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Commentary

COVID-19 and Alzheimer's Disease: What Is the Connection?

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Abstract. Wang et al. found that elderly COVID-19 patients were at risk of AD. The following facts suggest a possible explanation: reactivation of herpes simplex virus type 1 (HSV1) and other herpesviruses can occur in SARS-CoV-2 patients; in cell cultures, HSV1 infection causes occurrence of many AD-like features, as does reactivation of latent HSV1 after addition of certain infectious agents; recurrent experimental reactivation of HSV1-infected mice leads to formation of the main features of AD brains, and to cognitive decline. These suggest that COVID-19 results in repeated reactivation of HSV1 in brain, with subsequent accumulation of damage and eventual development of AD.

Keywords: Alzheimer's disease, COVID-10, herpes simplex virus type 1, infections, reactivation, vaccinations

The article by Wang et al. linking COVID-19 to Alzheimer's disease (AD) [1] is of great interest, especially in view of the many lines of evidence linking herpes simplex virus type 1 (HSV1) to AD. Some of these are described below, together with the proposal that infection-induced reactivation of latent HSV1 in brain of elderly people is the pathway that links the two diseases.

Many studies reveal a number of features common to both AD and COVID-19. The type 4 allele of the gene for apolipoprotein E (*APOE* ε4) is a major susceptibility factor for AD and in COVID-19, it confers a risk of severe disease. SARS-CoV-2, like AD, causes *inter alia* neurocognitive impairment, olfactory dysfunction, excessive fatigue, and anxiety symptoms, and autopsies of COVID-19 patients' brains and brains of experimentally infected animals have shown various types of neuropathological damage. The latter include severe acute effects on neuronal function and viability, and neuroinflammation, which impairs neurogenesis in the hippocampus [2]. SARS-CoV-2 infects astrocytes and to a lesser extent neurons, and the viral genome has been detected in the brain of some sufferers [3, 4]. Intriguingly, it has been suggested that insults such as infections and pollution might reactivate not only latent viruses but also endogenous retroviruses which, on chronic activation, may eventually lead to cognitive impairment and dementia in genetically susceptible people [5]

There are many reports that COVID-19 leads to reactivation of HSV1 and of varicella zoster virus (VZV) (see, e.g., [6–11]). In the case of AD, several epidemiological studies have shown that infections in general increase risk of the disease [12–17], and there is some evidence also that certain types of vaccination might decrease AD/dementia risk [18–21].

As to experimental data implicating HSV1 infection and reactivation of HSV1 from latency in the subsequent development of AD, HSV1 infection of cultured neural-type cells was found to lead to accumulation of the main components of the characteristic features of AD brain, amyloid-β, and AD-like tau [22, 23]. HSV1 infection of brain models, 3D hiNSC cul-

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tures, causes occurrence of these and several other AD-like features [24] and in these models, VZV [25] and other infectious pathogens (Cairns, Itzhaki, and Kaplan, to be published) reactivate quiescent HSV1, with consequent expression of AD-like phenotypes. Further, in HSV1-infected mice, repeated reactivation of the virus by thermal stress leads to the production of AD-like features—formation of amyloid-β, AD-like tau, and neuroinflammation markers (astrogliosis, IL-1β, and IL-6), irreversible cognitive defects and eventually to occurrence of an AD-like phenotype [26].

The rationale for considering that HSV1 might be involved in AD was based firstly on the fact that in the rare but very serious acute disease that HSV1 causes in brain, herpes simplex encephalitis, the main regions most affected are those most affected also in AD [27]. Secondly, HSV1 is a very common virus, infecting about 80% of the population by age 60: after infection, it remains in the body for life, known to reside in the peripheral nervous system (PNS) in latent form, where it is reactivated by events such stress, infections, and immunosuppression, causing direct viral damage and also inflammation. HSV1 reactivation in the PNS causes herpes labialis (cold sores), though in only some 25–40% of those infected; the other 60–75% are asymptomatic. (Asymptomatic infection occurs in other infectious diseases, including SARS-CoV-2, though many people seem unaware that "infect" does not necessarily mean "affect".) The prevalence and persistence of HSV1 meet the pre-requisites for a proposed cause of AD: high prevalence and late onset.

Investigation of the linkage between HSV1 and AD started in 1991 when HSV1 DNA was discovered (using PCR) in latent form in brain of a high proportion of elderly people, including AD patients [28]. (In fact, HSV1 DNA had been detected previously in human brain, in immunosuppressed HSV1-seropositive patients, as revealed by *in situ* DNA hybridization; it was absent in brains of seronegative and/or non-immunosuppressed subjects, suggesting that immunosuppression caused reactivation of latent HSV1 in brain [29].) Later, it was discovered that HSV1 in brain of *APOE* ε4 carriers conferred a high risk of AD (and that *APOE* ε4 was a risk for herpes labialis, caused usually by HSV1 [30]. More recently, many other studies using very diverse techniques have supported these observations, and the concept that HSV1 in brain of *APOE* ε4 carriers is a major cause of AD, resulting from repeated reactivation of the virus in brain (as in the PNS) leading to cumulative damage, including cognitive decline, and thence, to the development of AD.

Among the many supportive findings on HSV1's link to AD, at least three population studies have found that HSV1 infection confers a risk of AD/dementia [31–33]. In contrast, there are several other studies that suggest that HSV1 does not confer a risk [34, 35]. However, the latter negative studies used less stringent criteria for HSV1-positivity and/or did not take into account *APOE* genotype, or that their "controls" almost certainly included a high proportion of infected but asymptomatic people; the latter would have diminished any difference in risk between "control" and infected groups.

A possible explanation suggested for the fact that infections in general increase the risk of AD was that infection-induced neuroinflammatory changes cause reactivation of latent HSV1 DNA present in brain [36]. Consistent with this proposal are the AD-like features caused by HSV1 in 2D and 3D cell cultures, the reactivating effects of infection with VZV [25] and the thermal-induced recurrent reactivations in infected mice; all of these are attributable to upregulation of cytokines [26].

As to vaccinations and dementia, the apparent protective effect of various vaccines against AD/dementia (including BCG in the case of bladder cancer patients [37]), and the finding that BCG vaccination reduces the frequency and severity of cold sores [38], implying an inhibitory effect on HSV1 reactivation, might result from a vaccination-induced decrease in severity and/or frequency of infection and consequent decrease in HSV1 reactivation [36].

I therefore propose that SARS-CoV-2 and other events that cause brain damage can trigger reactivation of latent HSV1 in brain, that repeated reactivations—particularly in *APOE* ε4 carriers—lead eventually to AD, and that vaccinations, by reducing reactivations, might reduce the risk of AD.

Thus the study of Wang et al. [1], and the relevant findings on the neuropathological consequences of COVID-19, together with the fact that COVID-19 can reactivate herpesviruses, and that HSV1 reactivations lead to AD-like phenotypic changes, support a role for HSV1 reactivation as a major consequence of COVID, as well as a major cause of AD. Further relevant information might be provided by investigating whether the proportion of HSV1-seropositive *APOE* ε4 carriers was higher in those patients who

progressed to AD than in those who did not progress to AD.

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CONFLICT OF INTEREST

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