

Encephalitis as a clinical manifestation of COVID-19: A Case Series

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Abstract

We present a case series of 5 patients who were found to have COVID-19 encephalitis. There is still no disease defining test for diagnosis so the mainstay of diagnosis is the exclusion of all common causes of encephalitis. Brain MRI and CSF analysis perform an ancillary in the diagnostic tools.

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Abstract

COVID-19 is a novel virus which causes a variety of clinical manifestations in the body some of which are still yet to be discovered. The main aim of our study is to highlight the neurological manifestations of COVID-19 as it is still new to the medical world and to emphasize the fact that the physicians have to be vary of the possibility that patients affected with COVID-19 can present with encephalitis during this modern world pandemic. Only a few case reports have been reported so far regarding the neurological manifestations of this novel virus which highlights the need of this study. We present a case series of 5 patients who were found to have COVID-19 encephalitis. There is still no disease defining test for diagnosis so the mainstay of diagnosis is exclusion of the all common causes of encephalitis. Brain MRI and CSF analysis performs an ancillary in the diagnostic tools. Our study also supports the use of IV Tocilizumab (4-8 mg/kg) and IV methylprednisolone (0.5-2 mg/kg) as treatment options having good results as the patients described in our case series responded well to this therapeutic combination. Our study also highlights the fact that the disease can have a good outcome with no long term neurological complications.

Keywords: COVID-19, Encephalitis, Neurological manifestation, Tocilizimab, Methylprednisolone, Polymerase Chain Reaction

Key Clinical Message: Brain MRI and CSF analysis perform an ancillary in the diagnostic tools. Our study also supports the use of IV Tocilizumab (4-8 mg/kg) and IV methylprednisolone (0.5-2 mg/kg) as treatment options having good results with favorable outcomes.

Introduction

COVID-19 has a very broad variety of clinical manifestations and signs and symptoms. Initially it was thought of affecting only the respiratory system but now it is known that it can affect a wide variety of body systems and manifest in a variety of ways. Acute respiratory distress syndrome (ARDS), thromboembolic syndrome, severe metabolic syndromes, severe acute tubular necrosis, electrolyte abnormalities, neurologic syndromes, and cardiac events, including myocarditis and arrhythmias, have all been linked to this new virus [1,13-14]. In March 2020, Beijing Ditan announced the first incidence of viral encephalitis linked to COVID-19 and through genome sequencing of the cerebrospinal fluid (CSF), COVID-19 presence was identified [2]. COVID-19 can cause non-specific symptoms such as headache, dizziness, taste and olfactory sensory disturbances, as well as particular syndromes such as encephalitis, acute transverse myelitis, meningitis, and stroke [3]. The neurological manifestations of COVID-19 can be caused by either direct invasion of the cells or by indirect mechanisms like inflammatory response and cytokine storm [4].

Our primary interest is that of encephalitis in COVID-19 affected patients. The presentation of COVID-19 encephalitis is the same as any other cause of encephalitis with patients showing features of fever, confusion, seizures and focal neurological signs. It can be diagnosed via MRI brain and CSF Polymerase Chain Reaction

(PCR) for COVID-19 genome. A variety of treatments including IV steroids, IV immunoglobulins and IV rituximab have been tried with variable outcomes [5].

We now present a case series of 5 patients who presented with COVID-19 encephalitis. It is important for physicians to be vary of the different neurological manifestations of COVID-19 and our case series will add more knowledge to it.

Case Presentation

Case no 1

Patient no 1 is a 48 years old male who presented with complaints of fever, confusion and one episode of seizure since the last 3 days. Patient had been suffering from sore throat, cough and shortness of breath from the last 12 days. He did not have any significant past medical history. He did not have any previous history of seizures before. On arrival he was having a fever of 103 F, blood pressure of 120/75 mm Hg, pulse of 103 bpm and a respiratory rate of 16/min. On examination he was not oriented in time place or person and his GCS score was 11/15. There was no neck stiffness or any focal neurological deficit. On chest auscultation there were bilateral crepitations as well. His lab and upon suspected encephalitis spinal fluid was done whose reports are as follows in **Table1**.

This lumbar puncture report presented a diagnostic dilemma as all the common causes of encephalitis were ruled out. Autoimmune workup, including anti-N-methyl D-aspartate (NMDA) receptor antibodies, anti-Ro antibodies, anti-La antibodies, antineutrophil cytoplasmic antibodies (ANCA) antibodies, and anti-Hu antibodies, were negative. As patient was having respiratory symptoms as well, a chest X-ray was ordered which showed bilateral homogenous peripheral shadows. A nasal swab COVID-19 Polymerase Chain Reaction (PCR) was ordered and it came back positive. Patient was suspected of having COVID-19 related encephalitis so a CSF COVID-19 Polymerase Chain Reaction (PCR) was done but it came back negative. MRI brain was also carried out which is given in

Figure 1.

