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REVIEW ARTICLE

MICROBES AND THE DEVELOPMENT OF DEMENTIA

MIKROORGANIZMY A ROZWÓJ OTĘPIENIA

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ABSTRACT

Introduction

Dementia represents one of the greatest challenges of modern medicine related to the ageing of the global population. The growing number of elderly people is contributing to an increase in the number of patients with dementing diseases, creating significant public health implications. The pathogenesis of diseases such as Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) or vascular dementia (VaD) is not fully understood. Recent theories suggest a possible involvement of microorganisms in the development of dementia.

Aim

The aim of this review is to assess the current knowledge of the likely contribution of microorganisms to the manifestation of dementia and their potential role as diagnostic and prognostic factors in the future.

Material and methods

Our review involved freely accessible databases: PubMed, Google Scholar, ScienceDirect, using keywords such as: dementia, microbes, virulent factors, neuroinflammation, neurodegenerative disorders.

Results

This review highlights the likely relationship between microorganisms such as Porphyromonas gingivalis and Helicobacter pylori and the development of dementing diseases such as Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies and vascular dementia.

Conclusions

Microorganisms including Porphyromonas gingivalis and Helicobacter pylori and their virulent factors are most likely to be involved in the pathogenesis of dementia diseases. Among these are lipopolysaccharide (LPS), gingipains and cytotoxin-associated protein A (CagA).

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STRESZCZENIE

Wstęp

Otępienie stanowi jedno z największych wyzwań współczesnej medycyny związanych ze starzeniem się populacji ogólnoświatowej. Rosnąca ilość osób starszych przyczynia się do zwiększenia ilości pacjentów z chorobami otępiennymi, co stwarza istotne implikacje dla zdrowia publicznego. Patogeneza chorób takich jak choroba Alzheimera (AD), otępienie czołowo-skroniowe (FTD), otępienie z ciałami Lewy'ego (DLB) czy otępienie nacznyniowe (VaD) nie jest do końca poznana. Najnowsze teorie sugerują możliwy udział mikroorganizmów w powstawaniu otępienia w tych chorobach.

Cel

Celem niniejszego przeglądu jest ocena aktualnej wiedzy na temat prawdopodobnego udziału mikroorganizmów w ujawnieniu się otępienia oraz ich potencjalnej roli jako czynników diagnostycznych i prognostycznych w przyszłości.

Materiał i metody

Nasz przegląd obejmował ogólnodostępne bazy danych: PubMed, Google Scholar, ScienceDirect, przy użyciu słów kluczowych takich jak: otępienie, mikroorganizmy, czynniki wirulentne, neurozapalenie, choroby neurodegeneracyjne.

Wyniki

W niniejszym przeglądzie zwrócono uwagę na prawdopodobną zależność między mikroorganizmami takimi jak Porphyromonas gingivalis i Helicobacter pylori a rozwojem chorób otępiennych takich jak: choroba Alzheimera, otępienie czołowo-skroniowego, otępienie z ciałami Lewy'ego i otępienie naczyniowe.

Wnioski

Mikroorganizmy m.in. Porphyromonas gingivalis i Helicobacter pylori oraz ich czynniki wirulentne najprawdopodobniej uczestniczą w patogenezie chorób otępiennych. Wśród nich wymienia się: lipopolisacharyd (LPS), gingipainy oraz białko A związane z cytotoksyną (CagA).

Słowa kluczowe: porphyropmonas gingivalis, helicobacter pylori, czynniki wirulentne, choroby neurodegeneracyjne

Introduction

Dementia is a significant public health challenge and an escalating burden due to the aging global population. It is a syndrome characterized by progressive impairment of cognitive functions, including memory, reasoning, and executive abilities. Rather than a single disease, dementia is best understood as a syndrome encompassing several subtypes, including Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and vascular dementia (VaD) (Guerreiro *et al.* 2020). The etiology of dementia is multifactorial, involving primary neurological, neuropsychiatric, and systemic medical conditions. It is frequently the case that multiple underlying pathologies converge in a single patient to produce the clinical manifestations of dementia (Błaszczyk

