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Editorial: Infection, inflammation, and neurodegeneration: A critical path to Alzheimer's disease, Volume II

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Editorial on the Research Topic

Infection, inflammation and neurodegeneration: A critical path to Alzheimer's disease, Volume II

Alzheimer's disease (AD) is the most prevalent cause of dementia, that represents one of the major health challenges for humanity, with significant social and economic implications. This complex and progressive neurodegenerative disorder is characterized by specific molecular hallmarks, as amyloid beta deposition and neurofibrillary tau tangles. The etiology of this disease is far from being fully understood, and the possibility of an infectious cause has long been debated.

Even Alois Alzheimer, himself, over 100 years ago studied *Treponema pallidum*, the causative agent of syphilis, a spirochete later associated with dementia (Noguchi and Moore, 1913). Oskar Fischer, a contemporary of Alzheimer and also a psychiatrist and neuropathologist, also suggested that microorganisms could form plaques in brain tissues (Fischer, 1907). Sporadic late-onset AD, accounting for ~95–98% of all cases of AD is thought to arise due to a multi-factorial interplay between genetic and environmental factors. Linkage has been identified to risk factors including ApoEε4 expression, chronic neuroinflammation, autoimmune mechanisms, oxidative and mitochondrial damage, cardiovascular factors, diabetes with insulin resistance, trauma to the blood brain barrier and selectively vulnerable brain insult. Thus, infection actually may be the overarching “unifying hypothesis” for sporadic late-onset AD, rather than other more mainstream hypotheses.

This Research Topic represents the efforts of the scientific community to better understand causative factors for sporadic late-onset AD, and lends itself to consider multiple elements and mechanisms participating in the pathogenesis of AD.

Among many factors that may drive the accumulation of amyloid and tau in AD, infectious triggers are some of the most significant and logical choices. In particular, the organisms likely to be involved in AD are those that can evade host immune defenses, gain entry to specific selectively vulnerable regions of the brain, and establish chronic/persistent and/or latent infection. Early studies of infection did not find in AD brains the direct evidence of viral nucleic acid sequences and antigens of cytomegalovirus, measles virus, poliovirus, adenoviruses, hepatitis B virus, and the influenza A and B viruses (Pogo et al., 1987), although other authors have shown the presence of HSV-1 (Ball, 1982; Itzhaki et al., 1997), *Borrelia burgdorferi* (Miklossy, 1993), and *Chlamydia pneumoniae* (Balin et al., 1998; Gerard et al., 2006) in AD brains. Besides that, over the years the hypothesis on the possible role of HSV-1 in AD has been supported by several *in vitro* studies, suggesting that HSV-1 infection and its multiple reactivation can trigger oxidative damage and progressive accumulation of neurotoxic products (Amyloid-beta and hyperphosphorylated Tau aggregates), leading to neurodegeneration and cognitive decline (see: Marocci et al., 2020). Moreover, host immunity and its decline with aging can have an effect on the control of HSV-1 viral reactivation from latency. Epidemiological studies of the IgG avidity index as an indicator of HSV-1 reactivation and the relationships between HSV-1-specific humoral immunity and cortical damage measured by MRI, even in relation with the host genetic pattern (see: Mancuso et al., 2019), allow one to hypothesize the possible protective role of antiviral IgG, although it remains to be confirmed by others.

Moreover, in the last twenty years, other different types of infections have been associated with dementing illnesses, including infection with *Treponema pallidum* (Miklossy, 2011), as well as *Cryptococcus neoformans* (Hoffmann et al., 2009), measles virus (Frings et al., 2002), and HIV (Zhou et al., 2010; Canet et al., 2018). More recently, several studies have correlated SARS-CoV2 virus in furthering the pathogenesis of AD (Fu et al., 2022). Intriguingly, the involvement of the microbiota in AD pathophysiology has also been gaining attention, as it may be a key factor influencing brain function; intestinal microbiota seems to interfere with A β assembly in brain (Wang et al., 2015), but even oral microbiota can play a role in onset and progression of AD (Sureda et al., 2020).

Local periodontal inflammation due to infection with *Helicobacter pylori* (Beydoun et al., 2021), the agent of gastric ulcers, or with *Porphyromonas gingivalis* (Elwishahy et al., 2021), in fact, can stimulate brain tissue inflammation (Dominy et al., 2019). Moreover, Wu et al. provided evidence *in vitro* that *Fusobacterium nucleatum* can increase TNF- α and IL-1 β expression in microglial cells, and also *in vivo* it can increase cognitive impairment, beta-amyloid accumulation and Tau protein phosphorylation in the cerebrum of an AD animal model.

The impact of systemic acute infections on neurodegeneration has been previously evaluated in animal models of chronic neurodegeneration (Cunningham et al., 2009), but only limited data exist on humans. The study of Silva et al. analyzed the neuroinflammatory response triggered by acute systemic inflammation in older subjects with dementia compared to cognitively healthy controls. Using PET imaging, the authors showed that the level of neuroinflammation due to acute systemic infection was reduced in subjects with dementia and/or delirium compared to cognitively healthy participants. Future investigations are warranted to confirm these observations, in order to clarify if “dementia” with changes in brain has a distinct neuroinflammatory profile possibly owing to immunosuppression within the brain in response to acute systemic infection.

Lei et al. conducted a systematic review and meta-analysis to determine the relationship between sepsis survivals and risk of dementia in elderly individuals. They determined that there was an increased risk of all-cause dementia in sepsis survival subjects suggesting the importance of an appropriate management and prevention scheme to preserve cognitive function.

Finally, Nelson explored the hypothesis that infections can contribute to AD through the generation of peripheral amyloids and/or neurovascular dysfunction. After a careful analysis of available data supporting the neurovascular dysfunction and blood-brain barrier permeability in AD, the author proposes in this interesting review a new “peripheral amyloid hypothesis” as a possible actor leading to cognitive impairment.

In summary, we are very grateful to the researchers that contributed with an article as well the reviewers who have contributed with their reviews to the quality of this Research Topic. Overall, this Research Topic and the entire contribution of literature to this hypothesis enables us to consider how infections, and consequently the host immune response, may play a significant role in the etiology of AD. We contend that consideration of infection and subsequent inflammation in the pathogenesis of AD may provide new avenues for intervention to both delay progression and, ultimately, prevent disease.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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