

Acute haemorrhagic necrotizing encephalopathy associated with COVID-19 in a patient with liver cirrhosis

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ABSTRACT

COVID-19 is emerging as a global pandemic and is a complex disease presenting with multi-organ involvement. Acute haemorrhagic necrotizing encephalopathy (AHNE) is a rarely reported phenomenon post-COVID-19 but is a rapidly progressing, fatal, haemorrhagic necrosis of the CNS parenchyma. Here, we present a very interesting case of a cirrhotic male patient with AHNE with COVID-19. Diagnosis of AHNE requires a multimodality approach and high index of suspicion in a patient suffering from SARS-CoV-2. Timely intervention and diagnosis may lead to a favourable outcome in the diagnosed cases. Future detailed studies in this direction may give an insight into this rare but important disease entity.

Keywords: AHNE, COVID-19, haemorrhagic, intervention, necrosis, pandemic

Introduction

Coronavirus disease (COVID-19) has emerged as a global pandemic affecting millions of people worldwide and is proving to be a greater danger than MERS and SARS-Coronaviruses. A plethora of symptoms have been described in the past few months, clearly indicating that COVID-19 is a complex disease, and not only a respiratory disease. It presents with a variety of unspecific symptoms so that the differential diagnosis encompasses a wide range of infections. The most common symptoms cluster of COVID-19 encompass: Respiratory: cough, sputum, shortness of breath, fever; Musculoskeletal: myalgia, joint pain, headache, fatigue; Enteric: abdominal pain, vomiting, diarrhoea; Muco-cutaneous (less commonly).^[1,2]

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A variety of viruses are known to invade central nervous system (CNS) such as HIV, influenza virus, flaviviruses, parainfluenza virus, arbovirus, cytomegalovirus, rhabdovirus, mumps virus, parvovirus B19, measles virus, herpes simplex virus, human T-cell leukaemia virus, coronaviruses (Co-V), etc., After entry into the host cells via angiotensin-converting enzyme (ACE-2) receptors, SARS-CoV-2 triggers the host immune response. Initially, the virus is encountered by the components of the innate immune system known as antigen-presenting cells (APC) like macrophages and dendritic cells. Increased circulating levels of pro-inflammatory cytokines, e.g., interferon γ , interleukin (IL- 1 β , IL-6, IL-2) and chemokines (CXCL10 and CCL2) are correlated with pulmonary inflammation and extensive lung involvement in SARS patients.^[3] There is also enhanced secretion of Th2-immune-oriented cytokines such as IL-4 and IL-10, whose main effect is to repress inflammation. Also, showing consistency with the cytokine release syndrome, dysregulation of the pro-inflammatory cytokine pathway, specifically involving IL-6 and TNF- α , was reported in the cerebrospinal fluid (CSF) of critically ill COVID-19 patients. Moreover, the inflammatory

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mediators damage the blood–brain barrier (BBB) and increase its permeability, making CNS vulnerable to complications like neuro-inflammation and encephalitis.^[3,4]

CNS involvement in COVID results in confusion, loss of consciousness, seizures, stroke, headaches, trouble focusing, changes in behaviour, etc., Late sequelae may lead to peripheral nerve issues, such as Guillain–Barré syndrome and inflammatory neurological conditions, such as acute disseminated encephalomyelitis, acute inflammatory demyelinating neuropathy and acute necrotizing haemorrhagic encephalopathy.

Acute haemorrhagic necrotizing encephalitis (AHNE) is a rarely reported phenomenon post-COVID-19 infection but is a rapidly progressing, fatal, haemorrhagic necrosis of the CNS parenchyma.^[5] The exact immuno-pathogenesis behind AHNE still remains unexplored but cytokine storm with a resultant dysregulation of the blood–brain barrier may be a likely causative mechanism.^[5-7]

Here, we report a very interesting and rare case of a cirrhotic male patient with acute haemorrhagic necrotizing encephalopathy (AHNE) with COVID-19.

Case Report

A 56-year-old male presented to the outpatient department on 6th June of our facility with chief complaints of fever, fatigue, malaise, mental disorientation, with respiratory distress for the last one week. The relatives gave the history of the presence of sore throat, dyspnoea, gastric upset, vomiting with on and off upper respiratory tract symptoms from last 14 days. He was a chronic alcoholic since last ten years and was diagnosed with liver cirrhosis eight months back. Liver transplant was advised to the patient at that time. He had no other medical problems and no previous surgical interventions. He had no significant travel history.

On clinical examination, the patient was febrile at 41.4°C, respiratory rate of 31 bpm, tachycardia at 121 bpm, blood pressure of 161/81 mmHg and oxygen saturation of 82% on room air. He was oriented to self but not to place and time; rest of the neurologic examination was unremarkable. Chest auscultation revealed bilateral coarse rales in both the lung fields. The patient required intubation and mechanical ventilation for severe hypoxic respiratory failure.

