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Research progress on the relationship between cognitive impairment and oral health

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Abstract: *With the intensification of the aging of population, the number of patients with neurodegenerative diseases such as cognitive impairment is increasing. Patients with cognitive impairment often have poor oral health, which previous studies have suggested that may be related to poor oral hygiene habits. However, studies in recent years have shown that oral diseases may accelerate the development of cognitive impairment through infections and other routes. In this article, the correlation and possible mechanisms of oral health including periodontitis, masticatory function, and oral mucosal disease and cognitive impairment will be elaborated.*

Keywords: *Cognitive impairment, periodontitis, masticatory function, oral mucosal disease*

Cognitive impairment refers to the pathological process of advanced intelligent processing of the brain related to learning, memory and thinking judgment, resulting in severe learning and memory impairment, accompanied by aphasia or apraxia or agnosia. Common neurodegenerative diseases in the elderly, such as Alzheimer's disease, Parkinson's disease, cerebrovascular disease, etc. are accompanied by symptoms of cognitive impairment.

Global rates of dementia are expected to increase three-fold by 2050. The World Health Organization (WHO) estimates that more than 50 million people are currently living with dementia around the world. Based on new data presented at AAIC, it is projected that global dementia prevalence will triple to approximately 152 million by 2050[1]. Most studies have shown that the incidence of periodontitis, the number of caries, and the number of missing teeth in this group are higher than in normal populations, which may be related to poor oral hygiene behavior habits [2]. However, a growing body of studies suggests that the presence of oral health problems can also affect cognitive impairment to some extent. Oral problems may not only be the result of cognitive impairment, but also be a risk factor for cognitive impairment [3]. Poor oral conditions can exacerbate the development of cognitive impairment, such as periodontitis, decreased masticatory function, and candidiasis [4-6].

1. Correlation between periodontitis and cognitive impairment

Systemic inflammation is associated with cognitive decline and the development of dementia [7]. Periodontitis is a common disease in oral diseases, which is an inflammatory disease caused by microorganisms that can lead to periodontal attachment loss[8, 9] .Periodontal bacteria can transfer from periodontal tissue into the bloodstream through blood-borne transmission or release of mediators of inflammation, leading to the development of bacteremia or systemic inflammation [10] .A large amount of epidemiological evidence has shown that there is a certain link with periodontitis and the occurrence of many systemic diseases such as diabetes, atherosclerosis and so on[11-13]. In recent years, studies between periodontal disease and cognitive impairment have also received increasing attention from scholars [4, 14, 15].

Guo Haiying et al. [16] performed a Meta analysis of the correlation between periodontitis and cognitive impairment, and the results showed that moderate or severe periodontitis was significantly associated with cognitive impairment (OR = 2.13), and their periodontal condition deteriorated significantly in patients with cognitive impairment. Cheng-En Sung et al. [17] conducted full-mouth periodontal examinations and cognitive function tests on 4663 participants aged 20-59. Divided into case groups and control groups based on periodontal conditions, studies have shown that after adjusting for all other factors, participants' periodontal status was significantly associated with an increase in cognitive

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test scores (trend p-values=0.014 and 0.038, respectively) indicating that periodontitis is significantly associated with impaired cognitive domains. Masanori Iwasaki[18] et al. have shown through a 5-year cohort study that the presence of heavier periodontitis exacerbates the extent of the original cognitive impairment over time. Some scholars have found that microorganisms of plaque biofilm can enter the brain through blood circulation and peripheral nerve pathways, thereby promoting the occurrence and development of cognitive impairment [19, 20]. Alzheimer's disease (AD) is a common disorder with cognitive impairment, it is related to the deposition of β-amyloid protein (Aβ) in the brain, and the occurrence of inflammation is also an important feature of the deposition [21]. It has been found that periodontitis not only accelerates the deposition of Aβ in the brain [22], but also the systemic inflammation produced by periodontitis also increases the risk of occurrence and development of AD [23-25]. A retrospective cohort study of National Health Insurance Research Database((NHIRD) in Taiwan found that long-term history of periodontitis was significantly associated with the development of AD [17]. Parkinson is also one of the most common disorders associated with cognitive impairment, and a five-year study showed that patients diagnosed with chronic periodontitis at baseline had an increased risk of developing Parkinson's disease compared to the normal population [26].