2022). In earlier years, research on dementia has focused on genetic predispositions – such as mutations in the APP, PSEN1, and PSEN2 genes, and on pathophysiological mechanisms, including the deposition of beta-amyloid plaques (Aβ) and tau protein aggregates in the brain (Van Cauwenberghe *et al.* 2016). However, a growing body of evidence highlights the critical role of microorganisms, both pathogenic and symbiotic, in the initiation and progression of neurodegenerative processes. Recent studies have increasingly emphasized the gut-brain axis (GBA), which underscores the multidimensional interplay between the gut microbiota and the central nervous system (CNS) (Seo and Holtzman 2024). The gut microbial communities play essential roles in maintaining physiological homeostasis and regulating metabolic processes, including immune system development, nutrient absorption, and vitamin synthesis (Bain and Cerovic 2020). Emerging evidence indicates that alterations in the gut microbiota, known as dysbiosis, are associated with dementia (Stadlbauer *et al.* 2020). Dysbiosis has been linked to chronic systemic inflammation, which may influence the brain via several mechanisms, including the release of proinflammatory cytokines (e.g. interleukin 6 (IL-6), tumor necrosis factor (TNF-α)), bacterial metabolites, and neural pathways such as the vagus nerve (Figure 1) (Anand *et al.* 2022). Furthermore, studies investigating bacterial pathogens Porphyromonas gingivalis have suggested their involvement in the pathogenesis of neurodegenerative diseases such as AD (Zhao *et al.* 2024).

The aim of this review is to analyze and synthesize current evidence regarding the role of microorganisms in the pathogenesis of dementia. Considering microorganisms as factors involved in the development of dementia opens new research opportunities and potential therapeutic pathways that could reduce the burden of neurodegenerative diseases in aging societies.

Clinical features of dementia

Dementia is characterized by an acquired, chronic loss of cognitive function caused by brain injury or disease, contributing to progressive impairments in thinking, memory, and behavior, often combined with emotional and language difficulties, hindering occupational or social function (Arvanitakis *et al.* 2019). According to the currently valid fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5), the diagnosis of dementia, defined as major neurocognitive disorder (MND), requires substantial impairment in at least one cognitive domain. The cognitive domains include complex attention, social cognition, language, learning and memory, perceptual-motor/visuospatial function, and executive functioning. Furthermore, to diagnose dementia, the clinician needs to ensure that it cannot be better explained by another mental disorder and that the cognitive impairment does not present exclusively in the context of delirium. Another important factor is the determination of the underlying etiology. On the other hand, a diagnosis of mild cognitive impairment (MCI) is established when there is modest impairment in at least one cognitive domain. In contrast to patients with dementia, individuals affected by MCI are still able to perform everyday activities individually but with great difficulties (Emmady *et al.* 2024).

Studies have demonstrated that healthcare professionals do not diagnose dementia or cognitive impairment properly enough. On the other hand, screening cognitive tests are useful tools to assess patients' cognitive status. One of the most commonly used is the Mini-Mental State Examination (MMSE), however, there are also other tests available: Montreal Cognitive Assessment (MoCA), ACE-R, Abbreviated Mental Test, Clock Drawing Tests, GPCOG, IQCODE, Mini-Cog test, Memory Impairment Screen, verbal fluency test, and others (Tsoi *et al.* 2015). Recent developments in nuclear medicine have provided other possibilities for dementia diagnosis. Positron emission tomography

