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Case Report

Encephalitis as a Clinical Manifestation of COVID-19: A Case Series

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Case report · Corticosteroids · COVID-19 · Encephalitis · Tocilizumab · Neurological manifestations

Abstract
COVID-19 is a novel virus which causes a variety of clinical manifestations in the body, some of which are 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 wary of the possibility that patients affected by COVID-19 can present with encephalitis. Only a few studies are available so far regarding the neurological manifestations of this novel virus which highlights the need for this study. We present a case series of 4 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 all the common causes of encephalitis. Brain magnetic resonance imaging and cerebrospinal fluid 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 possible treatment options with good results, as the patients described in our case series responded well to these medications.

Introduction

COVID-19 has a wide variety of clinical manifestations and signs and symptoms involving various systems of the body. This novel infection has been associated with acute respiratory distress syndrome, thromboembolic syndrome, severe metabolic syndromes, severe acute tubular necrosis, electrolyte abnormalities, neurologic syndromes, and cardiac events, including

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myocarditis and arrhythmias [1]. The first case of COVID-19-associated viral encephalitis was reported in March 2020, and through genome sequencing of the cerebrospinal fluid (CSF), COVID-19's presence was identified [2]. The neurological manifestations of COVID-19 can include either nonspecific symptoms like headache, dizziness, taste and olfactory sensation disturbance, or specific syndromes like encephalitis, acute transverse myelitis, meningitis, or stroke [3]. These can be caused by either direct invasion of the cells or indirectly due to 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 similar to other causes of encephalitis, with patients showing features of fever, confusion, seizures, and focal neurological signs. It can be diagnosed by magnetic resonance imaging (MRI) of the brain and CSF polymerase chain reaction (PCR) for the COVID-19 genome. Various treatments, including intravenous steroids, immunoglobulins, and rituximab, have been tried with variable outcomes [5]. Herein, we present a case series of 5 patients with COVID-19 encephalitis managed with intravenous tocilizumab and methylprednisolone.

Case Presentation

Patient 1

Patient 1 was a 48-year-old male who presented with sore throat, cough, and shortness of breath for 12 days. Also, he had fever and confusion for 3 days, and an episode of seizure. His past medical history, personal history, and drug history were unremarkable. On arrival, he had a temperature of 103°F, blood pressure of 120/75 mm Hg, pulse rate of 103 bpm, respiratory rate of 16/min, and a GCS score of 11/15. His systemic examination was unremarkable except for bilateral crepitations on chest auscultation. He had no neck stiffness or focal neurologic deficits.

His laboratory findings are mentioned in Table 1. The patient was suspected of having encephalitis, so an MRI of the brain and lumbar puncture were ordered. MRI of the brain showed gyral swelling and hyperintensities in the right mesial temporal lobe, suggestive of encephalitis (shown in Fig. 1). The findings of the lumbar puncture are given in Table 2. Also, we did an autoimmune workup, including anti-NMDA receptor antibodies, anti-Ro antibodies, anti-La antibodies, ANCA antibodies, and anti-Hu antibodies, which were negative. These investigations were carried out to rule out the common causes of encephalitis. As the patient had respiratory symptoms, we did a chest X-ray, which showed bilateral homogenous peripheral opacities. A nasal swab COVID-19 PCR was ordered, which was positive. The patient was suspected of having COVID-19-related encephalitis, so a CSF COVID-19 PCR was done, but it was negative.

Based on clinical evaluation and investigation reports, we made a diagnosis of COVID-19-associated encephalitis. He was treated with a single dose of IV tocilizumab 400 mg (4–8 mg/kg) followed by IV methylprednisolone 1 g (0.5–2 mg/kg) for 5 days. The patient's condition improved and was then discharged. On follow-up after 1 month, the patient was doing well, and there were no residual neurological signs.

