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SHORT COMMUNICATION

Central nervous system reactivation of herpesviridae family in patients with COVID-19

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Abstract

The objective of this study is to describe our COVID-19 patients with herpesviridae reactivation in the central nervous system (CNS). Four patients were described including two with acute encephalitis and two with acute encephalomyelitis. Three of four patients had abnormal findings on neuroimaging studies. One of four patients died, one survived with major neurological sequelae, and two others fully recovered. Herpesviridae reactivation in the CNS in patients with COVID-19 is a rare but serious coincidence. The optimal therapeutic management has not been investigated and until more information is available, it is prudent to treat these patients with appropriate antivirals with or without anti-inflammatory agents.

Keywords Herpesviridae · SARS-CoV-2 · COVID-19 · Encephalitis

Introduction

Coronavirus disease 2019 (COVID-19) is a disease spectrum with a wide variety of clinical manifestations Baj et al. (2020). From the beginning of the COVID-19 pandemic, neurological involvement has been described as a frequent and frightening presentation of the disease. It occurs in 14–57% of patients hospitalized with COVID-19 Hensley et al. (2021). While encephalopathy and cerebrovascular accidents are among the most commonly reported neurological complications of COVID-19, cohorts of COVID-19 patients with neuropsychiatric syndromes only rarely identified patients with encephalitis or meningitis caused by SARS-CoV-2.

The estimated incidence of encephalitis in a large Spanish COVID-19 cohort was 0.1% in general and 0.35% in the group admitted to intensive therapy units. Despite its overall rarity, it has been shown that encephalitis occurs more commonly in association with COVID-19 than the influenza viruses or other respiratory tract infections (hazard ratio: 1.41, 1.03–1.92) Taquet et al (2021). Histopathologically, only few post-mortem studies were able to detect SARS-CoV-2 virus within the neural capillary endothelial cells Paniz et al. (2020); others found little evidence of viral replication within the central nervous system (CNS) (Kantonen et al. 2020; Solomon et al. 2020). Thus, direct viral invasion is considered a possible yet unlikely mechanism of CNS involvement. Most reports suggest an inflammatory-mediated mechanism for COVID-19-associated para- and post-infectious encephalitides (Achar and Ghosh 2020; Ye et al. 2020).

The frequency of concomitant neuroinfections or subsequent reactivation of other neuroinvasive viruses in COVID-19 patients with neurological manifestations is not yet known. Here, we describe 4 patients with COVID-19 who presented with different neurological syndromes associated with CNS reactivation of herpesviridae family members from our prospective cohort of community-acquired central nervous system infections in Mashhad, Iran.

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Case presentation

Case 1

A previously healthy 34-year-old man presented with progressive neurological symptoms of gait and speech difficulties, and blurred vision within 2 weeks of a mild viral prodrome. He had close contact with a COVID-19-infected family member. On admission, he was alert and oriented. Neurological examination revealed direction-changed nystagmus, and gait and bilateral limb ataxia, accompanied with dysarthria and increased deep tendon reflexes but no sensory deficits. Chest CT scan was normal. Brain MRI showed bilateral non-enhancing confluent T2/FLAIR hyperintensities in the periventricular white matter and corticospinal tracts (Fig. 1A–C). Cerebrospinal fluid (CSF) analysis revealed 1/μL leukocytes, 6 erythrocytes/μL, protein 73 mg/dL, glucose 67 mg/dL, IgG 172.1 mg/dL, and CSF IgG index of 1.18. Using Neuro 9 multiplex real-time PCR, cytomegalovirus (CMV), adenovirus, herpes virus (HSV) 1 and 2, varicella zoster virus (VZV), enterovirus, parechovirus, human herpes virus (HHV) 6 and 7, and parvovirus B19 were negative in the CSF but Epstein–Barr virus (EBV) DNA came back positive. SARS-CoV-2 RNA was also detected in the CSF using TaqMan probe–based real-time, reverse transcription PCR. During the following weeks, the patient developed multiple cranial nerve palsies (bilateral cranial nerve (CN) VI and left CNs VII, IX, and X), aphasia, and spastic paraparesis with increased deep tendon reflexes in all four limbs. Intravenous immunoglobulin (IVIG) and high-dose steroids led to partial recovery of deficits but symptoms recurred after a few days. Given that the patient had progressive neurological signs and another positive test result for CSF EBV DNA PCR, he was started on a 14-day course of ganciclovir. Four-week follow-up brain MRI showed significant decrease in the aforementioned T2/FLAIR white matter lesions (Fig. 1D–F). The patient was discharged to rehabilitation service for treatment of the remaining neurological sequelae including dysarthria, spastic paraparesis, and urinary incontinence. Four-month follow-up showed significant improvement of the cognitive and motor skills with neurorehabilitation (Table 1).

