

Periodontal Disease and Neurodegeneration: The Possible Pathway and Contribution from Periodontal Infections

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ABSTRACT

Neurodegeneration is a process in which the neurons lose its structure, function and ultimately the death of the neurons follows. Various neurodegenerative diseases like Alzheimer's, Parkinson's etc., are thus gaining enormous interest in health plans. Scientists are in search of finding the various markers to detect the onset of neurodegeneration. So far, Amyloid-beta (A β) and neurofibrillary tangle are the two markers found in most neurodegenerative diseases. Besides that, neural inflammation is also considered as one of the parameters for the onset of neurodegeneration. Inflammation may be caused either by insult of central nervous system or by peripheral infections. Numerous microbes get a chance to enter into the brain due to bacterial infection especially periodontal infection. The current review summarises the role of periodontal infection and the mechanism via which it contributes for neurodegeneration.

Keywords: Alzheimer disease, Amyloid-beta, Gingivitis

INTRODUCTION

Most developed countries including UK and North America are mostly prone to be affected with the periodontal disease [1,2]. Periodontal disease is basically classified into two types: (1) Gingivitis; (2) Periodontitis [3]. Gingivitis meant for the infection and inflammation of gingiva without any irreversible damage to the underlying deeper periodontal structure. In the earliest stage, the infection affects only the gingiva, which later spread to the deeper parts of supporting tissues. In periodontitis the detachment of periodontal ligament from the cementum occur, which subsequently leads to apical migration of junctional epithelium, pocket formation, gingival recession and alveolar bone destruction that finally results into tooth loss, if not treated properly [4].

The virulence of periodontal pathogens is determined by the type of toxins released by them and the type of inflammatory substances gets activated in response to it. Periodontal disease is basically a chronic infectious disease that has been linked to various systemic inflammatory conditions. In different organ systems, migration of periodontal pathogens like *Porphyromonas gingivalis* from mouth to brain contributes for low but persistent level of local inflammation. Liberation of reactive oxygen/nitrogen species also takes place when innate immune responses are activated by A β [5] from cell walls of bacteria [6]. The pathogen further increases the concentration of proinflammatory cytokines like Tumour Necrosis Factor α , (TNF- α) reduces the anti-inflammatory mediators like interleukin 1 [7] and also increases the concentration of C Reactive Protein (CRP) [8]. An elevated concentration of cytokines are resulted in patients of Alzheimer's Disease (AD) which is because of acute and chronic inflammatory responses in body [4,7]. Studies revealed that there is higher incidence of periodontal disease (periodontitis) in patients with neurodegenerative disorders [9,10] and there is an increase in the expression of higher amyloid precursor proteins in periodontitis [11,12] and higher deposition of plaques of A β in the elderly population [13]. Thus, periodontal infection leads to survivability of harmful microbes, loss of beneficial microbes in the oral cavity ultimately leading to the decreased immunity of host and oral health related quality of life in an elderly population [14].

Aetiology and pathogenesis of neurodegenerative diseases are not well characterised; however, inflammation is thought to play a

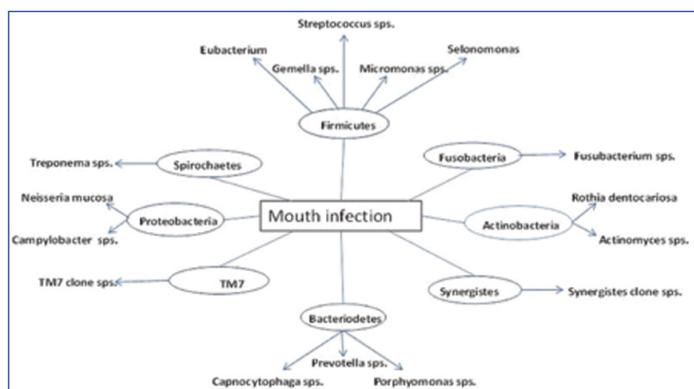
remarkable role. Studies have revealed that peripheral infections e.g. periodontal diseases can accelerate the onset and progression of neurodegenerative diseases; although, mechanisms of pathway through which it affects, are not well understood [2,6,12-15]. The objective of this review is to present possible pathway and contributions between periodontal diseases and pathogenesis of neurodegeneration and also to discuss the role of free radicals in prevention and treatment of periodontal disease induced neurodegeneration.