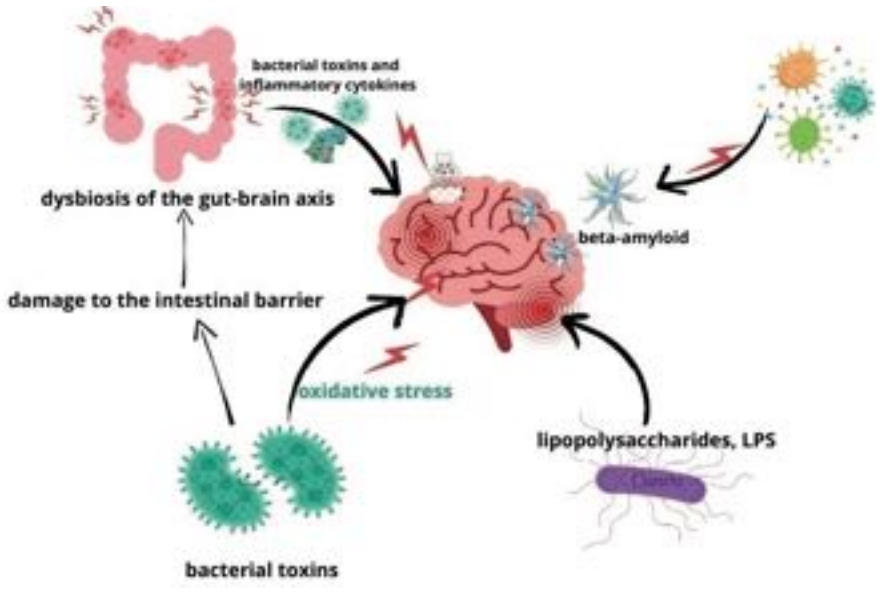

Figure 1. Mechanisms linking microorganisms with dementia. Illustration of the mechanisms linking mie croorganisms with dementia. It presents processes such as dysbiosis of the intestinal microbiota, damage to the gut-brain barrier, direct infections, neuroinflammation and the formation of beta-amyloid deposits.

(PET) plays an important role in the early and specific diagnosis of dementia, contributing to suitable medical management and clinical prognostication (Burkett *et al.* 2022). Since dementia is characterized by neuronal cell loss, currently, there is no curative treatment for this disorder. Nevertheless, therapeutic interventions are used to alleviate the behavioral and cognitive consequences of dementia (Hafiz *et al.* 2023). Indeed, patients affected by dementia often suffer from neuropsychiatric symptoms, which include depression, apathy, aggression, anxiety, irritability, sleep disorders, aberrant motor behaviors, delusions, and others (Radue *et al.* 2019). A 2024 Lancet Commission report provided recommendations for people with dementia stating that neuropsychiatric symptoms should be treated using activity and care-coordinated multicomponent interventions (Livingston *et al.* 2024). Moreover, patients suffering from AD or DLB should use cholinesterase inhibitors and memantine. Interestingly, the Commission determined fourteen risk factors for developing dementia and proposed various actions to reduce dementia risk, such as cognitively stimulating activities, education, hypertension prevention, depression treatment, reduction of air pollution, alcohol consumption, and cigarette smoking. These actions might be promoted by healthcare professionals, contributing to a decrease in dementia prevalence.

Dementia biomarkers

In the early stages of dementia, symptoms may be subtle and inconspicuous, often not becoming apparent until they begin to significantly impair the patient's quality of life. Initially, these symptoms can be misattributed to normal aging processes, thereby delaying the recognition and diagnosis of the condition. As a result, the early diagnosis of dementia remains a major challenge in the field of neurology. For this reason, the identification of reliable diagnostic and prognostic biomarkers has been a focal point of research worldwide for many years.

One of the leading theories of AD pathogenesis suggests that the aggregation of Aβ plays a central role in the development of the disorder. As a result, Aβ has been extensively studied as a potential biomarker in brain imaging, cerebrospinal fluid (CSF) and blood

analysis. PET imaging enables the quantification and localization of Aβ deposits in the brain through the selective binding of the Pittsburgh Compound-B (PiB) ligand. The Aβ40/ Aβ42 ratio in CSF can serve as a valuable diagnostic tool, as it is a highly effective predictor of amyloid positivity in PET imaging. However, there is high costs and invasiveness associated with imaging and CSF analysis. Recent studies have demonstrated that the ratio of plasma APP669-711/Aβ1-42 and Aβ1-40/Aβ1-42 can effectively reflect beta-amyloid burden in the brain (Nakamura *et al.* 2018). Another critical biomarker of AD is neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated tau (p-tau) protein. These intracellular aggregates disrupt microtubule stability, compromise axonal transport, and contribute to neuronal dysfunction and degeneration. P-tau is a relatively specific biomarker for AD, as its concentration in CSF correlates with the extent of NFTs pathology. However, elevations in total tau levels in CSF may reflect not only NFT accumulation but also neuronal and synaptic damage, which occurs in various neurodegenerative disorders as well as in traumatic brain injuries.

