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Perspective

Does periodontitis really play a role in dementia? - Novel evidence from molecular insights

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Periodontitis is a disease characterized with acute and chronic inflammatory condition which invades the periodontal apparatus. It results from a complex interplay of bacterial infection and host response, often influenced by lifestyle, systemic diseases, and genetic factors. Many epidemiological researches have shown evidence of a link between severe periodontitis and several systemic diseases. Diabetes mellitus and cardiovascular diseases are two of then.[1,2] Dementia is a silent disorder that might start from midlife and eventually manifest as symptomatic dementia in late-life.[3] Some Epidemiological studies investigated the co-occurrence of periodontitis and dementia.[3] But this conclusion may be misled by periodontitis caused by disability to keep oral hygiene in patients with dementia. Others found that pathogens of periodontitis had been discovered related to dementia through study of antibody to pathogens and clinical measurements of periodontitis.[4]

Hypotheses had been proposed to explain the pathophysiological mechanisms between periodontitis and dementia,[5] yet no direct evidences were produced.

Recent study by Dominy et al. has provided evidence for causality of periodontitis in Alzheimer's disease.[6] Oral infection of *porphyromonas gingivalis* (*Porphyromonas gingivalis)*, a key pathogen of chronic periodontitis, has been shown to resulted in brain colonization and increased amyloid β peptide $(A\beta)_{1-42}$ formation in mice. The cysteine proteases of gingipains, the major virulence factors produced from *P. gingivalis* are demonstrated to be neurotoxic both in *in vivo* and in *in vitro*, and blocking this virulent protease may reduce production of $A\beta_{1-42}$ and neuroinflammation. In addition, gingipain immunoreactivity was significantly enhanced in brains of Alzheimer's disease individuals,[6] which further confirm the role of bacteria-secreted neurotoxins with and without immunoresponses may critically contribute to the pathogenesis of dementia at least in part.

Several pathological mechanisms of chronic periodontitis to increase incidence of the dementia are proposed, including the penetration of periodontal pathogens and virulent factors, increase of inflammatory mediators, and induction of atherosclerotic changes.[5] The periodontal pathogens have been detected in postmortem brains of

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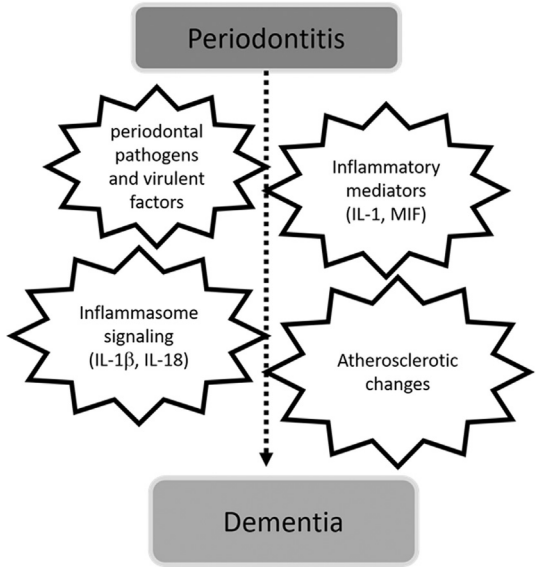

Fig. 1 Role of periodontitis in the pathophysiological mechanisms of dementia. Periodontitis is proposed to induce dementia through penetration of periodontal pathogens and virulent factors, increase of inflammatory mediators, activation of brain inflammasome, and enhancing brain atherosclerosis.

cognitive deficient people. The access routes may through blood—brain barrier, peripheral nerves, and cerebral fluid. Furthermore, the pathological pathogens produce toxins that impact our immune systems then increase more accumulated toxic Aβ peptides and phosphorylated tau protein in brain. The experimental study has demonstrated more Aβ peptides and phosphorylated tau protein accumulation with memory impairment in hippocampus of Alzheimer's mice with periodontitis induced with periodontal pathogen. Besides, the periodontitis produces proinflammatory cytokines that may cause neurodegeneration.

The NLRP3 inflammasome was found to play a role in the pathogenesis of Alzheimer's. NLRP3 inflammasome increase maturation and secretion of interleukin (IL)-1β and IL-18, leading to inflammatory responses. NLRP3 inflammasome is both activated by pathogen or antigen in brain cells. Interestingly, recent study found that NLRP3 inflammasome was upregulated in patients with periodontitis,[7] suggesting the possibility that periodontitis may lead to the genesis of dementia via activation of brain inflammasome. Several agents were under investigated to inhibit inflammasome activity, which may lead to novel therapeutic strategy for periodontitis-induced dementia.

Microphage migration inhibitory factor (MIF), secreted from macrophage during stimulation of bacterial antigens was considered as an inflammatory cytokine. MIF was suggested to play an important role in the pathogenesis of dementia since MIF immunolabeling in microglial cells is associated with amyloid peptide plaques.[8] The epidemiology study showed that MIF was higher in cerebrospinal fluid of dementia participants with cognitive impairment.[9] Thus, MIF-related inflammation may directly contribute to the genesis of amyloid pathology. Peritonitis is a key disease increase circulatory MIF, which supports the pathological role of periodontitis in dementia.

In conclusion, as shown in Fig. 1, periodontitis may increase the risk of dementia through bacteria-released neurotoxin, activation of NLRP3 inflammasome, inflammatory cytokines (MIF, IL-1) and pathologic immune responses. Accordingly, targeting periodontitis-activated novel molecules and periodontitis control is expected to reduce the risk of dementia in aging, and treating periodontitis should have positive effect in preventing dementia and controlling its progress.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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