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Doctoral dissertation

Analysis of the correlation between periodontal inflammation and Alzheimer's disease – the role of infectious agents and the activation and response of peripheral immune cells

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SUMMARY

Alzheimer's disease (AD) is the most common dementia type worldwide, accounting for 60 to 80% of all cases. Unfortunately, as average life expectancy increases, the number of dementia cases is also increasing, for which age is the most significant risk factor. Currently, AD is considered one of the most serious social and economic challenges requiring urgent intervention. For many decades the amyloid cascade hypothesis dominated AD research, indicating that deposits of amyloid-beta peptide (Aβ) in the brain play a major role in the pathophysiology of AD. However, recent findings have significantly altered this view. Nowadays, AD is considered not only as neurodegenerative disease of the brain but rather as systemic disease, as it affects both the central nervous system and systemic processes. Changes in the inflammatory response in the brain, as well as in the adaptive and innate immune responses, seem crucial for fully understanding its causes.

An additional source of inflammatory molecules in the brain may be infections, including those involving the oral cavity, such as periodontal disease (PeD). As a result, PeD and changes in the composition of the oral microbiota may play a key role in the pathogenesis of AD. Due to the close anatomical location of the oral cavity and the brain, there is a possibility of infiltration of the brain by periopathogens and their metabolites. This contributes to the development of inflammation in the brain, leading to the activation of resident immune cells, accumulation of pathological proteins including Aβ, neuronal death, and neurodegeneration. Preliminary studies confirm that inflammation caused by periopathogens may be one of the factors accelerating the development of AD, but the relationship between these two disorders has not yet been fully explained, justifying the need for further research in this area. AD is a leading cause of mortality worldwide; therefore, expanding knowledge about the role of the oral microbiome and immune response in the pathogenesis of AD is crucial.

The main objective of this study was a comprehensive analysis of the interdependencies between AD and PeD at the clinical level, the functioning of peripheral immune cells, and at molecular and microbiological levels. Understanding these mechanisms is important for developing new, effective therapies that stop or delay disease progression. The relationship between PeD, inflammatory activation, and

clinical parameters in AD was determined using an *ex vivo* model of isolated peripheral blood leukocytes (PBLs), which were assessed for activation and immune response to bacterial and viral antigens. The study utilized lipopolysaccharide from the periopathogen *Porphyromonas gingivalis* (LPS-PG) and the indicatory virus VSV (*vesicular stomatitis virus*) to determine the level of innate immune response. Subsequently, an analysis of pro- and anti-inflammatory molecules was conducted, as well as the expression levels of genes associated with activation and regulation of the inflammatory response. The relationship between clinical parameters in AD, gene polymorphisms associated with the immune response (hyper-inflammatory phenotype), and the species composition of the oral microbiota was also examined.

Based on the analysis of clinical parameters, it was found that there is a close relationship between the occurrence of AD and PeD, and that the burden of periodontal inflammation in patients with dementia may significantly affect the deterioration of cognitive functions and progression of AD. The conducted studies established that significant changes occur in the composition of peripheral immune cells during the course of AD, which may be associated with the weakening of patients' innate immunity. Following infection of cells with the indicatory virus VSV, patients with AD exhibited significantly lower concentrations of secreted pro-inflammatory cytokines, suggesting that they generally have lower innate immunity than healthy individuals. However, it was not found that the burden of periodontal inflammation was associated with the level of innate immunity in cognitively healthy individuals. At the molecular level, peripheral immune cells of patients with AD were characterized by decreased production of inflammatory mediators while exhibiting a rapid immune response to a bacterial antigen (LPS-PG). A significantly greater release of inflammatory mediators was observed in individuals with AD than in cognitively healthy individuals, which may indicate that the cells of patients with AD undergo hyperactivation. Additionally, increased expression of the *AP-1* gene among AD patients may be associated with the increased periodontal inflammation, which could explain the higher expression of cytokines in response to LPS-PG. Differences were also observed in the composition of the oral microbiota between cognitively healthy individuals and those with AD. Patients with AD were characterized by a higher proportion of *Bacteroidetes* bacteria and lower *Proteobacteria* than cognitively healthy individuals.

The conducted studies confirm that PeD, as an infectious and inflammatory disease, is an additional significant burden on the immune system of patients suffering from AD. This affects the overall condition and status of peripheral immune cells and leads to the persistence of chronic low-grade systemic inflammation. Therefore, a priority in the field of mental health should be the implementation of diagnostics for periodontal inflammation (PeD) among individuals with cognitive impairments and dementia, especially of the Alzheimer's type (AD). It should be also considered to permanently include periodontal treatment in the protocol for managing patients with dementia and those exhibiting mild cognitive impairments. Medical personnel, such as nurses, psychiatrists, and dentists, should be trained and continually inform patients about the necessary of prevention of PeD to avoid future mental health consequences.