FTD is a heterogeneous disorder with different clinical phenotypes, considering the behavioural form (bvFTD) and primary progressive aphasia (PPA). Due to the aggregation of specific proteins, FTD can be divided into: FTLD-TDP (frontotemporal lobar degeneration associated with TDP-43) , FTLD-TAU (frontotemporal lobar degeneration associated with TAU protein) and FTLD-FUS (frontotemporal lobar degeneration associated with FUS protein). The most common subtype of FTD is FTDL-TDP. The pathogenesis of FTLD-TDP is characterized by the accumulation of hyperphosphorylated and ubiquitinated TDP-43, which forms toxic, insoluble aggregates. TDP-43 aggregates in the brain are characteristic of FTLD-TDP, however, the use of TDP-43 as a biomarker is challenging, as it predominantly aggregates in neurons and is not always released in significant amounts into the CSF and blood (Katisko *et al.* 2022). The potential marker for all subtypes of FTD is neurofilament light chain (NfL), which is released into the extracellular space as a result of neuronal damage, from where it can enter both the CSF and bloodstream. Serum levels of NfL have consistently been found to be elevated in patients with FTD with higher levels in patients with FTLD-TDP than with FTLD-TAU. (Abu-Rumeileh *et al.* 2018, Weintraub *et al.* 2021). Furthermore, NfL levels also correlate with disease severity, with higher concentrations reflecting a more advanced clinical phenotype. An additional advantage of NfL as a biomarker is its ability to detect the disease up to 15 years prior to the onset of clinical symptoms (Gifford *et al.* 2023).

The pathogenesis of DLB is primarily driven by the pathological aggregation of α-synuclein which forms insoluble structures known as Lewy bodies, suggesting that α-synuclein could have potential as a biomarker for the disease. However, while total α-synuclein levels in CSF are typically reduced in patients with DLB, these levels can overlap with those observed in control groups and individuals with other neurodegenerative conditions, which reduces the specificity of α-synuclein as a definitive diagnostic marker for DLB (Hanson 2021). Nevertheless, recent studies have shown that oligomeric α-synuclein, when measured in combination with tau protein, holds more promise as a specific biomarker in differentiating DLB from AD (van Steenoven *et al.* 2018).

In case of VaD, its pathogenesis has been linked to malabsorption of cobalamin leading to elevated levels of homocysteine (Hcy), an amino acid whose excessive accumulation contributes to vascular endothelial dysfunction and increased cerebrovascular risk. Hyperhomocysteinemia has been implicated in promoting atherosclerosis, oxidative stress, and neuroinflammation, all of which may exacerbate cerebrovascular pathology and cognitive decline (Nillson *et al.* 2013). Furthermore, clinical studies suggest that elevated Hcy levels are associated with an

