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Infection, neuroinflammation and interventions for healthy brain and longevity

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Abstract

Alzheimer disease (AD) is a disastrous neurodegenerative disease for which presently no consensus exists neither for the etiology nor for the efficacy of treatments. The amyloid hypothesis of the disease pathogenesis predominated during decades stating that amyloid beta (A β) formation and oligomerization is the major cause for AD. Recently, beside the amyloid plaques and neurofibrillary tangles, the neuroinflammation was added as a derivative of these misfolded proteins. However, the recent clinical failure of trials targeting the A β raised again the hypothesis of a possible infectious origin for AD. Even if this hypothesis was first evoked already by Alois Alzheimer, it is not yet fully accepted. Many studies have supported that microorganisms, including spirochetes, herpesviruses and *Porphyromonas gingivalis* play a role in AD and beta-amyloid peptide (A β) is an antimicrobial peptide. These data gave new impetus to the infection hypothesis. In this chapter we will discuss why the amyloid hypothesis by itself does not explain AD, how the infection hypothesis may induce AD, and what are the consequences for a healthy brain considering the numerous treatment avenues for improving the quality of life of the older subjects.

Key words: Infection, Alzheimer's disease, Parkinson's disease, Viruses, Bacteria, neuroinflammation, Vaccination

1. Introduction

As the population is aging, the neurodegenerative diseases are concomitantly increasing (Armstrong 2019). These are progressive diseases causing cognitive alteration starting with memory and language and finally progressing to the complete loss of the patient's personality and functioning (De Marchi et al. 2023). This represents a huge burden to the society. It was recognized for a long time that neuroinflammation represents one of the common convergences of neurodegenerative diseases; however, the origins leading to this neuroinflammation were not clear for decades (Shir and Day, 2022; Zheng W et al. 2023, Han et al. 2024). Finally, it seemed that misfolded proteins produced during neurodegenerescence such as Amyloid beta peptide ($A\beta$) or α -synuclein were considered the major causal factors (Prusiner, 1984). Therefore, the central hypothesis of the development and progression of neurodegenerative diseases was that pathologically formed peptides lead to neuroinflammation which in turn decreases the numbers and functions of synapses, kills the neurons, and results in clinically apparent cognitive disorders (Kepp et al. 2023). Recently, other theories have been put forward, such as the infection origin which will lead to inflammation and only after that the $A\beta$ will be secreted and perpetuate the neuroinflammation (Tran, Lee and Cho, 2022). There are now tentative efforts to use this pathway for therapeutic interventions. In this chapter we will explore the data supporting the infection hypothesis of neurodegenerative diseases, how it relates to neuroinflammation and what could be done to maintain the brain healthy throughout life.

2. The amyloid cascade hypothesis

When Alois Alzheimer described the pathological hallmarks in the postmortem brain of the lady in her 50s, he did not know that he was describing the later called Alzheimer's disease (AD) (Alzheimer et al. 1907). The two main pathomorphological hallmarks were the amyloid plaques and the neurofibrillary tangles. The amyloid plaques are made from oligomeric $A\beta$ peptides which straight after the formation of the monomeric $A\beta$ start to fibrillate and become oligomeric. The plaques are considered as a sort of extracellular agglomeration of these misfolded proteins (Armstrong 2009). The neurofibrillary tangles are made of hyperphosphorylated tau protein inside of the neurons. They are very toxic for neurons and when they accumulate in great proportion, they kill the neuron and therefore decrease the number of synapses which is one of the first pathological and functional characteristics of AD.

It is now very well known that the $A\beta$ peptide is able to induce the tau protein hyperphosphorylation by different signaling pathways, including the PPA2, GSK-3 β and the CDK5 among others (Ekinici and Shea, 2000).

In the meantime, another characteristic of AD and of many other neurodegenerative diseases is the presence of an inflammation in the brain. This neuroinflammation was already noted by Alzheimer himself. This is the ultimate common pathway for all the neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS (Ranschoff 2016, Guo et al. 2020).

