OXFORD

QJM: An International Journal of Medicine, 2022, 222–227

https://doi.org/10.1093/qjmed/hcac060
Advance Access Publication Date: 23 February 2022
Original paper

ORIGINAL PAPER

Post-COVID-19 HSV encephalitis: a review

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Summary

Background: Herpes simplex virus encephalitis (HSVE) is one of the most common infectious causes of sporadic encephalitis. Coronavirus disease (COVID-19) has been associated with immune dysregulation of the host that might increase the risk of infections like HSVE following SARS-CoV-2 infection. There is paucity of literature on post COVID-19 HSVE. This study was conducted with the aim of analyzing the clinical presentation, brain imaging, and outcome of patients presenting with HSVE within 6 weeks of COVID-19 and providing a comprehensive review on the possible mechanisms of post-COVID-19 HSVE.
Methods: This observational study included patients who had laboratory-confirmed HSVE (type 1 or type 2) and a history of COVID-19 within the previous 6 weeks. Patients were followed up for 3 months.
Results: Eight patients were included and all of them had type 1 HSVE. The mean latency of onset of neurological symptoms from being diagnosed with COVID-19 is 23.87 days and a majority of the patients have received injectable steroids with a mean duration of 6.5 days. Behavioral abnormality was the commonest neurological presentation and typical brain imaging involved T2 FLAIR hyperintensities of the medial temporal lobes. All patients received intravenous acyclovir 10 mg/kg every eight hourly for atleast 14 days. One patient with concomitant rhinocerebral mucormycosis succumbed while the majority had a complete recovery.
Conclusion: Possible immune dysregulation in COVID-19 may increase the susceptibility of HSVE in patients with a history of recent SARS-CoV-2 infection. The clinical manifestations and laboratory findings of HSVE in such patients are similar to typical HSVE.

Introduction

The coronavirus disease (COVID-19) pandemic has put the world in the doldrums and the puzzle of its various extrapulmonary manifestations as well as sequelae seems to be unsolved till date. The paradoxical immune state in COVID-19 is one such piece of the puzzle, which warrants extensive research. The debate of hyperinflammation versus immunosuppression in COVID-19 demands attention for further therapeutic strategies in severe ailment.[1] Herpes simplex virus encephalitis (HSVE) has been attributed to a breach in the host immune system resulting in protean neuropsychiatric manifestations. The authors hereby report a series of eight cases of HSVE in patients with a history of COVID-19 within 6 weeks, with a

Received: 8 February 2022; **Revised (in revised form):** 17 February 2022

comprehensive outlook on clinical presentation, brain imaging, therapy and outcome on a background of a critical review on existing literature on HSVE. The possible role of COVID-19-induced immune dysregulation contributing to HSVE has also been explored considerably in this article.

Material and methods

After obtaining institutional ethical committee clearance, this observational study was conducted from May 2021 to November 2021. The inclusion criteria comprised patients presenting with acute encephalitis syndrome (AES) with a history of COVID-19 within the previous 6 weeks and a positive polymerase chain reaction (PCR) for HSV type 1 or type 2 in cerebrospinal fluid (CSF). The case definition of AES included a person of any age, in any geographical region, at any time of the year presenting with acute onset fever and any change of mental status and/or new onset of seizures (excluding febrile convulsion). Confirmation of COVID-19 was obtained through a recorded document of positive reverse transcription-PCR for SARS-CoV-2 from oropharyngeal and nasopharyngeal swab. COVID-19 was classified as mild when only upper respiratory symptoms and/or fever in absence of any hypoxia were recorded. Moderate COVID-19 was considered in patients with breathlessness and oxygen saturation of 90 to $\leq$93% on room air, which required hospitalization, while severe COVID-19 was implicated in patients with breathlessness and oxygen saturation of $\leq$90% on room air. The inclusion of patients presenting with AES within 6 weeks of COVID-19 was justified by the possibility of peak immune dysregulation as observed in post-acute COVID-19 syndrome by 4 weeks and adding up the incubation period of around 2 weeks in case of HSVE.[2] After obtaining written informed consent from the patients' kin, detailed history regarding demography, symptoms, time course and evolution of the disease, past medical history, comorbidities were obtained followed by a thorough neurological examination as per prefixed proforma. The patients were investigated with contrast-enhanced magnetic resonance imaging of the brain, an electroencephalogram (EEG), CSF assay and other supportive investigations on requirement. The patients were followed up for 3 months after hospitalization to assess the outcome. Data were collected retrospectively and analyzed on the MS Excel platform. Given the rarity of association of COVID-19 with HSV encephalitis, the authors reviewed the existing literature on PubMed and Medline databases using Medical Subject Headings terms 'HSV encephalitis' or 'HSVE' and 'COVID-19' or 'SARS-CoV-2'.

