LETTER

Role of HHV-6 subtypes in accelerating EAE progression

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We enthusiastically read the article in PNAS by Leibovitch et al. (1), in which they show that intranasal inoculations with human herpesvirus (HHV)-6A and HHV-6B accelerate the onset and severity of experimental autoimmune encephalomyelitis (EAE). They performed an outstanding job in utilizing marmosets to mimic the multiple sclerosis (MS)-like symptoms rather than female C57BL/6 mice. Although the creativity of their work is undeniable, several points exist that are worth mentioning.

It is allegedly known that EAE imitates MS-like symptoms and shares many pathological manifestations with MS; however, the central organ affected in this animal model is the spinal cord (2) rather than the brain. When it comes to the study of Leibovitch et al. (1), neither MRI scan nor immunohistochemical section was provided from spinal cord tissue.

Similar to the expanded disability status scale, which is a method of quantifying disability in MS and monitoring changes in the level of disability over time (3), there is a particular ranking score for EAE animal models, representing their disability status. Such a ranking would have been beneficial to monitor the disease progression/alleviation in response to external insults/medications.

The main focus of the authors is on the infiltration of $CD8^+$ T cells into the brain of the marmoset to attribute their functions to disease duration. Numerous research studies have highlighted the pivotal role of $CD4^+$ T cells in the induction of EAE and its propagation (4). The application of anti-CD4 antibodies would have provided a better understanding of the impact of the presence of proinflammatory cells on disease duration.

Leibovitch et al. (1) make a comparison across the groups in terms of the T1 lesion burden as a proportion of total lesion volume. They show that the HHV-6B animals have a significantly higher mean fraction in comparison with the HHV-6A or control animals. It should be noted that the level of significance at 0.05 would not be acceptable to display such a discrepancy among the animals.

Altogether, we believe that further studies are warranted to elucidate the precise mechanism of HHV-6 in the pathogenesis of MS.

1 Leibovitch EC, et al. (2018) Herpesvirus trigger accelerates neuroinflammation in a nonhuman primate model of multiple sclerosis. *Proc Natl Acad Sci USA* 115:11292–11297.
2 Kim JH, et al. (2006) Detecting axon damage in spinal cord from a mouse model of multiple sclerosis. *Neurobiol Dis* 21:626–632.
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4 Chitnis T (2007) The role of CD4 T cells in the pathogenesis of multiple sclerosis. *Int Rev Neurobiol* 79:43–72.

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