Patient 2

Patient 2 was a 63-year-old female with complaints of fever and confusion for 2 days and 3 episodes of seizures in the last 24 h. Also, she had nasal stuffiness, rhinorrhea, sore throat, and body aches for the last 10 days. She was a known case of hypertension and poorly controlled type 2 diabetes mellitus. Her personal history and drug history were unremarkable. She had a temperature of 102.6°F, blood pressure of 105/72 mm Hg, pulse rate of 102

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Table 1. Summary of the laboratory investigations of all the cases

Laboratory investigation	Unit	Reference value	Case 1	Case 2	Case 3	Case 4
WBC	Cells/mm^3	4,000–11,000	13,000	17,000	14,000	16,000
CRP	mg/mL	0–5	87	102	68	112
D dimers	ng/mL	0–200	810	1,318	984	1,118
Ferritin	ng/mL	30–400	1,245	865	1,311	754
LDH	U/L	140–280	564	653	486	560
Random blood sugar	mg/dL	120–140	119	112	108	102
Blood culture			Negative	Negative	Negative	Negative
Urine culture			Negative	Negative	Negative	Negative
Urine toxicology			Negative	Negative	Negative	Negative
HIV antibodies			Negative	Negative	Negative	Negative
Rapid plasma reagin			Negative	Negative	Negative	Negative

bpm and a GCS of 11/15. Physical examination revealed throat hyperemia and lung crepitations on the left side. She had no neck stiffness or focal neurologic deficits.

Her laboratory findings are mentioned in Table 1. The patient was suspected of having encephalitis, so an MRI of the brain and lumbar puncture were ordered. MRI of the brain was suggestive of encephalitis (shown in Fig. 2). The findings of the lumbar puncture are given in Table 2. Also, we did an autoimmune workup, including anti-NMDA receptor antibodies, anti-Ro antibodies, anti-La antibodies, ANCA antibodies, and anti-Hu antibodies, which were negative. These investigations were carried out to rule out the common causes of encephalitis. A chest X-ray was done, which showed bilateral opacities, which were more on the left side. A nasal swab COVID-19 PCR was ordered, and it was positive. The patient was suspected of having COVID-19 encephalitis, so a CSF COVID-19 PCR was ordered, and it came back positive.

Based on clinical evaluation and investigation reports, we made a diagnosis of COVID-19-associated encephalitis. She was then treated with a single dose of IV tocilizumab 400 mg (4–8 mg/kg) followed by IV methylprednisolone 1 g (0.5–2 mg/kg) for 5 days. The patient failed to show any improvement. Another dose of IV tocilizumab was repeated, and methylprednisolone 1 g IV was continued for another 5 days. The patient's condition improved and was then discharged. On follow-up after 1 month, the patient was doing well, and there were no residual neurological signs.

Patient 3

Patient 3 was a 38-year-old male with the complaints of shortness of breath and chest pain for the last 12 days. Also, he had complaints of fever and drowsiness for the last 4 days. His past medical history, personal history, and drug history were unremarkable. He had a temperature of 101.3°F, blood pressure of 120/75 mm Hg, pulse rate of 96 bpm, respiratory rate of 18/min, and a GCS of 10/15. His physical examination was unremarkable apart from bilateral chest crepitations. There was no neck stiffness or focal neurologic deficits.

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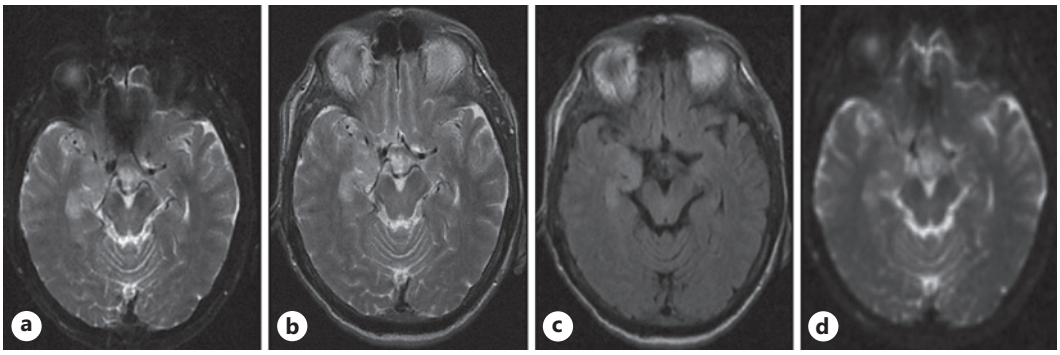

Fig. 1. a, **b** Axial T2Wl demonstrates gyral swelling and hyperintensities in the right mesial temporal lobe, in particular the uncus and part of the hippocampus consistent with encephalitis. **c** Axial FLAIR demonstrates hyperintensities in the same areas. **d** Axial ADC map shows facilitated diffusion in the right mesial temporal lobe.