Microflora Altered during Mouth Infection

Various microbes are found in the oral cavity of a healthy human being. The plethora of microflora residing as commensal in human being is appraised to have outskirt the total number of cells in the body [16]. It is the inherent property of oral cavity which provides the opportunity for miscellaneous growth of microbiota. The microbes have two habitat preferences for them, one being the shedding (mucosa) and other being the solid surfaces (teeth or dentures) [17]. The microbiota includes Bacteroidetes, Firmicutes, Tenericutes, Actinobacteria, Proteobacteria, Euryarchaeota, Chlamydiae, Spirochaetes, Streptococci, Actinomycetes, *Veillonella*, and Diphtheroids, and gram negative anaerobic rods [17]. In humans the oral cavity found to contain over 700 species [18]. Out of 700 species, the periodontal pocket contains more than 400 species, and the rest 300 species are found to be present at other oral sites like mucosal membranes, lesions, tongue, and endodontic infections, which was established on the analysis of 16S rRNA clones [18]. The eight different phyla contribute for oral infection, which includes Firmicutes, Synergistes, Spirochaetes, Actinobacteria, Proteobacteria, Bacteroidetes, Fusobacteria and TM7 phylum [Table/Fig-1] [19].

Immune Invasion

Bacteria present in the oral cavity invade host immune barrier by destroying the complement fragments. A complex of complement proteins includes C1-C9, which together form Membrane Attack Complex (MAC). Members of this family have the ability to create pore across the membrane. Bacterial infection degrade C3 and C5 protein by a trypsin-like cysteine proteinases named gingipains [20], which avoids the opsonisation mechanism mediated by the C3b



[Table/Fig-1]: Various microbial family contributing for oral infection.

by attaching on the surface of the bacterial cell walls. Mostly the gingipains are found to be present on the surface of the bacterial cell wall and degrade complement proteins of host [21]. Gingipains prevent its degradation by complement mediated lysis by attaching to C4b binding protein [21]. Gingipains are major cause in the development of periodontitis, by mediating swelling and destroying the tissue in the periodontium of teeth [22]. *P. gingivalis* infection leads to two types of gingipains. One is specific for lysine binding (Kgp) and another is specific for arginine (Rgps) depending upon the specificity for their cleaving sites [20].

The main key for host pathogen interaction during infection is the recognition of Lipopolysaccharides (LPS). LPS are the main signals present over cell wall of pathogens and this recognition is mediated via a receptor of host cell surface that is toll-like receptor, after which the enzymes as well as toxins of microbes, get access to the blood stream of host through the ulcerated epithelium of the periodontal pocket. From there gram-negative bacteria enter to the bloodstream by releasing toxins and inducing immune response by releasing proinflammatory mediators such as TNF- α , prostaglandin E₂, and interleukin-1 β , γ -interferon [23]. The elevated levels of infectious agents which decrease the self-tolerance capacity of host organism leading to the onset of autoimmune disease [24].

Poor oral hygiene and periodontal pathogens seem to influence the incidence of various systemic disorders [4] e.g., the receptors in the oral mucosal surface encourage attachment and colonisation of respiratory pathogens which subsequently leads to lower respiratory tract and lung infection [25]. Studies have also found that there is an increase in inflammatory serum markers such as IL-6 fibrinogen and CRP in patients having periodontitis than patients without periodontitis [26]. In the same way, chronic periodontitis and disorders of metabolism are the key to systemic inflammation and insulin resistance [27].

Periodontitis proceeds to neurodegenerative diseases by microbial or inflammatory infection (2). In the first mechanism, by neuronal pathways, *T. denticola* multiplication affects branches of the trigeminal nerve [2,28]. In the second method by release of inflammatory molecules like CRP, IL-6, IL-1 β , IL8 and TNF- α inflammation increases in brain [28].

