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Exploring the Association between Oral Microbiome and Mild Cognitive Impairment: A Narrative Review

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Abstract

Objective: Some studies have investigated the association between oral microbiome and mild cognitive impairment (MCI). However, there needs to be more narrative reviews synthesizing this evidence. This study aimed to bridge this gap in the current knowledge. Methods: A comprehensive search was conducted on PubMed (MEDLINE) to identify studies examining the association between the oral microbiome and MCI. Search parameters and inclusion criteria were clearly defined, encompassing terms related to the oral microbiome, MCI, and their association. Two authors independently selected relevant studies and performed data extraction. Result: Four studies were included. Two cohort studies and two case-control reported an association between the oral microbiome and MCI. Conclusion: Based on the evidence synthesized from the included studies, the review suggests an association between MCI and the oral microbiome. Specifically, all included studies identified significant differences in the abundance of specific microbial species between individuals with MCI and those with normal cognitive function, underscoring the potential role of these species in neuroinflammatory diseases.

Keywords

Microbiota, Neurocognitive Disorders, Neuroinflammations, Alzheimer's Disease, Cognitive Dysfunction, Neuroinflammatory Disorder

1. Introduction

Alzheimer's disease (AD), which is characterized by many cognitive impairments such as dysfunction of memory and intellectual disabilities, is affecting over 55 million people in 2020 and is going to duplicate every 20 years [1] [2]. AD is caused by extracellular deposits of β-amyloid (Aβ) in the brain with reactive microgliosis, intracellular neurofibrillary tangles with loss of neurons, and synaptic disorders [3].

Mild cognitive impairment (MCI) is the reversible phase between normal cognitive status and dementia [2]. Individuals with MIC are at a higher risk for dementia (1% - 2%) and identified by higher cognitive alternations at their age and education level; however, they don't show disability in daily life tasks [1] [2]. MCI is valued clinically as it is a predictor for dementia [4].

The oral microbiome consists of over 1000 species of bacteria, viruses, fungi, and protozoa, with the microbiome as the dominant percentage [5]. Although the womb of the fetus is usually sterile, recent studies found intrauterine environment colonization of oral microorganisms, particularly in amniotic fluid, in approximately 70 % of pregnant women. The first contact of the newborn baby with microorganisms is during delivery and from the microflora of the uterus and vagina of the mother. Besides, the oral cavity of newborn babies is inoculated with microorganisms from the first feeding, which starts the process of the possession of oral microflora. However, the oral microorganism seems to be affected by the environment. In other words, the oral microbiome is altered remarkably in composition and activity. It develops dynamically with the host, as the host's diet, PH changes, interaction among microorganisms, and gene mutations affect the oral bacteria [6]. Disturbance in the balance of diversity in the microbial population and healthy microbes or increasing pathogenic microbes would lead to oral dysbiosis [5]. This condition can cause oral diseases such as periodontitis, dental caries, gingivitis, and oral lesions [5]. Oral microbes, which are directly affected by infection and the indirect impact of inflammation, could lead to neurological diseases [2] [7]. Several human studies showed oral bacteria in brain samples with AD diagnosis. It has been investigated that the higher IgG levels against oral pathogenic microbes in AD patients [8] [9]. Moreover, in AD patients, the diversity of oral microbes decreases [8].

Most previous studies on the relationship between oral microbiome and cognitive diseases enrolled AD patients, and few studies worked on MCI patients. However, the association between oral microbiome and MCI as a contributing factor for AD is important to find preventive strategies for AD and treatment for MCI. This narrative review aims to synthesize existing research on the association between oral microbiome and MCI.

2. Methods and Materials

For this narrative review, an extensive search of the PubMed database was conducted to identify relevant studies investigating the association between the oral

microbiome and mild cognitive impairment (MCI). The aim was to provide a comprehensive summary and synthesis of the existing literature on this topic.

2.1. Search Strategy

The search terms included combinations and synonyms related to the oral microbiome, MCI, and their association. Terms such as 'oral microbiome,' 'oral flora,' 'oral microorganisms,' 'mild cognitive impairment,' 'cognitive decline,' and 'cognitive dysfunction' were used. Boolean operators (AND, OR) were employed to combine the search terms, and truncation and wildcards were used to capture variations in word endings.

2.2. Data Extraction

Two reviewers independently conducted the data extraction process. The extracted information included the first author, year of publication, study design, sample description, and main findings of each eligible study. This information was compiled to create a comprehensive summary of the literature.