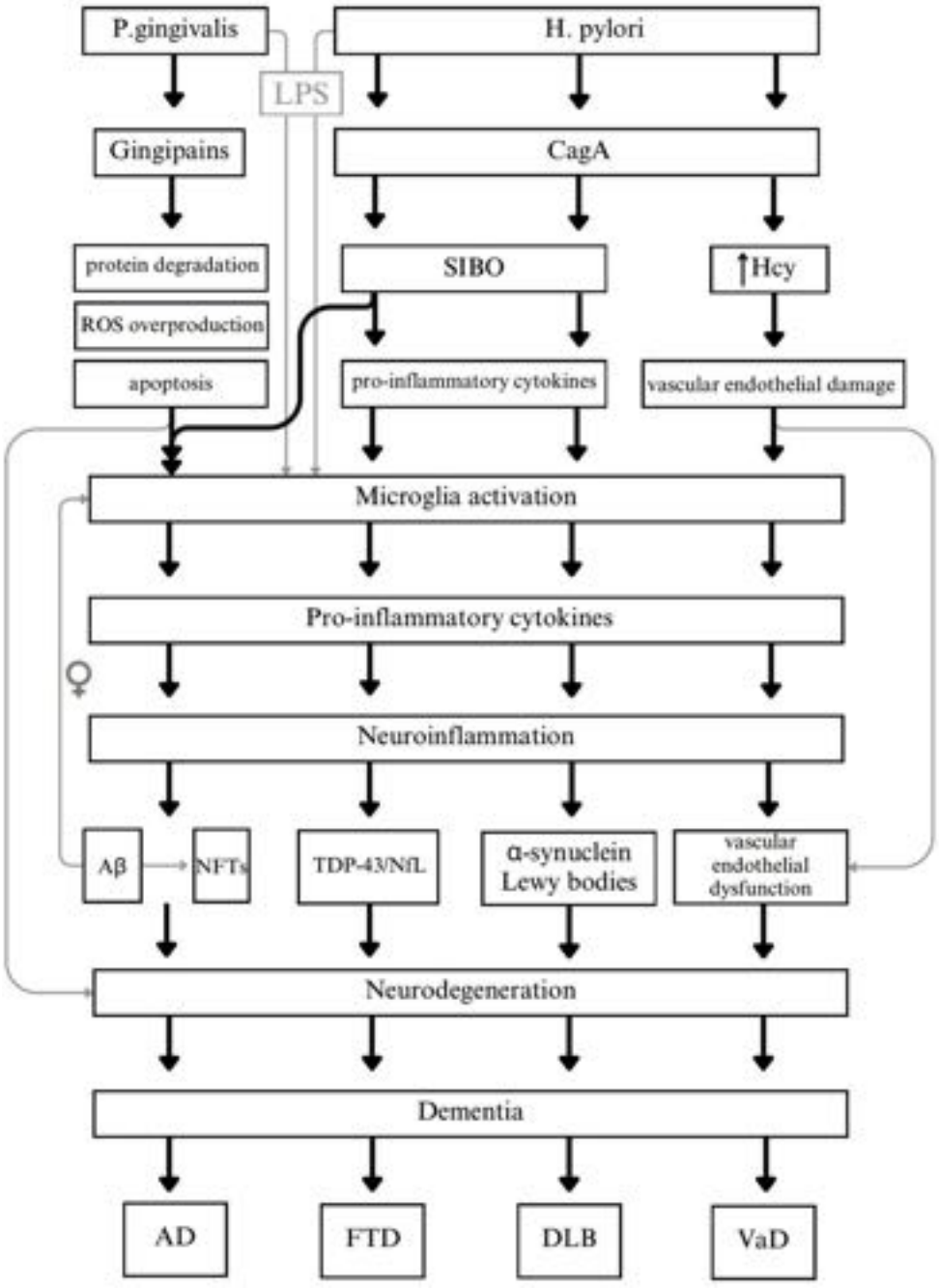

Figure 2. Detailed mechanisms linking microorganisms with AD, FTD, DLV and VaD. LPS – lipopolysaccharide, CagA – cytotoxin-associated protein A, SIBO – small intestinal bacterial overgrowth, ROS – reactive oxygen species, Hcy – homocysteine, Aβ - beta-amyloid plaques, NFTs – neurofibrillary tangles, TDP-43 – TAR DNA-binding protein 43, NfL – neurofilament light chain, AD - Alzheimer's disease, FTD – frontotemporal dementia, DLB – dementia with Lewy bodies, VaD – vascular dementia.

increased risk of progression from MCI to dementia (Zuliani *et al.* 2024).

Emerging research also highlights the potential role of infectious markers in the pathogenesis and progression of various neurodegenerative diseases. Evidence suggests that microbial infections, viral pathogens, and associated inflammatory responses may contribute to neurodegenerative processes by triggering immune activation, promoting protein misfolding, and exacerbating neuronal damage.