Patient was then treated with a single dose of IV Tocilizumab 400 mg (4-8 mg/kg) followed by IV methylprednisolone 1g (0.5-2 mg/kg) for 5 days. Patient responded very well to this treatment and his conscious level improved and he became oriented to time place and person. Patient did not have any further episodes of seizure after that. Patient was then discharged to nursing care at home and after a follow up period of one month, patient was totally oriented and there were no residual neurological signs as well.

Case No 2

Patient no 2 is a 63 years old female who presented with complaints of fever and confusion from the last 2 days and had 3 episodes of seizures in the last 24 hours. She has a background history of hypertension and poorly controlled diabetes. She had signs and symptoms of upper respiratory tract infection like nasal stuffiness, rhinorrhea and sore throat and severe body aches from the last 10 days. On examination she had a fever of 102.6 F, blood pressure of 105/72 mm Hg and a pulse rate of 102 bpm. Her throat examination showed red hyperemic throat. On her central nervous system examination she was not oriented in time, place or person and had a GCS of 11/15. She did not have any neck stiffness or any focal neurological deficit. On chest examination she was having predominantly left sided chest crepitations. Her lab and upon suspected encephalitis spinal fluid was done whose reports are as follows in

Table 2.

Autoimmune workup, including anti-N-methyl D-aspartate (NMDA) receptor antibodies, anti-Ro antibodies, anti-La antibodies, antineutrophil cytoplasmic antibodies (ANCA) antibodies, and anti-Hu antibodies, were negative. These investigations were carried out to rule out the most common and important causes of encephalitis and it came back negative. As patient was having URTI features as well so a chest X-ray was done which showed bilateral opacities more on the left side. A nasal swab COVID-19 Polymerase Chain Reaction (PCR) was ordered and it came back positive. Patient was suspected of having COVID-19

encephalitis so a CSF COVID-19 Polymerase Chain Reaction (PCR) was ordered and it came back positive. MRI brain was also carried out which is given in

Figure 2.

Patient was then treated with a single dose of IV Tocilizumab 400 mg (4-8 mg/kg) followed by IV methylprednisolone 1g (0.5-2 mg/kg) for 5 days. Patient failed to show any improvement. Another dose of IV Tocilizumab was repeated and methylprednisolone 1g IV was continued for another 5 days. Patient responded very well to this treatment and her conscious level improved and she became oriented to time place and person. Patient was then discharged to nursing care at home and after a follow up period of one month, patient was very much improved. She was totally oriented and her conscious level was fully back to normal with a GCS of 15/15. She did not have any residual neurological deficit as well.

Case no 3

Patient no 3 is a 38 years old male who presented with complaints of fever and drowsiness for the last 4 days. He had no significant past medical history. He was having shortness of breath and chest pain from the last 12 days. On examination he had a fever of 101.3 F, blood pressure of 120/75 mm Hg, pulse rate of 96 bpm and respiratory rate of 18/min. He had a GCS of 10/15 and was not oriented in time place or person. He did not show any evidence of neck stiffness or any focal neurological deficit. His lab and upon suspected encephalitis spinal fluid was done whose reports are as follows in **Table 3**.

Autoimmune workup, including anti-N-methyl D-aspartate (NMDA) receptor antibodies, anti-Ro antibodies, anti-La antibodies, antineutrophil cytoplasmic antibodies (ANCA) antibodies, and anti-Hu antibodies, were negative. All common causes of encephalitis were ruled out through these lab investigations. His chest x ray was done which showed bilateral opacities and nasal swab COVID-19 Polymerase Chain Reaction (PCR) came out positive. He was suspected of having COVID-19 encephalitis so CSF COVID-19 Polymerase Chain Reaction (PCR) was also ordered but it came back negative. MRI brain was carried out which is given in

Figure 3.

Patient was then treated with a single dose of IV Tocilizumab 400 mg (4-8 mg/kg) followed by IV methylprednisolone 1g (0.5-2 mg/kg) for 5 days. Patient responded very well to this treatment and his conscious level improved and he became oriented to time place and person. Patient was discharged to nursing care at home and after a follow up period of one month, patient was totally oriented and there were no residual neurological signs as well.

