Covid-19 (Figure 3).

We have reviewed these expert recommendations and created a comprehensive algorithm for the diagnosis and treatment of Covid-19 (Figure 3).

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, moxifloxacin, and abietirust. 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 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 encephalitis (HSE) commonly presents with fever, seizure, altered mental status, and focal neurologic deficits.[1] HSV infects the frontal and temporal lobes, causing necrosis and inflammation. With treatment, HSE mortality is 5-15%, and 60-80% of survivors experience permanent neurologic 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).[1] 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.[4] COVID-19 pneumonia has a mortality rate of 2-8% in patients experiencing HSV coinfection (odds ratio 5.27).[5] HSV reactivation in Covid-19 patients is associated with increased mortality.[6] A report of 7 severe Covid-19 patients with HSV reactivation with fulminant hepatitis as an opportunistic sequela in severe Covid-19.[7]

DISCUSSION

Both HSV and SARS-CoV-2 have been shown to trigger new infection or latent reactivation of the host via a histone methyl/phospho switch.[15,17] 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 upon activation of Toll-like receptors.[8] 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, including histone phosphorylation and causing sympathetic excitation.[11-12] HSV reactivates HSV-1 through inhibition of the NTRs, blocking cap-dependent mRNA translation. Hypoxia selectively promotes mTORS-mediated hypophosphorylation and inactivation of the 4E-BP1 translational repressor. This results in downregulation of the cap-dependent mRNA transcript pool by reactivation of HSV-1 mRNAs 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 HSV, which can lyse[14] and reactivate through the effects of Interleukin-1β on gene expression.

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-CoV-2 can lead to HSV reactivation, likely through the effects of fever and hypoxia on gene expression and use of glucocorticoids in Covid-19 treatment.

REFERENCES


Figure 1. MRI images demonstrating bilateral hyperintensity due to inflammation and necrosis from HSV encephalitis

Figure 2. HSV Encephalitis Treatment Algorithm

Figure 3. Covid-19 Treatment Algorithm

Figure 3. Covid-19 Treatment Algorithm

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