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CASE REPORT

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

Rahul Handa[1] · Satyan Nanda[1] · Atul Prasad[1] · Rajiv Anand[1] · Man Mohan Mehndiratta[1] · Dhruv Zutshi[1] · Aarti Pahuja[1] · Rajesh Kumar Pandey[1] · Payal Mittal[1] · Sachal Sharma[1] · Sujata K Dass[1] · Prabhjeet Kaur Bedi[1] · Pankaj Kumar Shah[1] · Bipan Sharma[1] · Nalin Malhotra[1]

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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

✉ Rahul Handa
rahulhanda0411@gmail.com

Satyan Nanda
satyannanda@gmail.com

Atul Prasad
atulprasad2004@yahoo.com

Rajiv Anand
anand_rajiv@hotmail.com

Man Mohan Mehndiratta
mmehndi@htmail.com

Dhruv Zutshi
dhruvzutshi@gmail.com

Aarti Pahuja
aarti.doc.01@gmail.com

Rajesh Kumar Pandey
rajeshmaitree2000@gmail.com

Payal Mittal
payal.mital0406@gmail.com

Sachal Sharma
drsachal@gmail.com

Sujata K Dass
sujatak.dass@blkhospital.com

Prabhjeet Kaur Bedi
prabhjeet14bedi@gmail.com

Pankaj Kumar Shah
drkumarpankajshah@gmail.com

Bipan Sharma
drvipansharma7@gmail.com

Nalin Malhotra
nalinmalhotra@gmail.com

[1] Department of Neurology, BLK Super Speciality Hospital, New Delhi, Jaipur, Rajasthan, India

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. Bedsides, 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,

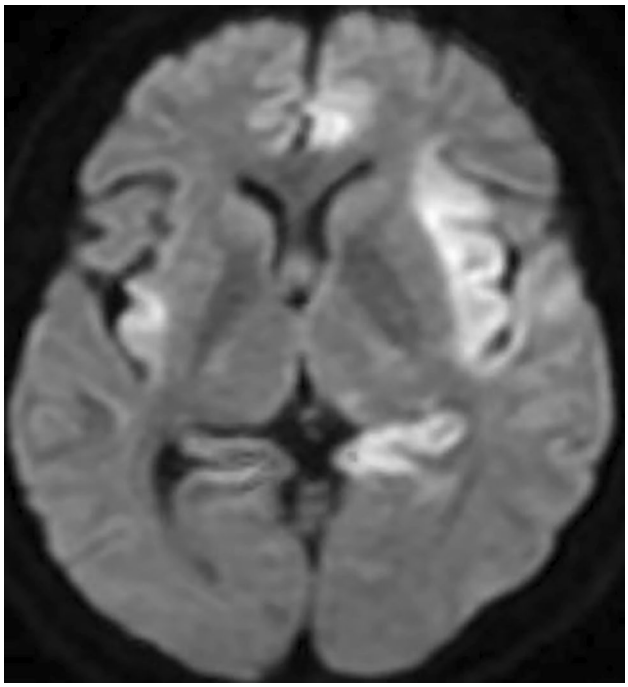

Fig. 1 MR DW image (done at admission) showing diffusion restriction involving both insula (left > right), left medial temporal and left frontal lobes