The amyloid cascade hypothesis was for a long time, because of the description of Alzheimer himself, the only and the true causal explanation for AD. However, because of the therapeutic failures targeting the A β peptide for decades, scientists started to doubt that A β may be the only cause of AD (Herrup 2015, Richard et al. 2021). Furthermore, many patients with AD diagnosis did not show A β peptide deposition (Rentz et al. 2010). In contrast, many cognitively healthy subjects including centenarians presented amyloid plaques in their brains. Finally, The Nun study showed that if the nuns had a clinical AD diagnostic, at autopsy vascular changes were always present, meaning that without vascular problems even if they had characteristic AD alterations in the brain no clinical diagnosis could be made (Snowdon 1997). Considering these scientific facts researchers started indeed to question from where A β could come and what its relationship with neuroinflammation is. The question raised whether the inflammation triggers the production of A β or the A β triggers the inflammation. Several lines of evidence point to the fact that inflammation precedes the production A β suggesting that A β is both a consequence and the cause (Fulop et al. 2023; Webers et al. 2020).

In the meantime, scientists have also found, that in the brain of AD patients, microbes could be directly shown therefore the plaques could represent a sort of biofilm that contains microbes (Miklossy 2016). Ruth Itzhaki's group was the first to show that HSV-1 DNA could be demonstrated in the plaques (Jamieson et al. 1991; Itzhaki et al. 1997). Later came the demonstration by other groups of the findings that gingipain from *P. gingivalis*, *B. burgdorferi* or *C. pneumoniae* may be also found in the plaques (Balin et al. 2018; Dioguardi et al. 2020). This was a big impetus to the infection hypothesis which was already evoked by Oscar Fisher in 1910 (Fischer O 1910).

The next scientific finding was in 2010 that A β peptide has strong microbicidal properties (Soscia et al. 2010). It was shown that A β can kill different sorts of microbes, including fungi and bacteria. Later the antiviral property of A β was shown against enveloped viruses such as HSV-1 (Bourgade et al. 2015). All this led to the infection hypothesis and subsequently to antimicrobial protection hypothesis (Fulop et al. 2018; Moir et al. 2018).

3. The infection hypothesis of AD

As mentioned above microbial remnants were found in amyloid plaques of diseased AD patients. However, these findings did not prove with no doubt that AD may be of infectious origin. Similarly the demonstration that A β is antimicrobial was not convincing enough to change or even weaken the amyloid cascade hypothesis. The recent homologation of two new monoclonal antibodies targeting efficiently the A β in the brain

even with only a very small clinical improvement shed further shadow on the infection hypothesis (Keep et al. 2023; Vaz and Sylvestre, 2020; Salloway et al 2022).

However, parallelly the research advanced and more and more evidence came that microbes may impact cognition. The last very important piece in the puzzle is the SARS-CoV-2 (COVID19) infection which has real clinical effects on persons being infected (Hampshire et al. 2024; Fanshawe et al. 2024). Many of the patients experienced confusion, brain fog, delirium, and other neurocognitive symptoms (Rudnicka-Drożak et al. 2023). It is still not known what the real toll of the SARS-CoV-2 virus on the development of AD will be in the long run. Many suspect that there will be a real boom of AD in a decade.

Another, important piece in the puzzle came from the rediscovery of the gut-brain axis (Chen et al. 2022). The observations corroborated that gut health will modulate not only the immune system in the brain but also contribute to the neuroinflammation and vice-versa (Megur et al. 2020; Liu et al. 2020). This is a powerful proof that microbiota may influence the brain health either beneficially or detrimentally (Wang et al. 2019).

3.1 What microbes are the most involved in AD development?

There are many different pathogens which were involved in the development of AD (Sita et al. 2021; Yadav et al.2022; Seacks et Wilcock 2020; Pieckut et al. 2022). Since many years some infectious disease in a long run have been related to various changes in cognition like *Treponema pallidum* for syphilis, HIV for AIDS and *Borrelia burgdorferi* for Lyme disease (Fulop et al. 2019; Tavasoli et al. 2023; Miklossy 2011). However, these diseases are not exactly recapitulating what is AD, but generate substantial neurocognitive disorders. It is to mention that since the treatment by antimicrobial agents of these diseases the incidence of dementia substantially decreased but the mild cognitive impairment remained.