Infection with periodontitis may lead to the occurrence of systemic infection in three ways [5]. First, oral pathogenic microorganisms: oral pathogens produce lipopolysaccharides of toxic products, resulting in the increase of glial cell, IL-1, TNF-a, and β-amyloid precursor proteins, and the degeneration of hippocampal pyramidal neurons, spatial working memory, and decreased hippocampal and temporal lobe size associated with lateral ventricle increases. Second, Inflammatory effect: Inflammation can cause an increase in cytokines, acute reactive proteins, complement, Thus stimulating the production of Aβ and contributing to aggregation. Third, Changes in blood vessels: Oral pathogens such as Porphyrinos gingivali, Streptococcus sanguis can lead to platelet aggregation, which is the main source of amyloid precursor proteins (APP), and platelet aggregation associated with cerebrovascular lesions may increase the production of Aβ in the brain.

In recent years, there have been more and more studies on Porphyrinos gingivalis (P.gingivalis) and AD. P.gingivalis is the main pathogen of chronic periodontitis, and scholars have found the presence of P.gingivalis in the brains of Alzheimer's patients [27]. P.gingivalis in the human brain drives NLRP3 inflammatory body activation, ASC spot aggregation, and subsequent Aβ plaque formation by releasing protein liposomals containing large amounts of gingival proteases (Gingipains). Aβ has been shown to be an antimicrobial peptide, a persistently high level of antibacterial Aβ caused by chronic gingival porphyria infections in the brain that may be toxic to host cells. Both human apolipoprotein (APOE) and tau are targets of gingipains hydrolysis, a mechanism that can produce neurotoxic APOE fragments in the AD brain that directly damage tau or either gingipains activates human proteases to act on tau, while tau truncation and fragmentation play a key role in inducing insoluble and hyperphosphorylated tau formation in AD [28].

Existing research suggests a latent correlation between periodontitis and cognitive impairment, and inflammation may be a key factor linking the two [5]. However, more sample size trials are needed to assess whether periodontitis may be a risk factor for the development or development of cognitive disorders that affect quality of life in older adults. Whether inflammation caused by cognitive impairment promotes the occurrence and development of periodontitis is also worth further study.

2. Correlation between masticatory function and cognitive impairment

The masticatory function is closely related to the number and location of teeth left in the mouth. The incidence of tooth loss is high in older adults, with a prevalence of 4.1 percent and a maximum of about 25 percent in adults aged 75 to 79 years[29], and the rate of tooth loss is higher in people with cognitive impairment than in non-cognitively impaired people [30].In recent years, several studies have suggested that masticatory function is associated with cognitive decline, tooth loss increases the risk of cognitive impairment and dementia [31-37].The number of posterior occlusal contacts has a greater impact on masticatory function, and the lack of posterior occlusal support has a greater impact on cognitive decline than other teeth [38] .

Gao Wei [39] et al. have concluded that after excluding socioeconomic factors and systemic health factors, the number of missing teeth is significantly correlated with cognitive impairment, and chewing dysfunction caused by tooth loss is a potential risk factor for cognitive impairment. Studies by foreign scholar Mónica G. Cardoso[40]et al. have also come to a similar conclusion: the higher the elderly population with functional chewing units, the higher the score of the mental status assessment scale, and

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the less degree of cognitive impairment. A 22-year study showed that a decline in masticatory function accelerates cognitive decline [41].

The causes of cognitive decline caused by decreased masticatory function are not yet clear. Experimental studies in animals have shown that the synaptic density of the cerebral cortex of mice with impaired masticatory function is reduced, the function of the cholinergic neurotransmitter system is disrupted, and the hippocampal acetylcholine (ACh) is associated with the spatial memory function of rodents [42, 43] .Chewing gum for 3 minutes with full chewing improves spatial working memory and episodic memory (assessed by immediate and delayed word recall) compared to chewing empty or not [44]. Executive function is a cognitive function in which the prefrontal cortex is highly involved. A significant negative correlation has been found between executive function and a component of the functional state of the reactive chewing system, temporomandibular joint disorders [45]. Normal masticatory function may be a protective factor in patients with cognitive impairment and neurodegenerative diseases, which may be due to the fact that chewing can increase cerebral blood flow and improve associated central nervous system and sympathetic activity [3, 46, 47]. In addition, studies have shown that removable dentures produce 30 to 60% chewability of natural dentitions, while full dentures are 10 to 40%. Fixed denture restorations produce relatively high chewing power compared to movable dentures [48]. However, even when a denture is worn after tooth loss, when the function of the chewing system is reduced due to the reduction in the number of teeth, the restoration cannot achieve the maximum bite force before the tooth loss [49-51].

