To the Editor—We appreciate the comments and excellent points of Drs Itzhaki and Klapper. It is indeed interesting to note that cytomegalovirus (CMV) only very rarely causes clinically evident central nervous system (CNS) infection in immunocompetent hosts. Therefore, given the finding of an association between CMV infection and Alzheimer disease (AD), alternate hypotheses of biological mechanisms should be considered. Our hypothesis is that lifelong periodic subclinical reactivation of latent CMV infection in the CNS produces a proinflammatory response, which is a contributory factor in the development of AD pathology, as manifested by amyloid beta (Aβ) plaques and neurofibrillary tangles. Evidence that reactivation occurs in the absence of symptoms in immunocompetent persons comes from several observations including detection of viral DNA in compartments outside the blood, as well as a marked increase in CMV-specific T cells with aging [1–3].

CMV is known to infect a wide variety of cells in vivo such as monocytes, macrophages, endothelial cells, and smooth muscle cells. In addition, CMV infects fibroblasts, astrocytes, and some neuroblastoma cell lines in vitro, which indicates tropism beyond lymphoid and epithelial cells and includes cells found in the CNS [4, 5]. Moreover, there is a growing body of evidence that CMV DNA is present in >90% of gliomas [6], and it was recently reported that glioblastoma patients receiving the antiviral drug ganciclovir, in addition to standard therapy, had increased survival [7].

One of our most striking findings was the association of interferon-gamma (IFN-γ) in the cerebrospinal fluid (CSF) with AD pathology and the observation that IFN-γ was detected in the CSF of >80% of CMV-seropositive subjects, whereas no IFN-γ could be detected in the CSF of any of the seronegative subjects. This suggests a role for inflammation in the CNS as a potential mechanism for the association of CMV with AD.

Because AD is a complex disease, and likely the result of multifactorial genetic and environmental factors, we believe that CMV reactivation is likely only one among many factors in the risk of disease. Indeed, Dr Itzhaki’s laboratory has reported very convincing evidence for the contribution of herpes simplex virus type 1 (HSV-1) infection to the development of AD, which we cited [8–10]. We do not have an explanation for the fact that we did not find the same associations for HSV-1 with IFN-γ, AD pathology, clinical diagnosis, and intracellular induction of Aβ that we found for CMV. Possibly there are differences among HSV-1 strains and infected cell types.

We would suggest that both viruses have the potential to be involved in the development of AD through the inflammatory response to viral reactivations in the CNS. Drs Itzhaki and Klapper cite a recent study that appears to support this hypothesis [11]. If that is the case, then perhaps ganciclovir, which is effective against both HSV-1 and CMV, might be the drug of choice for a therapeutic trial, despite the fact that it has greater toxicity than acyclovir. However, we would suggest that development of vaccines against both viruses would be the better long-term strategy.

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References


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