Chapter 20
Periodontal Disease as a Possible Risk Factor for Alzheimer's Disease

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Abstract Periodontal disease is a localized infectious disease caused by periodontal disease-related bacteria, such as *Porphyromonas gingivalis*. Recently, Periodontal disease is known to cause systemic spread of chronic inflammation and exacerbate lifestyle-related diseases such as ischemic heart disease, diabetes mellitus, and obesity, while the inflammatory response plays a large role in the development of neurodegenerative conditions such as Alzheimer's disease (AD).

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Mild systemic inflammation has been reported to increase an individual's risk of AD. Inflammation has been thought to spread through the circulatory system and CNS. The increased amounts of inflammatory mediators in the blood are transmitted to the brain and may activate the microglia in the brain. Chronic inflammation in periodontal disease and periodontal disease-related bacteria are transmitted and spread to the brain via a certain mechanism, which might then exacerbate the AD. Periodontal infections are treatable, and thus this may be relevant for preventing and delaying the progression of AD. In this super-aging society, periodontal disease measures will become increasingly important.

Keywords Alzheimer's disease • Amyloid β protein • Chronic inflammation • Cognitive impairment • Lipopolysaccharide • *Porphyromonas gingivalis* • Proinflammatory cytokine • Senile plaque

20.1 Introduction

Rather than systemic diseases being the risk factors for periodontal disease, periodontal disease has been shown to cause systemic diseases, including lifestyle-related diseases. To date, periodontal disease has been reported as a risk factor for diabetes mellitus (DM), cardio- and cerebrovascular disease, aspiration pneumonia, premature and low birth weight infants, bacterial endocarditis, glomerulonephritis, arthritis, and palmoplantar pustulosis [1–5]. The following three pathways are assumed to be the mechanism of the systemic spread of periodontal disease: direct action of bacterial body and toxin of periodontal disease-related bacteria at the local periodontal site that spread to target organs through the hematogenous route or respiratory tract [4]; the action of inflammation-inducing substances such as cytokines, which are produced by the inflammatory response within periodontal tissue or immune response that spread hematogenously to the target organs [5]; and a pathway that results in intracerebral spread through the nervous system [6, 7]. There are various data on intravascular infiltration of periodontal disease-related bacteria and its spread to target organs thus far, but its mechanism of affecting diseases is not fully understood. On the other hand, the inflammatory response has been known to play a large role in the progression of cerebrovascular disorder and dementia, conditions that often occur in the elderly [8–10]; however, the effect of periodontal disease is not fully understood.

Taking other published studies into consideration, here we discuss our most recent analytical results of the correlation between periodontal disease and Alzheimer's disease (AD) in a mouse model in this study.

20.2 Current Status of AD in Japan

More than 30 million people in Japan are >65 years old. In a study group of the Ministry of Health, Labour and Welfare (2013), the number of patients with dementia was 4,620,000 people, while another four million people in the general population are estimated to have it. This number is expected to increase in the future. Among them, 60–70 % patients have AD, which becomes an urgent issue in an advancing aging society such as that in Japan. The current situation of AD involves the absence of an effective prevention method as well as a fundamental treatment method [11].

20.3 Inflammation and AD

In addition to aging and genetic mutation, AD is affected by accumulation of amyloid β protein (Aβ) caused by intracerebral inflammation [12]. Further, Aβ deposits also cause inflammation, which results in the progression of synapse disorders and neuronopathy. In recent years, mutations of the *TREM2* gene, which controls the inflammatory response, has been found in patients with AD, renewing the importance of the inflammatory response in the development of AD [13]. Chronic inflammation is also thought to play an important role in the development of central nervous system (CNS) diseases. The long-term use of non-steroidal anti-inflammatory drugs is known to prevent the occurrence of neurodegenerative disease. Its effect in delaying the progression has been observed in an epidemiologic study and animal experiment [14]. The immune system of the CNS is extremely simple and is not acquired. Accordingly, the immune response is served by the innate immune system.

Microglia are cells of the macrophage system that possesses a phagocytic capacity that plays a central role in the intracerebral innate immune response. The microglia digest the accumulated Aβ in the brain and remove it from the brain. These cells produce cytokines such as active oxygen, interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), i.e., inflammatory response promoting molecules that are known to promote neurodegeneration in AD [15, 16]. On the other hand, they also produce anti-inflammatory molecules such as IL-4 and IL-10, which are thought to provide a neuroprotective role in addition to controlling the inflammatory response [17]. Therefore, microglia are important cells in the control of AD status.

Separately from the exacerbation of AD status due to intracerebral inflammation, mild systemic inflammation has been reported to reduce cognitive function and hippocampal capacity and increase the risk of AD [18–20]. Inflammation has been thought to spread through the circulatory system and CNS. The increased amounts of inflammatory mediators in the blood are transmitted to the brain and may activate the microglia in the brain. The TNF-α level is increased in the blood of patients with AD and reportedly correlates with reduced cognitive function [21, 22].