Results

A total of eight patients were included in this study. The mean age of distribution was 39.12 years and three patients were female (37.5%). Among the individuals, four patients (50%) had comorbidities and a majority of them were hypertensive (75%). All patients with comorbidities were on regular medications barring one (Case 7). Considering the severity of COVID-19 pneumonia among the affected individuals, four patients (50%) had a severe illness and were managed in an intensive care setup, while the remaining patients had a mild and moderate illness in equal distribution and patients with mild illness were managed conservatively in home isolation. The mean latency of onset of neurological symptoms from being diagnosed with COVID-19 was 23.87 days. Six out of eight patients received injectable steroid therapy for COVID-19 and the mean duration of steroid therapy was 6.5 days. The majority of the patients (62.5%) were afebrile on admission; however, all patients had a history of fever prior to the onset of neurological symptoms. The clinical profile of the patients with post COVID-19 HSV encephalitis has been summarized in Table 1.

Neurological presentation

The commonest neurological presentations in this series were behavioral abnormalities (62.5%) followed by altered sensorium (50%). Meningism was noted in two patients (25%) while focal seizure with impaired awareness was reported in only one patient (12.5%). Similarly, only one patient had episodic visual hallucinations. Three patients had nausea and vomiting.

Absolute lymphocyte count

Lymphopenia was a consistent finding in the majority of the cases (75%) and the mean absolute lymphocyte count was 792.75/cumm.

Brain imaging

All except one patient had abnormal brain imaging. The most common abnormality detected on magnetic resonance imaging (MRI) brain was T2FLAIR hyperintensities in the medial temporal lobes (Figure 1A and B), seen in half of the patients

