VIEWPOINT

Can Infections Cause Alzheimer Disease?

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Author Audio Interview

A new model of the pathogenesis of Alzheimer disease (AD) is challenging the old. New disease models do not always *replace* old models. Instead, the new sometimes *completes* the old.

The Old Model

Amyloid-β, Tau, and APOE

The pathogenesis of Alzheimer disease (AD) remained a mystery for 80 years. However, in recent decades, 3 molecules have been found to play crucial roles: amyloid-β (Aβ), found in plaques; tau, found in neurofibrillary tangles; and apolipoprotein E (APOE).[1] Individuals who carry 2 copies of the allele for *APOE*E4* are about 10 times more likely to develop the disease than those who have no copies of this allele.

Proponents of the old model postulate that the production of Aβ stimulates both the development of tau neurofibrillary tangles and neuroinflammation—and that Aβ, tau, and inflammation each lead to the destruction of neurons and synapses. Yet it remains unclear how Aβ, tau, and APOE interact to produce pathology and whether neuroinflammation is a contributor to or only a reflection of pathogenesis.

Neuroinflammation

Although controversial at first, today there is little doubt that neuroinflammation is present in AD. Multiple components of inflammation can damage neurons and synapses: cytokines and chemokines, reactive oxygen species, activation of the classical and alternate complement pathways, and activation of cyclooxygenase 2. In addition, biomarkers of inflammation are upregulated most prominently in those areas of the brain that are most affected by AD neuropathology: the frontal and temporal neocortex and limbic system. In short, neuroinflammation is *associated* with the neurodegeneration seen in AD, and recent research suggests it may precede neurodegeneration.

But what triggers the inflammation? Neuroinflammation can occur in response to the buildup of Aβ. It also can occur in response to the neurodegeneration.

A proposed new model, however, suggests yet another trigger for neuroinflammation: infections of the brain, and infection elsewhere in the body that activates the immune system in the brain. This hypothesis could reorient the direction of future research and practice. But what is the evidence for it?

The New Disease Model

Infection Triggers Neuroinflammation and Then AD

Infection by neurotropic microbes—particularly agents capable of producing an ineradicable infection, like herpesviruses—theoretically could trigger chronic neuroinflammation. Several gene variants that impair the immune response to infection appear to be more common in individuals with late-onset AD and could foster a smoldering, recurrent reactivation of latent infection. However, this is difficult to prove in humans.

Herpes Simplex Virus Types 1 and 2 in AD

Multiple reports link herpes simplex virus type 1 (HSV-1) to AD. DNA of HSV-1 may be found more often in the brains of individuals with AD than in healthy and disease controls[2]; the viral DNA is especially prominent adjacent to Aβ plaques.

How might HSV-1 be linked to Aβ, tau, and APOE? In vitro, HSV-1 infection of neuronal and glial cells can impair autophagy (degradation of cellular protein), which in turn leads to the accumulation of both Aβ and tau—and the accumulation of both is reduced by treatment with acyclovir.[3] In *human* organoids, "minibrains," infection with HSV-1 is followed by the production of tau and the development of plaque-like structures laden with Aβ—both of which are reduced by treatment with acyclovir.[4,5] In vivo, HSV-1 infection of mice leads to the production of Aβ deposits and cognitive deficits but the pathologic changes are not pathognomonic of AD.

Some investigators have found HSV-1 DNA more often in the brains of people with AD who are *APOE*E4* allele carriers. That is plausible: a few studies suggest that *APOE*E4* carriers may be at additional risk of HSV-1–related cold sores and HSV-2–related genital ulcers. Thus, *APOE*E4* carriers may have difficulty controlling HSV-1 or HSV-2 infections and also are more likely to develop AD—raising the possibility that the former might explain the latter.

Some epidemiological evidence also links HSV-1 and HSV-2 to AD. One study identified more than 8000 people 50 years or older with newly diagnosed HSV-1 or HSV-2 infections, matched them to 3 controls without such a history, and followed up the study participants for a decade.[6] The 8362 who had contracted HSV-1 or HSV-2 infections earlier in life, compared with the 25 086 who did not, had a greater relative risk of dementia later in life (adjusted hazard ratio [HR], 2.56; 95% CI, 2.35-2.80). Most provocative, among 7215 people whose symptomatic herpes infections had been treated with antivirals, the rate of subsequent dementia was lower than the rate among the 1147 people not treated with antivirals (adjusted HR, 0.092; 95% CI, 0.079-0.108), with a significant dose-response relationship.[6] This was an uncontrolled observational study in just one community, with a relatively short follow-up period. Moreover, the reported 91% relative reduction in the rate of dementia is so substantial that it is hard to believe. Nevertheless, it is important to see if this finding can be replicated.

