Systemic Exposure to Lipopolysaccharide from Porphyromonas gingivalis Induces Bone Loss-Correlated Alzheimer’s Disease-Like Pathologies in Middle-Aged Mice

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Background: Alzheimer’s disease (AD) and bone loss are clinically exacerbated. However, the mechanism of exacerbation remains understood.

Objective: We tested our hypothesis that periodontitis is involved in the exacerbation, contributing to AD pathologies.

Methods: The bone, memory, and inflammation in bone and brain were examined in 12-month-old mice after systemic exposure to lipopolysaccharide from Porphyromonas gingivalis (PgLPS) for 3 consecutive weeks.

Results: Compared with control mice, bone loss in tibia (26% decrease) and memory decline (47% decrease) were induced in mice with a positive correlation after exposure to PgLPS (\( r = 0.7378, p = 0.0011 \)). The IL-6 and IL-17 expression in tibia was negatively correlated with the bone volume/total tissue volume (\( r = -0.6619, p = 0.0052; r = -0.7129, p = 0.0019 \)), while that in the cortex was negatively correlated with the memory test latency (\( r = -0.7198, p = 0.0017; p = 0.0351, r = -0.5291 \)). Furthermore, the IL-17 expression in microglia was positively correlated with Aβ42 accumulation in neurons (\( r = 0.8635, p < 0.0001 \)). In cultured MG6 microglia, the PgLPS-increased IL-6 expression was inhibited by a PI3K-specific inhibitor (68% decrease), and that of IL-17 was inhibited by IL-6 antibody (41% decrease). In cultured N2a neurons, conditioned medium from PgLPS-stimulated microglia (MCM) but not PgLPS increased the productions of AβPP, CatB, and Aβ42, which were significantly inhibited by pre-treatment with IL-17 antibody (67%, 51%, and 41% decrease).

Conclusion: These findings demonstrated that chronic systemic exposure to PgLPS simultaneously induces inflammation-dependent bone loss and AD-like pathologies by elevating IL-6 and IL-17 from middle age, suggesting that periodontal bacteria induce exacerbation of bone loss and memory decline, resulting in AD progression.

Keywords: Alzheimer’s disease, amyloid-β, bone loss, interleukin-6, interleukin-17,
lipopolysaccharide from *Porphyromonas gingivalis*, memory decline, microglia, systemic inflammation