DOI: 10.1002/jmv.28689

COMMENTARY

JOURNAL OF MEDICAL VIROLOGY WILEY

Herpes simplex virus and SLE: Though uncommon yet with significant implications

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KEYWORDS

autoimmunity, herpes simplex virus, human herpes viruses, infection and autoimmunity, systemic lupus erythematosus

To the Editor,

The relation between infectious agents, particularly viruses, with autoimmunity and autoimmune diseases, has been extensively studied during the last decades. Recently, the association was shown to be even stronger during the pandemic of COVID-19, as the causative virus, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has been linked to severe autoimmune sequela in infected individuals. The concerned consequences in patients with COVID-19 were documented during the acute viral infection, throughout the long recovery phase (so-called post-COVID syndrome), as well as secondary to the vaccines of COVID-19.[1] Actually, the autoimmune nature of SARS-CoV-2 has been vastly reported in the medical literature and it is beyond the scope of our current paper.[2] However, it shows the strong bond between infection and autoimmunity. Subsequently, with a deep interest in the field, we analyzed the article of Chang et al.[3] concluding that there is no correlation between herpes simplex viral infections and systemic lupus erythematosus (SLE) in terms of causality using Mendelian randomization.

In fact, SLE as a syndrome represents a spectrum of chronic systemic autoimmune conditions affecting almost every organ system and characterized by the production of a wide variety of autoantibodies. In terms of etiology, or more precisely, triggers of the disease, various infectious agents especially viruses were linked to the emergence of SLE. We have previously shown, by a real-life bigdata analysis, a strong and significant correlation between SLE and hepatitis C virus compared to controls.[4] Moreover, infections in general were found in remarkable association with SLE besides increasing the mortality rated in hospitalized patients with SLE.[5] When it comes to herpes viruses and autoimmunity, the topic can be addressed in two main levels. The first is related to the correlation between herpes viruses and autoimmunity in general, whereas the second level concerns SLE and herpes viruses.

Human Herpes Viruses (HHVs) are widely spread DNA viruses infecting high proportion of the general population. The family is well known of causing latent and active infection determined by the competency of the immune system of the infected individual. Epstein–Barr virus (EBV) was demonstrated to serve as a risk factor for developing multiple sclerosis (MS) in certain age groups while Human Herpes Virus 6 (HHV-6), another HHV, inferred a risk for the disease in all age groups.[6] In fact, the mechanisms regarding the role of HHV-6 in MS has been considerably investigated.[7] For instance, HHV-6 was found to provoke autoimmunity through several mechanisms like its capability of lysing infected cells, and hence exposing high amounts of cell antigens presenting to the immune system. HHV-6 can also cause an irregular expression of the histocompatibility molecules resulting in the presentation of self-antigens. Another hypothesized mechanism by which HHV-6 contributes to autoimmune diseases is through molecular mimicry where viral proteins produced are similar, in various degrees, to self-proteins. The latter results in cross-reactive T cells with the ability of recognizing both viral and self-antigens.

Meanwhile, HHVs are responsible for a significant number of aspects in SLE. In terms of susceptibility to developing SLE, both EBV and CMV serve as important players in this regard.[8] Structural proteins of the viruses were shown to modulate the risk of SLE in genetically predisposed individuals. Interestingly, other members of the HHVs were directly and indirectly linked to SLE including Herpes Simplex Virus (HSV). In contrast to the findings presented by Chang et al.[3]; Reis and colleagues illustrated a significant importance of both primary and reactivation of HHVs in patients with SLE.[9] By enrolling 71 SLE patients classified into active and non-active disease, serum samples were evaluated by PCR for the detection of HHVs including

HSV-1 and HSV-2. Based on the results, the authors emphasized the need to check for the presence of HSV-1 and HSV-2 in patients with SLE presenting with atypical symptoms.

Having said that, we do agree that HSV-1 and HSV-2 are not as common as other members of the HHVs, particularly EBV, in terms of etiology, pathogenesis, and exacerbation of SLE. Nevertheless, their implication in SLE should not be underestimated. This association comes to a greater attention due to the critical importance of CNS infection in SLE, as it carries a high mortality rate and constitutes a clinical challenge in the differential diagnosis of SLE-related CNS disease (termed neuropsychiatric lupus).[10] While the latter is treated with high doses of immunosuppression, the high mortality in the former could be worse under immunosuppressive treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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