If we consider AD, some viruses were specifically considered as causative microbes (Bruno et al. 2023). The most well-known viruses are the Herpes viruses and among them the HSV-1 is described to be the most involved (Godhardt et al. 2023; Piotrowski, Tucker and Jacobson, 2023; Athanasiou et al. 2022). This enveloped DNA virus was demonstrated in the amyloid beta plaques already in the 90s (Itzhaki et al. 1997). This virus can reproduce almost all the pathological hallmarks of AD. It would colonize the trigeminal node and remain latent and only propagate when the immune surveillance is becoming weakened. HSV-1 infection profoundly affects neuron physiology. The virus is remaining mainly latent in the neuronal system, but the reactivation is very frequent. In vitro studies indicate that in neuronal cells HSV-1 triggers intracellular Ca^{2+} signaling promoting amyloid precursor protein (APP) phosphorylation via GSK-3 β activation and in turn the amyloidogenic APP processing leading to extra- and intracellular accumulation of A β and other APP cleavage products. These possibly activate different pathways affecting the transcription of neurotoxic genes, DNA repair mechanisms, expression of synaptic proteins, and neurogenesis. HSV-1-induced GSK-3 β activation

was also linked to tau phosphorylation in human neuroblastoma cells, and hyperphosphorylated tau was shown to accumulate into nuclei of infected cells. Interestingly, a recent article showed transient tau phosphorylation in HSV-1-infected primary hippocampal neurons isolated from adult mice (Wozniak, Frost and Itzhaki 2009). HSV-1 infected animals particularly resembled an AD-like phenotype, showing also cerebral A β hyperproduction and deposition in plaques, signs of neuroinflammation, increased levels of oxidative stress damage and epigenetic alterations, paralleled by progressive and irreversible cognitive deficits. Furthermore, HSV-1 replication can be effectively inhibited by antiviral drugs such as acyclovir (ACV), penciclovir, foscarnet, and BAY 57e1293. These drugs, targeting viral DNA replication, in turn greatly reduced also HSV-1-driven tau phosphorylation and A β formation in *in vitro* models of infections (Wozniak MA et al. 2011). The infection of the neuronal models by VZV induced indirectly the reactivation of the HSV-1 infection (Cairns, Itzhaki and Kaplan. 2022).

Besides this experimental evidence there are also human data which incriminate HSV-1 as an infectious agent causing AD (Harris et Harris 2018). The findings, as mentioned, of HSV-1 DNA in post-mortem brains opened the way to further target it as potential causative agent. An observational retrospective cohort study on electronic health databases in Taiwan supported this chance. This study reported a 2.56-fold higher risk of developing dementia, including AD, over a 10-year follow-up period in Taiwanese individuals newly diagnosed with HSV infection in 2000. In contrast the persons who were treated by valacyclovir had a reduction in their risk of developing AD (Tzeng et al. 2018). Recently, Loveheim et al. (2019) published results from a nested case-control study investigating if herpes antiviral drugs could prevent AD incidence in a very small, but well-characterized cohort in terms of APOE ϵ 4 and HSV-1 carriage status. Their results, again, indicate an association between antiviral treatments (in this case even preventive) and a lower risk of AD (Hemmingsson et al. 2021; Linard et al. 2022). A recent clinical trial (ClinicalTrials.gov identifier NCT02997982) has evaluated the efficacy of valacyclovir (the most effective and bioavailable antiviral to treat HSV infections) to improving cognition and functions in HSV seropositive AD patients (Weidung et al. 2022).

More complex and long-lasting study design underlies the NCT03282916 trial started in February 2018. This is a randomized, double-blinded, placebo-controlled phase II proof-of-concept trial enrolling 130 participants with mild AD and HSV seropositivity (IgG and IgM). Valacyclovir (2.0 to 4.0 g/day in 65 participants) or placebo (in 65 subjects) administration lasting for 78 weeks over which changes in cognitive parameters as well as PET imaging (to detect cerebral amyloid accumulation and tau phosphorylation) are assessed as primary and secondary outcomes, respectively.