Synthesis:

The findings from the included studies were synthesized narratively. Key themes, patterns, and trends identified from the literature were summarized and presented in a coherent narrative. The emphasis was placed on providing an overview of the existing evidence regarding the association between the oral microbiome and MCI, highlighting the main findings and implications.

3. Results

We included four studies that met the criteria for this narrative review.

3.1. Characteristics of the Included Studies

Table 1 provides an overview of the included studies. The studies were conducted in different regions, including Europe (Switzerland and Sweden) [10] [11], Asia (China) [2], and North America (United States of America) [12]. Two were case-control studies [2] [10], while the others were cohort studies [11] [12]. The sample sizes ranged from 68 to 154 participants. Two studies enrolled patients with both MCI and Alzheimer's disease (AD) [10] [11], while the other studies focused solely on MCI patients [2] [12].

Control groups in the study included cognitively normal individuals [2] [10] [12] and accompanying partners of cognitive impairment patients [11].

3.2. Diagnosis and Sample Collection

The diagnosis of MCI in the included studies was based on various criteria, including the Peterson criteria [2], Winblad criteria [10], Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) [11], and the Uniform Data Set (UDS) [12]. Saliva samples were used for microbial analysis in two studies [2] [11]. In contrast, one study collected samples from the deepest or most

represented periodontal pocket [10], and the other study used oral swabs from multiple oral sites, including the dorsal tongue, hard palate, buccal mucosa, and keratinized gingiva [12].

3.3. Association between Oral Microbiome and MCI

3.3.1. Bacterial Diversity

Regarding alpha diversity indices, one study found that the ecological community of the normal cognition group was richer, with no significant difference in the distribution and abundance of taxa between the two groups. Additionally, the beta diversity showed no significant difference between the groups [2]. In contrast, another study suggested that MCI was significantly associated with higher alpha diversity, particularly in the subgingival microbiome. The beta diversity also exhibited significant differences between the study groups [10]. However, one study did not observe remarkable differences in bacterial diversity among the groups [11]. Furthermore, one study examined both alpha and beta diversity but found no significant differences in either index [12].

Table 1. Overview of included studies.

First author (year)	Country	Characteristics of participants	Diagnosis of MCI	Oral microbiome sampling	Study type	Results
Da *et al.* (2023)	China	MCI = 47 Cognitively normal = 47 Male = 46 Mean age = 73.58 ± 5.25 yo	Peterson criteria	Non-stimulated saliva	Case-control	Gemella haemolysans and Streptococcus gordonii were lower while Veillonella unclassified_Veillonella and Fusobacterium sp._HMT_203 were higher in MCI
Holmer *et al.* (2021)	Sweden	AD = 46 MCI = 40 Subjective cognitive normal = 46 Cognitively healthy = 63 Age = 50 - 80 yo	Winblad criteria	Deepest periodontal pocket	Case-control	Treponema, Prevotella, Campylobacter were higher in MCI Rothia aeria, Corynebacterium durum and several members of Actinomycesgenus were lower
Batthini *et al.* (2020)	Switzerland	Participant = 78	MMSE, chemosensory and CDR	Non-stimulated saliva	Cohort	Depletion of bacterial taxa in MCI Prevotella tannerae, Filifactor alocis and Porphyromonas gingivalis decreased in MCI Cardiobacterium valvarum is increased
Yang *et al.* (2020)	United States of America	MCI = 34 Control = 34 Male = 27	All components of UDS	Soft tissue oral swab	Cohort	Pasteurellacae family were more abundant in MCI and Lautropia Mirabilis lower

3.3.2. Species Difference

One study identified specific species that were significantly enriched in the cognitively normal group, including Streptococcus gordonii, Gemella haemolysans, Peptostreptococcus stomatis, Cardiobacterium hominis, Bosea vestrisii, Prevotella sp._HMT_317, and Olsenella uli. In the MCI group, species such as Megasphaera micronuciformis, Kingella denitrificans, Aggregatibacter sp._HMT_458, Neisseria unclassified_Neisseria, and Fusobacterium sp._HMT_203 were more abundant [2]. Another study found higher levels of Treponema, Prevotella, and Campylobacter in the MCI group compared to the control group, while Rothia aeria, Corynebacterium durum, and several members of the Actinomyces genus were more abundant in controls [10]. The linear discriminant analysis effect size (LEfSe) analysis in one study showed a depletion of certain bacterial taxa in MCI compared to other groups. Specifically, Prevotella tannerae, Filifactor alocis, and Porphyromonas gingivalis were decreased, while Cardiobacterium valvarum was increased. Leptorichia wadei (L. wadei) also increased abundance from cognitively normal with a lower chemosensory score to MCI [11]. In another study, the Pasteurellaceae family was more abundant in the MCI group compared to the control group, whereas Lautropia mirabilis showed the reverse pattern [12].

