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## **Viruses - a major cause of amyloid deposition in the brain**

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### **Key words**

Alzheimer's disease, Amyloid beta peptide, viruses, Microbes, antimicrobial hypothesis,

## **Highlights**

1. The amyloid beta hypothesis is outdated
2. Viruses have been implicated as a putative cause of Alzheimer's disease (AD)
3. Viruses contribute either directly or indirectly to amyloid beta production and Tau phosphorylation as well as to neuroinflammation which are the putative hallmarks of AD
4. Due to their antiviral effects, amyloid beta peptides are useful but during the disease development, when a threshold is crossed, they become detrimental
5. Treatment should aim at preventing the neurotropic viruses to become latent in the brain, by early enough vaccination
6. AD is an inadequate name that should be replaced by Chronic Brain Failure (CBF) of neurodegenerative type.

## **Abstract**

Alzheimer's Disease (AD) is claimed to be the most frequent dementia type affecting mostly older subjects. The pathological hallmarks of AD are the amyloid beta plaques, the neurofibrillary tangles mainly composed by phosphorylated Tau and neuroinflammation mediated mainly by glial cells. Clinically, AD is a syndrome with a spectrum of various cognitive disorders. There is a complete dissociation between the pathology and the clinical presentation. The pathological hallmarks do not explain the cognitive decline. Therefore we need a disruptive new approach to be able to prevent and treat AD. The first step is to abandon the appellation AD which directly reflects the causative involvement of amyloid beta and switch to the Chronic Brain Failure (CBF) of neurodegenerative type. Since decades, we have known that viruses are involved in the pathogenesis of AD. There is an academic resistance to admit the role of viruses/microbes in the pathogenesis of AD since the temporal causality via the contributing pathways between infection and clinical presentation have not been demonstrated directly. It will be imperative to demonstrate longitudinally the sequence of events which leads from chronic infection to cognitive decline and to discover biomarkers and to build algorithms to integrate in a complex system the sequence of events for future effective precision medicine-based treatments.

## **Introduction**

Alzheimer's disease (AD) has been known for more than 100 years. Dr Alois Alzheimer made the first description of what became later the Alzheimer's disease. He described the pathological characteristics of this disease, namely the amyloid plaques and the neurofibrillary tangles (1). Later it was discovered that these plaques were made from amyloid beta peptide ( $A\beta$ ). This is a by-product of the processing of the Amyloid precursor protein (APP) found in most cells but most particularly in neurons. What Dr Alzheimer described was, indeed, as we know presently, the familial form or early-onset AD, but not the more common sporadic late-onset AD.

In the familial form of AD, certain mutations in the gene coding the amyloid beta peptide give rise to a distinctly pathological form of  $A\beta$  which forms plaques called senile (amyloid) plaques. During the clinical progression of the disease, these amyloid plaques increase in number and extension all around the brain starting from the entorhinal region in the temporal lobe. The observation of Dr Alzheimer, despite being made in a familial case, has been directly applied to all dementia cases and so the Alzheimer's disease became since the 80s the most frequent cause of dementia (2). It is of note that Dr Alzheimer described other important changes in the brain such as atherosclerotic changes, neurofibrillary tangles and suspected that an infectious origin/contribution may be plausible. A few years later Dr Oskar Fischer made the same assumption (3). Nowadays whatever is the cause, every cognitive disorder occurring in a sporadic manner in older subjects has become the so-called AD. Furthermore, the discovery by Dr Alzheimer of the amyloid plaques as a hallmark with the neurofibrillary tangles gave rise to the amyloid cascade hypothesis which has dominated over decades the whole field in clinical and in fundamental research (4-6).

### **What is the amyloid cascade hypothesis?**

This hypothesis is based on the sole fact that  $A\beta$  is produced by the amyloidogenic processing of APP in neurons and its deposition, by its self-fibrillation property as plaques in the brain. This amyloidogenic pathway follows the successive processing of APP first by  $\beta$ -secretase followed by  $\gamma$ -secretase processing. The ultimate product of this processing is an  $A\beta$  with either 40 or 42 amino acids (7). They may be cytotoxic and induce a strong neuroinflammatory process via glial cells. In this case, the microglia in the brain try to eliminate these peptides by phagocytosis. The TREM2 receptor of the microglia are the most important in this process. However, as the disease progresses, the microglia become less and less capable of eliminating this toxic peptide but remain hyper-activated through their other surface receptors and this induces neuroinflammation. There are several risk factors which contribute to the defective clearance of  $A\beta$  peptides including the ApoE4 genotype, alterations in the microglia innate immune genes, the senescence of the microglia, and most importantly, aging (8-11).

Aging is considered as the most important risk factor for the development of AD. Aging by the inflammaging (low grade, chronic, clinically non-manifest inflammation)

phenomenon creates numerous molecules that favor AD such as the production of free radicals and inflammatory mediators that will alter the functioning of the microglia including their ability to perform phagocytosis (12). Furthermore, senescence of microglia also contributes to the development and progression of plaques. Recently a new type of microglia was discovered namely the disease associated microglia (DAM). These microglia instead of being protective during the progression of the disease become pathogenic (13).

These changes with aging contribute to the A $\beta$  induced inflammation in the brain (neuroinflammation). The scavenger receptors of the microglia are constantly stimulated by the amyloid peptides and ultimately produce pro-inflammatory mediators. These inflammatory mediators create a vicious circle by stimulating and maintaining inflammation while this inflammation increases the production of A $\beta$ . This phenomenon is a normal element of the innate immune memory process and under normal circumstances comprises a beneficial activity of the microglia however, through successive activation (reactivation of latent viral infections) microglia become dysregulated by epigenetic and immunometabolic changes leading to pathological outcomes, especially chronic neuroinflammation which destroys synapses and neurons (14,15).

The amyloid cascade hypothesis has been experimentally proved in animals mainly in the genetically engineered AD mouse model. However, in humans this hypothesis could never be demonstrated as the cause of AD. The amyloid cascade hypothesis depends on the second half of the process namely when the A $\beta$  peptide is already present in excess and inducing various pathological processes. However, this theory has not answered the fundamental question of AD: what causes/initiates the production of A $\beta$  peptides which could be the key for the treatment/prevention of this devastating disease.

### **What are the arguments against the amyloid beta hypothesis?**

Since we use images to confirm our clinical diagnosis of AD it has been shown that many AD cases exist without any A $\beta$  plaques and vice versa, that is, many non-AD subjects may have substantial A $\beta$  deposits as plaques (16). This should be a powerful argument against the amyloid beta hypothesis as the pathology could not be linked to clinical cognitive decline. However, this has not been taken into consideration and conceptually has not been accepted as a sufficient argument against this basic theory.