Other viruses such as HHV6/7, CMV, HCV, H5N1, H1N1 and already mentioned SARS-CoV-2 are also involved. The latter, since the pandemic COVID19, became a very strong candidate to induce neurocognitive disorders which resembled AD (Ciaccio et al. 2021; Lin 2022) but resolved shortly after the infection. However, the long COVID is still

reproducing some prominent clinical features of AD including memory problems and brain fog (Pszczółowska et al. 2024, Ecartot et al. 2023).

Not only viruses but also bacteria and fungi are incriminated in AD (Zhou et al. 2023; Pauwels and Boer 2023). There are sufficient data to involve several bacteria, starting with the *P. gingivalis* (the main agent for periodontitis) and continuing with *Chlamydia pneumoniae* and spirochetes such as *Borrelia burgdorferi* (Hayashi et al. 2019; Singhrao and Olsen, 2019; Liu et al. 2024; Cichońska, Mazuś and Kusiak 2024; Chacko et al. 2022; Sanchini et al. 2023). The most studied is the relationship between periodontitis and AD. *P. gingivalis* infective elements were also found in higher quantity in post-mortem brain of AD patients (Dominy et al. 2019). This bacterium is residing in the mouth and propagating to the brain by the trigeminal nerve and via the thalamus to other cerebral regions. However, it is of note that the *P. gingivalis per se* could never be demonstrated in the brain. In contrast, the other bacteria could be found in the brain associated with the plaques. The bacterial infection is also reproducing all the hallmarks of AD, namely the production of A β , p-tau and neuroinflammation. Recently, it became evident that the bacterium should not be present in the brain but some bacterial products such as the outer membrane vesicles (OMVs) may recapitulate the pathological effects of bacteria (Zhang et al. 2021; Xie et al. 2023a,b; Gong et al. 2022).

One of the other major sources of bacteria, as already mentioned, is the gut (Liu et al. 2024). The communication between the gut and the brain is known as the gut-brain axis, where the gut influences the brain physiology and vice versa (Park et al. 2024; Ghosh et al. 2024). In case of dysbiosis, the gut becomes leaky and pathogens as well as their metabolic and cleavage products may by several ways disseminate to the brain for inducing a neuroinflammation. Therefore, the peripheral inflammation may induce the CNS inflammation and vice versa. These effects mimic somehow the sickness behavior syndrome (O'Callaghan and Miller 2019).

3.2 How these microbes may influence the brain for the development of AD?

The routes by which pathogens may be introduced in the brain which is efficiently protected by the peripheral and the central nervous system (CNS) immunity were also elucidated. The microbes either directly or via their metabolites may finally arrive in the brain either by the nasal-brain or vagal-brain axis. As this is a chronic stimulation and not simply an acute infection it is supposed that the microbes involved are latent and may constantly reactivate and induce the production of A β which in turn may perpetuate the already existing neuroinflammation caused by the infection. It can be also conceptualized that not the pathogens themselves are penetrating the brain, but their different metabolites or products. The most well-known mediators are the LPS and the outer membrane vesicles (OMV) originating from various microbes (Anwar 2023; Feng et al. 2013; Ge et al. 2022; Levine et al. 2023; Sait 2021; Wongshitratt et al. 2023).

Therefore, many ways exist to influence the brain, occurring through the incoming and outgoing branches of the vagus nerve, which represents the major modulatory pathway;

through the generation of metabolites including short-chain fatty acids and bioactive peptides as well as the modulation of transmitters (e.g., serotonin and acetylcholine) by the microbiota; through the secretion of cortisol by the HPA in case of stress, which can affect intestinal motility, integrity, and mucus production, leading to changes in gut microbiota composition. This alteration, in turn, may affect the CNS through the modulation of stress hormones, through the propagation of the pro-inflammatory cytokines and chemokines.