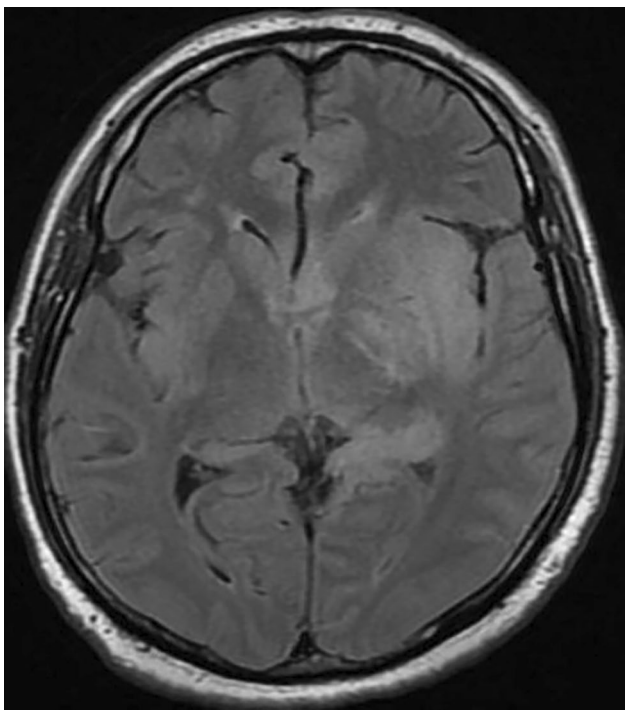

Fig. 2 MR FLAIR image (done at admission) showing asymmetric hyperintensities involving both insula (left > right), left medial temporal and left frontal lobes

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.

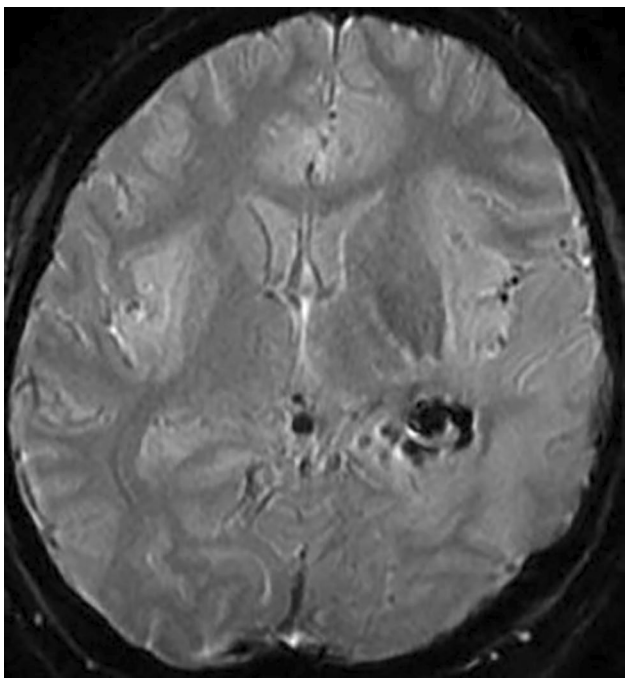

Fig. 3 MR susceptibility weighted (SW) image (done 5 days after admission) showing haemorrhagic areas in left medial temporal lobe

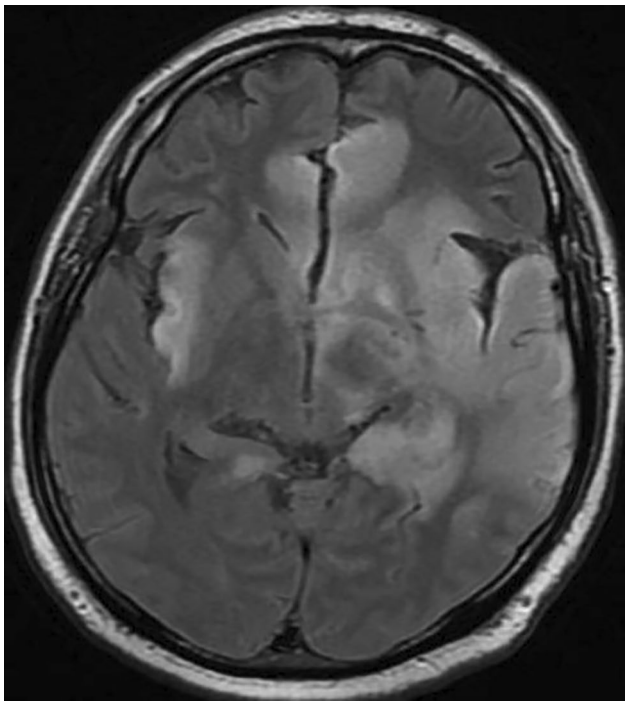

Fig. 4 MR FLAIR image (done 5 days after admission) showing asymmetric hyperintensities involving both insula (left > right), bilateral medial temporal (left > right) and bilateral frontal (left > right) lobes along with mass effect

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.

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