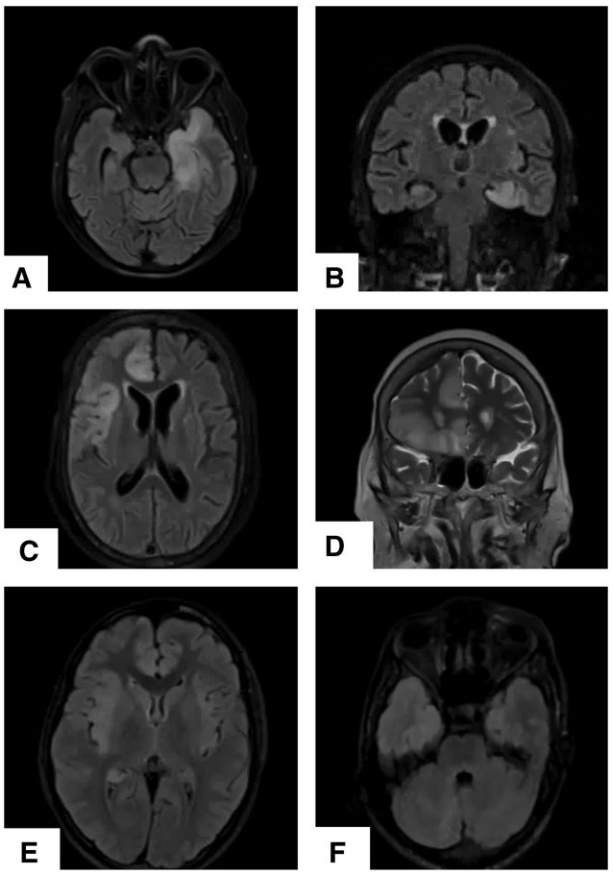

Figure 1. MRI brain T2FLAIR sequence revealing asymmetric medial temporal hyperintensities (left>right) (**A**). T2FLAIR hyperintensities visible in bilateral medial temporal regions (left>right) (**B**), right medial frontal and insular cortex (**C**) and right medial frontal and orbitofrontal regions (**D**). T2FLAIR hyperintensities noted in bilateral medial frontal and insula (**E**) and bilateral medial and anterior temporal regions (right>left) (**F**).

(asymmetric in two cases and symmetric in two cases). Other areas involved were medial frontal, orbitofrontal and insular cortices (Figure 1C and D). Diffusion restriction in the involved areas was visible in three cases. Asymmetric signal changes were observed in four patients. One patient (Case 7) had an incidentally detected invasive fungal sinusitis, which was histologically diagnosed as rhinocerebral mucormycosis (RCM).

Electroencephalogram

Periodic lateralized epileptiform discharges (PLEDs) were observed in EEG record of two patients (25%) and one of them had bilateral PLEDs. Diffuse slowing of background activity was observed in four patients (50%) with asymmetric slowing in one case. Right temporal spike and slow-wave discharge was observed in one patient. One patient had normal EEG.

CSF assay

All patients, except one, had lymphocytic pleocytosis with a mean cell count of 12.14/cumm. CSF protein was elevated in all patients with a mean CSF protein concentration of 70.75 mg/dl. CSF glucose was within normal limits in all of the patients. All of the patients were positive for HSV type 1 in CSF HSV-PCR analysis.

Antiviral therapy

All patients were treated with intravenous acyclovir 10 mg/kg every eight hourly for a minimum duration of 14 days; however, one patient (Case 7) succumbed on day 9 of therapy. Treatment was initiated within 5 days of symptom onset in all of the patients.

Outcome

Five patients (62.5%) had complete recovery after 3 weeks of admission, while two had partial recovery. One patient had persistent behavioral abnormality while another patient had impairment of new learning. One patient (Case 7) who was incidentally diagnosed with RCM succumbed to sepsis with multiorgan failure on day 9 of hospitalization.

A summary of investigations, treatment and outcome of patients with post COVID-19 HSV encephalitis has been tabulated in Table 2.

Discussion

Herpetic infections (predominantly HSV-1) have been recognized as one of the most commonly identified etiologies of sporadic encephalitis.[3] HSV usually gains access through mucosa or breached skin, and subsequently infects the sensory neurons via the glycosaminoglycans on the cell surface and cell adhesion molecules, and ultimately reaches the dorsal root ganglion through retrograde axonal transport.[4] The pathogenic mechanisms of access of HSV to the central nervous system are poorly elucidated. The suggested routes of neurotropism include retrograde transport via the olfactory or trigeminal nerves, contralateral spread via anterior commissure or viremia.[5,6] However, increased predilection of orbitofrontal and mesial temporal lobe involvement in HSV encephalitis negates the possibility of hematogenous dissemination and favors the olfactory route of transmission, though robust data are unavailable. The innervation of meninges by the trigeminal nerve may also explain the involvement of the aforementioned areas.[7] There is no clear consensus regarding whether primary infection per se or reactivation of latent HSV in the trigeminal ganglia or within brain parenchyma leads to the manifestation of HSVE. In the majority of the cases, the viral strain causing herpetic skin lesions has been reported to be different from the strain causing encephalitis in the same patient suggesting the probability of primary infection.[8] Damage of the nasal mucosa by SARS-CoV-2 may increase the risk of HSV transmission in patients with a recent history of COVID-19.

