

## Microbes Causing Alzheimer's Diseases

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### ABSTRACT

Alzheimer's disease (AD) is a degenerative, progressive and disabling disease that affects the central nervous system (CNS), being the main cause of dementia worldwide. The symptoms of the AD are due to progressive loss of cholinergic function due to neuronal cell death mainly in the hippocampus cerebral cortex and other different regions of the brain leading to reduction of cholinergic function and clinical deregulation of thought process and memory. It is now known that the development of the disease is the result of these complex environmental and genetic interactions in which gut microbiota plays a special role. The role of microbes and chronic inflammation in the pathogenesis of Alzheimer' disease (AD) has been postulated by many authors. On the other hand, several studies have reported the main role of *H. pylori* infection and/or GUT microbiota alteration in promoting chronic inflammation, thus possibly influencing both occurrence and evolution of AD. In this article, we analyze the most important and recent studies performed on this field both on humans and animals and provide possible pathogenic explanations.

Keywords: Alzheimer's disease, Microbiota, *H. pylori*, Inflammation, Amyloid, Dysbiosis.

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### INTRODUCTION

Alzheimer's disease (AD) is a degenerative, progressive and disabling disease that affects the central nervous system (CNS), being the leading cause of dementia in the world [1] [2]. The symptoms of AD are due to progressive loss of cholinergic function due to neuronal cell death mainly in the hippocampus cerebral cortex and other different regions of the brain which regulate thought process and memory [3], [4], [5], [6]. The role of microbes as a possible cause of acute and chronic diseases has been investigated by many researchers for a long time; indeed, bacteria and viruses have been demonstrated to affect organs even far from the primary site of infection, especially through translocation and/or molecular mimicry mechanisms. Gut microbiota is a complex system of microorganisms showing an unequal distribution from the mouth to the anus and covering several biological functions. Overall, it is composed by viruses, bacteria, yeasts and protozoa, all living in

relative harmony, but more information is now available concerning bacterial community. On this subjects, two main dominant families have been recognized, such as *Firmicutes* and *Bacteroidetes*, along with other less represented species, including *Clostridia*, *Proteobacteria*, and *Actinobacteria*. *Helicobacter* species are classified among *Proteobacteria* and include a wide range of subspecies colonizing stomach, gut, and bile. *H. pylori* is the most known species and is the main cause of gastritis, peptic ulcer and gastric cancer in humans, while some authors place *H. pylori* among the GUT microbiota species, since in some specific conditions, it may act as a symbiont. This is the case of allergic asthma and/or atopic dermatitis, showing a negative correlation with *H. pylori* infection, possibly due to the stimulation of the Th1 and the suppression of the Th2 immune response, thus promoting inflammation but alleviating allergic reactions. GUT microbiota composition may vary among healthy and unhealthy

individuals. In normal subjects, GUT microbiota lives in *eubiosis*, meaning maintaining diversity, richness and relative abundance. In this way, GUT microbiota and host co-exist in a cooperative systemic aggregation model, both contributing to regulating the barrier effect, metabolism, immunocompetence and tolerance, and influencing synthesis of many substances including neurotransmitters, drug metabolism and even behavior conditioning. However, all factors able to alter *eubiosis*, such as the massive use of antibiotics and/or anti-acids, the impairment of the immune system or the alteration of the integrity of the GI mucosal barrier, are able to produce a pathological condition called *dysbiosis*, which in turn is strongly related to the occurrence of both GI or extra-GI diseases, including neurological disorders, through the promotion of a pro-inflammatory status<sup>13</sup>. This is why some researchers explored the possibility that *H. pylori* infection and/or intestinal dysbiosis, persisting for decades, may possibly influence both occurrence and development of Alzheimer disease (AD). In this article, we analyze the most important and recent studies performed on this field and provide possible pathogenic explanations.