Case 2

A 19-year-old married woman presented to the emergency department with confusion and fever. Her symptoms started 2 days after her child recovered from a transient episode of fever, myalgia, and symptoms suggestive of gingivostomatitis. Subsequently, she developed fever, sore throat, myalgia, and a few oral ulcers. After 2 days, she noticed weakness in both her legs, numbness up to above the umbilicus, and difficulty in urination. Three days later, she was admitted to the hospital with lethargy and fever. She had a history of paraparesis, with a sensory level, and urinary retention 1 year prior current symptoms that resolved spontaneously after 1 week, before seeking medical attention. On admission, she was febrile and lethargic and had neck stiffness. Neurological examination revealed flaccid paraplegia, bilateral neutral plantar responses, and a sensory level at T6. Chest CT scan was normal. Her brain MRI was unremarkable but spine MRI showed a long segment (C2-T9) non-enhancing central cord hyperintensity on T2/STIR (Fig. 1G–J). CSF analysis revealed leucocytes: 7/μL, erythrocytes: 17,000/μL, protein: 71 mg/dL, and glucose: 50 mg/dL. CSF PCR for CMV and VZV (AmpliSens®, Russia) and SARS-CoV-2 (TaqMan Real-Time PCR Kit for N and RdRp genes) were negative but positive for HSV-1 DNA (AmpliSens®, Russia). SARS-CoV-2 DNA PCR on nasopharyngeal specimen using TaqMan Real-Time PCR Kit for N and RdRp genes also revealed positive results. CSF anti-MOG, CSF anti-AQP4, and ANA profile were negative. Her consciousness returned to normal on day 4 of hospitalization while she was on empirical ceftriaxone, vancomycin, and dexamethasone for a presumed bacterial meningoencephalitis. During the second week of hospitalization, she received high doses of steroids presuming recurrent idiopathic transverse myelitis, before CSF HSV-1 DNA PCR reported positive. Limb motor forces continued to improve on IV Acyclovir which was added to the high-dose steroid in the third week. One-month follow-up showed full recovery of memory and cognitive skills.

Case 3

A 54-year-old man presented to the emergency department with fever and behavioral change. Two weeks prior to admission, he developed fever, cough, and myalgia. SARS-CoV-2 RNA PCR on nasopharyngeal secretions using TaqMan Real-Time PCR Kit for N and RdRp genes showed positive results and he was diagnosed with COVID-19. One week later, he started experiencing headache, delusions, and hallucinations as well as fever. On physical exam, he was febrile, awake but agitated, inattentive, and disoriented. Motor system examination was normal and no focal neurological deficit was evident. CSF analysis was significant for leukocyte 580 cells/μL, 95% lymphocytes, 5% polymorphonuclears, protein 139 mg/dL, and glucose 41 mg/dL. Other laboratory examinations showed serum interleukin-6 134 pg/mL, CRP 16 mg/dL, ESR 24, procalcitonin 1.7 ng/mL, WBC 12,400/μL, polymorphonuclears 88%, lymphocytes 9%, Hb

