodontitis may contribute to the development of Alzheimer's Disease pathology through three interrelated processes. They are the direct effects of pathogenic products, the inflammatory response to these pathogens, and the effect on vascular integrity. These processes have been demonstrated to impact microglial activation, the production and formation of β-amyloid protein and tau protein, and cerebrovascular pathology [Fig-1].

Pathogenic Products

The cell walls of Gram-negative bacteria contain Lipopolysaccharide(LPS) that induces a number of host defenses. Lipopolysaccharides stimulate certain inflammatory cytokines that are associated with microglial activation and altered processing of amyloid precursor protein.[5] Animal studies show that chronic infusion of LPS into rat brains may result in long lasting inflammatory reaction with pathological changes like increased number of activated astrocytes, increased number and density of reactive microglia, increase in IL-1β, TNF-β, and beta amyloid precursor protein, the degeneration of hippocampal pyramidal neurons, impairment in spatial working memory.

Inflammation And Alzheimer's Disease

The presence of primed microglia may influence the response of the brain to systemic infection. It is hypothesized that in Alzheimer's Disease and other neurodegenerative diseases, microglia become activated, leading to higher production of inflammatory mediators and chronic overreaction to subsequent stimuli. Microglia release many inflammatory mediators in the brain including acute phase proteins, complement factors, prostaglandins, free radicals, and cytokines. β-amyloid peptides in the brain may also potentiate monocyte transmigration from blood to brain.[6] β-amyloid is aggregated as oligomers and fibrils which have varying neurotoxicity.

Griffin and colleagues[7] proposed that IL-1 is critical to the processing of amyloid precursor protein, favoring continued amyloid β deposition. IL-1 also contributes to the phosphorylation of tau protein favoring tangle formation, increases production of nitric oxide synthase fatal to cells, and increases the production of acetyl- cholinesterase responsible for the breakdown of acetylcholine which is important in learning and memory function. Beta secretase, a protease that cleaves amyloid precursor protein and results in toxic β-amyloid peptides, may also be upregulated by inflammatory mediators.[8]

Kamer et al[9] hypothesized that TNF-alpha and elevated antibodies to periodontal bacteria would be greater in Alzheimer's Disease compared to normal controls and their combination would aid clinical diagnosis of AD.

Infectious Pathogens And Alzheimer's Disease

Treponema bacteria, a family of gram negative spirochetes commonly associated with Periodontal Disease was found in the brains of Alzheimer's.

Disease patients with greater frequency than in non-Alzheimer's Disease controls.[10] Antigens for two types of treponema were found in the trigeminal ganglia, pons, and hippocampus possibly indicating that the bacteria reached the brain via the trigeminal nerve. Viral infection may also be a risk factor for AD, particularly herpes viruses. HSV-1 also contribute to the formation of amyloid plaques and abnormally phosphorylated tau protein possibly by attenuating the processing of amyloid precursor protein into toxic β-amyloid peptide.[11]

CONCLUSION

It is proposed that bacterial and viral infections commonly found in Periodontal Disease may impact the brain, either directly or via systemic signals to the brain, and contribute to the development of Alzheimer's Disease. Periodontal infections may result in harmful pathogenic products leading to systemic inflammatory responses. Elevated systemic inflamatory response may contribute to the exacerbation of existing brain pathologies. Infections may also contribute to vascular pathology with the potential to impact brain function. If systemic infection and inflammation have been proved by longitudinal studies to be the contributors of Alzheimer's Disease, several preventive measures and treatment strategies would be implied.

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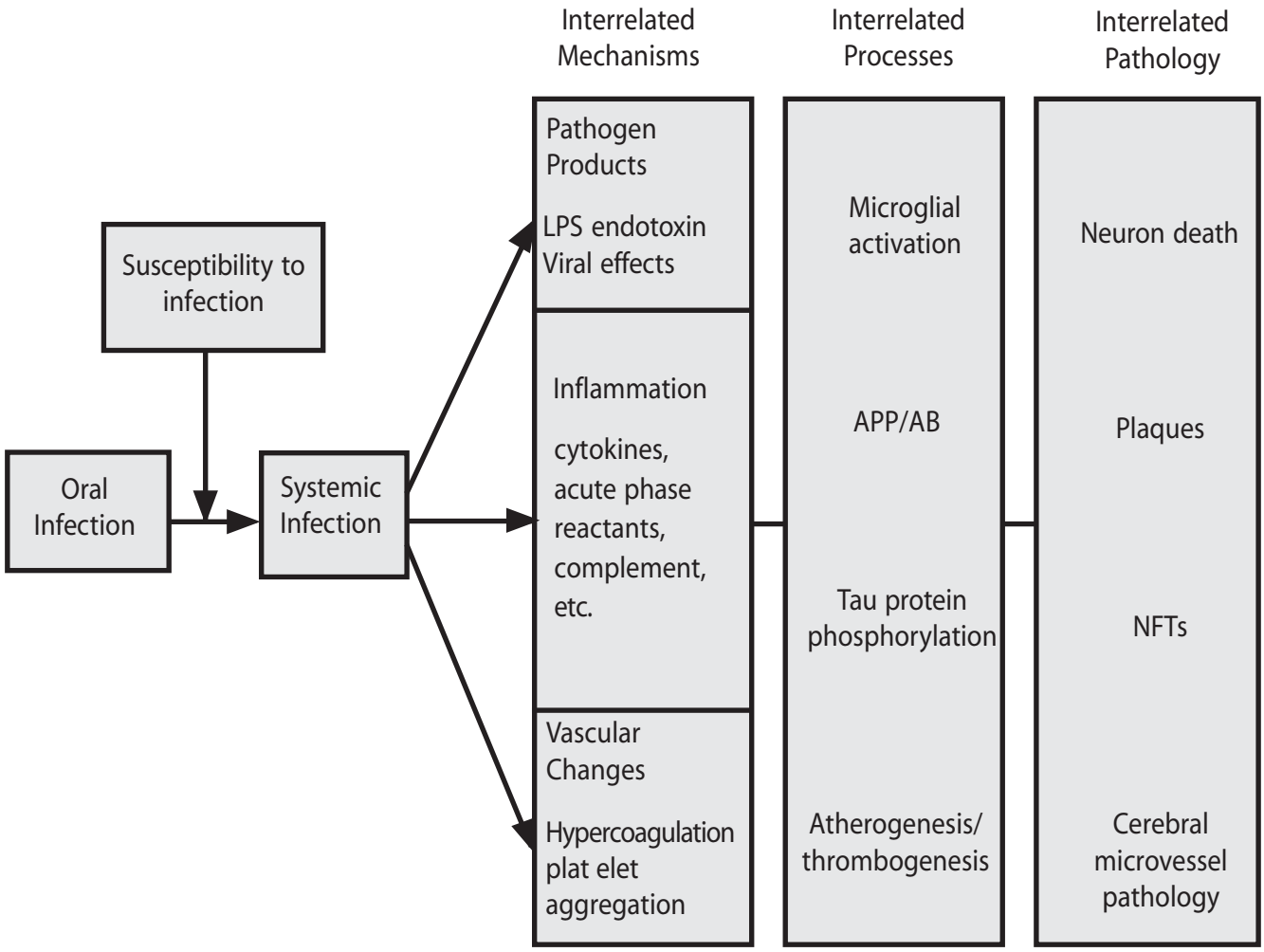

Fig-1: Proposed pathways between periodontal infection and Alzheimer's disease pathology

Abbreviations: LPS-lipopolysaccharide, APP-Amyloid precursor protein, AB-amyloid beta, NFTs-neurofibrillary tangles