Table 2. Summarizing the CSF findings of all the cases

Spinal fluid	Units	Reference value	Case 1	Case 2	Case 3	Case 4
Color		Colorless	Colorless	Colorless	Colorless	Colorless
WBC	Cells/mm^3	0–5	57	76	63	59
Lymphocytes	%		81	79	86	77
Neutrophils	%		19	21	14	23
RBC	Cells/mm^3	0	342	423	297	400
Proteins	mg/dL	15–45	80	95	73	65
Glucose	mg/dL	40–70	76	64	61	52
Glucose as percentage of serum glucose	%	50–70	63	57	56	51
Opening pressure	cm H_2O	5–20	14	18	12	16
Gram stain		Negative	Negative	Negative	Negative	Negative
HSV 1 and 2 PCR		Negative	Negative	Negative	Negative	Negative
Cryptococcal antigen		Negative	Negative	Negative	Negative	Negative
CMV PCR		Negative	Negative	Negative	Negative	Negative
VDRL		Negative	Negative	Negative	Negative	Negative
COVID-19 PCR		Negative	Negative	Positive	Negative	Negative

His laboratory findings are mentioned in Table 1. The patient was suspected of having encephalitis, so an MRI of the brain and lumbar puncture were ordered. MRI of the brain showed signs suggestive of encephalitis (shown in Fig. 3). The findings of the lumbar puncture are given in Table 2. Also, we did an autoimmune workup, including anti-NMDA receptor

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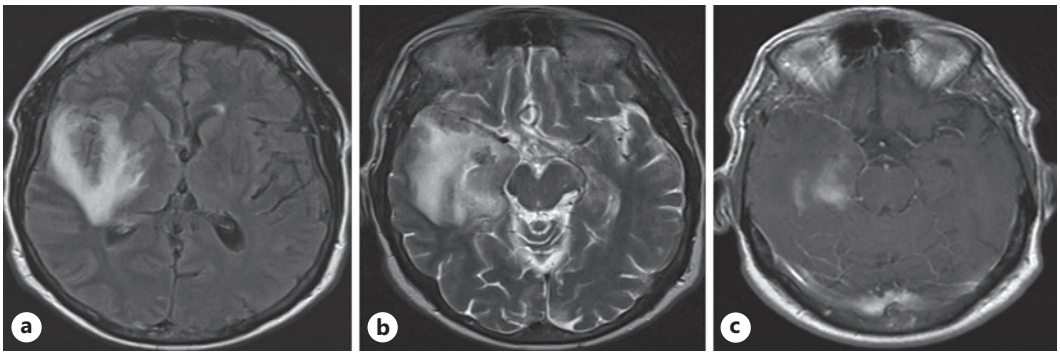

Fig. 2. a Axial FLAIR demonstrates hyperintensities involving the right mesial temporal lobe, insular cortex, and basal ganglia with axial T2WI (**b**) showing hyperintensities consistent with encephalitis. **c** Post-contrast T1WI shows patchy areas of enhancement in the mesial temporal lobe.

antibodies, anti-Ro antibodies, anti-La antibodies, ANCA antibodies, and anti-Hu antibodies, which were negative. These investigations were carried out to rule out the common causes of encephalitis. His chest X-ray showed bilateral opacities, and nasal swab COVID-19 PCR came out positive. He was suspected of having COVID-19 encephalitis, so CSF COVID-19 PCR was also ordered, but it came back negative.

Based on clinical evaluation and investigation reports, we made a diagnosis of COVID-19-associated encephalitis. He was then treated with a single dose of IV tocilizumab 400 mg (4–8 mg/kg) followed by IV methylprednisolone 1 g (0.5–2 mg/kg) for 5 days. The patient responded very well to this treatment and was then discharged. On follow-up after 1 month, the patient was doing well, and there were no residual neurological signs.