The innate immune system serves as the first line of defense and mounts an initial response till adaptive immunity comes into play. Dimerization of Toll-like receptors bound to viral motifs known as pathogen-associated molecular patterns leads to a cascade of events producing interferons (IFNs), tumor necrosis factor and various proinflammatory cytokines.[9] Defective immune response to HSV or immune dysregulation increases the susceptibility to HSVE. Priming of adaptive immunity subsequently leads to recruitment of activated leukocytes and results in consequent tissue destruction and neurological sequelae. The virus tends to remain in a latent state in the host via inactivation of lytic-phase genes and evasion of host immunity with the aid of specific CD8+ T cells in trigeminal ganglia. Immune dysregulation may lead to reactivation, and consequently the virus travels to tissues innervated by the infected dorsal root ganglia.[10] IFNs play a key role in regulating the immune cascade and delayed induction of IFN by SARS-CoV-2 in animal models led to pulmonary infiltration by macrophages, whereas blockade of IFN signaling led to markedly reduced infiltration. Impaired production of IFN in severe COVID-19 may lead to an imbalance between the proinflammatory macrophages and the macrophages which facilitate repair.[11] High levels of neutralizing antibodies against the spike protein of SARS-CoV-2 have been associated with marked deficiency of repair-facilitatory macrophages with upregulation of proinflammatory macrophages in the lungs of patients with severe COVID-19.[12] Profound depletion of natural killer cells in COVID-19 has been attributable to dysregulated IFN response to an extent. Lymphopenia with functional exhaustion of $CD4^+$ and $CD8^+$ T cells due to defective IFN production has been reported in COVID-19.[13] Regulatory T cell counts have an inverse correlation with disease severity in COVID-19. Dysregulation of the host interferon response may allow latent herpes virus to reactivate in patients with recent COVID-19.[14–16] Immune dysregulation has been reported in patients with diabetes and some studies have reported increased prevalence of herpesvirus infection in diabetic individuals.[17] In this series, two patients were diabetic, one of them (Case 7) had poor glycemic control and was concomitantly detected to have RCM and HSVE. Considering the long-term effect of SARS-CoV-2 on host immune response, baseline diabetes may also lead to immune dysfunction and make the host susceptible to HSVE.

The role of corticosteroids in the management of moderate to severe COVID-19 has been indispensable and hence incorporated in major treatment guidelines as per mortality and morbidity benefit offered by corticosteroids, despite delayed viral clearance and slight propensity of secondary bacterial infections.[18] However, a meta-analysis concluded that mortality was greater among 21 350 patients with COVID-19 who were treated with corticosteroid for a duration of 3–12 days due to prothrombotic influence and adverse drug reactions, compared to patients who did not receive corticosteroids.[19] Corticosteroids appear to be a double-edged sword and hence judicious use should be advocated in patients with COVID-19, with no data supporting long-term use of corticosteroids till date.[20] Recently,

Table 1. Clinical profile of patients with HSV encephalitis after COVID-19 infection

Patient	Age, sex	Comorbidities	Severity of COVID-19	Latency of onset of neurological symptoms from being diagnosed with COVID-19	Duration of steroid therapy received for COVID-19 (days)	Neurological presentation	Febrile on admission
Case 1	21, M	Nil	Severe	26	5	Behavioral abnormalities, loss of episodic and immediate memory	No
Case 2	33, M	Nil	Severe	28	10	Anterograde amnesia, altered sensorium	No
Case 3	28, F	Nil	Severe	23	7	Altered mental status, nausea, vomiting	Yes
Case 4	54, M	Hypertension	Moderate	32	5	Altered sensorium, meningism	Yes
Case 5	49, F	Diabetic	Mild	30	Nil	FIAS, behavioral abnormality	No
Case 6	16, M	Nil	Mild	17	Nil	Hypersomnolence, behavioral abnormalities, nausea, vomiting	No
Case 7	68, F	Hypertension, diabetes, chronic kidney disease	Severe	21	7	Meningism, altered sensorium, behavioral abnormalities	Yes
Case 8	44, M	Hypertension	Moderate	14	5	Visual hallucinations, behavioral abnormalities, nausea, vomiting	No