Moreover, it is now well established that neuroinflammation which is also a hallmark of AD, precedes the development of the real established AD pathological hallmarks (amyloid plaques and neurofibrillary tangles). This neuroinflammation is characterized by the chronic activation of glial cells, upregulation of pro-inflammatory cytokines such as IL1 $\beta$ , and infiltration by peripheral immune cells (innate and adaptive) in the brain (17). This neuroinflammation is due to the activation of the immune process by A $\beta$ , whose production has been induced by local or systemic infections, and especially by chronic local or systemic inflammation (18,19). Therefore, this immune-inflammatory response occurs well before any classical pathogenic hallmarks of AD but it is a cause and a consequence

of the production of A $\beta$ . This initiates a vicious circle where A $\beta$  as a stress response protein is produced in reaction to an insult which most probably is an infection that must be eliminated (20). This infection has mediated the production, misfolding, fibrillization, and eventually the formation of plaques by A $\beta$ . Therefore, amyloid is only a consequence, and not a cause of the whole process.

The establishment of this inflammatory process is not depending at all on the supposed alteration of the immune system with aging (immunosenescence) as mentioned earlier because it is a beneficiary process as maintaining the stressors and most specifically the acute and latent infections in a controlled state. This is occurring through the activation and the establishment of the trained innate immunity which most of the time independently from the adaptive immunity may control the infection or the reactivation however in most of the time specifically direct the adaptive immune response to be more efficient. This time dependent dynamic and sequential progression of the immune reaction is essential to the maintenance of the healthy cognition but in the meantime prepares the ground to a certain dysfunction culminating in a spectrum of clinical and neuropathological evidence.

All parts of the innate immune response are involved in this process but most particularly the interferon signalling pathways. Type I interferon is an essential molecule to combat virus infections and its cellular machinery and pathways involving most particularly the mitochondria are entirely solicited. The recent discoveries linking infections to  $\beta$  amyloid and the defense/detrimental mechanisms via the IFN pathways have been disentangled (). Their involvement will be more extensively discussed in the HIV and SARSCoV2 sections. However, at this stage we should mention that recently it was described that IFN-I signaling represents critical module within the neuroinflammatory network of AD and prompts concerted cellular states that are detrimental to memory and cognition (Roy et al. 2022). This happens via a feed-forward A $\beta$ -plaque-IFN-A $\beta$  loop whereby inflammation stimulates factors that further exacerbate AD pathology, where amyloid fibrils harboring nucleic acids (NA), activate this IFN-I response pathway (Roy et al. 2020). These new observations once more reinforce the idea that the immune system is able to fight and maintain the latent and recurrent infections controlled but at some point, due to complex genetic and environmental constellations this inflammation becomes detrimental and will manifest as a clinical, so called, AD spectrum syndrome.

The next much more powerful argument is the failure of the hundreds of clinical trials aiming to cure AD by eliminating A $\beta$  plaques from the brain using monoclonal antibodies or by passive immunization (21). These treatments are based on the Amyloid cascade hypothesis which states that A $\beta$  as the cause of the disease. In fact, these treatments resulted in fantastic improvement in experimental animals. However, in human subjects they were complete flops. Although these treatments may reduce the A $\beta$  load, they did not result in any clinical improvement for the patients (22). This fact may again underline that A $\beta$  may be eliminated but the cognition of the treated subjects did not change over the follow-up. Therefore, the pathogenic role of A $\beta$  peptides is very dubious. However, it should be mentioned that at that late stage of the disease (concerning the patients mostly included in

the trials) probably the brain damages are so deep that no cognitive improvement could be expected by just the elimination of A $\beta$ . Rather than being beneficial, anti-A $\beta$  treatments could lead to serious side effects (e.g. amyloid-related imaging abnormality (ARIA)-E (edema) and -H (hemorrhage) (23). In the first trial, some individuals died from encephalitis. These failures in the monoclonal treatments underlined again the incorrectness of the A $\beta$  hypothesis.

Finally, this theory never took into consideration the physiological role of A $\beta$ . From an evolutionary perspective it would be unimaginable that a peptide is produced in most mammals, and yet has no physiological role. Amyloids are everywhere in nature and have various physiological roles suggesting that in humans this should be identical (24). It is well known that even microbes possess amyloid like structures for their self-defence (curli) (25). The curli are the most well-known amyloid peptides which protect bacteria from destruction. Even in virus membranes, there exist amyloid like structures which physiologically interfere with cellular necroptosis and help perpetuate viral survival (26). Therefore, A $\beta$  should also have a physiological role in the brain. Indeed, it is important to mention that A $\beta$  possesses several essential physiological functions as a) being part of the innate immune response as an antimicrobial peptide; b) possessing a protective role against brain injury; c) contributing to sealing the blood brain barrier during injury; d) depending on its form, it may be angiogenic and e) finally being antitumorigenic by promoting cell death (27,28). Of course, as with many other things too much of a good thing may become a bad thing. It is clear with the progression of the pathology, A $\beta$  accumulation may become harmful and contribute to the development as well as the progression of AD.

All these arguments militate against the A $\beta$  hypothesis, but it is still strongly ingrained in the scientific and clinical community dealing with AD. The biggest questions never answered by this hypothesis are from where the increased quantity of A $\beta$  beta amyloid is originating and what is the magnitude of the increased quantity of A $\beta$  necessary to induce clinical AD. It has been supposed by contamination/continuation from the familial AD model that sporadic AD is identical but occurring later in life. One of the very important studies which tried to answer this question was the Nun study (29). This study clearly demonstrated that clinical AD was never diagnosed without vascular pathological changes in the brain of these AD subjects. This pioneering study also demonstrated the similarities between the pathogenesis of AD and atherosclerosis namely infections and chronic inflammation. Since that time, it is well recognized that the atherosclerosis risk factors are also risk factors to AD, therefore AD may not be a consequence of A $\beta$  accumulation (30). However, the experimental/clinical evidence was not efficient to shake the AD community to accept new ideas.

### **What triggers the production of amyloid beta peptide beyond physiology?**

First we should consider how the amyloid beta is produced. There are two pathways to process the membrane bound Amyloid precursor protein (APP). The first is non-amyloidogenic meaning that the external part of the APP is cleaved in a sequential manner by the  $\alpha$ -secretase followed by the  $\gamma$ -secretase. The second is the amyloidogenic pathway



which starts with the internalisation of the APP in endosomes where they are cleaved by the  $\beta$ -secretase followed by the  $\gamma$ -secretase processing (7). This gives rise to various amyloidogenic peptides mainly to those of A $\beta$ 1-40 and the A $\beta$ 1-42 secreted in the extracellular space mostly linked to exosomes (31). Researchers observing the failure of the treatment of AD which targets the amyloid beta were thinking that it should have some important reason for its production even if the clinical AD will never develop.

Researchers became interested in studying the composition of amyloid plaques as they observed that various infections either acute or chronic lead to cognitive changes which could resemble those observed in AD (32). Therefore, the thought emerged that infections (viruses and bacteria) may induce the production of A $\beta$  (33). Initial experiments showed the presence of the HSV-1 DNA in autopsy brain followed by the demonstration in amyloid plaques (34,35). This was a revolutionary observation relating for the first time AD plaques to a viral infection. Later other experiments demonstrated that other pathogens especially *Borrelia burgdorferi*, *Chlamydia pneumoniae* followed by *Treponema denticoli* may also be observed in the plaques (36-38). These plaques were then viewed as a sort of cemetery for these microbes in the form of biofilms. For a long-time these discoveries were contested as these microbes infect most people but not all of them develop AD. Of course, at this stage the link was missing.