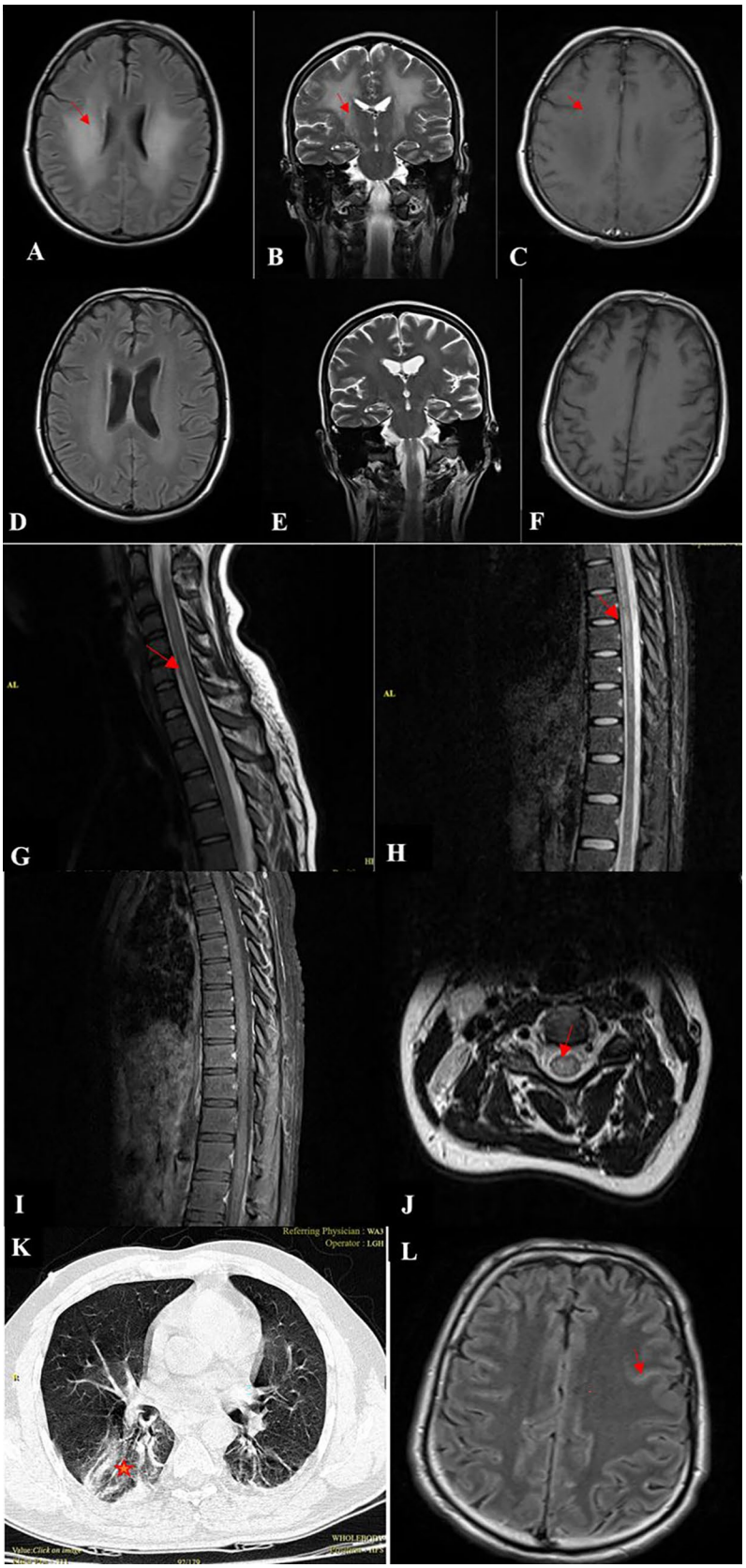

Fig. 1 On admission, brain MRI of patient no. 1 (**A–C**). FLAIR (**A**), T2W (**B**), and T1W with contrast (**C**) sequences show confluent high signal intensities in the deep white matter of periventricular and corticospinal tracts bilaterally. No evidence of enhancement is seen. Four-week follow-up brain MRI of patient no. 1 (**D–F**). T2W/FLAIR signal hyperintensities are decreased significantly in the deep white matter of periventricular and corticospinal tracts (**A, B**) and no enhancement in T1W post contrast (**C**). Spine MRI of patient no. 2 (**G–J**). Sagittal T2W (**A**), STIR (**B**), T1W post contrast (**C**), and axial T2W (**D**) images showed a long segment (C2-T9) central cord hyperintensity on T2/STIR images with no contrast enhancement. Chest CT scan and brain MRI of patient no. 3 (**K–L**). Chest CT scan shows consolidation in the right lower lobe (red asterisk) with peribronchial thickening (**A**) and brain MRI shows high signal sulci (red arrow) in the frontoparietal region on axial FLAIR image (**B**)