For the evaluation of masticatory function, there are instrumental assays, chewing peanuts methods, etc. which require the help of measuring instruments or tools, and the operation is complex. In 1990, the Dutch scholar Eichner proposed the Eichner Index [52], which is based on the location of the missing teeth and the support area of the bite of the teeth for classification, the molar area and the anterior molar area of the upper and lower jaws are used as the 4 occlusal support areas, and the presence or absence of the occlusal area is used as the criterion for classification. Studies have shown that the Eichner classification can express the masticatory function well [53, 54]. It is also widely used in clinical research [54-56]. However, further research is needed to improve our current understanding of the relationship between chewing and cognitive function.

3. Correlation between oral mucosal disease and cognitive impairment

The oral mucosa of the elderly is in poor condition [57, 58]. Oral mucosal diseases such as ulcers, denture stomatitis, and candidiasis are found to occur more frequently in cognitively impaired populations than in normal [5, 59-61].

Oral fungal infections are an opportunistic infection and is common in the elderly, especially oral candidiasis. With an increase in the geriatric population, there is a sharp increase in severe systemic fungal infections in this age group [62]. Oral fungi are found in periodontal pockets, in the root canal, on the mucous membranes, and on dentures. Denture stomatitis is common in older adults wearing dentures that are heavily contaminated with fungi, which can be a source of systemic mycosis [63, 64]. Depending on the variety of fungi detected in the AD brain, fungal infection is clearly identified as a causative agent and risk factor for AD [65-67]. Scholars have found that candida infection leads to an increase in the body's acetaldehyde production, and elevated acetaldehyde levels may be involved in the formation of sasolino and its metabolites in the brain, leading to the destruction of substantia nigra dopaminergic cells, thus affecting the progression of cognitive impairment [7]. Animal experiments have shown that blood-borne infections caused by Candida albicans can cause damage to the central nervous system of mice, leading to memory impairment, the mechanism of which may be fungal-induced glial granulomas: Focal glial hyperplasia around fungal cells and deposition of amyloid precursor proteins and amyloid β peptides. The formation of these granulomas is accompanied by increased production of cytokines IL-1β, IL-6, and tumor necrosis factor, as well as increased phagocytosis of microglia, resulting in the infection of brain [68]. In addition, research by Jos éAntonio [69]et al. found that more than 70% of patients diagnosed with cognitive impairment or dementia have symptoms of dry mouth of varying degrees. This may be related to the medications taken by people with cognitive impairment.

Recent studies have found that there may be early markers of cognitive impairment on the oral mucosa. Since the buccal mucosa originates from the ectoderm along with the central nervous system, the buccal mucosa may reflect potential changes in the pathology of central nervous system diseases. Studies have shown that individuals clinically diagnosed with AD and not taking any medications have significantly different buccal cell group characteristics compared to age- and sex-matched controls:

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neutral lipid content, Basal cells, cleft cells, and concentrated chromatin cells are significantly reduced (the latter two are biomarkers of cell death) [70-72].Another study found that phosphorylated Tau protein (p-Tau) and Tau transcripts were found in the oral mucosa of cognitively impaired subjects in higher amounts than in healthy subjects [73, 74] (Abnormal hyperphosphorylation of the Tau protein in the brains of patients with AD, losing normal biological function.).Scholars have found that oral keratin 14 and multiple blood markers of AD are found in patients with mild cognitive impairment and in patients with confirmed AD. Buccal cells have the potential to become a new diagnostic method for early identification of individuals with MCI and AD[75].Compared with cerebrospinal fluid and serological markers, the extraction of buccal cells is more minimally invasive or even non-invasive, which provides new ideas for the diagnosis of cognitive impairment, and further research is needed.

4. Conclusion

Periodontitis, decreased masticatory function, and oral mucosal diseases may cause impairment of cognitive function. With the intensification of the aging of the population, the cognitive health problems and oral health problems of the elderly are gradually emerging, and once the cognitive impairment is diagnosed, the cost and energy spent on follow-up treatment are very large, which is also a challenge for families and medical resources. Therefore, it is more necessary for us to pay attention to this problem early and intervene in oral health problems as early as possible. However, more clinical and epidemiological evidence is needed to further explore the correlation between cognitive impairment and oral health traits.

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