Review Article

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NEURODEGENERATIVE DISORDERS AND PERIODONTITIS: A MECHANISM BEHIND THE LIAISON

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ABSTRACT:

Neurodegeneration, the slow progressive dysfunction and loss of neurons and axons in the central nervous system, is the primary pathological feature of acute and chronic neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Periodontal disease is a condition that causes inflammation and destruction of the gums, alveolar bone, and other structures that support the teeth. Periodontitis constitutes a peripheral oral infection that can provide the brain with intact bacteria and virulence factors and inflammatory mediators due to daily, transient bacteraemia. If and when genetic risk factors meet environmental risk factors in the brain, disease is expressed, in which neurocognition may be impacted, leading to the development of neurodegenerative disorders. Here, we review the mechanistic link between Neurodegenerative disease and periodontal disease.

Keywords: Periodontitis, Neurodegeneration, Inflammation, Neuronal damage

INTRODUCTION:

Neurodegenerative disorders are the chronic conditions of the central nervous system (CNS), that often leads to motor problems and dementia. Studies have revealed that neurodegenerative conditions including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) have a symptomatic phase that may be present for some years before the onset of the clinical syndrome [1]. Periodontal disease is a condition that causes inflammation and destruction of the gingiva, alveolar bone and other structures that support the teeth. The etiology of periodontitis is complex involving the presence of pathogenic bacteria found in dental plaque evoking host immune response [2]. The inflammatory process in periodontitis extends from the gingiva (gums) into deeper connective tissues, resulting in the loss of connective tissue and bone. Periodontitis is basically a result of inflammation caused due to wide array of pathogenic microorganisms. These microorganisms release numerous proteolytic enzymes, resulting in destruction of soft and hard tissues supporting the teeth. Release of lipopolysaccharides from the gram negative bacteria results in the expression of proinflammatory factors/cytokines like (Interleukins) IL1α and 1β, IL6, TNFα, prostanoids, matrix metalloproteinase (MMP)[3]

MECHANISMS OF MICROORGANISMS INVOLVED IN PERIODONTITIS

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1. Periodontal bacteria and their products could be aspirated, which could induce pulmonary pathology.

2. Periodontal pathogens have the capability to gain access to systemic circulation and subsequently colonize different distant anatomic sites in the body.

3. Periodontal bacteria and their products can disseminate through systemic circulation in pregnant woman inducing inflammatory changes and resulting in preterm low birth weight infants.

4. Chronic adult periodontitis has been associated with several conditions including increased risk of atherosclerotic complications, myocardial infarction, stroke, poorly controlled diabetes mellitus, and Neurodegenerative disease.

5. The host response also plays a vital role in inducing systemic effects by producing a multitude of inflammatory mediators including cytokines that gain access to the systemic circulation [4].

NEURODEGENERATIVE DISORDERS

Alzheimer's disease (AD) is a fatal neurodegenerative disease associated with elderly age group and a major health problem in the geriatric subject's worldwide. The incidence of AD significantly increases with age, reaching almost 50% in subjects aged 85 years [5]. AD is characterized by the formation of extracellular amyloid β peptide (AβP) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein, leading to gradual loss of neuronal synapses and ultimately neuronal degeneration with diminution of essential neurotransmitters [6]. Genetic aberration causes increased expression of the amyloid precursor protein (APP) gene which could be a risk factor for late onset of AD [7].

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder and is the second most common progressive neurodegenerative disorder after Alzheimer's disease. It has a prevalence rate of 0.5–1% among people older than 65 years [8]. The disease results in the selective loss of dopaminergic neurons within the substantia nigra (SN) of the midbrain. With the progression of disease, there is a gradual degeneration of neurological connections in nigrostriatal pathway, producing motor, cognitive and psychiatric symptoms [9].

Huntington's disease is a neurodegenerative disorder that affects primarily adults. It is inherited as an autosomal dominant disease manifested with physical, cognitive and mental deterioration, which is eventually fatal [10].The main cause of this syndrome is a dynamic mutation based on a specific repetitive sequence of cytosine, adenine, and guanine in exon 1 of the huntingtin gene.

PATHOGENESIS OF ALZHEIMER'S IN PERIODONTITIS

Plausible mechanism of Alzheimer's in periodontitis are Metastatic spread of gram negative bacteria from the oral cavity to the brain via neuronal pathways, Periodontal disease increase the risk of cerebrovascular injury to brain, Genetics:- Polymorphisms in the Interleukin 1 gene family and weight loss and wasting associated with periodontal disease may contribute to cognitive decline [11].

Inflammation is known to play a pivotal role in this process. The flora of periodontal disease consists largely of gram-negative bacteria. Current research has identified brain receptors specific for gram-negative bacteria. Brain infections by gram-negative bacteria have been linked to Alzheimer's etiology, specifically late-onset Sporadic AD. A recent histologic study demonstrated the presence of gram-negative Chlamydia pneumonia in cells of an infected brain region in 17 of 19 post mortem Alzheimer's brains, while brains of controls were not infected [11]. The microorganisms in the dental plaque can enter brain either through blood stream or via peripheral nerves. These microorganisms and their products elicit an inflammatory mechanism within the CNS. It is generally accepted with appreciable evidence that presence of inflammation in the CNS results in cognitive impairment, such as that seen in AD. This inflammatory impairment is attributed to cytokine arbitrated interactions between neurons and glial cells. Cytokines released due to inflammation include IL family, TNFα, transforming growth factorβ, and chemokines (monocyte chemotactic protein, IL8, macrophage migration inhibitory factor, and monokine induced by γinterferon) that have also been implicated as serum and plasma biomarkers for pathogenesis of AD [12].