3.3 The final common way for microbes to lead and maintain AD

Immunity is also critically involved in the initiation and progression of AD. Specifically, toll-like receptors (TLRs) and peptidoglycans (PGNs) mediate the immune response towards microbes by acting as sensors of microbial components. A local immune activation can, throughout different pathways, lead to an immune activation in different organs, including the brain (Goldeck et al. 2016; Le Page et al. 2018). This low-grade immune activation has been implicated in the pathophysiology of some forms of depression and neurodegenerative disorders such as AD and Parkinson's disease (PD). All the microbes mentioned as suggested to participate in AD pathogenesis, can induce the activation of the brain immune defense system. The primary defense is maintained by microglia with the contribution of the astrocytes. These cells are activated and try to get rid of the microbes (Qin et al. 2021). There are several types of these cells through the disease progression which will develop and becoming from beneficial to neurotoxic (Keren-Shaul et al. 2017; Spiteri et al. 2022; Javanmehr et al. 2022). This happens during the decades of microbial stimulation of the brain immune system joined by the peripheral systemic inflammatory cells including monocytes and T cells, which are contributing to perpetuate the chronic inflammation and destroying the near by neurons (Fung et al. 2017; Mary, Mancuso and Heneka 2024). Therefore, at the beginning the beneficial and necessary neuroinflammation becomes detrimental as the infections is not cleared and becomes chronic (Franco, Sagar, Bokhari 2024).

All the inflammatory pathways will be activated including the NF κ B pathway leading to the pro-inflammatory cytokines' production (Sun et al. 2022). In the meantime, the NLRP3 inflammasome pathway is also activated leading to the ASC and Caspase-1 activation and resulting in the IL-1 pro-inflammatory cytokine production. This inflammasome activation is one of the hallmarks of AD and of other neurodegenerative diseases (Lünemann et al. 2021).

Therefore, chronic neuroinflammation is the common endpoint for all infections in the brain to perpetuate the pathology and the progression of AD (Li et al. 2024; Kandpal et al. 2024; Dias-Carvalho et al. 2024; Melchiorri et al. 2023). Neuroinflammation during the progression is not only maintained by the reactivation of the infections per se as well as by their mediators, but also the inflammaging occurring at a low-level during aging as well as the immunosenescence (Martorana et al. 2012; Mohapatra et al. 2023; Bowirrat A 2022; Kumar et al. 2024; Dyer et al. 2024; Bauer, Pawelec and Paganelli 2024). Even if these processes are not the cause of AD neuroinflammation they may contribute

depending of the whole body circumstances (Zhang et al. 2024). Furthermore, one of the main fuels of inflammaging is cellular senescence (Guerrero 2021; Hanley et al. 2024). The constantly activated microglia in the brain become senescent, meaning that they do not divide nor die but secrete pro-inflammatory products (Filgueira et al. 2012; Liu 2022; McFarland and Chakrabarty 2022; Wissler-Gerdes et al. 2020). Thus, it was suggested that with aging, as the main risk factor for AD, the microglia enter in cellular senescence and contribute further to neurodegeneration (Lau et al. 2023; Hu et al. 2022). However, it could not be demonstrated so far without any doubt that these processes play any role in human brains.

3.4 What is the role $A\beta$ in the context of the infection hypothesis of AD?

$A\beta$ is considered as the foundational pathogenic factor of AD (Hardy and Allsop, 1991). However, all trials aiming to decrease it in the brain failed to produce beneficial effects (Mehta et al. 2017; Kim et al. 2022; Doggrel 2024). They were very efficient to decrease $A\beta$ in the brain but did not produce desired clinical effects and even sometimes lead to harmful effects such as ARIA (Salloway et al. 2022). Therefore, it was hypothesized that $A\beta$ may also have some physiological effects (Jeong et al. 2022). Indeed, as mentioned earlier it was shown that $A\beta$ is an antimicrobial agent which can be microbicidal towards viruses, bacteria, and fungi (Soscia et al. 2010; Bourgade et al. 2016). It is a very efficient antimicrobial agent and therefore is now considered as part of the innate immune system of the brain. The mechanism of its action is still debated as it can be a direct suppression of the enveloped microbes by direct killing of the microbes, it can by the fibrillation process entrap the microbes and stop their propagation, or finally, it can coat the surfaces and inhibit the attachment of the microbes to the neurons (Bourgade et al. 2022). Experimental evidence exists *in vitro* and *in vivo* to support these contentions and gave rise to the antimicrobial protection hypothesis (Moir et al. 2018).

The case of AD as a neurodegenerative disease caused by microbes is not unique and the antimicrobial properties of $A\beta$ is not unique neither among the other neurodegenerative diseases. Therefore, the research was also extended to other neurodegenerative diseases such as Parkinson's disease (PD).