Later it was discovered by the group of Tanzi that A $\beta$  is physiologically a part of the innate immune defense as they demonstrated strong antimicrobial properties (27). This was a major discovery as they demonstrated that A $\beta$  could inhibit infections by bacteria and *Candida albicans*. These observations further added weight to what had been discovered earlier in the plaques. Later the group of White as well as our group demonstrated that A $\beta$  has a strong antiviral activity (39). These observations may be integrated into what is found in nature as from plants to bacteria amyloid is used as an antimicrobial peptide (40). These observations further reinforced the link between infections and A $\beta$  (41,42).

The next step was to demonstrate that indeed viruses may induce the production of A $\beta$  which kills them (35,43,44). Our group has demonstrated in vitro that HSV-1 infection of neurons but not microglia produce A $\beta$ , and that the neuronal supernatants may inhibit the infectivity of HSV-1 (20). These findings completed the circle namely that infections are triggering the production of A $\beta$  as a defense mechanism which will decrease the microbial charge helping the development of robust microglial and adaptive immune response (45). The link between infections and the production of A $\beta$  beside the activation of BACE was shown via the production of pro-inflammatory cytokines which could in turn induce the formation of interferon-induced transmembrane protein-53 (IFITM3) in neurons and astrocytes (46). This IFITM3 will bind and stimulate the  $\gamma$ -secretase activity resulting in increased A $\beta$  production. This is an even more important observation as this again links neuroinflammation induced by infections to increased A $\beta$  production via the pro-inflammatory mediators. Recently another mechanism was described which links the production of A $\beta$  to HSV-1 which is the production of the miRH1 which inhibits Ubr1 which is a ring -type E3 ubiquitin ligase of the ArgN-end rule pathway leading to the

degradation of proteins bearing “destabilizing” N-terminal residues including the neurodegeneration-related A $\beta$  (47). However, when the microbial charge becomes overwhelming, or there is constant reactivation (chronic infection) coupled to inefficient microglial function, A $\beta$  becomes pathological and induces the typical pathological hallmarks of AD.

### **Which are the most important viruses involved in AD**

Viruses can directly infiltrate the CNS, activate microglia and astrocytes, as well as attract peripheral immune/inflammatory cells which all contribute to neuroinflammation which is one of the hallmarks of AD (48). The consequence of this direct invasion by viruses of the CNS is either the apoptosis of neurons or their destruction for further invasion. However, some viruses are able to hide themselves using latency factors and survive for decades and reactivate from time to time (49-52). There are several viruses which have been incriminated. Most studies in this context consider the Herpesviridae, HIV, influenza, but other reports mentioned that the Japanese and West Nile encephalitis viruses may also be initiators (**Table 1**).

#### *HSV-1 and 2*

HSVs belong to the alpha Herpesviridae. The most important studies were done with HSV-1. This Herpesviridae is particularly studied because it is so widespread and because latent virus resides in the trigeminal ganglia (53). Infection with HSV-1 accumulates with age and about 70% of persons above 65 years have been infected and become carriers (54). This is an enveloped double stranded DNA virus which enters the cells by fusion of their membrane using the gB and gD proteins on their surface. HSV-1 may infect various tissues including mouth, face, nose, and the central nervous system (55). Once the primary-infection has resolved in immunocompetent subjects, HSV-1 establishes a latency state which means that it can reactivate following any stress situation (51). Trigeminal ganglion and nuclei are the privileged site for latency from where the virus via the sensory neurons may propagate to the thalamus and the sensory cortex (56). Infection and repetitive reactivation thus increase the risk of A $\beta$  induction and phosphorylated Tau (pTau) production concomitantly with neuroinflammation, synapse destruction, leading ultimately to clinically significant cognitive decline resembling what is called AD (57). These processes may be accentuated under certain circumstances by aging. It should also be mentioned that HSV-1 may also infect the central nervous system via hematological dissemination through the blood-brain barrier (BBB) (58).

The group of R. Itzhaki contributed essential knowledge to our understanding of the role of HSV-1 in AD development. They have demonstrated that the viral DNA is an integrative part of amyloid plaque (34,35). This signifies that HSV-1 in some way may contribute to amyloid plaque formation. This may occur through the induction of A $\beta$  production inside cells and when cells are destroyed, they may release the A $\beta$  which can then aggregate and imprison HSV-1 DNA. Furthermore, cells stimulated by HSV-1 may produce extracellular A $\beta$  which in turn may destroy/trap the viruses being enclosed in the nascent amyloid

plaques. In either way A $\beta$  acts as an antiviral amyloid peptide decreasing the infectivity of HSV-1 but in the meantime contributing to neuroinflammation and amyloid plaque formation and deposition. Through these 2 potential mechanisms, HSV-1 favors the production of A $\beta$  as well as its accumulation which is originally protective but becomes harmful through time. Therefore, A $\beta$  is a natural defence against HSV-1 that may become pathogenic if it accumulates (41,59,60).

A $\beta$ , if produced in great quantity or aggregated through the influence of the virus may also contribute to plaque formation. It is significant to mention that A $\beta$  by itself may self aggregate. This aggregation can occur inside infected neurons and therefore the neurons will not be able to destroy these aggregates by autophagy. The viral glycoprotein K may also directly bind A $\beta$  and favor its fibrillization (61). We should also mention that this plaque formation may also be beneficial by isolating the virus and its products. Therefore, this is a double edge sword.

Interestingly, beside the stimulation of A $\beta$  production, HSV-1 may also directly stimulate GSK3 $\beta$  mediating pTau production (62). HSV-1 can also induce neuroinflammation either directly by stimulating the production of pro-inflammatory cytokines and free radicals or by the production of A $\beta$  which contributes to activation of microglia scavenger and pattern recognition receptors. The GSK3 $\beta$ , via the intracellular Ca signalling activation, induces several pathological processes participating in the development of AD such as the increase of secretases activities involved in A $\beta$  production, the phosphorylation of APP, and inducing defects in the autophagic process further contributing to A $\beta$  accumulation (63).

Furthermore, among the risk factors described for AD, the ApoE4 allele was shown to be the most powerful and most frequent genetic risk factor for developing AD while concomitantly these AD patients could be more susceptible to be infected by HSV-1 (33,64,65). Interestingly, almost all HSV-1 negative AD patients do not have the ApoE4 allele. Therefore, the simultaneous presence of both HSV-1 and ApoE4 represents an increased risk for the development of AD (66). Moreover, by regulating cholesterol transport, ApoE4 modulates the production of A $\beta$ , the cholesterol content of the lipid rafts and the clearance of A $\beta$  through the BBB (67). Lipid rafts also serve as an entry place for viruses into neurons. Therefore, cholesterol metabolism orchestrated by ApoE4 and the susceptibility for virus entry and APP pathologic cleavage are intimately linked.

