

Is AD caused by viral infection?

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There are now about 100 experimental studies by several groups (including some 40 or so from RFI's group), using diverse approaches, which explicitly support - directly or indirectly - the hypothesis that herpes simplex virus type 1 (HSV1) is involved in AD. HSV1 is a neurotropic virus which infects 80-90% of humans by the age of about 60. Once infected, a person harbours the virus for life. It resides in latent form (i.e., dormant) in the peripheral nervous system (PNS) in the trigeminal ganglia but can reactivate under circumstances such as stress and immunosuppression, and in some 25% of infected people it then causes cold sores (herpes labialis). In very rare cases ($\sim 1-3/10^6$), it causes the severe brain disease, herpes simplex encephalitis (HSE)

The first relevant study, in 1991, revealed by PCR that HSV1 DNA is present in latent form in a high proportion of elderly brains, including those of AD patients. It was subsequently found that HSV1 in brain of carriers of an APOE- $\epsilon 4$ allele confers a major risk of AD. The presence of HSV1 DNA in many elderly normal brains as well as in AD brains does not invalidate a role for HSV1; many microbes infect far more people than they affect, so "controls" might be infected but are asymptomatic; i.e., 'infect' does not necessarily mean 'affect'. Later, studies on intrathecal antibodies in the elderly (which are known to be long-lived after HSE), confirmed viral presence in brain, and showed also that HSV1 reactivation from latency can occur in brain (as well as in the PNS), quite probably recurrently; thus, HSV1 is not just an inert passenger in the aged brain,.

The main concept is that HSV1 reactivates periodically in brain under certain conditions such as stress, immunosuppression, peripheral infection etc. Reactivation leads to a productive infection, which causes both direct and also inflammatory damage, and viral spread. Repeated reactivation would cause cumulative damage - perhaps a limited, localised type of HSE, culminating in the development of AD in APOE- $\epsilon 4$ carriers. (Significantly, APOE- $\epsilon 4$ is a risk factor for cold sores.)

HSV1 DNA presence in human brains has been confirmed by 5 other groups, another confirmed the HSV1-APOE- $\epsilon 4$ association in AD, and yet another showed a trend. Further, studies on HSV1-infected APOE-transgenic mice found that APOE- $\epsilon 4$ transgenic animals display a greater potential for viral damage.

Diverse approaches - cell biological, genetic, epidemiological and virological - have subsequently been used to investigate the role of HSV1 in AD. These indicate that HSV1 does indeed reactivate in human brain and that it induces AD-type damage. Data on HSV1 DNA in CSF, which remains for only one week post-HSE (unlike long-lived HSV1 antibodies), suggest that reactivation of the virus is far more frequent than expected merely from the frequency of HSE. Other CSF studies have shown that biomarkers of AD are more similar to those of HSE patients than are those of patients with other brain infections. Also, in immunosuppressed leukaemic patients, brain specimens revealed HSV1 DNA in those who were seropositive, but not in those who were seronegative, nor in non-immunosuppressed subjects.

HSV1 infection of a wide variety of cells in culture, including human neuronal-type, causes accumulation of beta amyloid ($A\beta$) and of abnormally phosphorylated tau (P-tau) - the main components respectively of the characteristic amyloid plaques and neurofibrillary tangles seen in AD brains. The increase in $A\beta$ probably occurs via activation of PKR and depression of BACE1 expression. Implicating HSV1 further in AD is the finding that HSV1 DNA is very specifically localised in amyloid plaques in AD brains. This association of viral

DNA with plaques does not prove causality, but considered together with the HSV1-induced formation of A β . it suggests that HSV1 is a major cause of A β formation in brain and of its toxic oligomers.

Several genome-wide association studies (GWAS) have examined genetic links between HSV1 and its host cells. They show that a limited number of genes, when combined, are strongly associated with AD, even though the effect of any single gene or SNP is very weak. Possibly these genes code for proteins that interact in various processes, leading to a synergistic effect on AD pathogenesis. Also, HSV1 might bind to many cell proteins, thereby modulating their expression, including many encoded by susceptibility genes for various neurological diseases, including AD.

Epidemiological studies have examined serum IgG and IgM, also IgG avidity index, and serological data relating to several different microbes; all show association between HSV1 reactivation and AD development, and between infectious burden and cognitive decline, with HSV1 particularly implicated. Cytomegalovirus (CMV) has been implicated also, possibly influencing immune response to other pathogens, thereby triggering the immune dysregulation involved in some age-related diseases, and suggesting specifically reactivation of HSV1 with CMV action and age.

There is evidence that A β has anti-bacterial action, as part of the innate immune system, and recently it has been shown to have specifically anti-HSV1 action; however, it is likely that if eventually over-produced, it becomes toxic. Other relevant, harmful effects of infection include dynamic interactions between HSV1 and amyloid precursor protein (APP), the precursor of A β , which would facilitate viral transport and interfere with normal APP transport and distribution; induction of toll-like receptors in HSV1-infected astrocyte cultures, which has been linked to the likely effects of reactivated HSV1 in brain; infection-induced acute or chronic inflammation in triple-transgenic mice, which would exacerbate tau pathological features, further supporting the triggering of inflammation by infectious agents in brain, leading to cognitive impairment via effects on tau.

Only 2 papers, 12 and 14 years ago, have challenged the data - specifically on viral presence in brain. No other opposing studies have since been published. One can conclude that there is overwhelming supportive evidence that HSV1 in brain of APOE-e4 carriers confers a major risk of AD.

