CASE REPORT

SARS-CoV-2-associated haemorrhagic encephalitis mimicking Herpes encephalitis

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Abstract
Although acute encephalopathy is quite commonly seen in patients of SARS-CoV-2 infection, encephalitis characterised by brain inflammation is relatively rare. Encephalitis caused by Herpes simplex type 1 is the most common cause of identified sporadic encephalitis, and early diagnosis and prompt treatment can prevent the devastating outcome. In this brief communication, we report a case of SARS-CoV-2 associated haemorrhagic encephalitis mimicking herpes encephalitis. In today’s pandemic era, it is especially important to distinguish herpes encephalitis from SARS-CoV-2-associated encephalitis as treatment and prognosis of both the conditions differ greatly. This case highlights the importance of suspecting SARS-CoV-2 infection in a patient presenting with clinical symptoms and brain imaging suggestive of Herpes encephalitis.

Keywords SARS-CoV-2 · Haemorrhagic encephalitis · Herpes encephalitis · Mimicking

Introduction
Neurological manifestations in SARS-CoV-2 infection are being increasingly described, and the projected prevalence of these complications is expected to far outweigh the neurological burden seen with severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle east respiratory syndrome coronavirus (MERS-CoV) in 2012 (Ellul et al. 2020). Although acute encephalopathy is quite commonly seen in patients of SARS-CoV-2 infection, encephalitis characterised by brain inflammation is relatively rare (Hassett et al. 2020). The mechanism responsible for
nervous system involvement in SARS-CoV-2 infection is still debatable (Krett et al. 2020). Encephalitis caused by herpes simplex type 1 is the most common cause of identified sporadic encephalitis, and early diagnosis and prompt treatment can prevent the devastating outcome (Tyler 2018). We herein report a case of SARS-CoV-2-associated haemorrhagic encephalitis mimicking herpes encephalitis.

Case report

A 46-year-old male, known case of hypertension on treatment was brought to emergency department of our hospital with chief complaints of fever of 1 week duration and altered sensorium and decreased verbal output for 4 days. On examination, his Glasgow Coma scale (GCS) was E2V3M4. Both his pupils were 2 mm and were reacting equally to light. Deep tendon reflexes were exaggerated in all four limbs with bilateral extensor plantar reflex. There were no signs of meningitis. He was intubated in view of poor GCS to protect the airway and to provide respiratory support. A clinical diagnosis of encephalitis was kept, and the patient was started on intravenous acyclovir, ceftriaxone, levetiracetam and supportive treatment. His routine blood investigations including complete blood count, liver and kidney function tests, glycosylated haemoglobin, creatinine phosphokinase, thyroid profile, serum procalcitonin and serum ammonia were within normal range. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were markedly elevated (60 mg/L and 72 mm/h respectively). Chest X ray showed confluent air space opacities scattered in periphery of bilateral mid and lower zones with interstitial septal thickening. Bed-sides, electroencephalography (EEG) showed background slowing with no epileptiform discharges. In view of altered sensorium, a brain magnetic resonance imaging (MRI) was advised which revealed diffusion restriction in left temporal, bilateral insular, left thalamus and left medial frontal lobes (Fig. 1). Asymmetric (left > right) hyperintensities were seen in bilateral insular, left frontal and left medial temporal lobe on fluid-attenuated inversion recovery (FLAIR) images (Fig. 2). Computed tomography (CT) chest showed irregular areas of consolidations more along the periphery with septal thickening and patchy ground glass opacities predominantly involving lower lobes of bilateral lung parenchyma. Ultrasound whole abdomen and 2D echocardiography did not show any abnormality. Blood and urine cultures at the time of admission were sterile. Cerebrospinal (CSF) fluid examination revealed lymphocytic pleocytosis (total cells: 163 with 100% lymphocytes with no RBC); elevated protein levels 90.8 mg/dl and normal glucose levels (45.2 mg%, corresponding serum glucose was 90 mg%). Multiplex polymerase chain reaction (PCR) panel for Herpes simplex virus 1 and 2, human Herpes virus 6, human parechovirus,
varicella-zoster virus; cytomegalovirus, enterovirus, Cryptococcus neoformans/gatti and bacterial meningitis panel for Streptococcus agalactiae, Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes, Escherichia coli k1 and Haemophilus influenzae were negative. CSF testing for Japanese encephalitis by PCR was negative. Gene X-pert for tuberculosis and cryptococcal antigen test were negative. Etiological evaluation for other infectious causes like Dengue, Chikungunya, typhoid and malaria were also negative. Covid-19 RT-PCR test from nasopharyngeal swab done on day 1 of hospitalization was negative but a repeat Covid-19 RT-PCR test done on the third day was positive. CSF examination for SARS-CoV-2 by RT-PCR could not be done as the facility was not available at our centre. Thus, in view of positive SARS-CoV-2 RT-PCR test, no epileptiform discharges on EEG and negative RT-PCR for Herpes virus 1 and 2 in CSF (done 5 days after the onset of neurological manifestations), a final diagnosis of SARS-CoV-2-associated haemorrhagic encephalitis was made, and the patient was started on intravenous steroids (dexamethasone), remdesivir and supportive treatment. Over the next 5 days, there was no improvement in sensorium of the patient, and thus, a repeat MRI brain was done which showed temporal evolution of changes seen in the first scan along with haemorrhage in the left temporal lobe associated with mass effect (Figs. 3 and 4). Patient’s family members were counselled about the benefit and risk of decompression craniectomy, but it was refused by the attendants. The patient continued to deteriorate neurologically and expired on day 10 of admission. The patient’s attendants were advised for the autopsy but they did not give consent for the same.