The question arises if so, many older people are infected by HSV-1 and it can be considered as a causal agent for AD why don't all these older subjects progress to AD. This is a complex question and new data seems to propose some tentative answers to this question. First, it seems that infection with HSV-1 is not sufficient to cause AD *per se* but could be a co-factor with other infections in certain individuals such as *P. gingivalis* (68). Secondly, most AD patients should also be ApoE4 positive. Third, it has been shown that perhaps it is not the virus itself, but its latent associated transcripts (LATs) and microRNAs could induce epigenetic, posttranslational, and metabolic changes important to provoke neurodegeneration (33). Fourth, the quantity of A $\beta$  and pTau produced locally and acting as seeding agents may be variable from one individual to the other. Fifth, the contribution

of chronic systemic inflammation/infection may be instrumental as this maintains a chronic neuroinflammation in a vicious circle as well as leading to virus reactivation. Finally, other risk factors may act concomitantly with HSV-1 to induce changes which lead to AD.

### *Influenza*

Influenza viruses are single stranded RNA viruses. The role of influenza virus seems at first glance counterproductive compared to the latent viruses mentioned above, namely HSV-1 and HSV-2. Influenza viruses do not seem to be directly involved in neurodegeneration. However, they contributed to the discovery of the antimicrobial activity of A $\beta$ . White et al (39) demonstrated that A $\beta$  is very efficient at protecting cells from influenza virus (H3N2 and H1N1) infections. They also showed that influenza virus induced A $\beta$  production and aggregation by similarities between A $\beta$  and the viral hemagglutinin. Later it was shown in epidemiological studies that influenza vaccination was able to protect against the development of AD (69), however it remains still controversial. It was also shown that after the Spanish flu pandemic the number of AD cases sharply increased. More recently, studies of virus exposure and neurodegenerative disease risk using national biobanks (70) demonstrated that even if multiple viruses were associated with neurodegenerative disease, influenza was the most frequently associated with various neurodegenerative diseases. Therefore, it should be recognized that influenza viruses A or B, may induce AD either directly by repeated brain infections when viruses undergo antigenic shift/drift or indirectly by a cytokine storm. It should be noted that influenza virus has also associated with another neurodegenerative disease namely Parkinson's Disease by phosphorylation and aggregation of alpha-synuclein which has also been shown to possess antimicrobial activities (72).

### *HHV-6, HHV-7 and EBV*

Readhead et al recently analysed post-mortem brains from four independent cohorts of AD patients by molecular and bioinformatics tools and found that herpes viruses were much more frequently present in AD brain than in controls (49). They were able to demonstrate the presence of HHV-6 and 7 as neurotropic viruses in the development and progression of AD. Epidemiological studies are also supporting that HHV-6 and HHV-7 were mainly found in post-mortem brain in AD patients (72). They may also establish persistence in the brain as well as in leukocytes. HHV-6A infection of neuronal cells, like HSV-1, contribute to increased A $\beta$  production and Tau hyperphosphorylation by altering autophagy in neurons.

EBV is also a persistent virus in the brain and its reactivation may cause A $\beta$  production and Tau phosphorylation concomitantly with the induction of neuroinflammation and neuronal death (73). Furthermore, it is interesting that AD patients have an increased number of EBV-positive circulating leukocytes. These viruses are also able to increase the oxidative stress and mitochondrial dysfunction of neurons leading to neuronal and synaptic dysfunction.

### *CMV*

CMV is a  $\beta$ -herpesvirus which persists for life following infection. It may infect many different cell types including innate immune cells such as microglia (52). CMV infection was also associated with increased AD either by directly infecting the brain and contributing to the A $\beta$  production during its reactivations or by decreasing the immune response in aging which indirectly will increase the risk of reactivation of other viruses such as HSV-1 or by the production of pro-inflammatory cytokines which maintain neuroinflammation (74).

### *HIV*

HIV is a retrovirus whose main targets are immune cells such as T cells and macrophages. As with some Herpesviridae, HIV also has the potency to develop latency (75). Therefore, when there is stress or decreasing immune surveillance the T lymphocytes start to produce new viruses. It is now well recognized that HIV may also infect the central nervous system and result is what is called HIV associated neurological disorder (HAND) (76). This syndrome has several clinical manifestations. However, since the inception of the introduction of high activity anti-retroviral treatment, the ultimate dementia stage is less frequent. HIV may transmigrate to the central nervous system in monocytes crossing the BBB.

There is still uncertainty whether HAND and AD may have the same roots, or they may somehow progress without each other. Nevertheless, it is well known that HIV proteins including Tat, gp120, or Cav-1 may either favor or inhibit in some circumstances the production of the A $\beta$  peptide (77). No doubt HIV inhibits A $\beta$  to avoid its antiviral activity (78). In other circumstances, however, it may favor it since Tat protein will inhibit the A $\beta$  clearing protein, the Neprilysin (79). On the other hand, deposition of Tau was observed when patients receive antiviral treatment. HIV infection induces A $\beta$  and phospho-Tau production leading to neuroinflammation which destroys synapses and causes neuronal death. It will be important to distinguish between HAND and AD in older subjects living with HIV or recently infected with HIV. This again demonstrates that even if A $\beta$  is produced, it may not be the only pathological inducer of AD as there are many clinical differences between HAND and AD.

### *SARS-CoV2*

The interest in virus mediated/induced/favored neurodegeneration leading to cognitive decline received a new impetus during the new COVID19 pandemic caused by the SARS-CoV2 (80). Even if it is mainly a respiratory virus, at least 25% of the infected individuals presented various neurological and cognitive symptoms. It took a long time to establish that some proteins of SARS-CoV2 may be neurotropic and found in the neurons/brain. The virus may infect the brain as other AD-associated viruses by the olfactory neuro-epithelium as many infected patients showed the symptom of loss of sense of smell. It is clear that this is an acute infection, but all of the above-mentioned viruses also start as an acute infection. Nevertheless, it is now accepted that SARS-CoV2 induces and may exacerbate inflammation in the brain by many ways including pro-inflammatory cytokine production

mainly IL1 $\beta$ , IL12, by modulation of ACE2 activities, by activation of glial cells and finally by causing ischemia which further contributes to A $\beta$  production (81,82). This process may lead to the exacerbation of an already existing latent infection causing some degree of neuroinflammation (83). Indeed, it was recently shown that HSV-1 infection may be awakened by a Herpes Zoster infection (84), or initiate itself a new neuroinflammatory process, epigenetic changes manifesting themselves as a cognitive decline decades later. Therefore, A $\beta$  and pTau deposits should be carefully monitored in COVID19 infected individuals years after the infection (de Erusquin GA, 2022).

