HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2017 June 04.

Published in final edited form as:

J Alzheimers Dis. 2016 ; 51(4): 979–984. doi:10.3233/JAD-160152.

Microbes and Alzheimer's Disease

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DISCLOSURE STATEMENT

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-0152).

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We are researchers and clinicians working on Alzheimer's disease (AD) or related topics, and we write to express our concern that one particular aspect of the disease has been neglected, even though treatment based on it might slow or arrest AD progression. We refer to the many studies, mainly on humans, implicating specific microbes in the elderly brain, notably herpes simplex virus type 1 (HSV1), *Chlamydia pneumoniae*, and several types of spirochaete, in the etiology of AD [1–4]. Fungal infection of AD brain [5, 6] has also been described, as well as abnormal microbiota in AD patient blood [7]. The first observations of HSV1 in AD brain were reported almost three decades ago [8]. The ever-increasing number of these studies (now about 100 on HSV1 alone) warrants re-evaluation of the infection and AD concept.

AD is associated with neuronal loss and progressive synaptic dysfunction, accompanied by the deposition of amyloid-β (Aβ) peptide, a cleavage product of the amyloid-β protein precursor (AβPP), and abnormal forms of tau protein, markers that have been used as diagnostic criteria for the disease [9, 10]. These constitute the hallmarks of AD, but whether they are causes of AD or consequences is unknown. We suggest that these are indicators of an infectious etiology. In the case of AD, it is often not realized that microbes can cause chronic as well as acute diseases; that some microbes can remain latent in the body with the potential for reactivation, the effects of which might occur years after initial infection; and that people can be infected but not necessarily affected, such that 'controls', even if infected, are asymptomatic [2].

EVIDENCE FOR AN INFECTIOUS/IMMUNE COMPONENT

- **i.** Viruses and other microbes are present in the brain of most elderly people [11–13]. Although usually dormant, reactivation can occur after stress and immunosuppression; for example, HSV1 DNA is amplified in the brain of immunosuppressed patients [14].
- **ii.** Herpes simplex encephalitis (HSE) produces damage in localized regions of the CNS related to the limbic system, which are associated with memory, cognitive and affective processes [15], as well as personality (the same as those affected in AD).

iii. In brain of AD patients, pathogen signatures (e.g., HSV1 DNA) specifically colocalize with AD pathology [13, 16, 17].

iv. HSV infection, as revealed by seropositivity, is significantly associated with development of AD [18–21].

v. AD has long been known to have a prominent inflammatory component characteristic of infection (reviewed in [22, 23]).

vi. Polymorphisms in the apolipoprotein E gene, *APOE*, that modulate immune function and susceptibility to infectious disease [24], also govern AD risk (reviewed in [25, 26]). Genome-wide association studies reveal that other immune system components, including virus receptor genes, are further AD risk factors [27–32].

vii. Features of AD pathology are transmissible by inoculation of AD brain to primates [33, 34] and mice [35, 36].

EVIDENCE FOR CAUSATION

i. In humans, brain infection (e.g., by HIV, herpesvirus, measles) is known to be associated with AD-like pathology [37–42]. Historical evidence shows that the clinical and pathological hallmarks of AD occur also in syphilitic dementia, caused by a spirochaete [4].

ii. In mice and in cell culture, Aβ deposition and tau abnormalities typical of AD are observed after infection with HSV1 [43–52] or bacteria [16, 53–55]; a direct interaction between AβPP and HSV1 has been reported [56]. Antivirals, including acyclovir, *in vitro* block HSV1-induced Aβ and tau pathology [57].

iii. Olfactory dysfunction is an early symptom of AD [58]. The olfactory nerve, which leads to the lateral entorhinal cortex, the initial site from where characteristic AD pathology subsequently spreads through the brain [59, 60], is a likely portal of entry of HSV1 [61] and other viruses [62], as well as *Chlamydia pneumoniae*, into the brain [63], implicating such agents in damage to this region. Further, brainstem areas that harbor latent HSV directly irrigate these brain regions: brainstem virus reactivation would thus disrupt the same tissues as those affected in AD [64].

GROWING EVIDENCE FOR MECHANISM: ROLE OF Aβ

i. The gene encoding cholesterol 25-hydroxylase (CH25H) is selectively upregulated by virus infection, and its enzymatic product (25-hydroxycholesterol, 25OHC) induces innate antiviral immunity [65, 66].

ii. Polymorphisms in human *CH25H* govern both AD susceptibility and Aβ deposition [67], arguing that Aβ induction is likely to be among the targets of 25OHC, providing a potential mechanistic link between infection and Aβ production [68].

iii. Aβ is an antimicrobial peptide with potent activity against multiple bacteria and yeast [69]. Aβ also has antiviral activity [70–72].

iv. Another antimicrobial peptide (β-defensin 1) is upregulated in AD brain [73].

Regarding HSV1, about 100 publications by many groups indicate directly or indirectly that this virus is a major factor in the disease. They include studies suggesting that the virus confers risk of the disease when present in brain of carriers of the ε4 allele of *APOE* [74], an established susceptibility factor for AD (*APOE ε4* determines susceptibility in several disorders of infectious origin [75], including herpes labialis, caused usually by HSV1). The only opposing reports, two not detecting HSV1 DNA in elderly brains and another not finding an HSV1–*APOE* association, were published over a decade ago [76–78]. However, despite all the supportive evidence, the topic is often dismissed as 'controversial'. One recalls the widespread opposition initially to data showing that viruses cause some types of cancer, and that a bacterium causes stomach ulcers.

In summary, we propose that infectious agents, including HSV1, *Chlamydia pneumonia*, and spirochetes, reach the CNS and remain there in latent form. These agents can undergo reactivation in the brain during aging, as the immune system declines, and during different types of stress (which similarly reactivate HSV1 in the periphery). The consequent neuronal damage—caused by direct viral action and by virus-induced inflammation—occurs recurrently, leading to (or acting as a cofactor for) progressive synaptic dysfunction, neuronal loss, and ultimately AD. Such damage includes the induction of Aβ which, initially, appears to be only a defense mechanism.

AD causes great emotional and physical harm to sufferers and their carers, as well as having enormously damaging economic consequences. Given the failure of the 413 trials of other types of therapy for AD carried out in the period 2002–2012 [79], antiviral/antimicrobial treatment of AD patients, notably those who are *APOE ε4* carriers, could rectify the 'no drug works' impasse. We propose that further research on the role of infectious agents in AD causation, including prospective trials of antimicrobial therapy, is now justified.

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