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Case Report

Early-onset herpes simplex encephalitis type 1 triggered by COVID-19 disease: A case report ☆,☆☆

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ABSTRACT

Coronavirus disease 2019 (COVID-19) causes a systemic inflammatory response and a temporary immunosuppression of hosts. Several reports have showed that reactivation of herpes simplex virus type 1 (HSV-1) is strongly associated with COVID-19. We present a case of a 66-year-old female, who developed HSV-1 encephalitis, showing impaired consciousness and typical MRI findings such as hyperintense lesions in the temporal lobe, insular cortices, bilateral medial frontal lobe on diffusion-weighted imaging, 7 days after the onset of COVID-19 symptoms. The number of cases of encephalitis in patients with COVID-19 is increasing. However, there has been limited reports of HSV-1 encephalitis following COVID-19, especially for cases with an interval of 7 days or less from the onset of COVID-19 symptoms to the onset of HSV-1 encephalitis. Our case highlights the importance of considering HSV-1 encephalitis in the differential when managing a patient with COVID-19-associated neurologic complications, even if it is in the early stages of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) can lead to host immune dysregulation. An immunosuppressed state in critically ill patients with COVID-19 has been reported to reactivate herpes simplex virus type 1 (HSV-1) [1], but the literature on HSV-1 encephalitis following COVID-19 is limited. In a previous report, neurologic symptoms from HSV-1 encephalitis occurred on average 24 days from the diagnosis of COVID-19 [2]. Herein, we describe a woman who presented with HSV-1 encephalitis 7 days after contracting mild COVID-19.

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Case report

A woman in her 60s was admitted to our hospital with mild-COVID-19 after presenting with fever up to 38.5°C for 5 days and a decreased oxygen saturation of 92% on room air on the day of admission. She was diagnosed based on the test result of Nicking Enzyme amplification reaction for SARS-CoV2 and it was most likely that the day of onset was when the fever started. She had no other symptoms such as headache, nausea, or impaired consciousness. Her chest computed tomography (CT) scan showed no evidence of pneumonia, and she was started on ritonavir-boosted nirmatelvir. Her past medical history included Hashimoto's disease and hyperlipidemia. The mutant strain of the SARS-CoV-2 virus was not identified, but we presumed it to be the Omicron strain based on the timing.

On hospital day 2, although her oxygen saturation and fever improved to 96% on room air and 37°C, respectively, she developed a headache and vomiting. The following day, she was noted to have a fever of 38.5°C and impaired consciousness. Her other vital signs were stable. Her neurological examination was notable for apathy, disorientation, impaired new learning, a positive jolt accentuation test, and nuchal rigidity. Laboratory tests revealed a low serum sodium of 127 mEq/L and a high vasopressin level of 6.0 pg/mL. The urine sodium was elevated at 87 mEq/L, and the urine osmolality was 523 mOsm/kg, consistent with the syndrome of inappropriate antidiuretic hormone secretion. The blood and urine studies were otherwise unremarkable. Cerebrospinal fluid (CSF) examination showed 28 white blood cells/μL with 94% lymphocytes and 6% polymorphonuclear leukocytes, 45.5 mg/dL protein, and 84 mg/dL glucose. No bacteria or neoplastic cells were present. However, 5 days after testing, results for the CSF polymerase chain reaction (PCR) test were returned and showed positive for HSV-1 and negative for other pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Furthermore, the assays for antibodies related to autoimmune encephalitis were negative (eg, anti-leucine-rich glioma-inactivated 1 protein (LGI1), contactin-associated protein-like 2 (CASPR2), N-methyl-D-aspartate receptor (NMDAR), myelin oligodendrocyte glycoprotein (MOG), aquaporin-4 (AQP4), amphiphysin, CV2, paraneoplastic antigen Ma2 (PNMA2 (Ma2/Ta)), Ri, Yo, Hu, recoverin, SRY-box transcription factor (SOX1), titin, Zic4, glutamic acid decarboxylase 65 (GAD65), and Tr). No abnormalities were visible on brain CT scan. Brain magnetic resonance imaging (MRI) showed marked hyperintense lesions in the right temporal lobe mainly involving the temporopolar and temporomesial regions, the right insular cortex, and the bilateral medial frontal lobe on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR). The apparent diffusion coefficient map in the corresponding regions showed low signal intensity (Fig. 1). The finding of the bilateral medial frontal lobe was prominent in the right hemisphere.

Since the broad differential diagnosis included cytokine storm encephalitis, autoimmune encephalitis triggered by COVID-19, and viral encephalitis due to SARS-CoV-2, HSV, or varicella-zoster virus, high-dose corticosteroids and acyclovir were started prior to receiving the CSF viral PCR and antibody results. Antiepileptic medications were added to treat nonconvulsive status epilepticus after electroencephalography showed diffusely slow and high-voltage waves.