Case No 4

Patient no 4 is a 52 years old male who presented with complaints of fever and drowsiness for the last 8 days. He also had 3 episodes of seizures in the last 2 days. He had a history of well controlled hypertension. He was having shortness of breath and body aches from the last 8 days. On examination he had a fever of 104.3 F, blood pressure of 130/85 mm Hg, pulse rate of 112 bpm and respiratory rate of 18/min. he had a GCS of 11/15 and was not oriented in time place or person. He did not show any evidence of neck stiffness or any focal neurological deficit. His chest examination showed bilateral crepitations as well. His lab and upon suspected encephalitis spinal fluid was done whose reports are as follows in **Table 4**.

Autoimmune workup, including anti-N-methyl D-aspartate (NMDA) receptor antibodies, anti-Ro antibodies, anti-La antibodies, antineutrophil cytoplasmic antibodies (ANCA) antibodies, and anti-Hu antibodies, were negative. All common causes of encephalitis were ruled out through these lab investigations. His chest x ray was done which showed bilateral opacities and nasal swab COVID-19 Polymerase Chain Reaction (PCR) came out positive. His CSF COVID-19 Polymerase Chain Reaction (PCR) was also ordered but it came back negative. He was suspected of having COVID-19 encephalitis as all the common causes of encephalitis had been ruled out in this patient making it a diagnosis of exclusion. MRI brain was also carried out which is given in **Figure 4**.

Patient was then treated with a single dose of IV Tocilizumab 400 mg (4-8 mg/kg) followed by IV methylprednisolone 1g (0.5-2 mg/kg) IV for 5 days. Patient initially did not respond very well to treatment. His fever settled down but his conscious level did not improve and he further had an episode of seizure in the hospital. Patient was then given another dose of IV Tocilizumab 400 mg and a further 5 days course of IV methylprednisolone 1 g was given. Patient responded very well to this treatment and his conscious level improved and he became oriented to time place and person. Patient outlook improved very much and was then discharged to nursing care at home and after a follow up period of one month, patient was totally oriented. There were no further episodes of seizures and there were no residual neurological signs as well.

Case no 5

Patient no 2 is a 57 years old female who presented with complaints of high grade fever and confusion from the last 2 days. She has a background history of hypertension, asthma and well controlled diabetes. She had sore throat and severe body aches from the last 10 days. On examination she had a fever of 104.6 F, blood pressure of 125/75 mm Hg, pulse rate of 98 bpm and a respiratory rate of 19/min. Her throat examination showed red hyperemic throat. On her central nervous system examination she was not oriented in time, place or person and had a GCS of 10/15. She did not have any neck stiffness or any focal neurological deficit. On chest examination she was having predominantly left sided chest crepitations and bilateral expiratory wheezes. Her lab and upon suspected encephalitis spinal fluid was done whose reports are as follows in **Table 5**.

Autoimmune workup, including anti-N-methyl D-aspartate (NMDA) receptor antibodies, anti-Ro antibodies, anti-La antibodies, antineutrophil cytoplasmic antibodies (ANCA) antibodies, and anti-Hu antibodies, were negative. These investigations were carried out to rule out the most common and important causes of encephalitis and it came back negative. As patient was having respiratory tract infection features as well so a chest x ray was done which showed bilateral opacities more on the left side. A nasal swab COVID-19 Polymerase Chain Reaction (PCR) was ordered and it came back positive. The clinical picture pointed towards a diagnosis of encephalitis so CSF COVID-19 Polymerase Chain Reaction (PCR) was also ordered but it came back negative. Patient was suspected of having COVID-19 encephalitis as all the other causes of encephalitis have been ruled out. MRI brain was also done and is given in

Figure 5.

Patient was then treated with a single dose of IV Tocilizumab 400 mg (4-8 mg/kg) followed by IV methylprednisolone 1g (0.5-2 mg/kg) for 5 days. Patient responded very well to this treatment and her conscious level improved and she became oriented to time place and person. Patient was then discharged to nursing care at home and after a follow up period of one month, patient was totally oriented, she did not suffer any episodes of seizures and there were no residual neurological signs.

Discussion

The primary effect of COVID-19 on the human body is on the respiratory system but it can inflict certain neurological manifestations as well [12]. Although the evidence on the neurological manifestations of COVID-19 is still scarce as it is rare, a study has documented that 36 of the patients having ARDS caused by COVID-19 had some forms of neurological manifestations [6]. COVID-19 can affect the nervous system in different ways which are classified into three main categories, CNS symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), peripheral nervous system (PNS) symptoms (hypogeusia, hyposmia, hypopsia, and neuralgia), and skeletal muscular symptoms [7]. Interestingly, the occurrence of neurological manifestations in COVID-19 affected patients depends upon the severity of the disease, greater the severity greater will be the likelihood of having the neurological manifestations [2].