As mentioned earlier chronic inflammation plays a mediating role after an infection was established and the organism is facing either its reactivation or other concomitant infections or any other stressful events. One common pathway between A $\beta$ , as an antimicrobial peptide of the innate immune response, and the inflammatory process generated is the interferon-induced transmembrane protein-3 (IFITM3 (Hur 2020)). The main role of this protein is to sequester the viral particles mainly in neurons and astrocytes as a defense mechanism, but in the meantime, it can also upregulate the  $\gamma$ -secretase which in turn increase the A $\beta$  production (Hur 2020). As described, the A $\beta$ -NA complexes are able to generate Type-1 IFNI either with its specific receptors or through the damage associated receptors which in turn display a dose-dependent neurotoxicity (Kessing and Tyor, 2015) This process has been demonstrated also in the HIV induced Hand (Thaney and Kaul, 2019).

Interestingly, Vavougiou et al (2021) has shown that SARSCoV2 was also able to induce the upregulation of IFITM3 which plays a double role either beneficial or detrimental role. This upregulation by SARSCoV2 of IFITM3 resemble of what was directly found in AD. In AD the A $\beta$ -NA complex by stimulating the IFN-gene signatures elicited the upregulation of IFITM3. This will activate the microglia independently of the virus involved. This complex is able to sustain the neuroinflammation either directly via the microglia activation or via the IFN related genes including IFITM3 leading to  $\gamma$ -secretase stimulation further increasing the A $\beta$  production. This outside – in trigger will 1 maintain the inflammation, 2 generate neuroinflammation, 3. Induce propagation through the brain via p-tau generation and finally, 4. Decrease viral clearance by interfering with the lysosomal/autophagosomal process perpetuating the viral infection (Nicholl et al. 2000; Cairns 2020, Orr and Odds 2013).

This feed-forward loop in the brain and the periphery accounts for a common pathway used by viruses to hijack/pervert the most important innate immune response against them, namely the Type I IFN system. This has been involved in the pathogenesis of virus induces Ad such as HSV-1 and further extended to HIV and SARSCoV2 by the group of Vavougiou et al. (2021). This idea is also in perfect alignment of the antimicrobial protection hypothesis put forward by Moir et al. ().

*Microbiome (gut brain and mouth brain axis)*

It is a well-known fact that problems with the gut have significant effects on brain functioning and vice versa (85,86). This is a bidirectional communication between the gut and the brain where alterations in one will affect the other. The microbiome is a complex population of bacteria, viruses and fungi with a weight predominance of bacteria, but probably 10 times more viruses or bacteriophages than bacteria (<https://doi.org/10.1016/j.coviro.2011.12.004>). The specific role of viruses is much less studied. There are several ways that they may interact with human cells. The first may be by direct translocation of the microbes to the brain either by the hematogenic or the vagal routes. Alternatively, microbial products such as LPS may mediate the effect of microbes on the brain. It has been observed that as sugar metabolism is decreasing in the AD brain while that of ketones is not (87). When gut dysbiosis occurs, ketone bodies produced by the normal microbiota are decreased due to the decrease in ketone producing bacteria further contributing to the progression AD. It was shown that in AD dysbiosis occurs, but probably this precedes the occurrence of AD (88). It was also shown that inflammation in the gut was largely associated with an increase of A $\beta$  peptide abundance as well as Tau accumulation in the brain and vice versa (89). The increased A $\beta$  also induces a disruption of the epithelial barriers leading to a leaky gut and inflammation. This is also a perfect example that peripheral chronic infection is involved in AD pathogenesis by the pathways mentioned.

The mouth brain axis is an even more direct way for bacteria or their products to enter the brain via the nerves of the oropharyngeal cavity to the brain. The most favored route is using the trigeminal nerve. Alternatively, microbes may also use the olfactory tract based on the Olfactory hypothesis. Oral dysbiosis and especially periodontitis has also been linked with the development and progression of AD (90,91). Besides the direct invasion of microbes, the neuroinflammation that may be induced may also contribute to the maintenance and chronicity of the pathological processes favoring the development of AD.

Therefore, all dysbiosis affecting the brain by any means initiates a mechanism leading to the production of A $\beta$  playing an essential role as antimicrobial peptide in the innate immune response and the initiation of neuroinflammation via microglial and astrocyte activation. However, the question is not yet settled whether dysbiosis is a consequence or a cause of AD.

**Clinical evidence that viruses may play a role in AD as a syndrome (AD spectrum)** There is only indirect clinical evidence that viruses may be incriminated in AD. One of the first studies revealed the Taiwanese epidemiological data demonstrating that persons suffering from HSV-1 infection and having received antivirals developed significantly less AD than those who were never treated (92). French, South Korean and Swedish studies also demonstrated similar results (93). However, some other studies could not confirm these findings. It is of note that no study involving antibiotics to treat bacteria has demonstrated similar effects.

It has been shown in many experimental settings that the A $\beta$  peptide may protect some species from infection. This was the case of a nematode which was protected from an

infection with *Candida albicans*. Similar situation has been demonstrated for mice which were infected by the bacteria *Salmonella typhimurium* (94). All these cases demonstrated that not only virus infections may initiate the production of A $\beta$  peptide but in turn this peptide may also protect against infection. These studies lead to the conceptualization of the antimicrobial protection hypothesis by Moir et al. ().

Vaccination could be a powerful means to prevent AD by preventing viral infections. The most powerful evidence, interestingly, comes from the preventive role of influenza vaccination on AD (95) as well as with VZV vaccination (96,97) and very recently of that of the BCG ().

### **What is the mechanism of action of the A $\beta$ peptide**

Different amyloids possessing antimicrobial activity act by various mechanisms. The first is the direct elimination of the microbe by A $\beta$  inserting into its membrane and forming pores which will mediate the death of the microbe (98). It will also interfere with the possibility for HSV-1 to attach or fuse with the host cell membrane to infect a cell. A second way is to form fibrils which are able to imprison the microbes and make it impossible for them to escape and continue their infectious activity (99). This is the mechanism that many scientists propose for amyloid plaques which become a biofilm cemetery which contain the microbes under control. This is one of the effective ways to control infection. However, this has a cost for the organism as the increase in the number or size of plaques that are surrounded by microglia will eventually attract astrocytes which will try to eliminate the imprisoned microbes by producing free radicals and pro-inflammatory mediators leading to neuroinflammation.

### **Why it is important to recognise viruses/microbes as causes of A $\beta$ peptides production?**

As mentioned earlier the amyloid cascade hypothesis stating that the increased production or decreased clearance of A $\beta$  peptide leads to amyloid plaques and consequently to neuroinflammation resulting in synapse destruction followed by the clinical manifestation of cognitive disorder has not led to clinical treatments (100). Despite the statements of the pharmaceutical industry and the beliefs of many scientists, nothing has emerged to alleviate the burden of this disease for the millions of afflicted people. Why it is so? No doubt, in our opinion, that by following the leads of the amyloid cascade theory it is only trying to understand and treat a consequence and not the cause.

Therefore, it is crucial to step back and try to discover and understand from where, why, and when A $\beta$  peptide is coming. The amyloid cascade hypothesis could be true per se, but at a very advanced stage of the disease. So, if we consider the origin of the A $\beta$  peptide, we should really first search for the causes of the A $\beta$  peptide production.