4. Parkinson's disease

PD has been also associated with cases of viral infection. Braak and colleagues (Braak et al. 2003) hypothesized that sporadic PD is triggered by pathogens that enter the body via the nasal cavity or are lodged in the gut, meaning that PD can be triggered in either the neurons of the nasal cavity or in the neurons in the gut (Braak et al. 2003). They advocate that the microbial products disrupt the immune response, causing immune activation and misfolding of α -synuclein in the periphery. From there, the misfolded α -synuclein aggregates and spreads toward the CNS via the olfactory tract or the vagal nerve (Rietdijk et al. 2017). Clinical data have found Lewy bodies in the olfactory bulb, dorsal motor vagal nerve, and enteric nervous system (Sharma et al. 2019), reinforcing the possibility that the disease spread from the periphery to the CNS and that, peripheral immune cells

and not brain immune cells, might be the first ones to react to misfolded α -synuclein occurring in the periphery.

In a longitudinal study, a positive correlation between increased blood levels of inflammatory chemokines CXCL12 and CX3CL1 and pro-inflammatory cytokine IL-8 and increased risk of PD was found (Li et al. 2022). Xu and colleagues measured serum levels of several inflammatory markers and found that PD patients had considerably higher levels of inflammatory cytokines IL-1 β and IL-33 in comparison to healthy controls suggesting that the inflammasome is actively activated. In the early-stage PD subgroup, the levels of these cytokines were even higher than in the late-stage PD subgroup (Xu et al. 2022). Moreover, serum levels of soluble TNFR1 were also increased in a sample of PD patients in comparison to healthy controls (Scalzo et al. 2009). Some studies may also relate PD to the influenza infections (Cocoros 2021).

5. What are the implications of the infection hypothesis of neurodegenerative diseases for the maintenance of healthy brain and longevity?

Based on the research findings it is now well-accepted that neurodegenerative diseases are initiated decades before the development of the clinically overt disease (Atri 2019). Therefore, one of the most important tasks for maintaining a healthy brain and favor longevity as a correlate that predictive biomarkers should be developed and being targeted (Yilmaz et al. 2020; Gracia et al. 2024; Lyon et al. 2024). These biomarkers or biosignatures should be developed at very early stages of the disease or even before any detectability of the disease. Therefore, a preventive strategy may be used to avoid the progression towards full-blown clinical AD. It is of note that these biomarkers should reliably represent the underlying physiological or pathological pathway to be able to decrease the risk of AD.

There are several tentative in longitudinal studies to find biomarkers which can be related to underlying mechanisms playing a role in the future development of the neurodegenerative diseases. However, until know the success of this discovery is limited because of the long period of incubation, because of the uncertainty around the exact pathomechanisms by which microbes are inducing the disease and finally because it can not be foreseen with certainty whether the disease will really develop. This underlines the heterogeneity of the physiological and pathological processes through disease development concomitantly to the aging process and points towards a personalized medicine approach.

However, as we know from the epidemiological and clinical evidence that microbes may be an initiator and the neuroinflammation is the common mechanism, we can act on these factors well before the clinical disease manifests itself.

We know since the FINGER study that the interventions taking into account the complexity of the neurodegeneration should be multimodal (Ngandu et al. 2015). This should include lifestyle factors, nonpharmacological and pharmacological interventions. The major lifestyle interventions are diet, exercise, bad and chronic stress reduction,

cognitive training. In real life these interventions mainly together are very difficult to achieve; however, people from birth should tend to implement the healthiest lifestyle possible. It is also evident that the healthy lifestyle may also be relative as we know that exercise per se can be very beneficial but in some circumstances it can be harmful. This depends on the type of exercise, the quantity of the exercise, the moment of life when it is practiced and the underlying physiological conditions. Therefore, there is no “one fits all” receipt for these interventions. The tendency, as in all interventions, is the personalization of the interventions tailored to the individual situations. These considerations may seem paradoxical in view of the overused and overestimated so called “healthy” lifestyle.