Discussion

Acute viral encephalitis is caused by direct viral invasion leading to brain inflammation which if left untreated can potentially lead to high morbidity and mortality. SARS-CoV-2 was detected by polymerase chain reaction in the cerebrospinal fluid of one of the first published cases of COVID-19–associated meningoencephalitis. Autopsy done on 8 patients with confirmed SARS-CoV-2 infection revealed the presence of SARS genome in the cytoplasm of hypothalamic and cortical neurons (Hassett et al. 2020). High-resolution post mortem MRI of 13 patients showed evidence of microvascular injury in the brain without evidence of direct viral invasion. (Lee et al. 2021) Although the exact mechanism by which SARS-CoV-2 virus affects the central nervous system is still debatable, several hypotheses have been proposed including neural expression of angiotensin-converting enzyme 2 (ACE2) receptors, retrograde neuronal transport, hematogenous spread, hypoxic injury or secondary to cytokine storm (Chalil et al. 2021).
Magnetic resonance imaging (MRI) is the imaging of choice in patients suspected of encephalitis, and abnormality can be seen in approximately 90% of patients with herpes simplex virus (HSV) encephalitis within 48 h of admission. MRI changes characteristic of HSV encephalitis include hyperintensities in cingulate gyrus and medial temporal lobe on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images along with haemorrhages. These MRI changes are quite specific for HSV encephalitis in patients who are confirmed by polymerase chain reaction (Solomon et al. 2012). Our patient had fever for 5 days followed by features suggestive of encephalitis. His changes on MRI were characteristic of HSV encephalitis, and thus, the patient was started on injection acyclovir. Lumbar puncture done 5 days after the onset of neurological manifestations to confirm the diagnosis and aetiology was suggestive of viral encephalitis (lymphocytic pleocytosis with elevated protein levels). Once his SARS-CoV-2 test came positive by reverse transcriptase polymerase chain reaction (RT-PCR) along with chest computed tomography (CT) scan suggestive of SARS-CoV-2 infection, the diagnosis was revisited and ultimately modified after cerebrospinal fluid examination (done 5 days after onset of neurological manifestations) revealed negative PCR for HSV 1 and 2 and EEG showed no epileptiform discharges. The presence of a negative multiplex PCR in CSF for HSV does not exclude a CNS herpes infection as reflected by per cent positive rate ranging from 82 to 96 for HSV-1 and HSV-2 detection by a multiplex PCR test (Liesman et al. 2018). However, in our patient, the possibility of this being a false negative is quite low on account of the florid MRI changes, CSF analysis performed on day 5 of illness showing pleocytosis and EEG showing no epileptiform discharges. Although, without an autopsy, this could not be certain.

Previous cases of SARS-CoV-2 associated encephalitis have reported non-enhancing to minimally enhancing, symmetrical T2 and FLAIR hyperintensities involving mesial temporal lobes and medial thalami (Chalil et al. 2021; Zambreanu et al. 2020). A systemic review of meningoencephalitis in SARS-CoV-2 showed similar CSF findings as in our case and reported temporal lobe hyperintensities on FLAIR as the most common neuroimaging finding (Mondal et al. 2020). Various treatment options have been used in the past for SARS-CoV-2-associated encephalitis including steroids, immunoglobulins and plasma exchange depending on whether encephalitis was considered to be para-infectious or post-infectious (Poyiadji et al. 2020). As our case had presented with fever with changes in chest CT scan suggestive of SARS-CoV-2 infection, he was started on high-dose steroids and Remdesivir along with supportive treatment. Although repeat brain MRI did not show any significant deterioration, patient’s oxygen requirement continued to increase, and ultimately, severe respiratory dysfunction due to SARS-CoV-2 led to his mortality.

Conclusion

Encephalitis is a rare but grave complication of SARS-CoV-2 infection which can closely mimic herpes encephalitis. This case highlights the importance of suspecting SARS-CoV-2 infection in a patient presenting with clinical symptoms and brain imaging suggestive of Herpes encephalitis.

Declarations

Competing interests The authors declare no competing interests.

References

Chalil A, Baker CS, Johnston RB et al (2021) Acute hemorrhagic encephalitis related to covid-19. Neurol Clin Pract 11(2):e147–151
Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T (2020) Neurological associations of COVID-19. Lancet Neurol 19(9):767–783. https://doi.org/10.1016/S1474-4422(20)30221-0
Hassett CE, Gedansky A, Migdady I, Bhimraj A, Uchino K, Cho SM (2020) Neurologic complications of COVID-19. Cleve Clin J Med Krett JD, Jewett GAE, Elton-Lacasse C et al (2020) Hemorrhagic encephalopathy associated with COVID-19. J Neuroimmunol 14(36):577326
Lee MH, Perl DP, Nair G et al (2021) Microvascular injury in the brains of patients with Covid-19. N Engl J Med 384(5):481–483
Liesman RM, Strasburg AP, Heitman AK, Theel ES, Patel R, Binnicker MJ (2018) Evaluation of a commercial multiplex molecular panel for diagnosis of infectious meningitis and encephalitis. J Clin Microbiol 56(4):e01927-17
Mondal R, Ganguly U, Deb S et al (2020) Meningoencephalitis associated with COVID-19: A systematic review. J Neurovirol 26:1–4
Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B (2020) COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology 296(2):E119–E120. https://doi.org/10.1148/radiol.2020201187 (Epub 2020 Mar 31)
Solomon T, Michael BD, Smith PE et al (2012) National encephalitis guidelines development and stakeholder groups. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. J Infect 64(4):347–373
Tyler KL (2018) Acute viral encephalitis. N Engl J Med 379(6):557–566
Zambreanu L, Lightbody S, Bhandari M et al (2020) A case of limbic encephalitis associated with asymptomatic COVID-19 infection. J Neurol Neurosurg Psychiatry 91(11):1229–1230

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