Herpes Simplex Encephalitis After Covid-19 Infection

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CASE PRESENTATION

A gentleman in his 60's presented to the hospital with dyspnea, fever, and hypoxia. He was diagnosed with Covid-19 pneumonia and treated with BiPAP, oxygen, dexamethasone, enoxaparin, budesonide, and albuterol. His hospital stay lasted 33 days. He was discharged home on oxygen and steroids. He returned to the hospital 3 days later with altered mental status. He was diagnosed with HSV encephalitis and treated with 2 weeks of acyclovir. Although his HSV resolved, he suffered temporal lobe necrosis and lasting neurologic dysfunction (Figure 1)

HERPES SIMPLEX ENCEPHALITIS

Herpes Simplex Virus (HSV) is the most common cause of encephalitis, accounting for about half of cases.[1] HSV is ubiquitous, with 47.8% of Americans testing positive for HSV-1 and 11.9% testing positive for HSV-2.[2] Most individuals are asymptomatic, but physiological stress can trigger new infection or latent reactivation. The most common symptoms of HSV are cold sores, especially on the mouth in HSV-1 and genitals in HSV-2. HSV encephalitis (HSE) commonly presents with fever, seizures, altered mental status, and focal neurologic defects.[1] HSV infects the frontal and temporal lobes, causing necrosis and inflammation. With treatment, HSE mortality is 5-15% and 69-89% of survivors experience permanent neurological deficits [1]. All encephalitis patients should be started on empiric acyclovir, and receive lumbar puncture with CSF viral testing. Treatment for HSV is intravenous acyclovir 10mg/kg every 8 hours for 14-21 days. [3]. We have created an algorithm for the diagnosis and treatment of HSV based on these guidelines (Figure 2).

COVID-19

Covid-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Symptoms include cough, fever, myalgia, headache, dyspnea, sore throat, diarrhea, nausea, loss of smell and taste, abdominal pain, and rhinorrhea. Mortality is about 1-2% in the general population, and higher in elderly people and individuals with comorbid conditions.[4] However, most cases resolve without treatment. The CDC recommends isolation at home until 5 days have passed, symptoms are improving, and no fever has been detected in the last 24 hours.[5] Outpatient treatment includes nirmatrelvir-ritonavir or sotrovimab.[6] Indications for hospitalization include severe dyspnea, hypoxia, and altered mental status. Treatment consists of oxygen, ventilation, dexamethasone, remdesivir, tocilizumab or baricitinib, acetaminophen, and anticoagulation.[7]. Nasal cannula and high flow nasal cannula can be used to maintain SpO2 90-96%. Indications for intubation and mechanical ventilation include hypercapnia, rapid deterioration, failure to improve on high flow oxygen, and hemodynamic instability.[8] We have reviewed these expert recommendations and created a comprehensive algorithm for the diagnosis and treatment of Covid-19 (Figure 3.

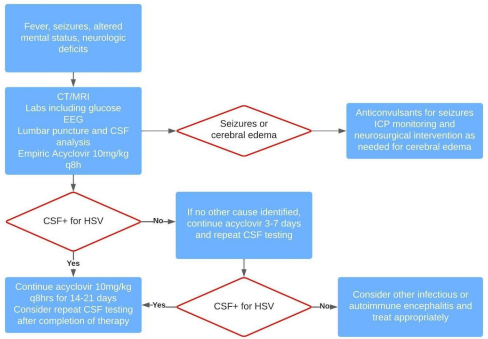

Figure 2. HSV Encephalitis Treatment Algorithm

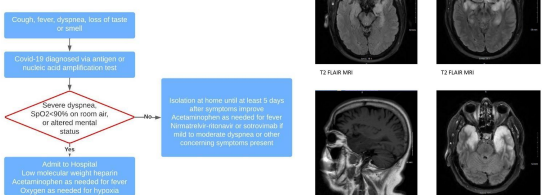

Figure 3. Covid-19 Treatment Algorithm

Figure 1. MRI Images demonstrating bitemporal hyperintensities due to inflammation and necrosis from HSV encephalitis

DISCUSSION

Both HSV and SARS-CoV-2 have the ability to infect the brain through retrograde axonal transport of viral particles and cell surface molecular mediated viral entry into neurons. [1,9-10] Possible mechanisms by which Covid-19 could trigger HSE include fever, hypoxia, and immunosuppression from dexamethasone therapy.

Fever may lead to HSV reactivation through the effects of Interleukin-1β on gene expression. IL-1β is produced by immune cells due to activation of toll-like receptors. IL-1β acts on the thermoregulatory center of the hypothalamus, causing an increase in body temperature. IL-1β leads to changes in neuronal gene expression, inducing histone phosphorylation and causing sympathetic excitation.[11-12]. Hypoxia can reactivate HSV-1 through inhibition of the mTOR pathway, blocking cap-dependent mRNA translation. Hypoxia selectively prevents mTORC1-mediated hyperphosphorylation and inactivation of the 4E-BP translational repressor. Products downstream of the cap-dependent mRNA transcripts repressed by 4E-BP help prevent HSV-1 reactivation through upregulation of host cell defenses and downregulation of viral gene expression.[13] An important consideration is whether or not SARS-CoV-2 itself can reactivate HSV. Many other viral infections can reactivate latent human herpes viruses, typically through co-infection and lysis of neurons. These viruses include other herpesviruses and HIV, which are lytic.[14] Coronaviruses however, are released through exocytosis and not lysis, and have not been shown to directly reactivate HSV-1.[9] The mainstay of Covid-19 treatment, dexamethasone is a powerful immunosuppressant which can lead to HSV activation by inducing apoptosis and lysis.[15-16] Dexamethasone induces apoptosis by downregulating the anti apoptotic proteins Bcl-2 and Bcl-xL, upregulating the pro apoptotic effectors Bak and Bax, and activating the apoptotic proteases caspases 2 and 3.[16] HSV Latency associated transcripts normally inhibit apoptosis through miRNA silencing of pro apoptotic mRNAs, and the process of apoptosis has been shown to reactivate HSV.[14] Additionally, dexamethasone, like endogenous glucocorticoids, activates c-Jun N-terminal kinase (JNK) which is involved in anti inflammatory pathways, but also turns on promoters of HSV lysis through a histone methyl/phospho switch.[15,17]

Previously described cases of SARS-CoV-2 and HSV-1 coinfection reported pneumonia, herpes labialis, gingivostomatitis, keratitis, encephalitis, and hepatitis as complications.[18-27] Studies show positive association between HSV-1 and Covid-19 infection.[26] Covid-19 is a risk factor for HSV-1 infection with 2.8% of patients experiencing HSV coinfection (odds ratio 5.27).[26,28] HSV-1 reactivation in Covid-19 patients is associated with increased mortality.[29] Case reports of HSV infection after Covid-19 vaccination have been published, but meta-analysis has shown no association between vaccination and HSV infection.[30] Only two cases of SARS-CoV2 and HSV-1 coinfection with encephalopathic manifestations have been described previously.[21-22]

In conclusion, Herpes Simplex Virus and Coronavirus are two common yet potentially devastating viruses. Although both are treatable, morbidity and mortality in Covid-19 pneumonia and HSV encephalitis remain high. Infection with SARS-CoV2 can lead to HSV reactivation, likely through the effects of fever and hypoxia on gene expression and use of glucocorticoids in Covid-19 treatment.

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