LETTER TO EDITOR

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# Role of Epstein-Barr Virus on Cognitive Impairment among Multiple Sclerosis Patients

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**Dear Editor,**

Approximately six million people in the United States are affected by neurological diseases (NDs), and their incidence and severity are linked to genetic and environmental factors [1]. Recent studies have implicated human herpesviruses, such as Epstein-Barr virus (EBV), as potentially infectious agents in the etiology of NDs [2, 3]. EBV is a neurotrophic virus that can infect astrocytes, neurons, and microglia [4]. Furthermore, infected B- and T-cells migrate through areas of the central nervous system, such as the glymphatic system and the nasopharynx, which could impact neuronal cell function [5, 6]. EBV infects B-cells, and there is growing evidence that B-cells play an important role in brain damage in some diseases, e.g., multiple sclerosis (MS) [1]. Demyelinating plaques associated with MS have been found to contain EBV. A high titer of the EBV nuclear antigen (EBNA) or an EBV infection also raises the risk of developing MS in the future [1].

Additionally, it has been noted that EBV seropositivity in MS is higher than 99% compared to 94% in adults, providing evidence that EBV may have contributed to MS early pathogenesis [7, 8]. B-cells and their activated offspring in the brain produce immunoglobulins and promote the clonal expansion of plasmablasts [9]. These antibodies that attack the myelin-producing glial cells and cause damage are discovered in MS patients' cerebrospinal fluid [9]. Additionally, MS patients frequently have anti-GlialCAM and anti-EBNA1 antibodies [8]. The integrity of the cortical gray matter structures may be impacted, and its atrophy may be accelerated by the B-cell follicles growing in the MS meninges and the presence of dysregulated EBV-infected B-cells [8, 10]. Previous reports indicated that imaging evidence (e.g., magnetic resonance imaging) of cortical atrophy could appear in the early stages of MS, despite the possibility of a delay between the onset of isolated cortical lesions and atrophy [10]. EBV can prevent B and T lymphocytes from proliferating, which causes neuroinflammation and demyelination when it infects neurons.

Additionally, it accelerates glial cell necrosis and degeneration [11]. Because anti-CD20 monoclonal antibodies are very efficient in treating MS patients, the involvement of B-cells in the onset of MS activity may be increasingly prominent [12]. These incidents support the association between EBV and MS [12]. Compared to the control group, anti-VCA and anti-EBNA-1 titers were considerably greater in MS patients. Higher anti-VCA titers were associated with older





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age and the female sex, while higher anti-EBNA-1 titers were associated with the male sex [13].

The relationship between exposure to EBV and cognitive performance has been studied, but the results have been mixed. Three tiny samples from a meta-analysis revealed a link between EBV and Alzheimer's disease (AD) [14]. In a recent study, EBV-specific T-cell receptors were found in the cerebral fluid of AD patients, and these receptors were strengthened by the increased antigen-specific clonal growth of CD8+ T-cells in AD [15]. Dickerson *et al*. evaluated the association between EBV and cognition in two studies involving 521 non-elderly and 229 individuals with schizophrenia, but they could not find a relationship [16]. In research involving 7000 young adults, EBV was also unrelated to cognitive function [17]. The confidence interval in the last two studies was considerable, making it challenging to interpret the findings. Even though the precise mechanism underlying the link between infection and AD is not fully understood, studies have suggested several potential mechanisms. According to some, herpesvirus infection may encourage the development of amyloid plaques in the brain [18]. According to Shim *et al*. a chronic EBV infection may play a role in the pathogenesis of AD, and an EBV antibody level may be employed as a potential biomarker for determining the likelihood of developing cognitive impairment [19].

It appears that EBV infection and its effect on demyelinating diseases could lead to degenerative processes in MS and cognition. Furthermore, new studies with new methods are needed to support the possibility of elevated EBV antibody titers with cognitive impairment among MS patients.

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**Conflict of Interest**

The authors have no competing interests.

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