A $\beta$  peptide has many physiological properties and among them the very important characteristic of possessing antimicrobial activity (101). If we admit this, it would be quite easy to conceptualize that an infection will be the trigger for its production. The first very



common infections are caused by viruses mainly the Herpesviridae. However other viruses may also initiate the production or the inhibition of these A $\beta$  peptides. This is also the case of HIV which causes a sort of dementia (i.e., HAND) where the A $\beta$  peptides also play a role hence relating this disorder to AD. In the meantime, as A $\beta$  peptide is also an antiviral peptide, then HIV may also inhibit its production at different stages of the disease. The very recent COVID19 pandemics involving the SARSCoV2 has been also demonstrated to stimulate the production of A $\beta$  () as well as once produced the A $\beta$  could bind to the S1 of SARSCoV2 may have negative impact on the infectivity of SARSCoV2 (Hsu JTA 2021), as we have shown the same mechanism in case of HSV-1 (Bourgade). This reinforces the antimicrobial protection hypothesis put forward by Moir et al () whatever is the infectious agent.

All these viral infections have been shown to share somehow similar molecular pathway converging on the innate immune system Type I interferon being the epicenter (Ahmed SSJ 2021, Alexander MR 2021, Vavougiou 2022, Lam SM 2021, Magusali M 2021, Yanf AC 2021, Zhou Y 2021). Type I IFN induction is initiating various response genes including ISG, OAS and IFITM families. These genes have been shown to be important players in the pathogenesis of AD and furthermore in various other viral infections such as by SARSCoV2, HIV, HSV-1 (Mgulai N 2021, Hur J-Y 2020, Varougiou 2021). This mechanism is meant to be protective but for any reason the viral infection per se or the viral products or the viral-generated PAMP/DAMP will pervert this protective mechanism. The dysfunction demonstrated of IFITM and OAS on a pathway level may abrogate the antiviral activity and furthermore may become pro-viral infection propagation factors (Shi G. 2021, Choi UY 2015, Roy EB 2020). It is mentioned that this perturbation in the ISG families seem to be a pan-tissue alteration as it is found at the level of neurons, peripheral immune cells, and microglia (Varougiou 2021x2, 2022, Jung HW 2020, Mavrikaki 2022). The converging point for this perturbation is the  $\gamma$ -secretase inducing the production of A $\beta$  (Svensson A 2010). Furthermore, there is a sort of association between A $\beta$  and nucleic acid which as complex or separately may upregulate IFITM3 which contributes to the stimulation of  $\gamma$ -secretase. This will initiate a vicious circle which will stimulate the production of A $\beta$  playing also an antimicrobial role and IFN production also as another antiviral molecule, however this may function as a protective mechanism at the beginning but may be perverted by the continuous presence of either participating molecules or becoming pro-viral. These mechanisms may explain how a viral infection may overcome the clearance of the immune system and become autonomous by sustaining itself by the increased A $\beta$ , ptau and neuroinflammation. This is in perfect alignment with the infection and antimicrobial protection hypothesis. Furthermore, this increased Type I IFN production also linking in a short and long term the infection and cognitive alterations via neuroinflammation synaptic loss and microgliosis (Erasquin GA 2022).

It should also be mentioned here that not only the viruses, but also other microbes may initiate the production of A $\beta$  peptide and especially those that cause long-term, or silent infections. This is the case most specifically for the mouth microbiota including *Treponema denticoli* and *Porphyromonas gingivalis*. We have also experimental evidence that *P.*

*gingivalis* may imitate the production of A $\beta$  from neurons in culture (unpublished data). These bacteria have been frequently detected in the brain of AD patients either related to plaques or directly to the neurons (102). Finally, *Borrelia burgdorferi*, the pathogenic bacteria causing Lyme disease and *C. pneumoniae* have also been incriminated in the AD pathogenesis by inducing the deposition of amyloid plaques (36,37).

Beside this direct evidence of the induction of the A $\beta$  peptide by microbes there is also evidence that this peptide may be induced by other insults occurring in the brain and particularly ischemia. Vascular risk factors are well known to contribute to the development and progression of AD. One of the possible ways that vascular factors, especially ischemia, may contribute to AD is the induction of the production of A $\beta$  peptide by damaged neurons (103). Therefore, it should be considered that A $\beta$  peptide is not only an antimicrobial peptide but also an acute stress protein which has various physiological functions.

This evidence underlines the importance to understand the role of the A $\beta$  peptide in the physiology which directly leads to the integration of these insults in the pathogenesis of AD. The acceptance of the fact that A $\beta$  peptide is produced in reaction to any insults to the brain we could be able to control, treat and prevent it. Consequently, we should not focus on the A $\beta$  peptide but to the insults which induce its production.

### **What is the cycle and the role of A $\beta$ peptide production?**

The A $\beta$  peptide plays different roles depending on the disease stage. It should be stated that a unique, uncomplicated viral infection will not lead directly to AD. Viral infections can also cause different consequences. HSV-1, as well as other viruses can cause encephalitis. This could also result in cognitive problems, but this is not AD. To induce AD, an infection this would need to enter latency or become a persistent infection. All incriminating infections or insults have the common property of chronicity and work by repetitive insults. At the beginning when the disease is at its prodromal or pre-clinical stages, A $\beta$  production may be detected but not the infection. The A $\beta$  peptide is a protective or anti-stress protein and may contain the insult. That is the reason why older subjects may have amyloid plaques without AD as these plaques have contained the disease (16). In other cases, the repetitive production of A $\beta$  peptide will overwhelm the threshold of the clearing capacity of the innate immune system of the brain. When this occurs, the deposition of A $\beta$  peptide becomes pathological because the immune system has been overwhelmed and neuroinflammation will start destroying synapses leading to the clinical manifestations of AD. In this setting the aging process may have co-contributing effects (104,105).

### **What are the consequences of the infection theory for AD**

If we accept that AD is not the AD that Dr Alzheimer described, we should abandon the term AD and only call the familial form AD as was suggested by Dr Alzheimer. Therefore, it is time to abandon the denomination of AD. We should replace it by another term which will not be biased by all these years of failure. We could suggest calling it by a generic term such as chronic brain failure (CBF) of neurodegenerative type. We can further refine

it if we precisely know the cause such as viral origin or infectious origin or toxic origin, but it probably would always have multiple origins as it will not be provoked by a single event, but rather by multiple or chronic insults. The concept of AD spectrum was first proposed even more since it is hypothesized that third of the very older subjects has LATE combined or not with AD ((Nelson PT et al. 2023). This could be a good appellation however again it is including AD which has strong connotation with the pathological hall mark of the disease/syndrome, namely A $\beta$  and pTau. We should drop the appellation of AD as a generic term.

Since we realize that A $\beta$  peptide production is secondary to another insult, we should search for this insult or insults in a thorough way to try to discover them. However, as with many age-related syndromes, we should admit that in many cases they are multifactorial. This means that on many occasions we will not be able to isolate just one cause.