4. Discussion

This narrative review aimed to provide an overview of empirical studies investigating the association between the oral microbiome and mild cognitive diseases. Four studies met the eligibility criteria and were included in this review.

The included studies used different sampling methods for oral microbiome sequencing, including non-stimulated saliva [2] [11], deepest pocket [10], and soft tissue oral swabs [12]. The diagnosis of MCI was based on different criteria in the included studies. One study [2] used the Petersen criteria, consisting of memory complaints usually corroborated by an informant, objective memory impairment for age, preserved general cognitive function, largely intact functional activities, and not being demented [13]. The other study [10] employed the Winblad criteria, which included characteristics of not being normal, not being demented, cognitive decline, and preserved basic activities of daily living [14]. Another study [11] utilized the MMSE, chemosensory probing, and CDR. The MMSE is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language [15]. The remaining study [12] applied the UDS neuropsychological measures, which consist of brief measures of attention, processing speed, executive function, episodic memory, and language [16].

Regarding the measurement of microbial diversity, three studies [2] [10] [12] considered both alpha and beta diversity, while one study [11] focused only on alpha diversity. Alpha diversity summarizes the structure of an ecological community with respect to its richness (number of taxonomic groups), evenness (distribution or abundance of the groups), or both [17]. Beta diversity is the

amount of variation in species composition among sampling units [18]. Although one study found the MCI group highest with observed richness index of alpha diversity, [10] the other study found the alpha diversity lower in MCI. [2] However, the other two studies [11] [12] did not observe any difference in MCI and normal cognitive group diversity. This discrepancy could be justified as the study with the highest diversity in the MCI groups [10] used samples from the deepest pockets, which can impact the results due to alterations in microbial diversity in pathogenic periodontal pockets [19]. This difference in sampling methods may also explain the observed beta diversity difference between cases and controls despite other studies not finding such differences. Additionally, the Shannon index of alpha diversity in all the other three studies did not show a significant difference between the groups [2] [11] [12]. The only contradiction lies in the richness of microorganisms, with one study finding a significant difference between MCI and cognitively normal groups [2], while the reverse is true for another study [12]. As a result, it can be concluded that microbial diversity does not show a significant difference between individuals with MCI and those with normal cognitive function in physiological saliva samples. However, this finding needs to be further investigated to confirm its validity.

All the included studies found differences between the oral microbiomes of MCI and cognitively normal groups. However, the bacteria that constituted the majority and their distribution did not follow the same trend across different studies. There are several potential explanations for this. Firstly, the different methods used to sample the oral microbiome could have contributed to the observed variations. Secondly, confounding factors, including microbial interactions, may not have been fully accounted for. Lastly, geographic differences could have had a remarkable effect on the oral microbiome's composition characteristics and internal structure [20].

In one study, Gemella haemolysans was significantly abundant in the normal group. The study suggested that this gram-negative bacterium possesses protein components in the culture supernatant that directly suppress the growth of Porphyromonas gingivalis and its virulence factor, gingipains, which are correlated with amyloid plaques [3]. Another study acknowledged the association between periodontal health and a greater abundance of Actinomyces and Rothia, as these two species were found to be higher in controls with healthier periodontal status compared to AD subgroups (such as MCI) with poorer periodontal health, suggesting a higher prevalence of periodontal diseases in groups with different degrees of cognitive dysfunction [10]. Additionally, another study indicated an increase in Leptorchia species, opportunistic bacteria, in MCI, which aligns with the increasing levels of several interleukins as an innate immune response in MCI [11]. Furthermore, one study showed an abundance of the Pasteurellaceae family, with species known for opportunistic pathogenesis and inflammation, in MCI. This family is associated with IL-1α, which has been significantly observed in neuroinflammatory diseases [12].

Previous literature has investigated the association between periodontal diseases and Alzheimer's disease (AD), but fewer studies focus specifically on MCI and the oral microbiome. Further research is needed to better understand the association between MCI and the oral microbiome, especially considering the high rate of progression from MCI to dementia. This knowledge could inform the development of new treatment approaches targeting the oral microbiome to address MCI.

5. Conclusion

This narrative review indicates an association between MCI and the oral microbiome based on the findings of the included studies. However, it's important to note the limitations inherent in the scope of this review, including the limited number of evaluated studies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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