Microbes and Neurodegeneration in various Diseases

During metabolism microbes interact with O₂ and metal ions to produce Reactive Oxygen Species (ROS) like peroxides, hydroxyl ions, superoxide anions [29]. ROS are produced by two pathways [30].

- (1) Direct interactions between REDOX-active metals and oxygen species;
- (2) Indirect pathway drives through metalloenzymes like xanthine dehydrogenase, nitric oxide synthase and phospholipases which are the activators of calcium.

ROS are very reactive in nature and initiate cell death in neurons as well as mediate mutations in DNA by interacting with it. Oxidative

stress creates cellular dysfunctions resulting information of toxic species like cholesterol oxides, peroxides, aldehydes, ketones and alcohols. Cholesterol oxide has a toxic effect on lymphocytes and macrophages residing on blood vessels [31]. ROS, a redox signal, generated because of the enzymatic reactions, and thus acts as a second messenger mediating a number of signalling systems [32]. Excessive ROS impairs intracellular calcium signalling leading to different apoptotic cascade, tissue injury, inflammation, brain injury and degenerative diseases [33]. Effect of ROS in various neurodegenerative diseases are explained below.

Alzheimer's disease (AD): Mutation in the amyloid precursor protein leads to deposition of small fragments of A β peptide in brain of AD patients [34]. Specifically ROS generated by pathogenicity of periodontal bacteria cause oxidative modification which generate abnormal soluble forms of A β from the membrane [35]. A variety of systemic changes were found in an experimental mouse model (ApoE null mouse) that was infected by *P. gingivalis* and *T. denticola*. In that study the brains of mice were found to contain the genomic DNA of *P. Gingivalis* and again chronic gingival was analysed by nucleotide sequencing method [36].

Parkinson's disease: In Parkinson's Disease (PD), there is accumulation of α -synuclein. Due to a missense mutation it leads to the destruction of dopaminergic neurons in the substantia nigra and the accumulation of intracellular inclusion bodies. The mutations in α -synuclein, which are parts of the deposits, is mainly mediated through the ROS generation during microbial infection in case of the oral periodontitis, which affects the expression of one enzyme dihydropteridinereductase, that maintains the production of dopamine [37]. With the onset of aging a dark brown pigment called, neuromelanin gets accumulated in substantia nigra of brain that accumulates metal ions, basically iron, which is an inflammatory agent. In Parkinson's disease, these metal accumulating agents are lost [38]. ApoE null mouse model is used to study Parkinson's disease. Studies to describe the strong intracellular labelling with C3 and C9, researchers use antibodies against C3 convertase and the membrane attack complex of brain tissue sections from the ApoE null mice. Microglia in both infected and uninfected groups, demonstrated solves the query [39]. Glia cells are more subjected to attack by MAC complex [40]. Opsonisation with complement activation fragments iC3b/C3b/C3d has also been found after local intravascular dissemination of *P. gingivalis* into brain tissue [41].

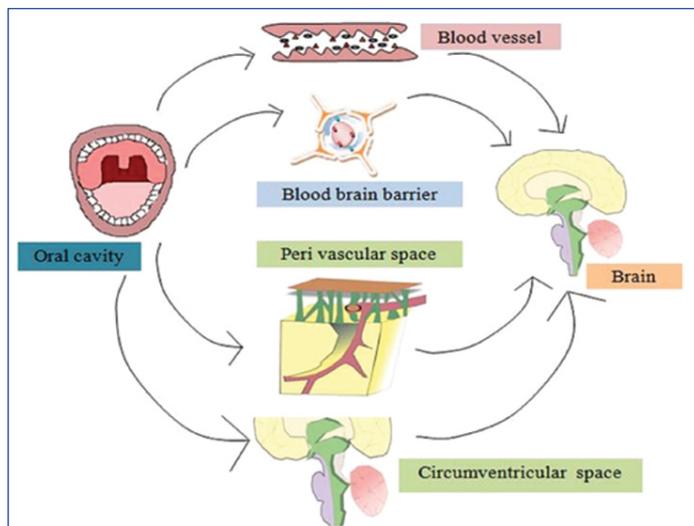
Relationship between Neurodegeneration and Periodontal Infection

Inflammation has principal role in the connection between periodontitis and neurodegenerative diseases. Inflammation is a protective mechanism that defends the body from external and internal agent or stimuli. In central nervous system, the main innate immune-defensive cells are resident microglial cell [42]. In systemic inflammation, inflammatory mediators are released that help in microglial cells activation [43], which leads to initiation of neurodegeneration. It suggests that periodontitis can direct the progression of neurodegenerative diseases similar to Alzheimer's disease, Huntington disease, Parkinson's disease by two plausible mechanisms [2].