If we accept this, we should search for biomarkers. This is imperative. This would also state that we no longer separate cognitive disorders as AD, vascular, etc but we should really consider their presentation. If we are able to base our diagnosis on their presentation we would be able to determine what are the pathways which lead to the specific cognitive alterations.

In this perspective it should be recognized that the infection theory put forward since decades lead to the antimicrobial hypothesis conceptualized by Moir et al in 2018 (Moir et al. 2018) explaining the role of A $\beta$  as being not a basically harmful protein but the initiator and effector of the first line innate immune response, as we have published this in 2016 (Bourgade et al). The contribution of the innate immunity either for the defense and later for the maintenance of the neuroinflammation through the activation of microglia and activated peripheral monocytes is also recognized (). As with many infections the timely and accurate acute innate immune response is very important to contain the pathogens before the development of the adaptive immune system. This gained even more recognition during the recent COVID19 pandemics. However, as it is mentioned by maintaining the constant stimulation by various viral products, DAMP, pTau, A $\beta$  or other connected agents leading to the chronicization of the neuroinflammation will continuously increase the neuronal degeneration. As this process before the clinical manifestations is lasting for decades now, we have the trigger, which is the infection or other stresses, the mediator which is the cerebral dysregulation syndrome and the clinical manifestation as an AD spectrum/syndrome as we have first proposed in our article integrating in the infection hypothesis the amyloid cascade hypothesis (Fulop 2018). By the work of many laboratories the mediating mechanism of the neuroinflammation via the IFN signaling pathways became more understandable and perhaps subject of targeted treatment.

## **Treatment**

If we consider that the infection hypothesis is correct therefore the use of various antimicrobial substances such as antibiotics, AMPs, antivirals, vaccines, epigenetic

modifiers become obvious (106,107). Unfortunately, we should recognize that until now only indirect evidence exists to support the use of these therapies.

The epidemiological data coming from the Taiwanese, French and Swedish studies all demonstrate that people who were treated with antivirals when they have an HSV-1 infection reduced the risk of developing AD. Furthermore, the above discussed vaccination against the most important latent viruses should be the major aim of the fight against AD. The antivirals, the fecal transplantation, the probiotics may be symptomatic treatments, but we need real disease modifying treatments.

### **Precision medicine**

Recently, a successful pilot project was published on the precision medicine approach to AD (108). This was just an application of what was advocated decades ago by the first multimodal intervention through the FINGER study (109). This study used simultaneous interventions to treat AD. The new approach is personalized for each patient and based on the determination of tailored potential contributing factors and targets. The pilot project was a targeted proof of concept trial using a small sample of patients. It is notable that the investigators assessed markers of inflammation, chronic infections, dysbiosis, insulin resistance and many other parameters associated with AD or MCI. They treated considering the most important contributors associated with cognition and assessed cognition every 3 months through 9 months of treatment. They found significant improvement by targeting specific patient-tailored cognition related targets, but obviously a larger confirmatory study is needed.

### **Why it is so difficult to accept that viruses and microbes are the cause of AD**

As in science any new approaches provoke resistance from the scientific community (110). Many new studies are produced to try to discredit new ideas. Recently a study was published demonstrating that A $\beta$  did not protect against HSV-1 infection in the mouse brain (111). Another study could not demonstrate the presence of viral DNA/RNA in post-mortem AD brains (112). The failure of some short-term antiviral treatments also contributes to discredit the infection hypothesis. The possible presence of polymicrobial etiology and multiple insults is another obstacle to recognition of the infection hypothesis.

Clearly, better recognition of the infection hypothesis would benefit from the direct demonstration on a long-term basis of the relationship between latent infection and clinically meaningful cognitive decline. This recognition is well accepted in acute microbial encephalitis. The role of the immune system is also sometimes difficult to understand. In acute infection its role is to eliminate the invaders, while in a long term run (chronic) infection of the immune system may become detrimental. Despite this is being fully accepted for other chronic inflammatory diseases, it has not yet been recognized in AD.

The complexity on the one hand of the multiple origins of AD associated genetic and environmental factors and on the other hand the complexity of the clinical manifestations

has become almost irreconcilable. If the present rigid clinical and pathological concept of AD is dropped, since they are known to be completely dissociated, then conciliation of these factors could ensue. Furthermore, the introduction of the role of aging further renders difficult the acceptance of an infectious origin, even if it is clear that immunosenescence and microglial senescence appears late in the process of cognitive decline. This is exacerbated by the lack of biomarkers which link infections to later cognitive disease development (**Figure 1**).

### **Conclusion and Perspective**

When there will be better acceptance of the infection hypothesis, science should focus on a better understanding of the molecular pathways linking infections, and especially viral infections, to the various hallmarks of AD. The pathways leading to A $\beta$  production should be more extensively uncovered. The multi microbial infection concept as well as the precision medicine concepts should be incorporated. We need a complex biological approach to be able to tackle the pathogenesis of this disease.

We should also step back from the disastrous name of the disease and concentrate on the cognitive consequences to be able to fit the pathology to the clinical findings and not vice versa. In this field we should recognize that AD is a syndrome with multiple cognitive manifestations which could be due to multiple causative origins including infections, trauma, and vascular stresses.

In the treatment domain it would be completely simplistic to think that one treatment will be miraculous. It should be accepted that, like in the precision medicine approach, we should develop multiple treatments for multiple targets. In this way we should treat acute as well as the latent infections. We should also treat the vascular problems. All this necessitates the development of truly personalized biomarkers and not only just A $\beta$  and pTau biomarkers.

Finally, the prevention should become the norm with lifestyle changes, vaccination and stress management.

### **Expert opinion**

Patients have been suffering for decades because of the inability of researchers to switch their mindset and accept the evidence that the amyloid hypothesis and resultant generated treatment have all failed. Now it is time to rethink our approach to AD. AD is a syndrome, and the origin is multifactorial. However, in a large part of the AD population the implication of one or more microbes, mainly viruses have been demonstrated. After infecting directly, the Central Nervous System (CNS) through the sensory pathway (i.e., olfactory bulb and trigeminal bulb), viruses induce amyloid beta production by several pathways. Amyloid beta is an ancestral, innate immune molecule used in many setting to protect brain cells (neurons). Indeed, the brain neurons produce amyloid beta to provide antimicrobial (antiviral) activity. Viruses can eventually escape this amyloid beta activity by inducing its fibrillization leading to plaque formation. Amyloid beta is the by-product

of various stresses among them the most important is chronic microbial infection. Since decades, we have known that viruses are involved in the pathogenesis of AD. This discovery was ignored and discarded for a long time. Now we should accept this fact, which is not a hypothesis anymore, and stimulates research community to come out with new ideas, new treatments and new concepts. The end of the story will be a precision medicine approach toward this devastating disease. If we can move away from the current dogma, we could make progress rapidly and significantly to be able, maybe, to definitively eradicate or severely curtail AD.