Virulent factors and the development of dementia

Virulence factors are molecules produced by pathogenic microorganisms that are crucial for the initiation and progression of many diseases. They include toxins, adhesins, and other molecules that facilitate attachment to, invasion of, and evasion of host immune defenses. These factors allow pathogens to colonize host tissues, overcome the natural resistance of the microbiome, and adapt the host environment to their advantage (Petersson *et al.* 2023). These molecules are not only critical for the pathogenicity of microorganisms but also represent potential targets for therapeutic interventions. Understanding their mechanisms is crucial for developing innovative strategies to combat infectious diseases and address challenges like antimicrobial resistance. Virulence factors have been implicated in mechanisms such as chronic inflammation, disruption of neuronal homeostasis, and amyloid pathology. The complement system, a critical component of innate immunity, becomes overactivated in response to certain bacterial and viral virulence factors, which leads to neuronal damage and synaptic loss. Pathogens expressing adhesins and other virulence factors can compromise blood-brain barrier (BBB), facilitating their entry into the CNS. Certain microbial virulence factors stimulate the production and aggregation of Aβ, a key pathological hallmark of AD. This process activates the complement system and promotes glial cell-mediated inflammation, further damaging neuronal networks. Microglia, the brain's immune cells, are activated in response to microbial virulence factors. While acute activation is protective, chronic stimulation leads to sustained neuroinflammation and neuronal injury. Persistent infections or continuous exposure to virulence factors exacerbate this microglial overactivation, creating a feedback loop that accelerates neurodegeneration (Shinjyo *et al.* 2021).

Virulence factors represent a significant but underexplored contributor to dementia pathogenesis. Through chronic neuroinflammation, BBB disruption and Aβ aggregation, these microbial components exacerbate neurodegenerative processes. Future research should focus on elucidating these interactions and developing targeted interventions to address this critical aspect of dementia etiology.

Porphyromonas gingivalis, can it cause the development of dementia?

Porphyromonas gingivalis is a gram-negative anaerobic bacterium that is one of the bacterial species that causes periodontitis (Verma *et al.* 2023). This disease is manifested by gingival swelling, vascular congestion, redness, the formation of periodontal pockets, and the progressive destruction of the bone and soft tissues that support the teeth (Fu *et al.* 2023). Periodontal disease is associated with various other disorders including rheumatoid arthritis, cardiovascular disease, type II diabetes and cognitive disorders such as early, middle and/or late dementia and AD (Nara *et al.,* 2021). Emerging evidence indicates a correlation between chronic periodontitis and dementia or sporadic AD (Shinjyo and Kita 2021; Verma *et al.* 2023).

Periodontal bacteria or bacterial particles can enter the brain through the bloodstream or peripheral nerves (Fu *et al.* 2023). Outer membrane vesicles (OMVs) carry various bacteria factors, such as gingipains and LPS, facilitating their delivery to various tissues within the host organism. Gingipains play

a pivotal role in neuronal degeneration by both indirectly activating microglia, thereby inducing chronic neuroinflammation, and directly damaging neurons through the overproduction of reactive oxygen species (ROS), protein degradation, and the promotion of apoptosis (Nara *et al.* 2021). The brain tissue of patients with AD showed higher levels of gingipains than non-AD subjects. A positive correlation was also found between the presence of gingipains and tau load as well as ubiquitin load (Dominy *et al.,* 2019). LPS stimulates cells to produce pro-inflammatory cytokines and its presence has been detected in the postmortem brains of AD patients, whereas it was not found in the brains of non-AD subjects (Poole *et al.* 2013; Verma *et al.* 2023). By activating microglia, LPS facilitates the formation of Aβ, the presence of which triggers a pathophysiological cascade that culminates in the hyperphosphorylation of tau and the accumulation of NFTs (Fu *et al.* 2023). P. gingivalis and its virulence factors not only promote the production of proinflammatory molecules, such as IL-1β, IL-6 and TNF-α, but also decrease the expression of anti-inflammatory mediators including IL-10 and IL-4. Higher level of pro-inflammatory cytokines lead to an increased level of inflammatory mediators in the brain, which directly contributes to neurodegeneration. Therefore, P. gingivalis and its virulence factor may have an impact on the development of dementia.