The target receptor via which the COVID-19 virus attaches to the cells is the ACE 2 receptor and after internalization of the virus into the cells, the RNA of the virus is released which then leads to translation and replication [8]. After entering the cells, the COVID-19 virus can damage the cells via 2 main mechanisms,

either via immune mediated damage due to cytokine storm or via severe hypoxia as a result of pneumonia and ARDS [9].

The diagnosis of COVID-19 encephalitis will require the isolation of virus from the CSF sample and it is generally very difficult because of the transient dissemination of virus in the CSF and very low titers which don't allow virus detection [6]. Similar pattern was also observed in our case series with only 1 out of 5 patients had a positive CSF COVID-19 Polymerase Chain Reaction (PCR) and the mainstay of diagnosis was the exclusion of all other important causes of encephalitis. MRI brain can also aid in the diagnosis of COVID-19 encephalitis and a wide range of MRI findings can be seen in COVID-19 related encephalopathy and they include leptomeningeal enhancement, ischemic strokes, and cortical fluid-attenuated inversion recovery (FLAIR) signals [10]. We also observed similar MRI findings in our patients.

The main treatment of COVID-19 encephalitis is supportive. However a variety of treatments like IV immunoglobulins, IV steroids, IV Tocilizumab and IV rituximab have been tried with variable outcomes [5]. In our case series the patients received IV Tocilizumab 400 mg (4-8 mg/kg) and a short course of IV methylprednisolone (0.5-2 mg/kg) resulted in drastic improvement in the outlook of the patient showing its efficacy as a treatment option. Neurological dysfunction may be persistent even after the acute illness has resolved and in a case series almost one-third of the patients were cognitively impaired at discharge and at follow up [11]. In our case series the patients had improved significantly at discharge and had no residual neurological damage on follow up after one month.

Conclusion

The COVID-19 can cause a variety of neurological manifestations and physicians have to be vary of them when they come across affected patients in this pandemic. There are no disease defining imaging findings on MRI brain and the yield of PCR analysis of CSF is low so basically it is a diagnosis of exclusion and we have to rule out the more common causes of encephalitis first to reach this diagnosis like we did in our study. There is not enough data present to definitely conclude whether there will be any permanent neurological damage or not, our study points us in the direction that complete recovery without any long lasting neurological damage is possible in such patients. To determine the exact efficacy and effectiveness of the current proposed treatment for COVID-19 encephalitis will require clinical trials but the result of our study show promising results of IV Tocilizumab (4-8 mg/kg) and IV methylprednisolone (0.5-2 mg/kg).

The purpose of our study is to highlight the importance of neurological manifestations of COVID-19 and to point to the fact that such a diagnosis has to be considered when a patient presents with such signs and symptoms. Our case series will add to the much deficient knowledge on the subject of neurological manifestations of COVID-19.

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DECLARATION OF CONFLICT OF INTERESTS

None

ETHICS APPROVAL

Need for ethical approval waived. Consent from the patient deemed to be enough.

CONSENT FOR PUBLICATION

Written informed consent has been taken from the patient which would be available upon the Editor-in-Chief's request.

AUTHORS CONTRIBUTIONS

MS, MH, MK, MJ, AH, NL, AQ, AAK, DM, NP, VJ, RS prepared the abstract, introduction, case, discussion, conclusion. MH, VJ and NP performed critical edits, revised the draft and prepared the final version of this manuscript which was approved by all authors.

DATA AVAILABILITY STATEMENT

None

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Figure Legends

Fig 1: MRI brain axial T2, FLAIR, echo planer and DWI. High signal FLAIR/T2 is demonstrated within the left mesial temporal lobe associated with mild gyral expansion, sulcal effacement and restricted diffusion.

Fig 2: MRI demonstrates extensive edema in the right temporal lobe with areas of intrinsic high T1 signal, in keeping with features of encephalitis.

Fig 3: MRI Brain shows increased T2 signal involving the right temporal lobe and insular cortex consistent with encephalitis

Fig 4: T2 and FLAIR hyperintense signal in bilateral lobes and bilateral caudate nuclei showing restriction diffusion on DWI, appearance is keeping with encephalitis.

Fig 5: Left Parietal lobe shows T2 and FLAIR hyperintensity which shows restricted diffusion on DWI, appearance suggestive of encephalitis.

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