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Correlation of Chronic Periodontitis with Alzheimer's Disease and Research Progress on Salivary Biomarkers

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Abstract: *Chronic Periodontitis (CP) is one of the most common chronic inflammatory diseases, caused by an oral flora imbalance, which leads to systemic chronic inflammation. Alzheimer's disease (AD), commonly referred to as 'senile dementia', is one of the most prevalent neurodegenerative diseases with an unknown etiology and latent onset in the elderly, posing a significant health challenge in aging societies. Epidemiological evidence indicates a correlation between CP and AD, and effective periodontal basic treatment can reduce the risk of AD to some degree. Current studies primarily suggest that CP may induce AD by amplifying neuroinflammation through systemic chronic inflammation or by direct invasion of CP-related pathogens into the brain, but the specific mechanism remains unclear, and there is a shortage of effective tools for early diagnosis of both diseases. Therefore, this paper summarizes the correlation studies between CP and AD and the possible mechanism of action, and emphasizes the feasibility of saliva as a biomarker of these two diseases, with a view to providing possible ideas for the early prevention and treatment of CP and AD.*

Keywords: *chronic periodontitis; Alzheimers disease; neuroinflammation; Porphyromonas gingivalis; saliva*

1. Introduction

Chronic Periodontitis (CP) is a chronic inflammatory condition characterized by microenvironment imbalance. On the basis of the fourth national oral health epidemiological data: periodontal disease incidence of various age groups in China are still in the high and increased with age and , is the leading cause of adult tooth loss[1]. A large amount of clinical data indicates that CP is closely associated with cardiovascular disease, inflammatory bowel disease, Alzheimer's disease, and other chronic conditions.

Alzheimers disease (AD), a neurodegenerative disease with unknown pathogenesis and latent symptoms, commonly known as "Alzheimer's disease", is divided into early-onset and late-onset, of which early-onset is mainly determined by genetic factors, while late-onset mainly occurs in people over 65 years old, and is influenced by the combined effects of risk and environmental factors [2].The key pathogenic mechanisms of AD include A β aggregation, Tau protein (Tau) hyperphosphorylation, and neurofibrillary tangles (NFTs). Inflammatory responses play a crucial role in the onset and progression of AD. The initial symptoms of AD are subtle and may manifest only in cognitive changes, making them easy to overlook and thus miss the optimal treatment window. Currently, there is no definitive treatment available[3]. The prevention and early treatment of AD are now recognized as crucial barriers. The World Health Organization has identified the aging population as a primary health concern for the elderly. Currently, there are approximately 55 million people worldwide living with dementia. A new case of dementia is diagnosed every three seconds, and by 2050, this number is expected to rise to 1.52 million. AD is the most prevalent type, accounting for about 60-80% of cases[4] . The number of AD cases in China is as high as 9.83 million, causing huge economic and social pressure on families and society, and posing a great threat to public health and sustainable development.

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2. Study on correlation between chronic periodontitis and Alzheimer's disease

Epidemiological studies have shown that CP is associated with AD. Studies have shown that the presence of CP increases the risk of cognitive decline in elderly individuals, and there is a significant correlation between the prevalence of CP and cognitive decline. Periodontitis is a risk factor for dementia, and it is more significant in men and women over 60 years old. There is an independent correlation between the degree of CP and low cognitive ability. Moderate to severe CP is significantly correlated with attention and executive function, and every 1mm increase in average clinical attachment loss (CAL) results in a decline in language ability and overall cognitive performance[5].

CP is one of the leading causes of tooth loss in adults, and as indirect clinical evidence to reveal the correlation between CP and AD, scholars have also noted the relationship between tooth loss and cognitive decline. Studies have suggested that a low number of remaining teeth (0-9) may be a predictor of dementia in later life, and a decreased number of teeth may increase the risk of developing AD. This correlation may be based on the effect of chronic inflammation on the central nervous system (CNS), or the decreased chewing function due to tooth loss, which reduces the intake of vitamins and nutrients, thus affecting the CNS. In addition, studies have shown that tooth loss can lead to a decrease in the volume of gray matter and white matter areas in the brain that are associated with memory, learning, and cognition.