Human Herpesvirus Types 6A and 6B

Both human herpesvirus (HHV) types 6A and 6B and type 7 (HHV-7) have been linked to AD. Prior to 2018, a few small studies had found an association, but others had not.

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In 2018, investigators studied brains from more than 1000 patients with either AD, progressive supranuclear palsy (PSP), or healthy aging. Other more common neurodegenerative diseases were not included. The team searched for DNA and messenger RNA (mRNA) from 515 known human viruses in postmortem entorhinal cortex and hippocampus—having no prior hypothesis as to which, if any, viral nucleic acid they might find.[7] Using bioinformatics tools to interrogate the massive data set, the team found higher levels of viral DNA and mRNA (indicative of active infection) from HHV-6A, HHV-7, and HSV-1 in people with AD than in those who had PSP or had aged healthfully. The DNA and mRNA load for HHV-6A correlated positively with clinical dementia scores and with the density of Aβ plaques and correlated inversely with the number of neurons.

However, 2 subsequent reports came to different conclusions. Another group analyzed the same large data set, using what it deemed superior bioinformatic techniques, and did not find that HHV-6A, HHV-7, and HSV-1 nucleic acids were more prominent among patients with AD.[8] A second team used molecular techniques to search for microbial DNA and mRNA in 3 large, independent repositories of AD and non-AD control brains and did not find a strong association between HHV-6A or HHV-6B and AD.[9]

The differing results on the abundance of HHV-6A or HHV-6B DNA and mRNA highlight the need for standardized and highly sensitive assays, as well as standardized procedures for brain sampling, when evaluating the possible role of these and other infectious agents in AD. For now, it remains uncertain whether HHV-6A, HHV-6B, and HHV-7 contribute to AD pathogenesis.

Other Microbes

Several other microbes also have been linked to AD, including varicella-zoster virus (VZV), hepatitis C virus, *Helicobacter pylori*, *Porphyromonas gingivalis*, *Chlamydia pneumoniae*, and fungal organisms. Given the number of very different organisms putatively linked to AD, it is easy to be skeptical that any of them are etiologic agents; however, these claims are consistent with a model that puts neuroinflammation, elicited by any of multiple microbes, at the heart of pathogenesis.

Tying Aβ to Infection

Amyloid-β is formed from the larger amyloid precursor protein (APP). The small Aβ molecule then forms soluble polymers that ultimately come together to form fibrils and fibrillar plaques. Neuroinflammation induces the production of Aβ; Aβ, in turn, elicits neuroinflammation, thus creating a vicious cycle.

Why would neuroinflammation stimulate the production of Aβ? Some investigators have suggested the "innate immune protection hypothesis." They argue that Aβ is capable of functioning as a natural antimicrobial peptide that is effective against not only viruses but also bacteria and fungi.[5] The polymers and fibrils can form a web that entraps invading pathogens. Whether Aβ actually performs such an antimicrobial function in the human brain remains unproven. The APP has been evolutionarily conserved in the animal kingdom for hundreds of millions of years; the potential antimicrobial benefits of Aβ might be a reason.

However, the smaller, soluble forms (oligomers) of Aβ are not only potential antimicrobials, they also are neurotoxic. Thus, the Aβ molecule has both beneficial and pathological effects.

Why would a neurotoxic molecule like Aβ have been evolutionarily conserved? Perhaps because Aβ's pathological effects typically become apparent only after age 60 years. That's well past childbearing age for women, and well past life expectancy until the 20th century. Thus, throughout most of human history, the pathological effects of Aβ would have had little effect on natural selection.

Conclusions

The old disease model remains valid: Aβ, tau, and APOE are important in the pathogenesis of AD, and neuroinflammation also is present. The parts of the new model that remain controversial are (1) whether neuroinflammation is a cause, rather than a consequence, of the amyloidosis, tau deposition, and ultimately neurodegeneration seen in AD and (2) whether, at least in some cases, infection may be the generator of neuroinflammation.

The new disease model is intriguing, but unproven. Possibly, further research may show that therapies targeting neuroinflammation (or, less likely, therapies targeting specific infectious agents) can prevent or even reverse AD. If that were to happen, the new disease model would not be replacing the old. Rather, the new would be completing the old.

ARTICLE INFORMATION

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