FIAS, Focal onset seizures with impaired awareness.

a resurgence of mucormycosis has been reported in patients with COVID-19 specifically from India and an unholy trinity of diabetes, injudicious use of corticosteroids and COVID-19 itself has been attributed to the increasing burden of the disease. Similarly, diabetes and injudicious use of corticosteroids may be held responsible to an extent in patients with COVID-19 for immune dysregulation and subsequent susceptibility to HSVE.

The neurological presentation in many patients with HSVE may be preceded by prodromal symptoms suggestive of local/systemic infection. The common manifestations of HSVE include fever, seizures, encephalopathy, headache with or without focal neurodeficits.[21] HSVE in patients tends to have less prodromal symptoms, less focal neurodeficits, extensive brain involvement, involvement of atypical sites of the brain, lesser degree of CSF pleocytosis, and higher mortality. The extensive brain involvement may be attributed to ineffective host immune response to curb the dissemination of HSV.[22] Lesser degree of CSF pleocytosis may occur due to the inability of the host to mount an effective immune response against HSV; however, pleocytosis may be absent in immunocompetent patients early in the course of disease.[21] In this series, one patient had normal CSF cell count and five patients had cell count less than $20/mm^3$.

Classical features in brain imaging of HSVE include symmetric or asymmetric involvement of medial temporal lobes, orbitofrontal cortex and insula, which are present in almost all of our cases except one. Atypical sites like parieto-occipital cortex, brainstem, internal capsule, thalamus and cerebellum may also be involved.[22] None of our patients had any atypical site involvement in brain imaging. Diffusion-weighted imaging may show restriction early in the course of illness; three cases in this series had diffusion restriction. Electroencephalogram in HSVE maybe variable and non-specific starting from periodic discharges, diffuse slowing of background, focal slowing and epileptiform discharges.[23] All these EEG changes were observed in different patients included in this study.

Early initiation of antiviral therapy is a critical modifiable factor for improving outcomes in HSVE. Intravenous acyclovir 10 mg/kg q8h for a duration of 14–21 days should be promptly initiated, even empirically as diagnostic evaluation of encephalitis should never delay antiviral therapy.[24] However, in many cases, mortality is inevitable despite antiviral therapy. As far as morbidity is concerned, HSVE leads to a great impairment of activity of daily living and postencephalitic neuropsychiatric sequelae are quite common (69–89%).[25] Poor prognostic factors include extremes of age, low level of consciousness at presentation, diffusion restriction in brain imaging and delay in initiation of antiviral therapy, In this series, intravenous acyclovir was initiated in all the patients within 5 days of symptom onset with a favorable outcome in most of the patients followed by a complete recovery in 62.5% cases and only one mortality. The patient who died had concomitant RCM and poorly controlled diabetes, which might have contributed to her demise. The patients who had partial recovery had impaired new learning (Case 2) and behavioral abnormality in the form of hypomania and hypersexuality (Case 8).

The COVID-19 pandemic has led to one very interesting observation in regard to an epiphenomenon that is the plethora of cases of invasive RCM. Many hypotheses and postulates have been forwarded including immunosuppressive effects of the virus or the associated therapy including use of corticosteroids, contamination from the oxygen supply link, so on and so forth. Although there is a lack of any concrete answer to the exact cause and effect relation, knowledge about such occurrences is definitely curious and ignites the scientific community to investigate closely so as to learn and be prepared when and if, it happens again. Being neurologists, as a group, who have been thrown inside this boiling cauldron of bizarre happenings over the last year and a half, the authors try to present another phenomenon or possibly epiphenomenon with an aim to investigate the rather uncanny clustering of an HSVE during the second wave of the pandemic, possibly when the delta variant of the virus was predominant. Possible causes of a sudden sharp