Helicobacter pylori and dementia development

Helicobacter pylori is a gram-negative bacterium, commonly found in a human stomach after being infected usually during childhood. There are two ways for H. pylori infection to occur – through ingestion or transmission from mother to fetus during pregnancy (Erickson *et al.* 2023). Frequently it causes chronic gastritis leading to pathological conditions such as gastric cancer, peptic ulcer disease or MALT lymphoma. Half of the world human population is infected with H. pylori (Malfertheiner *et al.* 2023). There are many pathogens associated with increased risk of developing dementia and H. Pylori is one of them (Roubaud Baudron *et al.* 2013). H. pylori infection pathomechanism is based on inducing production of interleukins, c-reactive protein (CRP), and TNF-α which promote neuroinflammatory response (Piekut *et al.* 2022). In vitro studies about H. Pylori infection influence were carried out with use of mouse neuroblastoma N2a cells – it turned out that infected cells contributed to increasing hyperphosphorylation of tau protein, which is one of the dementia and AD causes. Those cells produce enhanced amount of presenilin 2 and Aβ42 and above that they activated glycogen synthase kinase-3β (Wang *et al.* 2015).

Another important mechanism in H. pylori infection leading to dementia involve bacteria OMVs, which are important in virulence as they let bacteria release toxins and enzymes to the host. Studies were carried out on Rosa26. tdTomato mouse model using Crerecombinase-labelled OMVs, that enabled detecting the OMVs distribution in a mouse body. This study has shown that OMVs reach not only stomach, but also kidneys, liver and brain. Cells with positive signal were found in brain cortex and hippocampus (Xie *et al.* 2023). This study also has shown increased amount of Aβ in OMVs-treated AppNL-G-F mice brain (mostly in CA1, CA2 and CA3 regions), which is typical for AD.

Those were some mechanisms that were found out in studies on how H. pylori infection may influence dementia development. There are also studies on humans that show H. pylori infection could affect cognitive functioning. Erickson *et al.* (2023) found out there is possible association between H. pylori seropositivity and dementia development as there were statistically significant results for H. pylori positive patients with worse results on the Reasoning task, which is used to measure cognitive functioning. There were also studies on correlation between H. pylori infection and Alzheimer disease. Douros *et al.* (2024) found in their study that the risk of AD after being infected with H. pylori was

increased on 11% in patients at age 50 years old or more. After a decade since H. pylori infection onset occurred, the risk of developing AD surged to 24%. There are few possible explanations for link between these two conditions. H. Pylori infection can induce intestinal dysbiosis, particularly small intestinal bacterial overgrowth (SIBO), which disrupts the gut-brain axis. This dysbiosis promotes the production of pro-inflammatory cytokines and activates pathological pathways that contribute to the development of neurodegenerative disorders, including dementia. Cobalamin malabsorption is commonly associated with H. Pylori infection, resulting in elevated Hcy levels that contribute to vascular endothelial damage. This endothelial dysfunction subsequently triggers microglial activation, which, through the release of pro-inflammatory cytokines, promotes chronic neuroinflammation. Furthermore, damage to the vascular endothelium disrupts normal blood flow and impairs oxygen delivery to neurons, leading to neuronal hypoxia, subsequent neuronal cell death and eventually to VaD. (Cárdenas *et al.* 2019).

Conclusion

The existing literature indicates a significant correlation between microbial infections and the pathogenesis of dementia, with particular emphasis on Porphyromonas gingivalis and Helicobacter pylori. Key mechanisms implicated in this process include chronic inflammation, protein degradation, and disruption of the BBB, all of which may contribute to disease progression. Consequently, the virulence factors of these microorganisms hold potential as biomarkers for the early detection and monitoring of dementia. Further research is required to elucidate the precise impact of these infections on neurodegeneration and to identify effective therapeutic strategies for affected patients.

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