- a) Periodontitis leads to systemic inflammation/infection;
- b) Bacterial and viral influence.

Both the mechanisms follow these three pathways [44], that are: (1) pathogen invasion and liberate of inflammatory mediators beginning from the oral cavity into the systemic circulation; (2) systemic inflammation occurred by periodontitis can affect the central nervous system through various possible ways; (3) the decline of dopaminergic neurons as well as activation of microglia occur in the substantia nigra which is located in midbrain [Table/Fig-2].

According to first pathway, under normal condition, the oral cavity acts as a physical, chemical, immunological barrier and prevents the entry of the microorganism. To increase the acute and chronic infection microbes have to acquire host system, for which it has to overcome all the barriers and then evade and spread infection [45]. Some specific bacteria form dental plaque or biofilm by stimulating



[Table/Fig-2]: Infection mode of pathogen from oral cavity to brain.

proinflammatory cytokines, including IL-1 β , IL-6 and TNF- α [45]. The proinflammatory mediator TNF- α expression increases in Alzheimer's disease and it is known to be the pivotal inflammatory cytokine. It facilitates the flow of events occurred in neuroinflammatory response. TNF- α exacerbates demyelination, inflammation, gliosis, cell death and Blood Brain Barrier (BBB) deterioration [7,45]. So TNF- α plays crucial role in the neurodegenerative disease. In advanced stages, periodontal disease may produce systemic inflammation. According to second pathway, an inflammatory response created both locally as well as systemically due to periodontal infection. From periphery the proinflammatory molecules are secreted help in boosting total pool of brain inflammatory molecules which are passed through systemic circulation and neural pathway or humoral pathway [3]. In the systemic circulation, proinflammatory molecules might enter the CNS through multiple pathways. They may enter the CNS through the areas of the brain which have no BBB (blood brain barrier) (circumventricular organ) [Table/Fig-3]. Also, sometimes through BBB, these molecules can enter the CNS by: (1) passing across fenestrated capillaries of BBB; (2) through transporters which is cytokine-specific; (3) BBB permeability increases; (4) brain endothelial cells activate and generate signalling molecules which associate with cytokine such as nitric oxide or prostanoids [3]. In humoral pathway, BBB is included. BBB allow any substance to pass from blood to brain. Due to infection the chances of disruption of BBB is high, which can lead to release of proinflammatory cytokines [46]. ROS and nitric oxide produced by activated microglial cell leads to dopaminergic neuronal death [3,46].

The principal cause of periodontitis is dental plaque which exists in biofilm form. The anaerobic species and gram negative bacteria colonise or invade the intact epithelium. Periodontal pocket give large surface area and ulceration in pocket lining help the pathogen to enter into systemic circulation [47]. In periodontitis, primarily some pathogens are involved. These are *Treponema denticola* (gram-negative, obligate anaerobic, pathogenic), *Porphyromonas gingivalis* (gram-negative, anaerobic, pathogenic), *Eikenella corrodens* (gram-negative, facultative anaerobic, pathogenic), *Fusobacterium nucleatum* (gram-negative, anaerobic, pathogenic), *Tannerella forsythia* (gram-negative, anaerobic, pathogenic), *Prevotella intermedia* (gram-negative, obligate anaerobic, pathogenic), and *Aggregatibacter actinomycetemcomitans* (gram-negative,