20.4 Periodontal Disease and AD

As mentioned earlier, chronic inflammation within peripheral organs might play a role in the exacerbation of the molecular pathogenesis of AD. One such inflammatory condition is periodontal disease. The inflammatory response that occurs in periodontal disease has been known to involve the development of various diseases, such as arteriosclerotic disease, DM, and obesity, and the incidence of premature and low birth weight infants [1–5, 23, 24]. In addition, periodontal disease has been reported to involve cerebral abscess formation [25]. Periodontal disease-related bacteria are spread systemically through the blood vessels and respiratory tract, suggesting its possible direct effect on the target organs. In addition, inflammatory mediators such as cytokines, which are produced in the local periodontal tissue, are carried hematogenously to the target organ and thought to worsen the inflammatory response.

There have been interesting reports on the correlation between AD and periodontal disease. *Porphyromonas gingivalis*, a periodontal disease-related bacteria, was found at high frequency in the autopsied brain tissue of patients who died of AD; however, it is not found in normal human brain tissue [26]. This result suggests that said bacteria spread hematogenously into the brain. *P. gingivalis* is a gram-negative anaerobic bacillus that possesses various toxins including lipopolysaccharide. Accordingly, it is known to cause a strong inflammatory response. In addition, the interesting finding is that a periodontal disease-related bacteria of the *Treponema* genus was found in the trigeminal ganglion, brainstem, and cerebral cortex; its frequency is said to be high in patients with AD in particular [6]. This finding suggests that periodontal disease-related bacteria can be directly transmitted into the brain and cause inflammation. The mechanism (hypothesis) of AD exacerbation due to periodontal disease is explained in Fig. 20.1. It will be important to analyze its detailed mechanism in the future. However, it is difficult to believe that AD is induced only by an inflammatory response due to periodontal disease and periodontal disease-related bacteria. Inflammatory responses are thought to aggravate the molecular level of AD, cause an earlier onset, worsen the degree of cognitive disorders, and cause faster progression, suggesting its action in modifying the disease status. The long-term use of anti-inflammatory drugs has been suggested to reduce the risk of AD onset [27].

Periodontal disease is the main cause of tooth loss; however, some reports have identified a correlation between tooth loss and AD. Tooth loss may be a risk factor for AD [28, 29]. Tooth loss reduces chewing function, which results in reduced cerebral blood flow and might lead to reduced cognitive function. However, tooth loss itself often does not accompany chronic inflammatory response, which suggests that the effects of tooth loss are not necessarily identical to those of periodontal disease. Oue et al. found that cognitive function was reduced by tooth removal in AAP transgenic mice, but there was no effect on the molecular pathology of AD [30]. On the other hand, when we induced periodontal disease in the same mouse, we found that intracerebral Aβ deposits increased and the intracerebral

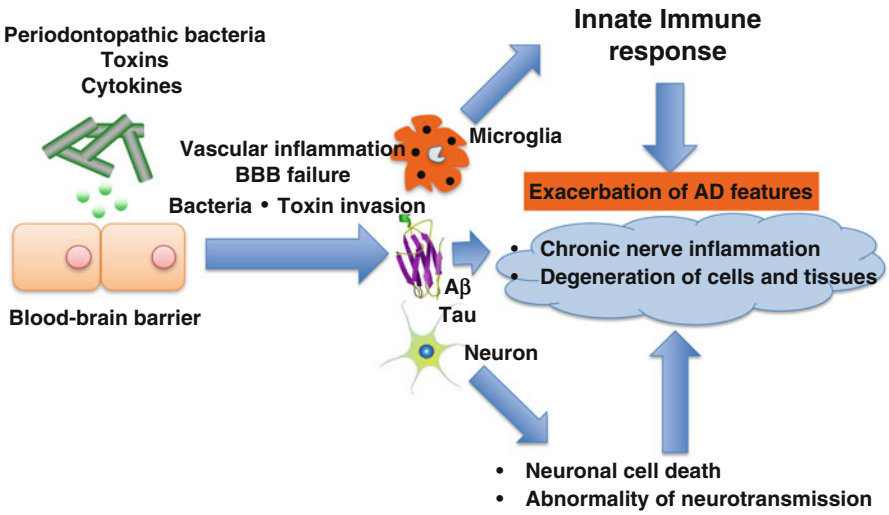

Fig. 20.1 Possible mechanisms by which periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease

inflammatory response was enhanced in addition to the reduced cognitive function. Both periodontal disease and tooth loss reduce cognitive function, but their molecular mechanisms are thought to differ.

20.5 Conclusion

All organisms survive by consuming food; the chewing function is therefore very important. This function not only supports life but could be important to the maintenance of cognitive function. In this modern aging society, preventing periodontal disease and maintaining oral cavity function will become increasingly more important.

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