Due to the ongoing COVID pandemic the patient was advised testing; naso- and oropharyngeal swabs were obtained and sent for RT-PCR of COVID-19. Routine blood investigations along with brain MRI were also prescribed in the patient. RT-PCR for COVID-19 turned out to be positive on both the naso- and oropharyngeal samples. Routine blood investigations revealed lymphopenia, raised CRP, D-dimer levels as well as raised serum amylase levels. Mild elevation of liver transaminases and hyperbilirubinemia was also noted.

Rest of the serological investigations including hepatitis, HIV, EBV were done as the patient had liver cirrhosis and came out as negative.

A high-resolution CT (HRCT) was advised which revealed ground glass opacities all over the lung fields, especially in the lower zones, confirming the diagnosis of COVID-19 infection [Figure 1: HRCT lung showing ground glass opacities representing COVID-19]. The patient was started with low tidal volume positive-pressure ventilation, a ten-day course of dexamethasone, a five-day course of Remdesivir and convalescent plasma. Remdesivir after 14 days of fever has shown beneficial effect in reducing viral load and mortality according to a recent study.^[6] A neurologic consultation was done for the persistent and worsening encephalopathy symptoms on 18th day of hospitalization, and a brain MRI was advised. Brain MRI revealed a large area of haemorrhage and necrosis involving left ganglio-capsular region and similar smaller area in the contralateral basal ganglia [Figure 2a and 2b: Brain MRI showing a large area of haemorrhage and necrosis involving left ganglio-capsular region and similar smaller area in the contralateral basal ganglia]. The final diagnosis came out to be AHNE with COVID-19 in the patient.

The patient was comatose and unresponsive to painful stimuli while on mechanical ventilation, with normal bilateral pupillary light, corneal and cough reflex. Repeat MRI was advised on 35th day for the worsening symptoms of the patient, and the resulting findings were most consistent with the diagnosis of AHNE in the setting of severe COVID-19 infection. The treatment regimen was further modified, and the patient apart from severe acute respiratory failure due to COVID-19 was also treated with vasopressors for septic shock along with haemodialysis for acute renal failure. On the 42nd day of hospitalization, his clinical condition worsened and still no response to painful stimuli was noted. Gradually, the patient succumbed to his clinical condition and died from cardiac arrest, refractory hypoxia and shock.



Figure 1: HRCT lung showing ground glass opacities representing COVID-19 infection

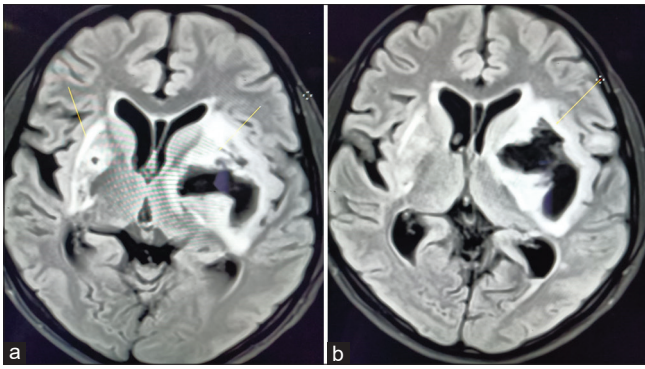


Figure 2: (a and b): Brain MRI showing a large area of haemorrhage and necrosis involving left ganglio-capsular region and similar smaller area in the contralateral basal ganglia

Discussion

With the increasing cases of SARS-CoV-2, it is no more primarily only a respiratory disease, rather it shows multi-organ involvement with varied clinical presentations. Both the central and peripheral nervous system's involvement are not infrequent. Some of the commonly encountered manifestations of COVID-19 infection are meningitis, encephalitis, seizures, ischemic and haemorrhagic stroke and persistent disorders of consciousness.^[7,8] AHNE is a very rare neurologic phenomenon occurring due to para-infectious and hyper-immune response to SARS-CoV-2 infection and is usually seen between one to two weeks after the onset of the upper respiratory tract infection after severe COVID-19. The true incidence of this rare entity is still unknown due to lack in recognition and timely intervention with neuroimaging studies due to deteriorating patients' clinical condition.^[9]

The present case report is among the very few cases reported till date of AHNE associated with COVID-19 infection in this part of the globe. Several studies have established that the human protein neuropilin-1 (NRP-1) is associated with invasion of SARS-CoV-2.^[10,11] It was hypothesized that the Co-V can bind to NRP-1, and the antibody that binds to this protein can block infection in the human cells. ACE-2 receptors are present in abundance in the enterocytes cells of the gut and direct connection of the enteric nervous system with the brain via vagus nerve provides an additional route for the entry of the virus to the brain.

AHNE associated with COVID-19 has been rarely reported in the past, and literature search shows only few cases in the adult as well as paediatric age groups.^[12-15] The SARS-CoV2 can directly infect and replicate in the intestinal cells that further trigger a peripheral immune response such as the excess release of cytokines. This cytokine storm along with direct viral invasion facilitates enteric inflammation and neuro-inflammation in the brain leading to varied neurological complications.^[14]

In the present case, the authors noted elevation in D-dimer and liver transaminases; some previous studies have also reported the

similar findings in COVID-19 infections associated with raised serum markers. A study by Zhou *et al.*^[15] revealed that an elevated D-dimer (>1 ug/L) is a risk factor for mortality in adult patients with COVID-19 infection at the time of admission.