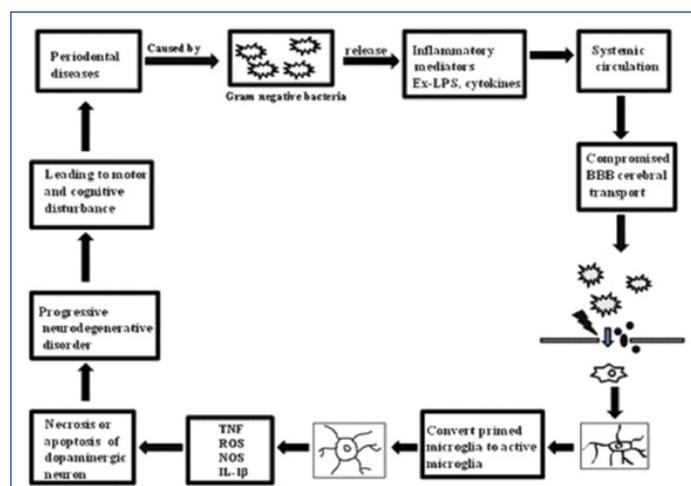
facultative anaerobic, pathogenic) [48,49]. Specifically *P. gingivalis*, *A. actinomycetemcomitans*, and *T. denticola* help in tissue invasion. Periodontal pathogens with their products are able to enter to the circulation predominantly in the ulcerated pockets, and subsequently in systemic circulation.

Bacterial associated products with proinflammatory molecules can enhance the brain proinflammatory cytokine pool. The gram negative bacterial LPS, readily recognise molecule to induce innate immune responses and CD14 receptor activate the peripheral proinflammatory cytokines. Several studies have shown that CD14 receptor found on specific area of the brain such as circumventricular areas, leptomeninges, and choroid plexus are exposed to systemic circulation [21,50]. LPS injected in intravenously and it up regulates CD14 receptors throughout the brain not only the specific areas which exposed to the LPS [50]. The breakdown of the BBB and the granulocytes or soluble molecules invasion might be caused due to systemic injection of LPS [51]. A reduced number of dopaminergic neurons resulted because of intranigral injection of LPS specially at substantia nigra [52]. Several studies shown that LPS-induced neurotoxicity is seen only in dopaminergic neuron not in GABAergic or the serotonergic neuron [52,53]. Altogether, the LPS is an essential cause for the development and progression of Parkinson's disease.

According to third pathway, the LPS of the gram-negative bacteria breached the BBB and provide the way of entrance for the macrophages and proinflammatory mediators, which developed active microglia from primed microglia. After activation of primed microglia, it produces several inflammatory mediators such as ROS, IL-6, TNF- α , IL-1 β and CRP. Elevated CRP and proinflammatory cytokines might stimulate glial cells via paracrine and/or autocrine pathways to produce additional P-Tau, A β 42 and proinflammatory molecules. Thus, a cycle is established in which inflammatory mediators play a dual role by both accelerating glial cells and triggering molecular pathways, might lead to necrosis and lastly dopaminergic neuron apoptosis. The dopaminergic neuron death marks the initiation and progression of neurodegenerative disease [2,3] [Table/Fig-3].

Antioxidants in the Prevention and Treatment of Neurodegenerative Disorders

Various antioxidants are used to prevent neurodegeneration. Polyphenols (PPs) have a unique property which is beneficial for health. PPs prevent degenerative diseases, any infectious diseases and also oral diseases via many mechanisms [54]. PPs are plant metabolites which are present in the form of fruits, seeds and leaves. They possess several phenol groups (i.e., aromatic rings with hydroxyls), which are derived from L-phenylalanine [54-56]. Polyphenols exert antibacterial and anti-oxidative property [57].



[Table/Fig-3]: Proposed pathway between neurodegenerative disease and periodontal disease.

Usually free radicals are neutralised by antioxidants like polyphenols so that it can diminish their destructive effects [58]. Most age related degenerative diseases caused due to oxidative damage, have protective role via PP [59].