Patient 4

Patient 4 was a 57-year-old female with complaints of sore throat and body ache for 10 days. She also had high-grade fever and confusion for the last 2 days. She was a known case of hypertension, asthma, and well-controlled diabetes. Her personal history and drug history were unremarkable. She had a temperature of 104.6°F, blood pressure of 125/75 mm Hg, pulse rate of 98 bpm, respiratory rate of 19/min, and a GCS score of 10/15. Physical examination revealed throat hyperemia and left-side chest crepitations with bilateral expiratory wheezes. There was no neck stiffness or focal neurologic deficits.

Her laboratory findings are mentioned in Table 1. The patient was suspected of having encephalitis, so an MRI of the brain and lumbar puncture were ordered. MRI of the brain was suggestive of encephalitis (Fig. 4). The findings of the lumbar puncture are given in Table 2. Also, we did an autoimmune workup, including anti-NMDA receptor antibodies, anti-Ro antibodies, anti-La antibodies, ANCA antibodies, and anti-Hu antibodies, which were negative. These investigations were carried out to rule out the common causes of encephalitis. Her chest X-ray showed bilateral opacities, more on the left side. A nasal swab COVID-19 PCR was ordered, and it came back positive. The clinical picture pointed toward a diagnosis of encephalitis, so CSF COVID-19 PCR was also ordered, but it came back negative. The rest of the systemic examinations were unremarkable.

Based on clinical evaluation and investigation reports, we made a diagnosis of COVID-19-associated encephalitis. The patient was then treated with a single dose of IV tocilizumab 400 mg (4–8 mg/kg) followed by IV methylprednisolone 1 g (0.5–2 mg/kg) for 5 days. The patient responded very well to this treatment and was then discharged. On follow-up after 1 month, the patient was doing well, and there were no residual neurological signs.

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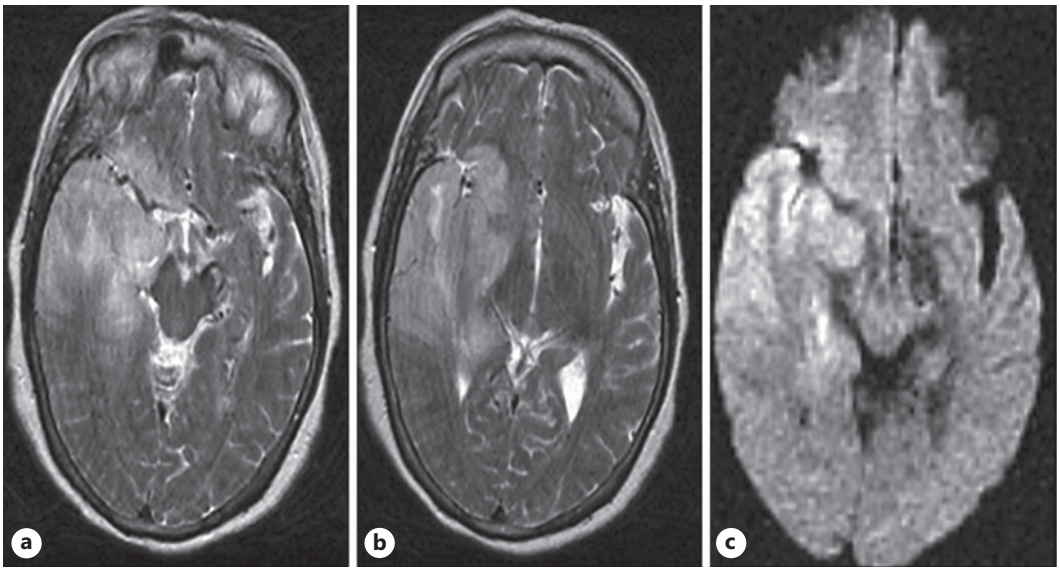

Fig. 3. a, **b** Axial T2WI shows gyral inflammation and hyperintensities involving the right temporal lobe, posterior aspect of the temporal lobe, and right basal ganglia with restriction of diffusion on the corresponding axial DWI image (**c**). There is a subtle mass effect on the brainstem with mild leftward midline shift.