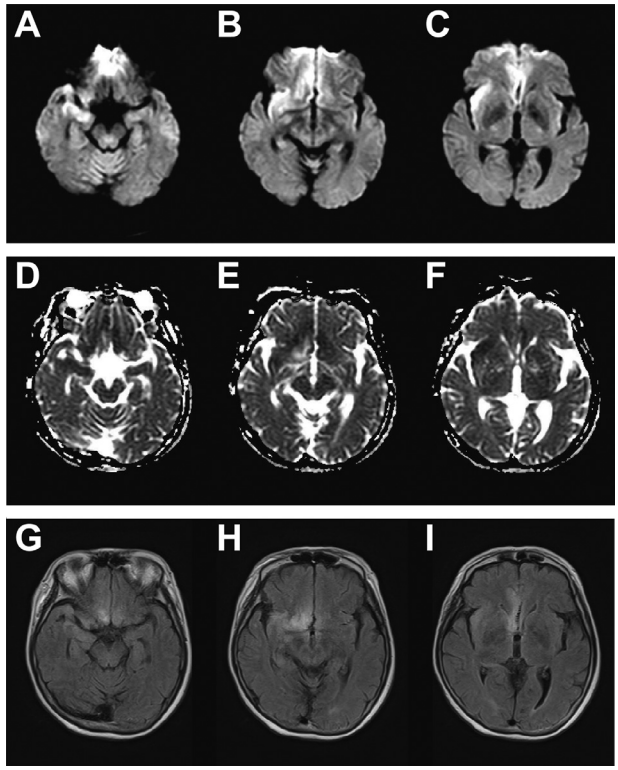

Fig. 1 – Cranial magnetic resonance imaging. (A-C) Axial diffusion-weighted imaging shows multiple hyperintensities in (A) the right temporal lobe, (B, C) the asymmetric bilateral medial frontal lobe, and the right insular cortex. (D-F) Hypointense signals on apparent diffusion coefficient maps and (G-I) hyperintense signals on fluid-attenuated inversion recovery are present in the corresponding lesions. The lesions in the temporal lobe were mainly involving the temporal pole and mesial temporal lobe.

The CSF results were positive only for HSV-1 5 days after the test, and the patient continued acyclovir and completed a 10-day course of steroids, based on previous reports of benefit [3]. After the initiation of treatments, the patient's fever was alleviated, and her consciousness gradually recovered. However, her apathy, impaired new learning, and disorientation persisted. The number of the CFS cells continued to increase despite 10 days of the treatments. The possibility of acyclovir-resistant HSV-1 was considered, and she required subsequent additional treatment with vidarabine. After additional treatments, the CSF PCR test for HSV-1 showed negative, and other CSF findings normalized 30 days after the admission. After the medication adjustment for NCSE and rehabilitation, the patient was discharged from our hospital on the 80th day of admission. At the time of discharge, her impaired consciousness, disorientation, and apathy fully resolved, although mild learning disabilities remained.