#### **Pathogenesis of Alzheimer's disease**

Inflammation is thought to play a significant role [7]. Its role can be primary [8], secondary, or a combination of both. For example, [9] showed that acute and chronic inflammation were able to induce Alzheimer's disease (AD) related pathology and cognitive decline in animal models. In this respect, in a thiamine-deficient model in which chronic inflammation and oxidative stress were early events, there was increased synthesis of antibodies (Ab) and amyloid plaques [10], and antioxidants reversed the increased production of Ab. Multiple reviews and animal studies support the concept that pro-inflammatory cytokines and lipopolysaccharide (LPS) are stimulators of Ab production and tau phosphorylation, and Ab and tau protein can induce increases in cytokine. However, other studies showed that

inflammation could be induced secondarily by the core AD pathological processes related to Ab cascade or tau related neurodegeneration.

Three lines of clinical evidence support the role of inflammation in AD: increased systemic inflammation, genetic data, and the presence of infectious/inflammatory peripheral conditions. Pro-inflammatory molecules including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- $\beta$  (TNF- $\beta$ ) were associated with and predicted poor cognition, cognitive decline, and dementia 2-25 years later. However, other studies failed to show these cytokines as predictors of cognitive decline [11]. This discrepancy may be explained by the heterogeneous inflammatory responses dependent on timing and individual differences in inflammatory genotypes. For example, we have shown lower cognition in subjects with periodontal inflammation than without [12].

However, among those with periodontal inflammation, cognitive losses were greater in those having IL-10-1082 AA/AG genotype [13]. Because subjects with IL-10-1082 AA/AG genotype produce less IL-10, an anti-inflammatory cytokine, IL-10-1082 AA/AG genotype qualifies for a pro-inflammatory phenotype. We also found that combination of the plasma TNF- $\alpha$  with antibodies to specific periodontal bacteria (index of bacteria exposure and host response) increased the discriminatory accuracy between normal (NL) and AD subjects [14]. These findings are consistent with Holmes [15] show that (a) peripheral infectious/inflammations are important in the pathogenesis of AD, and (b) perhaps, it is the combination between both peripheral infections/inflammations and the magnitude of the host response, that is critical in understanding the pathophysiology of AD.

Second, genome-wide association studies show that several genes encoding proteins of the inflammatory immune system (PICALM, CLU, CR1, CR2, TREM2, and CD33) are associated with AD [16]. Third, peripheral infections and inflammation are associated with and

predict cognitive decline and AD. Infectious agents such as cytomegalovirus [17] and herpes virus are associated with AD pathology and cognitive dysfunction/AD and increase the risk for AD. Peripheral inflammations with significant inflammatory burden such as diabetes, obesity, metabolic syndrome, and atherosclerosis are also associated with cognitive dysfunction and are now accepted risks for AD [18].

### **The Role of Herpes Simplex Virus Type 1 (HSV1) in Alzheimer's Disease (AD)**

Dr. Itzhaki's laboratory first discovered in 1991 that HSV1 DNA is present in a high proportion of the brains of both AD patients and elderly normal subjects [19]. Subsequently, six other groups detected HSV1 in human brain [20]. The fact that HSV1 is present in elderly normal people as well as AD patients does not preclude a viral role. Most viruses infect far more people than they affect: genetic factors can determine who is asymptomatic and who suffers disease. Indeed, [21] found that HSV1 DNA in the brains of carriers of an apolipoprotein E-4 (APOE-4) allele confers a high risk of developing AD.

A study by another group [22] confirmed the HSV1-APOE-4 association in AD, and work on HSV1-infected APOE-transgenic mice has shown that APOE-4 animals display a greater viral load, and a greater potential for viral damage [23]. Significantly, APOE-4 is a risk also for cold sores [24]; [25], which are usually caused by HSV1 in the peripheral nervous system, suggesting that the damage caused by HSV1 is greater, or that repair is lesser, in APOE-4 carriers.

Subsequently, the Itzhaki lab detected intrathecal antibodies to HSV in cerebrospinal fluid (CSF) of a high proportion of AD patients and healthy elderly people [NB., anti-HSV antibodies found in CSF are known to be long-lived after herpes simplex encephalitis (HSE)]. This indicated that HSV1 can actively replicate in brain, causing damage both directly and via inflammatory processes [26]. It was proposed that reactivation of HSV infection in brain is possibly recurrent, so that damage accumulates, leading eventually to the gradual

development of AD. The next discoveries revealed direct links between HSV1 damage in cell culture, and the damage seen in AD brain. The Itzhaki lab and several other groups found that Ab and P-tau [27]; [28] and the relevant enzymes that produce them increase greatly in HSV1-infected cell cultures [29] [30].