Table 1 Patients' characteristics

	Case 1	Case 2	Case 3	Case 4
Main clinical characteristics	Gait and speech difficulties, blurred vision, vertigo, fever, headache and myalgia, nystagmus, ataxia, dysarthria, and cerebellar signs	Urinary retention, fever, confusion, weakness in both legs, numbness up to above the umbilicus, lethargy, neck stiffness, flaccid paraplegia, bilateral neutral plantar response and sensory thoracic level	Fever and abnormal behavior, headache, delusions and hallucinations, disorientation, agitation	Fever and abnormal behaviors, confusion, agitation, nonsensical speech
Imaging findings	*Bilateral confluent T2/FLAIR hyperintensity in the periventricular white matter and corticospinal tracts without contrast enhancement*	Long segment (C2-T9) central cord hyperintensity on T2/STIR with no contrast enhancement	High signal sulci in the frontoparietal region on T2/FLAIR images	Normal brain MRI
Primers and probes	*Multiplex Neuro 9 Real-Time PCR kit* for nucleic acid detection of CMV, EBV, adenovirus, HSV 1 and 2, VZV, enterovirus, parechovirus, HHV 6 and 7, and parvovirus B19 TaqMan Real-Time PCR Kit for nucleic acid (N and RdRp genes) detection of SARS-CoV-2.	AmpliSens®, Russia real-time PCR kit for nucleic acid detection of HSV, VZV, EBV, and CMV TaqMan Real-Time PCR Kit for nucleic acid (N and RdRp genes) detection of SARS-CoV-2	®Novingene, Iran real-time PCR kit for nucleic acid detection of HSV Viruses AmpliSens® MTC-diff-FRT, Russia real-time PCR kit for nucleic acid detection of *M. tuberculosis complex* TaqMan Real-Time PCR Kit for nucleic acid (N and RdRp genes) detection of SARS-CoV-2	AmpliSens®, Russia real-time PCR kit for nucleic acid detection of HSV, VZV, EBV, and CMV TaqMan Real-Time PCR Kit for nucleic acid (N and RdRp genes) detection of SARS-CoV-2
CSF analysis	WBC: *1/μL* RBC: *6/μL* Glucose: *67 mg/dL* Protein: *73 mg/dL*	WBC: *7/μL* RBC: *17,000/μL* Glucose: *50 mg/dL* Protein: *71 mg/dL*	WBC: *580/μL* *Lymph: 95%* RBC: *200/μL* Glucose: *41 mg/dL* Protein: *139 mg/dL*	WBC: *0* RBC: *0* Glucose: *85 mg/dL* Protein: *32 mg/dL*
TLC (10^3 mcL)	555	1024	1125	1056
D-dimer (ng/mL)	-	-	2800	3530
LDH (U/L)	-	632	1019	1187
CRP (mg/dL)	159	3.1	16	41
Complications	Deep vein thrombosis	None	Nosocomial pneumonia, mechanical ventilation	None
Clinical outcome, GOS	3	5	1	5

11.9 mg/dL, platelets 211,000/µL, AST 30 U/L, ALT 34 U/L, and LDH 1019 U/L. Brain MRI showed high signal sulci in the frontoparietal region on T2/FLAIR images. HSV-1 DNA PCR on CSF using a commercial HSV 1 and 2 real-time PCR kit (®Novingene, Iran) was positive but SARS-CoV-2 RNA PCR using TaqMan Real-Time PCR Kit for N and RdRp genes and *M. tuberculosis* complex DNA PCR using AmpliSens® MTC-diff-FRT PCR kit revealed negative results. Since the result of HSV-1 DNA PCR on CSF found positive, CSF was not tested for other viruses. CSF culture was negative for bacterial and fungal pathogens. SARS-CoV-2 RNA PCR on nasopharyngeal secretions was repeatedly positive. The chest CT scan on admission revealed consolidation in superior segments of bilateral lower lobes suggestive of an aspiration pneumonia instead of pneumonia caused by SARS-CoV-2. He received intravenous acyclovir, ceftriaxone, and dexamethasone. During admission, he developed respiratory distress and underwent mechanical ventilation. At that time, the chest radiography showed progression of pulmonary infiltrates to bilateral airspace lesions on middle and lower lung zones. Intravenous piperacillin-tazobactam and remdesivir were started and ceftriaxone discontinued. Multidrug-resistant *Klebsiella pneumoniae* was isolated from respiratory secretions. Over the following days, his admission was complicated with multiorgan dysfunction eventually leading to death on the 14th day of hospitalization.

