Neurotherapeutics (2018) 15:415–416
https://doi.org/10.1007/s13311-018-0625-4

COMMENTARY

Association of Herpes Viral Infections, Antiherpetic Therapy, and Dementia: Real or Alternative Fact?

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Published online: 26 March 2018

In the manuscript by Tzeng et al. [1], in this issue of Neurotherapeutics, the authors took advantage of a national database in Taiwan established through the National Health Insurance Program. The program includes 99% of the total population, which is approximately 23 million clients. Using this database, they retrospectively identified 8362 subjects over a 10-year period with newly diagnosed herpes simplex virus (HSV) infection, which included both genital and non-genital infections. Thus, both HSV-1 and HSV-2 infections were included. The population was further divided into three groups based on the clinical subtype of dementia: microvascular disease, Alzheimer's disease, or other causes of dementia. The authors compared this population with well-matched controls at a ratio of 1:3; thus, there were 25,086 controls. They found that all three types of dementias had an increased risk with either HSV-1 or HSV-2 infection. There was no association between the herpes virus infections and the risk factors for vascular disease except for within the category of "other dementia." This association was lost when patients who developed dementia within the first 5 years after the infection were excluded. Importantly, however, the authors analyzed the data to determine if there was an effect of antiviral therapy on the development of dementia. They claim that antiherpetic medications can reduce the risk by nearly 90.8% and that prolonged therapy had a better outcome.

The study has several caveats. It is retrospective in nature, which inherently poses issues with proper diagnosis, selection bias for treatment, variable duration of therapy, lack of any neuroimaging studies, or identification of genetic risk factors. Despite the caveats, the current study opens up new questions regarding the role of peripheral herpes viral infections in CNS disease even though it does not settle the debate. The major question to ask is why would herpes virus infection in the genitalia or on the lips lead to dementia. There was nothing to suggest that these patients had meningitis or encephalitis that was clinically apparent. One would have to postulate that the virus establishes a chronic or persistent infection in the brain to cause cognitive deficits. However, given what we know about these viruses, this would be highly unlikely. The other possibility is that any viral infection could set up a systemic inflammatory process. Activation of the innate immune responses in the brain could be detrimental particularly in older individuals. This type of immune activation might not be specific for herpes viral infections. In fact, many infections in the elderly such as pneumonia or sepsis can precipitate cognitive decline that continues after adequate treatment of the infection. It is not clear if minor infections can also pose a risk [2, 3]. In the present study, both HSV-1 and HSV-2 were associated with increased risk for dementia, and there was an increased risk for all types of dementia suggesting a non-specific nature of the association. In another study using the same database, herpes zoster ophthalmicus, which is caused by varicella zoster virus, was also associated with an increased risk for dementia [4]. There is another body of literature that claims a more direct association based on the demonstration of gene products of HSV-1, chlamydia pneumonia, and spirochetes in the amyloid plaques in the brain. It is postulated that these products may either facilitate the formation of the plaques or set up a chronic neuroinflammatory process (reviewed in [5]). However, the mere presence of these antigens does not establish a causative role.

Despite these caveats, since there is no currently available treatment for age-related dementias or Alzheimer's disease, if a small subgroup could benefit from antiviral treatment, where the drug is relatively innocuous, it could still have a major public health impact. For these reasons, further investigations are necessary to conduct a properly designed prospective study to examine the association between herpes virus infections, antiviral therapy, and dementias, and to determine if there is a causative

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link. This will likely take many years to complete. In the meantime, is there anything we can do? At the least, it might be safe to say that patients who develop herpes viral infections should be treated with appropriate antiviral drugs.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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