One other very important preventive aspects of the neurodegenerative diseases proved to work is vaccination (Lehrer et al. 2022, Ecarnot et al. 2023; Lopthatananon et al. 2021; Zhao et al. 2024). There is now ample evidence that certain if not all vaccinations may reduce the risk of neurodegenerative disease development, especially that of AD. So far this was shown for the influenza vaccination, VZV and pneumococcal vaccination. This not only decrease the risk and incidence of AD but support the infection and inflammation pathomechanisms of AD. Furthermore, even a study showing that the BCG vaccination in case of subjects suffering from bladder cancer when excluding the cancer-related mortality has shown decrease in AD incidence (Weinberg et al. 2023). Thus, today vaccination seems to be the most powerful preventive intervention, of course combined to the other mentioned for maintaining healthy brains. Each older subject should be encouraged to be vaccinated as much as they can. More vaccines need to be developed for presently orphan microbes including HSV-1 (Preda et al. 2023)

The intermittent use of antibiotics and antivirals even if it was not purposefully used to prevent AD were shown to reduce the risk of AD (Loeb et al. 2004; Devanand 2018). Most specifically the antibiotics such as Doxycycline and Rifampin and the antiviral acyclovir were shown in large epidemiological and small RCT studies to decrease the risk for AD. The success of antivirals in HIV to decrease the HIV-related dementia and mostly convert it in HAND underlines the efficacy of the antiviral treatment to prevent dementia but also suggest that this is not enough to avoid the later neurocognitive manifestations of the infection (Fulop et al. 2019; Gelman 2015). The use of anti-inflammatory drugs on the long run in inflammatory diseases such as rheumatoid arthritis led to a substantial reduction of AD (in t' Veld et al. 2001). These results sharply contrast the small intervention studies using the same medications in AD, however confirming that once the pathophysiological neuron destructive and inflammatory process is initiated it is very difficult to efficiently intervene (in t' Veld et al. 1998; Meyer et al. 2019). Therefore, the interventions should target the very early stages of the neurodegenerative process.

However, the use of medications could be another palliative alternative that can be complementary. Indeed, several anti-inflammatory drugs are currently being tested in different neuroinflammatory diseases (Wang et al. 2019). On the other hand, other drugs are also being tested because of their anti-inflammatory potential, highlighting several

from the family of antibiotics, plant derivatives, antagonists of chemokine receptors, etc. This strategy has the advantage of using already available drugs, which makes the pharmaceutical development process much faster. It should be emphasized that most of them are used in established clinical neurodegenerative diseases as there is no reliable measure of the outcomes to indicate their efficiency for decreasing or modulating the pathological process (Fulop et al. 2021).

6. Conclusion

The lack of knowledge of the exact cause(s) of neurodegenerative diseases including AD and PD and the failure of the amyloid or α -synuclein hypotheses led to new hypotheses including the infection hypothesis. There are ample experimental and clinical proofs pointing to the role of various infective agents in the development and progression of both AD and PD. However, the acceptance of this theory is difficult. There is clear need to develop biomarkers which can predict the role played by microbes in the progression of AD which in the meantime may be druggable. A huge scientific effort is devoted to this research. These biomarkers may also be predictive of the brain health, resilience, and robustness. Biomarkers suggesting AD development from the baseline are actually badly needed.

In the meantime, some well-recognized preventive measures may be applied to maintain brain health and decrease the risk of AD. Among them the vaccination has a privileged role as was recently demonstrated for several different commonly used vaccines.

Furthermore, the intricate interplay between inflammatory processes occurring in the CNS and peripheral tissues contributes significantly to the development and progression of various inflammatory diseases. This reciprocal relationship is particularly evident in the context of obesity, stress, neurodegenerative diseases, and metabolic disorders. The CNS can sense peripheral inflammation through intricate signaling mechanisms, triggering a cascade of neuroinflammatory responses that can further exacerbate peripheral inflammation. Conversely, peripheral inflammation can be transported to the CNS via immune cells or soluble mediators, leading to neuroinflammation and neuronal dysfunction. Understanding and targeting these bidirectional interactions hold immense potential for therapeutic interventions aimed at ameliorating the impact of inflammatory diseases on both the CNS and peripheral tissues and consequently help to diminish and prevent the suffering of millions of patients affected by AD or PD.

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