Case 4

The last case was a 24-year-old 37-week pregnant woman who presented with fever, behavioral change, and unintelligible speech 1 week after a febrile prodrome. On admission, she was febrile (38 °C) and tachypneic (20/min) with oxygen saturation of 92% in room air. On neurological examination, she was confused and agitated with a Glasgow coma scale (GCS) score of 10/15. Laboratory examinations revealed white blood cell count of 6600/µL (neutrophils, 77% and lymphocytes, 16%), hemoglobin of 15.4 mg/dL, platelets of 304,000/µL, ALT of 228 U/L, AST of 532 U/L, ALP of 471 U/L, LDH of 1187 U/L, d-dimer of 3530 ng/mL, CRP of 41 mg/L, and ESR of 43 mm. Serum and urine toxicology screen were negative. Chest CT scan showed diffuse bilateral peripheral ground glass opacities involving about 30% of the lungs. Since the pattern of involvement on chest images was classic for COVID-19 and SARS-CoV-2 was detected on nasopharyngeal secretions using real-time RT PCR for N and RdRp genes, no test was performed for other respiratory viral pathogens on her respiratory secretions. She underwent an emergency cesarean section under general anesthesia due to the development of fetal distress and delivered a healthy baby. Brain MRI was normal and CSF analysis was unremarkable. CSF was negative for VZV, EBV, CMV DNA, and SARS-CoV-2 RNA but positive for HSV-1 DNA (AmpliSens®, Russia). She received intravenous acyclovir and steroids. On the 14th day of hospitalization, she was fully conscious but had some recent memory difficulties. Five-month follow-up showed full recovery of neurologic symptoms without any sequelae.

Discussion

Here we described four patients with acute COVID-19 who presented with an encephalitis (2 cases) or an encephalomyelitis (2 cases) syndrome probably due to concomitant herpesviridae (EBV or HSV-I) reactivation in the CNS. Although SARS-CoV-2 RNA was found in the respiratory secretions of all patients, only 2 showed concomitant pulmonary involvement and in one patient SARS-CoV-2 RNA was also found in the CSF. CSF pleocytosis was mild in all but one patient. Three of four patients partially recovered while on steroids and before institution of antiviral treatment.

Although COVID-19-related encephalopathy Berlit et al. (2020) might explain behavioral change in these patients, this syndrome most commonly occurs in the setting of severe COVID-19, mostly due to hypoxia, sepsis, severe systemic inflammation, renal failure, and cytokine storm Berlit et al. (2020). Only one of our patients presented with severe pulmonary involvement of COVID-19; however, neurological symptoms developed before respiratory involvement in this patient and marked inflammatory CSF changes are not consistent with the diagnosis of encephalopathy. Encephalitis and encephalomyelitis caused by SARS-CoV-2 are other possible explanations; however, neuropathological studies have not been able to show direct viral invasion of the CNS by SARS-CoV-2 infection (Kantonen et al. 2020; Solomon et al. 2020).