Further, it was found that Ab deposition occurs in the brains of HSV1-infected mice. They next investigated the proximity of HSV1 DNA to amyloid plaques in human brain, and found a striking co-localisation [31], 90% of plaques contained HSV1 DNA, and in AD brains, 72% of the viral DNA was associated with plaques (only 24% in elderly normal brains, perhaps reflecting reduced Ab production or greater clearance). These findings, taken together with Ab accumulation after infection, suggest that HSV1 causes the formation of toxic Ab species and plaques, and support a causal role for HSV1 in AD.

The HSV1-induced increase in Ab suggests that at least initially, the peptide at low levels might act as part of the innate immune system's response to HSV1, perhaps protectively as a "bioflocculant," i.e., binding neurotoxic agents [32], or as an antimicrobial peptide [4], although, in the latter study, its toxicity precluded accurate assessment of any antiviral activity. However, in view of recent positive findings [6] [7], it seems likely that the extent of Ab's antiviral activity is determined by both its preparation method and its aggregation state. In any case, though, Ab eventually becomes toxic, presumably when overproduced, and when oligomerization occurs.

Another important discovery was that HSV1 infection reduces expression of presynaptic proteins synapsin-1 and synaptophysin and decreases synaptic transmission; these inhibitory effects on synaptic function were dependent on GSK-3 activation and subsequent intraneuronal accumulation of Ab [23]. Now, following almost three decades of disregard of, or opposition to, the role of HSV1 in AD, there are well over 130 publications using diverse approaches genetic, immunological and virological

that support this concept, as well as Dr. Itzhaki's proposal that AD could be treated with antiviral agents.

#### ***Chlamydia pneumoniae* and AD**

Another organism that has been linked to AD is *C. pneumoniae*. In this case, the bacterial DNA has been found (in some studies) to be present in brain of a very high proportion of AD patients but in only very few age-matched normals, indicating a greater susceptibility to entry and infection of brain by the bacterium (and possibly also to damage by the latter) in AD patients rather than, as with HSV1, a greater susceptibility to damage of the nervous system. The first report of an association of *C. pneumoniae* with AD demonstrated by PCR that the DNA of the organism was present in 90% of postmortem brain samples examined from late-onset AD [2]. As compared to these results, only 5% of postmortem brain samples from age-matched, non-AD, control individuals contained DNA from *C. pneumoniae*.

In one study, PCR was conducted using highly specific and sensitive probes for sequences of *C. pneumoniae* chromosomal DNA [54]. PCR positivity was detected in samples obtained from at least one area demonstrating neuropathology (e.g., temporal cortices, hippocampus, parietal cortex, pre-frontal cortex) as well as, in four cases, areas less often demonstrating AD pathology (e.g., cerebellum). Interestingly, in the latter four cases, severe neuropathology was observed throughout, while in the two AD brains that were PCR-negative, very mild pathology was observed [22].

In addition to PCR, other techniques such as immunohistochemistry and electron microscopy were used to determine if *C. pneumoniae* antigens or the organism itself were present in the brain tissues [32]. These analyses demonstrated in AD samples, but not in control samples, that antigens for *C. pneumoniae* were apparent within perivascular macrophages, microglia, and astroglial cells in areas of the temporal cortices, hippocampus, parietal cortex, and pre-frontal cortex. Electron microscopy revealed chlamydial inclusions that contained elementary and

reticulate bodies. Immunoelectron microscopy verified *C. pneumoniae* in the samples following labeling of the organism with a monoclonal antibody to an outer membrane protein. Immunogold labeling was not evident in the comparable control sections negative by PCR. Frozen tissue samples were analyzed by RT-PCR to determine whether RNA transcripts from *C. pneumoniae* could be identified.

Culturing was successful from two different AD brains and negative from two control brains [19]. Taken together, these data suggested that *C. pneumoniae* was present in areas of AD neuropathology, was viable from AD brain tissues, and was capable of being cultured from those tissues. Pneumonia as a cause of death for AD patients in the original study of *C. pneumoniae* associated with AD was documented in 4 of 19 cases, with one of the four expiring from aspiration pneumonia [10]. Although pneumonia is a fairly common cause of death among AD patients, there were few differences between the AD and control populations available to the investigators.

