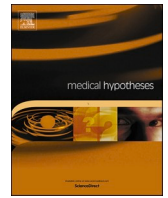




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Letter to Editors

**Ethnicity and the relationship between covid-19 and the herpes simplex viruses**

A B S T R A C T

The pathogen burden, defined by the frequency of antibodies to several viruses and a parasite, is greater in Hispanic whites and black populations than it is in non-Hispanic whites, in the USA. The poor and those without higher education also have higher pathogen burdens. The most frequent pathogen that was measured, was the Herpes simplex virus type 1 (HSV-1). This virus can inactivate most of the elements in the immune system, that are designed to protect against the incursions of viruses, bacteria and other pathogens. HSV-1 can also damage the blood brain barrier (BBB), which prevents the entry of pathogens into the central nervous system. Without the help of HSV-1, the COVID-19 virus may not be able to cause serious illness or death in humans. A prophylactic treatment to contain HSV-1, could be vital in the fight against COVID-19.

The COVID-19 pandemic has dominated the thoughts of people around the world. It appears to be totally indiscriminate. However, there is increasing evidence to suggest that COVID-19 mortality amongst ethnic minorities is disproportionately high. Stebbins et al. in a paper on: “Persistent socioeconomic and racial and ethnic disparities in pathogen burden in the United States, 1999-2014” [1] examined data from 17,660 participants in the National Health and Nutrition Survey. They looked at the “Pathogen Burden”, which was arrived at by taking the number of positive serologies for cytomegalovirus (CMV), herpes simplex viruses -1 (HSV-1) and HSV-2, human papilloma virus and the parasite: *Toxoplasma gondii* and dividing by the number of parasites tested, giving a percent-seropositive for each participant. They examined sex- and age-adjusted mean pathogen burdens from 1999-2014, stratified by race, ethnicity, poverty to income ratio (PIR) and educational attainment. Those with a PIR < 1.3, had mean pathogen burden (MPB) 1.4-1.8 times those with a PIR > 3.5, with no change over time. Disparities in education had even greater effect, with the MPB among those that had less than a high school education being around twice that of those who had completed more than a high school education. Non-Hispanic black, Mexican American and other Hispanic participants had a mean pathogen 1.3-1.9 times that of non-Hispanic Whites. They demonstrated that the socio-economic and racial/ethnic disparities in pathogen burden have persisted over 16 years, with no sign of the gap closing. This disparity could depend on the number of contacts that people make within these societies. Living in extended families, more crowded housing and congregating for religious and other ceremonies, could account for some people making more contacts than others.

The most frequent pathogen in the pathogen burden is HSV-1. The HSV's, apart from causing genital and oral lesions, and encephalitis, have other abilities, which are more relevant in the present context. Especially pertinent, is the effect of HSV on the immune system. In “Herpes simplex virus evasion of early host antiviral responses”, Tognarelli et al. [2] review the actions by which HSV-1 and HSV-2 can avoid or inactivate most of the host's antiviral responses. Natural killer cells (NK) are one of the first lines of defence against viruses and tumour cells. They can recognise and destroy virus infected cells that either lack the expression of major histocompatibility complex 1 molecules or express

NK activating molecules on the cell surface, because abnormal cellular processes betray infection. HSV's target NK and NKT cells and also macrophages, because these cells are likely to play a key role in controlling HSV infection. Dendritic cells are important immune cells that promote and regulate immune responses by modulating the activity of innate and adaptive immune cells. They can then activate CD4+ and CD8+ T cells. These and other cells, that participate in the bodies response to viruses are either destroyed or inactivated. Obesity is accompanied by a systemic, chronic, low-grade inflammation as well as dysfunction of innate and adaptive immune cells [3]. NK cells as well as innate lymphoid cells and invariant NK cells can all participate in the obesity-induced inflammation and insulin resistance [4]. There is an impaired functionality and phenotype of NK cells under obese conditions. The impact of impaired NK cell physiology on obesity-associated diseases, especially the increased susceptibility to viral infections, the increased risk of cancer and impaired response to treatment could be important. Bond [5] suggested that HSV is the cause of chronic fatigue syndrome (CFS), irritable bowel syndrome and fibromyalgia and this was confirmed by Pridgen et al. [6] who found that treatment with a nucleoside analogue such as famciclovir, combined with celecoxib, an anti-inflammatory drug, with antiviral activity, was effective in all three disorders. A review by Eton-Fitch et al. [7], analysed the results of 17 studies of natural killer cell profile and cytotoxic function in CFS. A consistent finding was impaired NK cell cytotoxicity. Aberrations in NK cell lytic protein levels and phenotype were also noted. These changes were consistent with those seen in HSV infection. A functional exhaustion of antiviral lymphocytes was found in COVID-19 patients [8]. The Total number of NK and Cd8+ T cells was markedly reduced in patients with COVID-19 infection. The function of these cells was exhausted in these patients. However, in patients convalescing after therapy, the number of NK and CD8+T cells was restored. COVID-19 infection may break down antiviral immunity at an early stage. Reactivation of HSV by COVID-19 could account for this.

The blood brain barrier is a biological and functional barrier in the central nervous system. It consists of astrocytes, pericytes and brain microvascular cells [9]. It plays a vital role in the pathogenesis of neurotropic viruses. It prevents viruses, bacteria, yeasts and other

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organisms from entering the brain. The static barrier functions and transportation systems of the blood brain barrier, are regulated by endothelial cells, pericytes and astrocytes, tight junctions and the basal lamina [10]. Apart from some more exotic viruses, such as: West Nile virus, Japanese encephalitis virus and Rift Valley fever and others such as human T cell leukaemia virus 1, rabies virus and human immunodeficiency virus which are not relevant to this argument, HSV 1 remains as the most frequent virus which can break down the blood brain barrier. Of particular interest, is that damage to the blood barrier occurs early in the course of human cognitive dysfunction [11]. It was shown that older adults with early cognitive dysfunction develop brain capillary damage associated with mural cell and pericyte injury, irrespective of beta amyloid and/or tau changes, suggesting that blood brain barrier breakdown is an independent, early biomarker of cognitive impairment, unrelated to beta amyloid and tau. I would suggest that blood brain barrier breakdown allows bacteria such as *Porphyrromonas gingivalis*, *Chlamydia pneumoniae* and spirochetes, yeasts and other viruses, such as COVID-19, to enter the brain.

A measurement of number of natural killer cells could be of value in screening people to distinguish those that would fare the worst when infected with COVID-19. Lower levels of NK cells would suggest a higher pathogen burden. While more detailed examination of these cells could reveal parallels with observations in COVID-19 patients.

It would also be of interest to check the alleles of apolipoprotein E, as the epsilon-4 allele renders people far more susceptible to developing Alzheimer's disease.

A treatment for HSV, especially prophylactic, could radically change the severity of the illness and the mortality resulting from COVID-19 infection. There are established treatments such as the nucleoside analogues, especially when given with another antiviral with a different mode of action. There are also other drugs and drug combinations which could be extremely effective.

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