Since the first year of the coronavirus pandemic, a growing body of literature described reactivation of herpesviridae family in COVID-19 patients (Xu et al. 2020; Ferreira et al. 2020; Tartari et al. 2020; Le Balc'h et al. 2020; Saade et al. 2021; Katz et al. 2021; Seeßle et al. 2021). In fact, herpesviridae reactivation has been reported as a relatively frequent incident in patients with COVID-19 adult respiratory distress syndrome (ARDS) Le Balc'h et al. (2020) and those admitted in the ICU for severe COVID-19 Saade et al. (2021). A more recent study identified 25 cases of HSV-1 and 16 cases of VZV reactivation among 889 confirmed COVID-19 cases Katz et al. (2021). Many of these studies attributed herpesviridae reactivation to the COVID-19-related immunomodulation. Available evidence showed that HSV-1 reactivates later in the course of SARS-CoV-2 infection, in parallel with a drop of innate antiviral responsiveness (Seeßle et al. 2021). It can be hypothesized that HSV evades the immune system while it is busy fighting SARS-CoV-2 infection. Whether

herpesviridae reactivation affects the outcome of COVID-19 patients is not clear but there is limited evidence that it does not change the outcome Saade et al. (2021) which has not been the case in our patients with CNS involvement. In a single center study in Brazil, 53 patients hospitalized with COVID-19 were evaluated for the prevalence of herpesvirus co-infection and its association with poorer outcomes and neurological symptoms. The study showed a prevalence as high as 79% for herpesvirus co-infection; however, it was not associated with poorer outcomes. In the case of HHV-6 co-infection, CNS-associated neurological symptoms were most prevalent in COVID-19 with herpesvirus detection. In this study, however, the CSF specimens of COVID-19 patients were not examined for viral DNAs Carneiro et al. (2022).

To the best of our knowledge, this is one of the first reports of COVID-19-associated herpesviridae reactivation in the CNS published in the literature to date. Another observational study described 8 patients with laboratory-confirmed herpes simplex encephalitis who had a history of COVID-19 within the previous 6 weeks and followed them for 3 months. In this report, all the patients received 14-day course of acyclovir and all but one with rhinocerebral mucormycosis survived Gupta et al. (2022).

In our first patient, neuroimaging findings were not characteristic for encephalitis caused by either EBV or SARS-CoV-2 Martelius et al. (2011); however, white matter lesions have been described both in EBV encephalitis Vyas et al. (2020) and in COVID-19-associated leukoencephalopathy (Elizondo et al. 2021; Sachs et al. 2020). So, it is difficult to attribute the neurological syndrome to either one of the viruses. The initial presentation of acute encephalomyelitis and a history of a prior myelitis attack led to a diagnosis of para-infectious CNS demyelinating disorder and start of high-dose steroids in the second patient. We presumed that the illness of her child was COVID-19 with oral lesions; however, HSV-1 can also manifest with similar syndrome. Nevertheless, it seems unusual for the patient to develop similar symptoms of HSV-1 as the second case. Both COVID-19-associated oral and gingival ulcer and inflammation (Wu et al. 2021; da Mota et al. 2021) and COVID-19-associated herpetic gingivostomatitis Kämmerer et al. (2021) have been described. Disease course and MRI findings are compatible with our primary diagnosis in this case; however, HSV-I reactivation in the setting of SARS-CoV-2 infection might explain presence of HSV-I DNA in the CSF and encephalopathy symptoms. Patient no. 3 had both inflammatory changes in the CSF and sulcal hyperintensity on MRI which presumed to be due to HSV-1 encephalitis, although we cannot exclude SARS-CoV-2 encephalitis. Patient no. 4 presented with psychotic features in the third trimester of pregnancy. Although this patient could be considered a case of COVID-19-associated encephalitis or encephalopathy, detection of HSV-1 in the CSF and response to treatment raised the possibility of neuroinvasion by this viral pathogen.

Presented cases raise the probability of herpesviridae reactivation in the CNS in relation with recent COVID-19. Further neuropathological studies are needed to evaluate this hypothesis and explain underlying pathophysiology of this phenomenon.

Conclusion

Our report highlights the importance of herpesviridae *reactivation* in COVID-19 patients and the uncertainties regarding its management. It is not clear how much herpesviruses contribute in producing CNS symptoms in this setting and whether they act as neuropathogens invading the CNS or as a benign bystander. The optimal therapeutic management has not been investigated and until more information is available, it seems prudent to treat these patients with appropriate antivirals with or without anti-inflammatory agents.

Declarations

Conflict of interest The authors declare no competing interests.

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