In addition, of the few cases for which pneumonia was a cause of death in both the populations, in no instance was *C. pneumoniae* documented as the etiologic agent. Thus, it appears unlikely that *C. pneumoniae*'s presence in AD tissues related to the patient's having a pneumonia caused by this organism at the time of death. Other factors may predispose a patient to long-term infection: these include the intracellular nature of the organism and the ease with which *C. pneumoniae* infections can become chronic and/or persistent in the body. As evidence indicated that the organism resided within cells in the parenchyma of AD brains and that some profiles of the organism showed atypia, these infections, most likely, were persistent in the brains of these individuals.

#### ***H. pylori* and Alzheimer' disease**

Chronic *H. pylori* infection might influence the development and course of AD via a wide variety of mechanisms. A cross-sectional study performed by

Beydoun *et al.*, 14, who analyzed data from the US national health and nutrition examination survey, explored the correlation between *H. pylori* positivity and cognitive performance among US adults. Results showed a poorer performance of *H. pylori*-positive 60-90 years old subjects, concerning verbal memory test compared to negative. Moreover, 20-59 years old infected non-Hispanic black and women performed worse on serial digits learning total errors compared to uninfected. This was a clear demonstration that *H. pylori* may, in some way correlate with cerebral function even if its causative role is still to be demonstrated.

In a study by Bu *et al.*, 15, they tested the hypothesis that AD may be associated to an infectious burden (IB) sustained by viruses (CMV and HSV-1) and bacteria, including *Borrelia burgdorferi*, *Chlamydia pneumoniae*, and *H. pylori*. They tested 128 AD patients and 135 healthy controls for serological evidence of those microorganisms, reporting a significant association between IB and AD. Concerning pathogenic mechanisms, they demonstrated higher levels of serum beta-amyloid protein (Ab), such as Ab40, Ab42 and total Ab and cytokines, such as TNFa, IL-1b, and IL-6 in subject positive to 4-5 infectious agents compared to uninfected. Similarly, Roubaud Baudron *et al.*, 16 examined both clinical and biological data of 53 patients with AD, testing the suggestion that *H. pylori* may alter the cognitive status by increasing

The role of chronic inflammation as a risk factor for AD development has been clearly established, as well as the influence of nutrition and metabolic syndrome<sup>34</sup>. On the other hand, all those conditions have been demonstrated to be associated with *H. pylori* infection and/or an imbalance of the GUT microbiota composition (Figure 1). Notably, *H. pylori* infection has been shown to alter gastric

Darko inflammation. Results showed a lower mini-mental state examination (MMSE) score ( $p=0.017$ ), higher plasma IL1b levels ( $p=0.025$ ) and increased gastric atrophy ( $p=0.020$ ) in infected subjects compared to uninfected a higher cognitive impairment in *H. pylori*-positive AD patients.

In another study, Wang *et al.*, 17 explored the possible correlation between *H. pylori* infection and the abnormal hyperphosphorylation of microtubule-associated protein tau, strongly implicated in AD pathogenesis. Interestingly, they found that *H. pylori* increase tau-hyperphosphorylation, which in turn is attenuated by the GSK-3 inhibitor, thus providing evidence of a potential role in the promotion of AD and opening the way for new *H. pylori* eradicating trials. Those data are also supported by animal studies; the same authors, in another trial<sup>18</sup>, tested the effect of *H. pylori* on cognitive function and Ab production in rats. They concluded that soluble surface fractions of *H. pylori* can impair cognitive functions and promote Ab42 formation, thus interfering with synaptic functions. More recently, Boziki *et al.*, 19 suggested that *H. pylori* may affect AD by interacting with Galectin-3, a glycan-binding protein implicated in several physiologic and pathologic processes, including cell signaling, proliferation, and migration as well as in the stimulation of immune response.

#### CONCLUSION

pH, thus influencing both gastric and GUT microbiota composition and promoting dysbiosis<sup>35,36</sup>, which in turn is now considered as a possible key point for AD occurrence and development. Indeed, bacteria have been shown to affect neurodegeneration by promoting inflammation, inducing molecular mimicry mechanisms and accumulation of Ab into the brain.

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