PARKINSON'S AND PERIODONTITIS

Studies have reported a higher prevalence of poor oral health and periodontal disease in subjects with Parkinson's disease [13, 14]. Due to motor impairment, patients may face difficulties in performing daily oral hygiene care procedures. In addition, cognitive disturbances commonly found in Parkinson's disease may also influence the quality and frequency of daily oral hygiene care by patients. The use of various medications causes alterations in quality and quantity of saliva which may be a further risk factor for poor oral health. Changes in salivary flow rates and difficultly in swallowing have also been shown to affect the oral self-cleansing mechanisms in patients with Parkinson's disease [15].

Patients with severe periodontal involvement with a higher level of bacterial colonisation, it is suspected that multiple episodes of bacteraemia occur per day. Periodontal pathogens and their products can induce pro-inflammatory cytokines including IL-1, IL-6 and TNF-a [16]. Periodontal pathogen

mainly comprises of gram-negative bacteria, and when active disease process is going on, minor trauma in the oral cavity can lead to bacteraemia and translocation of bacteria systemically. Hence, the Lipopolysaccharides from these bacteria and the inflammatory mediators may breach the Blood brain barrier (BBB) [16, 17]. After the disruption of BBB and with the entry of macrophages and pro-inflammatory mediators, the primed microglia may get converted into active microglia. Once activated, these may, in turn, produce various inflammatory mediators such as TNF-a, IL-1b, IL-6, iNOS and ROS. Once these mediators are produced, they might lead to necrosis and finally apoptosis of dopaminergic neurons present in the SN of midbrain. Death of the dopaminergic neurons marks the initiation and progression of Parkinson's disease. [9].

HUNTINGTON'S AND PERIODONTITIS

Chronic periodontitis would be a potential source of neuronal damage through its proven ability to generate low-grade systemic inflammation and spread to the brain periodontal pathogens through hematologic and neural routes. Both situations predominantly activate the innate immune system by microglial M1 phenotype polarization and alternative pathway activation of the complement system, which ultimately enhances microglial activation with consequent release of cytokines and reactive oxygen species. According to Ellrichmann *et al.* [10], this would produce astrogliosis (hypertrophy and an increase in the astrocyte proliferation in response to proinflammatory stimuli) [18]. Thereby, both systemic inflammation and the same Huntington's disease exacerbate the promoted brain inflammation. This neuroinflammation produces neuronal injury due to:

- Activation of apoptotic pathways.
- TAU protein hyperphosphorylation.
- Increased amyloidogenesis.

Injured neurons would release damage associated molecular patterns at later stages of the death process, promoting microglial activation in the brain, and therefore neuronal injury, leading to cognitive impairment [20] .

CONCLUSION:

Overall this review clearly demonstrates that inflammation caused by periodontal pathogens and cytokines could serves as a liaison between periodontitis and neurodegenerative disorders. However; in the literature, there are no animal studies specifically addressing the causal relationship of periodontal inflammation to neurodegerative diseases.

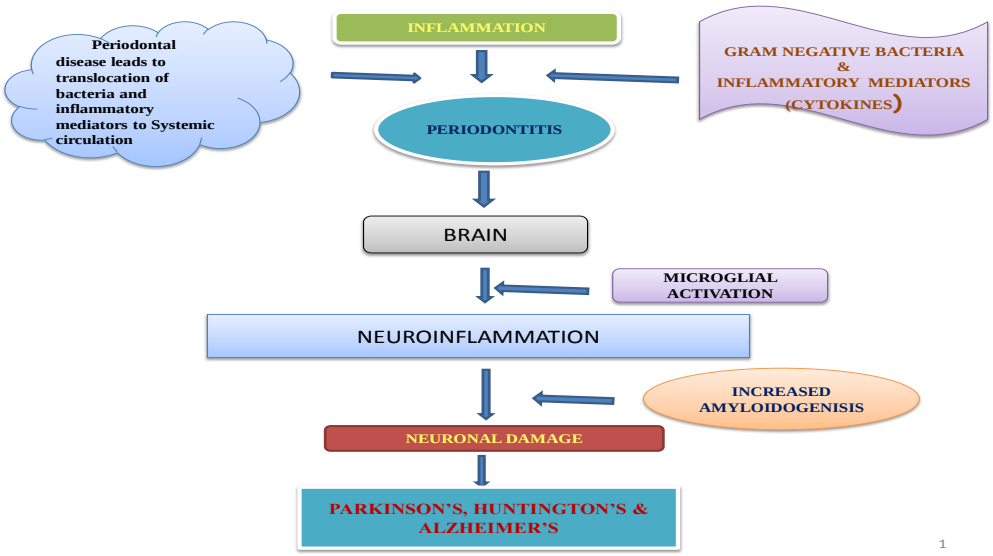

Fig.1 Liasion Behind Periodontitis And Neurodegenerative Disorders

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