3. Possible mechanisms of action between chronic periodontitis and Alzheimer's disease

Currently, the mechanism of action of CP is generally believed to involve AD, which is divided into two main categories, through the indirect effects of chronic systemic inflammation, where long-term bacterial infection induces chronic systemic inflammation that spreads to the CNS and amplifies neural inflammation induced by long-term bacterial infection spread to CNS and amplify neural inflammation; Or bacteria directly infect the CNS via the blood-brain barrier, trigeminal nerve, etc.

The blood-brain barrier (BBB) is composed of important blood capillary endothelial cells, the basement membrane, pericytes, and astrocytic foot processes, is the important guarantee to realize the central nervous system steady state. Damage to the blood-brain barrier (BBB) is a key factor in the pathogenesis of AD. Damage to the blood-brain barrier (BBB) can lead to oxidative and inflammatory reactions in the brain, accelerating the production of Aβ through the activation of related enzyme systems, such as β - and γ -secretases.

3.1. Periodontitis pathogens amplify neuroinflammation through chronic systemic inflammation and induce AD

Generally, in patients with severe chronic periodontitis who have 28 teeth, the area of the periodontal pocket lining can reach 50 to 72 square centimeters, and the permeability of the periodontal epithelium also increases. Repeated episodes of bacteremia, caused by daily chewing, flossing, or tooth loosening, exacerbate the inflammatory state. This chronic inflammatory response can invade the brain through various pathways, leading to an intensified central inflammatory response and ultimately to neurodegenerative diseases. An important cause of neuroinflammation is peripheral infection, while periodontitis, as a common chronic inflammation, affects most middle-aged and elderly people in the world, and oral diseases (especially CP) may be modifiable risk factors for systemic chronic inflammation. It is worth noting that the positive blood culture rate among tooth extraction patients with CP (79.40%) was significantly higher than that among tooth extraction patients without CP (56.50%), indicating that periodontitis can indeed cause peripheral infection.

3.2. Periodontal pathogens and their virulence factors directly invade the central nervous system

More than 700 microorganisms have been isolated from the human oral cavity, and among the many kinds of periodontal pathogens, P. gingivalis is considered to be the key pathogen of CP. In addition, researchers have detected important pathogenic factors and gum protease (Gingipains, GP) of P. gingivalis in the brains of AD patients. This reveals that periodontal pathogens not only affect brain function by raising the level of systemic inflammation but can also directly enter the brain in a particular way and damage the CNS. P.gingivalis is composed of outer membrane vesicles (OMVs) secreted by Gram-negative bacteria, which are composed of outer membrane components, intracellular signaling molecules, iron absorption related proteins and various toxic factors (GP, LPS, etc.). Currently, some

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OMVs are linked to focal oral infections and the pathogenesis of AD. GP, LPS, and their participation in iron intake by proteins provide a molecular pathogenic mechanism, which includes the formation of amyloid plaques in the brain, neuronal tangles, and iron-related cell death.

4. Salivary biomarkers of CP and AD

Saliva is a highly complex and crucial body fluid, containing numerous living substances, including DNA, RNA, proteins, metabolites, and microorganisms.It serves as a medium for salivary function and as a marker for disease diagnosis and detection. The proportion of substances in saliva is dynamic and influenced by external stimuli. Normally, a healthy adult produces about 500-1,500 ml of saliva per day. Studies have shown that saliva is mainly secreted into the mouth by the large salivary glands controlled by the autonomic nervous system, and its initial liquid mainly comes from the intercellular fluid, while the final mixed liquid flowing into the mouth mainly comes from the intercellular fluid and blood. Consequently, various substances present in the blood can also be detected in saliva. It is also proved that it is feasible to use saliva instead of blood, cerebrospinal fluid and other body fluids for noninvasive disease detection.Currently, the screening, diagnosis, and monitoring of various diseases using drug group technology have become research hotspots.

