Introduction

For twenty-five years, professor Ruth Itzhaki's research on microbes as a possible cause of Alzheimer's diseases was dismissed and ridiculed. The idea that there could be a potential bridge between two starkly different fields–virology and neurodegeneration–seemed absurd at the time. Now, Itzhaki's work is the backbone of an ongoing, cutting-edge trial on antiviral treatments for Alzheimer's at Columbia University.

Microbes as Triggers

Evidence supporting Ithaki's theory points to herpes simplex virus 1 (HSV-1) as a driving factor in Alzheimer's disease. HSV-1 is mainly transmitted orally, and causes what is commonly known as cold sores. The mechanism of invasion is as follows: the virus invades the body, burrows into the central nervous system, and remains latent within the brain (Cox, 2023). When activated, it causes an acute inflammatory response. This activation can take place due to periods of stress, including head injuries, immunosuppression, and other comorbid infections. The multiple reactivations lead to sufficient brain damage and inflammation, facilitating the spread of the infection.

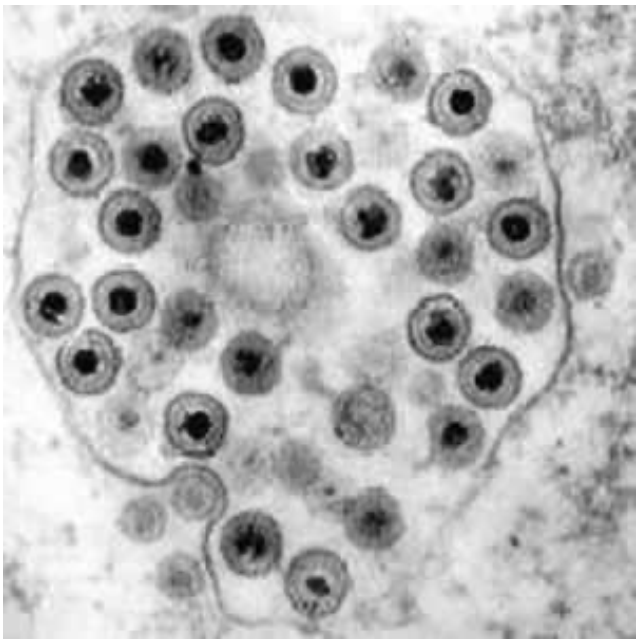

Figure 1. Herpes Simplex Virus (UTMB Home. n.d.).

While any pathogenic microbe can theoretically have a trigger role (and various bacteria have been suspected of this), there are shocking similarities in the brain regions affected by Alzheimer's Disease and the herpes simplex virus 1, leading scientists to believe that it might be implicated in the pathogenesis of Alzheimer's Disease. HSV-1 was found in the temporal, frontal, and hippocampal regions of both AD individuals and individuals only infected with HSV (Tyler, 2021). Additionally, According to Johns Hopkins Medicine, HSV-1 is very common, affecting up to fifty to eighty percent of American adults. The asymptomatic nature of the viral infection often renders it undetectable.

HSV-1 was notably the first microbe to be detected in the human brain, in both patients who were diagnosed with Alzheimer's and those who were not. This is a clear indication that infection by the herpes simplex virus 1 alone is not enough to cause disease, and another factor can determine the degree of damage caused by the virus (Itzhaki, 2022).

The VZV Pathway

A study by Tufts University suggests that another form of herpes virus, varicella zoster virus, may be one of the causative factors (Blanding, 2015). As reported by the National Institute of Health, more than ninety-five percent of people have been infected with varicella zoster virus (abbreviated VZV) before the age of twenty, usually in the form of chickenpox (Tyler, 2021).

To better understand the relationship between HSV-1, VZV, and Alzheimer's disease, Tufts researchers modeled the brain with sponges made of silk and collagen, and populated these sponges with neural stem cells. They found that neurons can be infected with VZV, but that wasn't enough to produce the characteristics of Alzheimer's disease. Interestingly, if HSV-1 was already present in a latent form, the exposure to VZV led to a reactivation of HSV-1 and a dramatic increase in both beta-amyloid proteins and tau proteins, a hallmark of Alzheimer's disease (Cairns et al., 2022).

Amyloid v. Microbial Theory

Until now, researchers have widely accepted what many call the amyloid theory as the cause of Alzheimer's disease. The amyloid theory holds that the disease can result from a buildup of amyloid beta peptides in the space between brain cells. The peptides are then cleaved from this space, allowing them to float freely and aggregate. If left untreated, the clumps aggregate into plaques, one of the defining characteristics of the disease (Cairns et al., 2022). Recent research has proved that the amyloid theory and the microbial theory are not necessarily mutually exclusive.

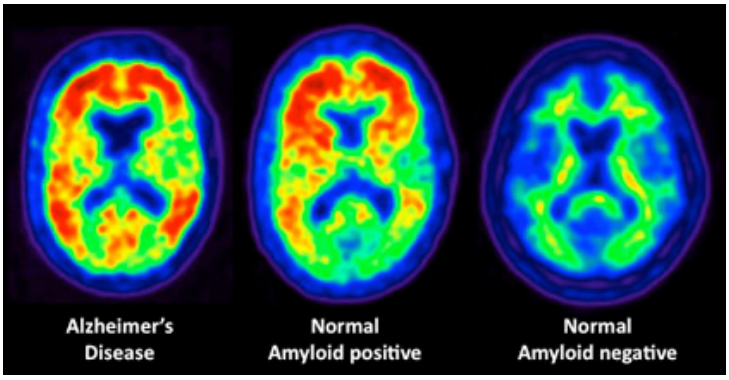

Figure 2. A PET scan by revealing the difference in presence of amyloid plaques between patients with Alzheimer's and those without (Yang, 2012).

A study by neurogeneticist Tanzi and colleagues showed that amyloid-beta has antimicrobial properties. Tanzi's study showed that this peptide was able to kill eight common pathogenic microorganisms, such as Streptococcus pneumoniae and Escherichia coli (Abbott, 2020). By glutinating and trapping various microbes, amyloid-beta is actually the brain's first line of defense, and only poses an issue when allowed to aggregate into plaques.

Aging brings the decreased ability to clear amyloid aggregates from in between neurons, allowing them to trigger a cascade of neuroinflammation. Furthermore, an age-associated waning immune system can allow microbes to proliferate more efficiently, catalyzing the development of the disease. Similarly, lifestyle risk factors of Alzheimer's, such as lack of exercise and social isolation, can also weaken the immune system and further decrease the body's ability to clear plaques (Yang, 2012).

Conclusion

Although the cause of Alzheimer's disease remains largely elusive, recent research into potential microbial origins has offered much-needed insights. Amyloid-beta plaques may be a side effect, rather than an actual cause of Alzheimer's, which could explain the relative ineffectiveness of amyloid-targeting drugs on patients.

Results of the study by Columbia University on valacyclovir, an antiviral treatment for Alzheimer's, are expected in early 2024. However, various studies have already shown the effectiveness of antivirals in preventing Alzheimer's, such as a 2018 study from Taiwan, which showed that people treated with antiviral drugs decreased risk of dementia nine-fold. Current research is now investigating the role of vaccinations in Alzheimer's.

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