MR features consist of multiple T2-hyperintense symmetrical lesions most frequently found in the ganglio-capsular region as well as thalami, putamina, periventricular white matter, cerebellum and brain stem tegmentum. Haemorrhage with necrosis and cavitation is usually encountered in the cases. The extent of lesions on the MRI has a direct correlation with patient prognosis, and the presence of haemorrhage with necrosis is particularly associated with a poorer prognosis, as is very much evident in our present case report.^[16,17]

Literature search reveals the treatment protocol usually followed in patients with AHNE consists of dexamethasone, with or without immunomodulation therapies such as intravenous immunoglobulin, plasma exchange or convalescent plasma.^[18] Recovery rates were more favourable in patients treated with immunomodulation and dexamethasone than those treated with dexamethasone alone. The patient in our case was also treated on a similar protocol but the severity of symptoms and extent of lesion made him succumb to his disease.

The limitation of this report is that we could not prove the direct evidence of the finding of SARS-CoV-2 in the CNS but we did obtain a positive PCR for SARS-CoV-2 at the initial stage of the disease in the patient. However, due to the clinical manifestations and MRI findings, we could postulate that this case represents an association between AHNE and SARS-CoV-2 exposure due to autoimmune-mediated mechanisms similar to other case reports reported in the past.^[19]

Conclusions

AHNE associated with COVID-19 is a rarely reported phenomenon both due to its complexity of diagnosis and lack of suspicion on the part of treating physician. Our present case report is among very few cases reported so far on this disease entity and throws light on the complex CNS involvement and pathogenesis in the cases of COVID-19. This case report will also be of great help to the primary care physicians by diversifying the knowledge about clinical manifestations in COVID patients and their timely management.

Abbreviations

COVID-19—Coronavirus disease; AHNE—Acute haemorrhagic necrotizing encephalitis; HIV—Human immunodeficiency syndrome, CNS—central nervous system; SARS-CoV-2—Severe acute respiratory syndrome coronavirus-2, BBB—blood-brain barrier, RT-PCR—real-time polymerase chain reaction.

Ethical considerations

Informed consent was obtained from the patient's son regarding the publication of images and clinical information in the

journal. He was informed of the confidentiality of the data. Ethical clearance was taken from the Ethics Committee of the Department of Medical Sciences at the university.

Consent to publish

The consent to publish has been obtained.

Author's contribution

S. S. performed literature search, data analysis and first draft of the manuscript and editing. USS contributed with the radiological findings, images and final draft of the manuscript and editing.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

Summary points

- CNS involvement in COVID results in confusion, loss of consciousness, seizures, stroke, headaches, trouble focusing, changes in behaviour, etc.
- AHNE is a rarely reported phenomenon post-COVID-19 infection but is a rapidly progressing, fatal, haemorrhagic necrosis of the CNS parenchyma.
- The exact immuno-pathogenesis behind AHNE still remains unexplored but
- Cytokine storm with a resultant dysregulation of the blood–brain barrier may be a likely causative mechanism.
- A 56-year-old male presented to the outpatient department of our facility with chief complaints of fever, fatigue, malaise, mental disorientation, with respiratory distress for the last one week
- He was a chronic alcoholic since last ten years and was diagnosed with liver cirrhosis eight months back.
- Routine blood investigations along with brain MRI was prescribed in the patient.
- RT-PCR for COVID-19 turned out to be positive on both the nasopharyngeal and oropharyngeal samples.
- A HRCT was advised which revealed ground glass opacities all over the lung fields, especially in the lower zones, confirming the diagnosis of COVID-19 infection [Figure 1].
- The patient was started with low tidal volume positive-pressure ventilation, a ten-day course of dexamethasone, a five-day course of Remdesivir and convalescent plasma.
- Brain MRI revealed a large area of haemorrhage and necrosis involving left ganglio-capsular region and similar smaller area in the contralateral basal ganglia [Figure 2a and 2b].
- The final diagnosis came out to be AHNE with COVID-19 in the patient.
- On the 42nd day of hospitalization, his clinical condition worsened and still no response to painful stimuli was noted. Gradually, the patient succumbed to his clinical condition and died from cardiac arrest, refractory hypoxia and shock.

- AHNE associated with COVID-19 has been rarely reported in the past and literature search shows only few cases in the adult as well as paediatric age groups.
- The present case report is among the very few cases reported till date of AHNE associated with COVID-19 infection in this part of the globe.
- Diagnosis of AHNE requires a multimodality approach in a patient suffering from SARS-CoV-2 presenting to the emergency department with worsening neurologic symptoms.
- Further studies and reporting of such cases will open new gates of knowledge and insight into this relatively new and rarely diagnosed phenomenon.

Data summary

No data was generated during this research or is required for the work to be reproduced.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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