Table 2. Summary of investigations, treatment and outcome of patients with post COVID-19 HSV encephalitis

Patient	Absolute lymphocyte count	MRI brain	EEG	CSF (cell count, predominant cells; glucose; protein)	Injectable acyclovir 10 mg/kg q8h initiation after symptom onset	Outcome (at 4 weeks)
Case 1	956/cumm	T2 FLAIR hyperintensities in bilateral medial temporal lobe (left>right)	PLED	3/cumm, lymphocytes; 68 mg/dl 58 mg/dl	Day 4	Complete recovery
Case 2	1200/cumm	T2 FLAIR hyperintensities in orbitofrontal, medial frontal, and insular region on right side with diffusion restriction	Asymmetric slowing of background	16/cumm, lymphocytes; 60 mg/dl 48 mg/dl	Day 2	Impaired new learning
Case 3	450/cumm	T2 FLAIR hyperintensities in bilateral medial frontal, medial temporal, and insular region with diffusion restriction	NAD	8/cumm, lymphocytes; 55 mg/dl 61 mg/dl	Day 4	Complete recovery
Case 4	900/cumm	T2FLAIR hyperintensity in left medial temporal lobe	Diffuse slowing of background	36/cumm, lymphoctes; 65 mg/dl 77 mg/dl	Day 1	Complete recovery
Case 5	600/cumm	NAD	Right temporal spike and slow-wave discharge	14/cumm, lymphocytes; 72 mg/dl 59 mg/dl	Day1	Complete recovery
Case 6	1000/cumm	T2FLAIR hyperintensities in orbitofrontal, anterior temporal and insular region (right>left) with diffusion restriction	BiPLED	26/cumm, lymphocytes; 59 mg/dl 96 mg/dl	Day 3	Complete recovery
Case 7	396/cumm	Extensive bilateral medial frontal hyperintensities with bilateral maxillary sinusitis and involvement of bilateral nasal cavity with destruction of non-contrast enhancing turbinate	Diffuse slowing of background	12/cumm, lymphocytes; 91 mg/dl 105 mg/dl	Day 5	Succumbed
Case 8	840/cumm	T2FLAIR hyperintensities in both medial temporal lobes	Diffuse slowing of background	6/cumm, lymphocytes; 70 mg/dl 62 mg/dl	Day 4	Behavioral abnormality

FLAIR, Fluid-attenuated inversion recovery; BiPLED, bilateral independent periodic lateralized discharges

spike have been postulated upon and a thorough literature review on various pertinent and important aspects has been looked upon.

We hypothesized that COVID-19 in conjunction with diabetes and steroid use might have paved the way for HSVE in our patients. Hence, we expected that the clinical profile, laboratory parameters and treatment response would be similar to those of HSVE in immunocompromised patients. However, the findings matched with the clinical presentation and imaging findings of typical HSVE in immunocompetent patients. The absence of marked CSF pleocytosis in our patients might signify a lack of robust immune response but can also be due to the early phase of HSVE. The outcome was favorable in this series. There is a paucity of literature regarding HSVE in patients with recent COVID-19 and this is supposedly the only series reported till date.

Conclusion

COVID-19 has baffled the world with its various manifestations and several sequelae, the mechanisms of which are yet to be elucidated. Immunosuppression or immune dysregulation after COVID-19 is still a matter of debate with anecdotal evidence. This series describes a comprehensive outlook on the clinical presentation, diagnostic evaluation and outcome of eight patients with HSV encephalitis within a period of 6 weeks of SARS-CoV-2 infection. The mechanism of post-COVID-19 HSVE is yet to be established, but breach of immune surveillance may be considered as a critical factor. There is a paucity of literature regarding the same and this seems to be a comprehensive case series on post-COVID-19 HSV encephalitis.

Conflict of interest. None declared.

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