The recent acceptance by the FDA of two new anti-A $\beta$  treatment of AD was acclaimed by a large part of the AD community and concomitantly strengthened the position of these believers in the amyloid cascade hypothesis and unfortunately again discredited the scientists trying to move away from this theory. The need in the population for a treatment is so strong that anything having the smallest effect is strongly supported by the public, however this completely occult the possibility to move forward with new concept generating new treatment.

Therefore, we should no longer question whether the infection hypothesis is proven or insufficiently proven, but science should ask how we could find ways to prove and consolidate it. We should implement strategies to eradicate chronic infections in the approach and treatment of AD when we have nothing to offer presently to these patients. So, wasting years to debate and discuss and try to convince each other instead of acting will lead to many new patients uselessly suffering from this sterile debate. We need to be inventive and audacious to dare to treat and approach patients in an innovative manner. Many patients will be grateful for this new innovative approach.

The most powerful help could be the recent SARS-CoV2 infection which had numerous neurological and cognitive consequences. We should use this for reinvigorating the infection hypothesis of AD as at long term we do not know what the effects of SARS-CoV2 will be on the development of AD. This should definitively help to boost the research and the financing of this poor child of AD research. The public should be also made aware of the possibility that other causes exist and may lead to more efficient treatment. Therefore, the next few years should be more helpful for this approach to AD and lead to new treatments and prevention.

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Each author individually read and contributed to the conceptualization, writing, and editing of the paper.

### **Conflict of interests:**

The authors declare no conflict of interest.

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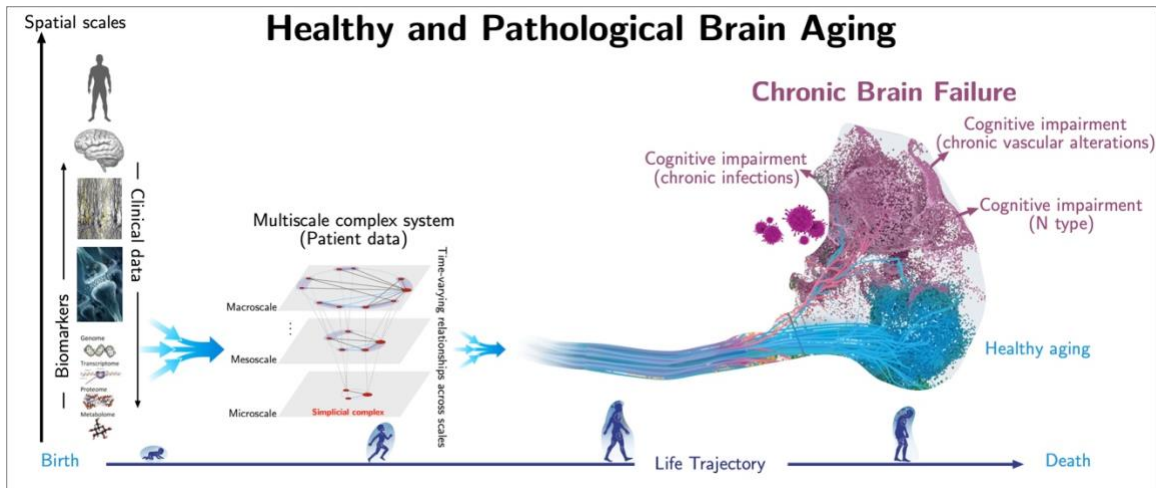
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## Tables

TABLE 1. Summary of the pathogens potentially involved in Alzheimer's disease

<b>Pathogen</b>	<b>Factors that could contribute to AD</b>
HSV-1/HSV-2	<ul style="list-style-type: none"> <li>- About 70% of person above 65 years old are infected.</li> <li>- After primo-infection, virus turns in latency, mainly in trigeminal ganglion and nuclei.</li> <li>- Repetitive reactivation is increasing the risk of increased amyloid beta peptide and pTau production concomitantly with neuroinflammation and synapse destruction.</li> </ul> <p>HSV-1 may also via the hematological dissemination infect through the BBB the central nervous system</p> <ul style="list-style-type: none"> <li>- Amyloid beta act as an antiviral amyloid peptide decreasing the infectivity of HSV-1 but in the meantime contributing to the neuroinflammation and amyloid plaque formation and deposition.</li> </ul>
Influenza	<ul style="list-style-type: none"> <li>- Virus induced the amyloid beta production and aggregation by similarities between amyloid beta and hemagglutinin.</li> <li>- Epidemiological studies show that influenza vaccination was able to protect against the development of AD.</li> </ul>
HHV-6/HHV-7	<ul style="list-style-type: none"> <li>- It was demonstrated the massive role of HHV-6 and 7 as neurotropic viruses in the development and progression of AD.</li> <li>- Epidemiological studies are supporting that HHV-6 and HHV-7 were mainly found in post-mortem brain in AD patients.</li> <li>- HHV-6A infection of neuronal cells contributes to the increased amyloid beta production and Tau hyperphosphorylation by altering the autophagy in neurons.</li> </ul>
EBV	<ul style="list-style-type: none"> <li>- EBV is a persistent virus in brain and its reactivation may cause amyloid beta production and Tau phosphorylation concomitantly with the induction of neuroinflammation and neuronal death.</li> </ul>
CMV	<ul style="list-style-type: none"> <li>- CMV infection was associated with increased AD either by directly infecting the brain and contributing to the amyloid beta production during its reactivations or by decreasing the immune response in aging which indirectly will increase the risk of reactivation of other viruses.</li> <li>- CMV increases the production of pro-inflammatory cytokines maintaining the neuroinflammation.</li> </ul>
<i>Treponema denticola/ Porphyromonas gingivalis</i>	<ul style="list-style-type: none"> <li>- These bacteria have been frequently demonstrated in the brain of AD patients either related to the plaques or directly to the neurons.</li> </ul> <p>Beta amyloid physiologically is part of the innate immune defense as they demonstrated strong antimicrobial properties.</p>

## Figures



**Figure 1. An abstract view of patients' life trajectory in both healthy and pathological brain aging.** From birth, the ca. 40 trillion human cells are interdependently organised across scales (from genetic to behavioral), hence forming a multiscale complex system with emergent properties (higher-order interaction networks) that evolve over time. This complex system constantly tries to maintain homeostasis (more generally, system invariance, which can be stationary or dynamic) in the form of a balance between its internal resources and external perturbations (stresses). A successful maintenance of this balance leads to healthy aging. In contrast, a maladaptation to various stresses leads to different pathologies, in particular, the syndrome of Chronic Brain Failure. Specifically, stresses involving chronic infections lead to a family of cognitive impairments, e.g., HSV-1, tertiary syphilis, HIV, etc. Other families of cognitive impairments involve other stresses, e.g., of vascular alteration origin and beyond. The overlap between these stresses via immune-inflammation makes often difficult to disentangle the exact role of these stresses, however the chronic infections play a fundamental role. The challenge of aging studies is to determine advanced experimental, clinical, mathematical and computational methodologies to identify key biomarkers from clinical data that lead to pathologies.