4.1. The CP

At present, more and more scholars are studying the salivary biomarkers of CP. Given the stability and relatively high quality of salivary DNA, it is feasible to develop salivary genomics as markers for periodontitis, such as multiple micrornas in salivary exosomes and exosomal methylation. Salivary proteomics in periodontal inflammation markers mainly some factors, such as saliva MMP - 9 and S100A8 or IL - 6, and the combination of MMP - 8 can be effective in the diagnosis of CP. In terms of saliva metabolism, studies have shown that the metabolism in the saliva of CP patients is very different from that of normal people. CP patients have specific characteristics of saliva metabolism, and the metabolic pathway leading to the disorder is mainly related to inflammation, oxidative stress, immune activation and bacterial energy metabolism. The combination of cadaverine, 5-oxoproline, and histidine yielded satisfactory accuracy in the diagnosis of CP, and 2-pyrrolidinic acid and butyryl putrescine were considered the most consistent metabolites reflecting the dysregulation of oral microbiota in patients with CP.

4.2. The AD

Salivary biomarkers for AD are currently focused on pathological markers of AD itself, such as Aβ40, Aβ42, total Tau protein, and phosphorylated Tau protein. Currently, it is widely believed that the level of A β 42 in the saliva of AD patients is higher than that in the control group, and A β 42 can be utilized to diagnose AD and predict the risk of its future progression. A large number of studies suggest that it is important to establish an efficient serological detection method for the early diagnosis of AD. For instance, Liang [6] et al. proposed a prediction model based on sphingosine-1-phosphate (S1P), ornithine, and phenyllactic acid. In addition by Yilmaz [7] and studies by Huan [8] and others have shown that salivary metabonomics can significantly distinguish between normal (CN), mild cognitive impairment (MCI), and impaired cognitive mild AD patients; Significant accumulation of cholesterol in the saliva of AD patients, coupled with high phenylalanine/tyrosine ratios, has been demonstrated to be a good indicator of AD .

4.3. Common metabolic markers of AD and CP

At present, there are few studies on the common salivary markers of AD and CP,and the occurrence and progression of both diseases are closely linked to the external environment. Therefore, salivary metabolomics has the potential to better monitor and jointly reflect the relationship between the two diseases from a microscopic perspective. Yang [9] et al. found that AD patients had a variety of adverse reactions, including cis-3-(1-cylethyl)-3, 5-cyclohexadiene-1, 2-diol, lauric acid, lignic acid,N, n-dimethylhydroxyethanolamine N, n-dimethylethanolamine n-oxide. It was also confirmed that the imbalance of specific bacterial flora in saliva significantly influenced the metabolic changes associated with AD.Qiu [10] and others suggest that, compared with CN and MCI patients, the severity of CP is greater in patients with AD, and for the first time, characterized AD and MCI patients based on the microbial community of dental plaque and the metabolic characteristics of gingival crevicular fluid using

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metabonomics, the results indicated that five types of bacteria and nineteen types of metabolites are associated with periodontal parameters in the progression of Alzheimer's disease (AD). The detection of purine, amino sugar, nucleotide sugar, lysine, galactose, phenylalanine, tyrosine, tryptophan, aminoacyl-trNA and pyrimidine metabolic pathways can be used for early warning of AD disease process, and provide a reliable basis for early warning of AD.

5. Summary

In recent years, the relationship between AD and CP has received increasing attention, and common mechanisms such as inflammation, oxidative stress, and immune activation have been proposed, which may be the link between the two; however, further studies are still needed to confirm this. With the advent of an aging society, the incidence of these two diseases is becoming more severe, and a wider population is being affected. Therefore, the development of early identification and diagnosis models is becoming increasingly urgent.

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