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A REVIEW OF EPSTEIN BARR VIRUS COINFECTION IN COVID-19 PATIENTS

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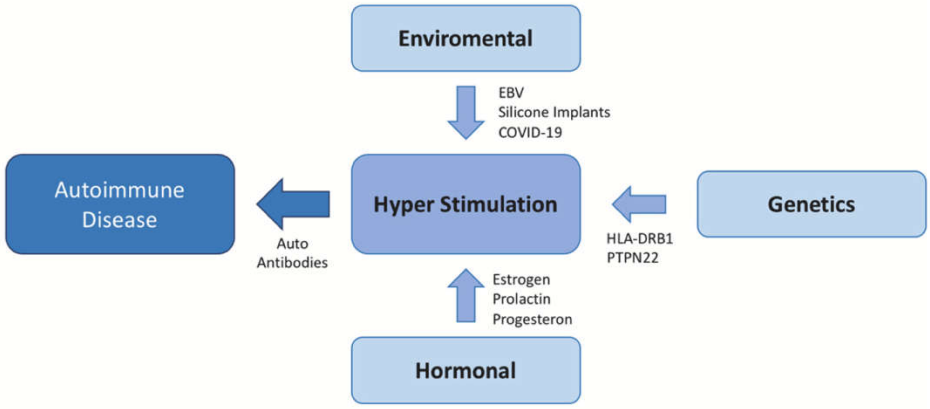
Abstract

Epstein–Barr virus (EBV) could tip an already compromised system into a self-perpetuating metabolic-oxidative stress-inflammatory spiral that could underly many of the symptoms of long COVID. Systemic reactivation of (EBV) may occur in novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Hence, In this review, we audit EBV coinfection in COVID-19 infected patients. A high proportion of COVID-19 patients have shown EBV reactivation and this may be associated with an increased risk of death. The mortality of COVID-19 patients complicated with EBV reactivation warrants to be addressed in a placebo-controlled randomized trial in the future.

Keywords: *Corona virus; EBV; Autoimmune; Coinfection*

INTRODUCTION

The onset of autoimmune diseases (AIDs) may be generated by a variety of factors through the creating a hyper stimulated state of the immune system. It is accustomed to classifying factors that affect the immune system into three primary groups: genetical, environmental and hormonal. Viruses are a substantial component of the environmental factors that affect the immune system. Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV) and human T lymphotropic virus 1 (HTLV-1) are examples of viruses with an established association to multiple AIDs. The autoimmune influence of these viruses is not atypical. There are many other viruses that are also associated with AIDs. The combination of a genetically pre disposed individual with a hyper stimulated state of the immune system may trigger an AID. [1]



EBV could tip an already compromised system into a self-perpetuating metabolic-oxidative stress-inflammatory spiral that could underly many of the symptoms of long COVID. [2] With this background in mind, we conducted a review of the studies and patients with confirmed history of COVID-19 infection that presented for symptoms concerning for EBV coinfection.

REVIEW

Mitochondrial Function & Covid-19 Infection

Mitochondria are key in the immune response. [3] It has been suggested that as SARS-CoV-2 may modulate mitochondrial function it may have a greater adverse effect in those with poorer mitochondrial health, such as the elderly and those displaying evidence of the metabolic syndrome. [4] Good mitochondrial health and reserve could well be important components in the resistance to SARS-CoV-2. Although there is building evidence for this, the idea is still not yet mainstream. [5]

EBV & "Long Covid"

However, it now seems that "long COVID" could also be related to reactivation of the **Epstein Barr Virus** (EBV), which lies dormant in a very high percentage of the population. [6] For instance, there is a correlation with impaired lymphocyte subpopulation count, EBV load and severity of disease [7], as well as evidence that EBV can induce angiotensin-converting enzyme 2 (ACE2) expression and SARS-CoV-2 entry to epithelial cells. [8] Critically, given that more than half of survivors of COVID-19 appear to have long term symptoms (post-acute sequelae of COVID-19 [PASC]) or "long-COVID", [9] the described association of EBV with mitochondrial dysfunction could play a key role in susceptibility and recovery from SARS-CoV-2. [10]

EBV & T Cells

Furthermore, the recent discovery that mitochondrial function is essential for sustained killing by cytotoxic T cells, for instance, of virally infected cells, is perhaps also suggestive, as EBV can also infect T cells. [11-12]

EBV & Chronic Fatigue Syndrome

The association between EBV induced chronic fatigue syndrome with mitochondrial dysfunction was suggested many years ago. EBV can alter mitochondrial dynamics and DNA replication. This therefore raises the possibility that reactivation of the EBV serves as a second mitochondrial "whammy", leading to a sustained inflammatory response and the classical symptoms of brain fog, tiredness and weakness. [13-15]

Structure of EBV

The EBV is a double-stranded DNA virus of the herpes family best known as the agent responsible for infectious mononucleosis. Referred to as one of the most common viruses in humans, it has a ubiquitous distribution of 90% among the world population. As an oncogenic virus, it is associated with a variety of lymphoproliferative disorders such as Burkitt's lymphoma, Hodgkin's lymphoma, T and natural killer (NK) cell lymphomas, and nasopharyngeal carcinoma. It is characterized by lifelong latency in B cells and intermittent recrudescence of lytic infection caused by stressors. [16-17]

The virus has the ability to switch from latent to lytic phase. The conversion process can be triggered by a variety of stimuli, including psychological stress. When the virus is reactivated, the patient may experience symptoms such as brain fog, fatigue, arthralgia, and skin rashes, among others. Recent studies suggest the possible interaction between SARS-CoV-2 and EBV. There have been a few hypothesizes regarding the mechanism of this interaction. One possible mechanism involves a decrease in CD8+ cells which are the primary cells responsible for immunity against EBV infection. CD8+ count to be significantly lower in patients with SARS-CoV-2/EBV coinfection and proposed the idea of reactivation due to the decrease in CD8+ cells. A correlation between reduced CD8+ T cells and NK counts, EBV DNA levels, and COVID-19 severity was observed in Paolucci et al. study. [18-19]

The potential role of EBV and its reactivation in the context of SARS-CoV-2 infection severity and long COVID is evident in the literature. Gold et al. published one of the first investigations on this topic. The authors suggested that the reactivation of the virus is observed soon after or within the initial phase of COVID-19 as demonstrated by positive titers of acute EBV infection antibodies in the screened individuals. The findings of this study reveal that 30% of COVID-19 patients showing symptoms of long-term COVID and SARS-CoV-2 may trigger other viruses that contribute to these symptoms. The results of the studies on the role of EBV and SARS-CoV-2 on disease severity has been conflicting. [20-21]

Systemic reactivation of Epstein–Barr virus (EBV) may occur in novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In a retrospective study, 1314 patients with confirmed COVID-19 were screened. These patients either died or were discharged. EBV reactivation was present in 55 of 217 patients. Patients with EBV reactivation have statistically nonsignificant higher mortality rate (12 [22%] vs. 18 [11%], p=.08). A high proportion of COVID-19 patients had EBV reactivation that may be associated with an increased risk of death. [22]

CONCLUSION

EBV could tip an already compromised system into a self-perpetuating metabolic-oxidative stress-inflammatory spiral that could underly many of the symptoms of long COVID. A high proportion of COVID-19 patients have shown EBV reactivation and this may be associated with an increased risk of death. The mortality of COVID-19 patients complicated with EBV reactivation warrants to be addressed in a placebo-controlled randomized trial in the future.

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