Polyphenol

Periodontal pathogens stimulate inflammation by which it increases the crevicular fluid production and chemotaxis of polymorphonuclear leukocytes, which inactivate the periodontal pathogen and release hypochlorous acid and singlet oxygen into the crevicular fluid [54]. Antioxidant activity of ascorbate, albumin and urate enhance the oxidative stress which is present in the crevicular fluid derived from plasma. Exterior factor or some systemic condition such as smoking, diabetics and metabolic syndrome induced local oxidative stress. Disequilibrium between oxidative stress and antioxidant activity leads to destruction of periodontal tissues [54]. Polyphenol helps to enhance the oral fluids antioxidant activity [59,58]. These observations suggest that antioxidant rich diet help in inhibition of periodontal development and progression, predominantly in subjects exposed to dietary and environmental sources of oxidative stress [60-63]. Studies further reveal the relation between the crevicular fluid and saliva antioxidative activity with periodontitis development. When antioxidant activities of crevicular fluid and saliva decrease, leading to the development of periodontal disease [64-66]. The PPs present in green or black tea which reside in the mouth for 2-5 minutes, it increases the saliva anti-oxidant capacity [67]. A daily dose of two grapes for up to two weeks can act as a great source in enhancing phagocytic activity of polymorphonuclear leukocytes [68]. PPs possess antibacterial activity against pathogens associated to periodontitis and help in prevention of biofilm formation even decrease pocket depth with local application. Several studies reveal that the green tea PPs inhibitory effect on the virulence factor which are produced from the periodontal disease causing anaerobic bacterium *Porphyromonas gingivalis* [69]. Daily consumption of tea PPs can be useful and practical method for the prevention of periodontal diseases.

Vitamin E (α -tocopherol)

Vitamin E is an antioxidant that breaks the extension of the free radical chain reaction in lipid regions of membrane. Studies revealed that it can be a potent drug for curing Alzheimer's disease [70]. Vitamin E is fat soluble in nature and comes into systemic circulation after getting absorbed from small intestine [71]. Vitamin E concentration in plasma level is maintained by liver through the absorption of LDL to the plasma. Transportation of LDL is through a transfer protein by α tocopherol [72]. If any genetic problem may appears in this protein, it may leads to vitamin E deficiency in human which induce peripheral neuropathy [73].

Vitamin C (Ascorbic Acid)

Vitamin C cannot be synthesised by human and other primates, while most mammals generate it endogenously in the liver [74]. Dehydroascorbate, which is the oxidised form of vitamin C, hydrolysis to form 2,3-diketo-L-gulonic acid and mediate release of carbon dioxide and components of pentose phosphate cycle. The synthesis of vitamin E can be mediated through renewal of vitamin C [75]. Vitamin C concentration is found to be high in brain. It is a cofactor of dopamine β -hydroxylase, and biosynthesis of catecholamine. It also acts as a free radical scavenger [76]. Vitamin C enters the brain and retain as ascorbic acid. The oxidised form of ascorbic acid is able to enter the BBB through GLUT1 receptor. The investigators concluded that, the blood concentrations of dehydroascorbic acid directly proportional to the vitamin C concentration in brain [12].

Recent literature has consistently shown an association between periodontal diseases and neurodegeneration [10-12]. So, the possibility that periodontal infections may contribute to

neurodegenerative diseases pathogenesis can't be excluded. Hence, more number of interventional studies and multicentre longitudinal studies, with large sample sizes should be carried out to prove causal relationship between periodontal infections and neurodegeneration. Also, preventive measures like use of antioxidants and supportive periodontal therapy should be taken to guarantee neurodegenerative patients a high quality of life.

CONCLUSION

Neurodegenerative disorders involve a complex pathophysiology and exact etiopathogenesis is still unknown. Presence of chronic inflammation has been suggested as a central mechanism for neurodegenerative disorders which is the common link between periodontal diseases and neurodegeneration. Like periodontitis, ROS is the key mediator in the progression of neurodegenerative disease which is released due to bacterial invasion into host cells. Possible pathway and contributions from periodontal infections and role of antioxidants in neurodegeneration have been discussed here. Presently, it may be stated that periodontal infections may pose as a potential risk factor for the development of neurodegenerative disorders. Patients, particularly of older age group should be strongly motivated towards oral hygiene maintenance and periodontal care, in mutual coordination of dental professionals and neurologist.

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