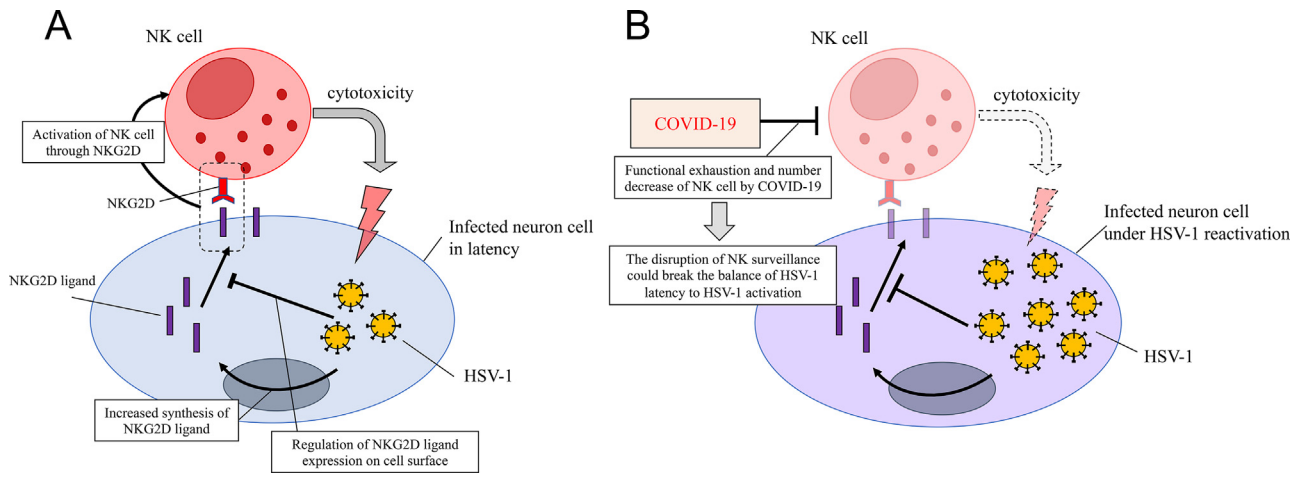

Fig. 2 – Proposed mechanism of HSV-1 reactivation triggered by COVID-19. (A) HSV-1 is known to avoid NK cell cytotoxicity by regulating expression of natural killer group 2D (NKG2D) ligand, which activates NK cell against infected cells, on infected cell surface. The regulation is thought to create a balance between NK cell activation and viral evasion which results in viral latency. (B) COVID-19 is known to cause functional exhaustion and decrease the number of NK cells. The disruption of NK surveillance could break the balance of HSV-1 latency and could possibly cause HSV-1 reactivation.

Discussion

HSV-1 generates a complicated balance with the host immune system, cycling between long latency periods and episodic viral reactivation. Eluding natural killer (NK) cell surveillance is one of many mechanisms of viral immune evasion. COVID-19 is known to exhaust the number and function of host lymphocytes, including NK cells, which could contribute to HSV-1 reactivation (Fig. 2) [4–7]. This is supported by reports of a greater than 40% prevalence of HSV-1 reactivation in COVID-19 patients, as detected by PCR analysis of respiratory specimens [8]. The neuronal damage by the reactivation of HSV described 2 mechanisms; “reactivation of a latent herpes virus” and “postinfectious immune inflammatory response” [9]. In our case, brain MRI showed scant white matter lesions, suggesting that the reactivation of HSV-1 following COVID-19 caused HSV-1 encephalitis due to direct virus neurotoxicity.

Although various neurological involvement during SARS-CoV-2 infection has been reported, encephalitis accounts for only 0.2% of all complications [10]. There is a growing body of literature on SARS-CoV2 induced cytokine storm encephalitis, post-COVID-19 autoimmune encephalitis, and direct CNS invasion of SARS-CoV-2 [11]. However, there are limited reports of COVID-19-associated HSV-1 encephalitis [2]. COVID-19-associated encephalitis has been reported to occur between 2 and 16 days after the onset of COVID-19 [12]. The onset of post-COVID-19 HSV-1 encephalitis from the diagnosis of COVID-19 was on average 24 days, which was longer than other types of COVID-19-associated encephalitis [2]. Therefore, cases of HSV-1 encephalitis that occur within 7 days of COVID-19 onset are rare. Our case occurred at an earlier stage of COVID-19 than previously reported cases of post-COVID-19 HSV-1 encephalitis.

In terms of MRI findings, our case showed typical patterns of HSV-1 encephalitis, which made it easier to include it into our differential. HSV-1 encephalitis typically involves lesions of the anterior and medial aspects of the temporal and orbital frontal lobes, usually more severely affected on one side. Additionally, extratemporal involvement occurs in up to 55% of patients, including the frontal lobe and the limbic system [13]. However, these findings on MRI are not specific to HSV-1 encephalitis, and may be seen in other encephalitides, including other types of viral or autoimmune encephalitis. As clinical features, patients with HSV encephalitis are more likely to present acutely with fever, and less likely with rash than those with other encephalitides [14]. In our case, considering the possibility of HSV encephalitis based on the clinical symptoms and imaging features, we were able to start acyclovir therapy on the second day of onset of encephalitis. It took 5 days to get the result of HSV-1 PCR on the CSF, thus we had to start HSV-1 treatment before the result were available. Early initiation of antiviral therapy for HSV is associated with favorable outcome of patients with HSV encephalitis [15]. If substantial improvement is not observed after 7 days of acyclovir admission, acyclovir resistant HSV should be suspected [16]. In our case, the combination therapy with acyclovir and vidarabine, an alternative treatment against HSV encephalitis [17], was finally effective. We believe that early initiation of treatment and the combination treatment have contributed to the clinical improvement of our case.

Conclusion

In this case, the location of the positive DWI and FLAIR lesions on MRI was typical of HSV-1 encephalitis, which led us to include it in our differential. However, the short interval of 7 days from SARS-CoV-2 infection to the onset of HSV-1 encephalitis made other known COVID-19-associated encephalitides more likely. The functional exhaustion of NK cells resulting from the

rapid progression of COVID-19 [18] suggests a potential mechanism for the early reactivation of HSV-1. Our case highlights the importance of maintaining an open mind to include HSV-1 encephalitis in the differential and initiate treatment against HSV-1 when managing a patient with COVID-19-associated neurologic complications.

Patient consent

Written, informed consent was obtained from the patient for publication of this case.

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