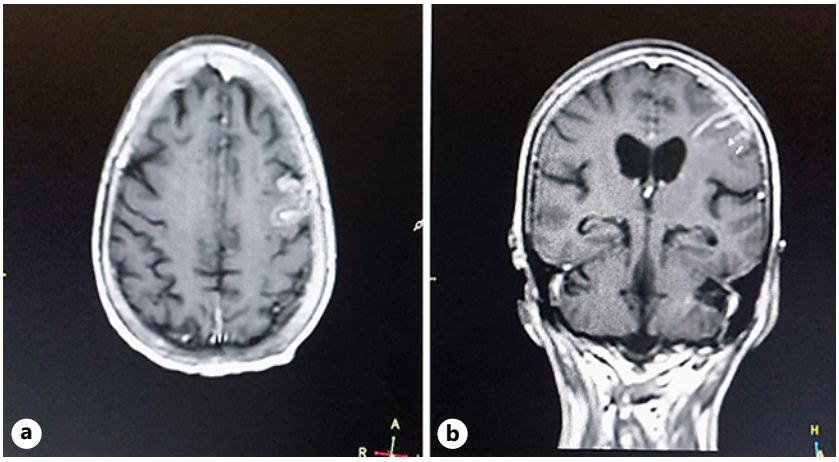

Fig. 4. Axial post-contrast T1WI (**a**) and coronal post-contrast T1WI (**b**) show abnormal areas of enhancement involving the sulci of the left parietal lobe with prominent localized meningeal enhancement.

Discussion

The primary effect of COVID-19 on the human body is on the respiratory system, but it can also inflict certain neurological manifestations. Although neurologic manifestations of the disease may be common, encephalitis is still rare and not frequently reported. A study has documented that 36% of patients with respiratory distress caused by COVID-19 had some form 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 symptoms (hypogeusia, hyposmia, hypoplasia, 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; the greater the severity, the greater the likelihood of having the neurological manifestations [2].

COVID-19 virus gets attached to the ACE-2 receptor, and after internalization of the virus into the cells, the RNA of the virus is released, leading to translation and replication [8]. After entering the cells, the COVID-19 virus can damage the cells via two main mechanisms: immune-mediated damage due to cytokine storm or severe hypoxia due to pneumonia and acute respiratory distress syndrome [9]. The encephalopathy associated with COVID-19 can result from either direct damage caused by the virus, an inflammatory response, or a post-infection autoimmune process.

The diagnosis of COVID-19 encephalitis is usually very challenging because of the transient dissemination of the virus in the CSF and very low titers, which do not allow virus detection [6]. A similar pattern was also observed in our case series, with only 1 out of 4 patients having a positive CSF COVID-19 PCR, and the mainstay of diagnosis was the exclusion of all other important causes of encephalitis. Based on the WHO definition, SARS-CoV-2 found in respiratory or other non-CNS samples with the exclusion of other possible causes is sufficient for diagnosing COVID-19 encephalitis [6]. MRI brain can also aid in diagnosing COVID-19 encephalitis, and a wide range of MRI findings can be seen in COVID-19-related encephalopathy. These include leptomeningeal enhancement, ischemic strokes, and cortical fluid-attenuated inversion recovery (FLAIR) signals [10]. The pattern described in our patients, demonstrating the involvement of the temporal lobes (and in 1 case, the insula) is very similar to those described in herpes virus type 1 encephalitis and in autoimmune encephalitis, which should be ruled out with appropriate laboratory investigations. Also, limbic encephalitis can present with similar clinical picture and MRI findings of hyperintensities on FLAIR and T2WI in the medial temporal lobes [11]. Herpes simplex encephalitis is indicated by cortical and subcortical temporal lobe hyperintensity on T2 and FLAIR weighted images, which is unilateral before developing into an asymmetric bilateral type [12]. Various other pathologies related to demyelination, endothelial lesions, and cytokine release syndrome can be observed in critically ill patients with COVID-19 with brain MRI demonstrating hyperintensity on T2WI with restricted diffusion in the subcortical and deep white matter, with small punctate hemorrhagic foci [13].

The primary treatment for COVID-19 encephalitis is supportive. However, various treatments like intravenous immunoglobulins, steroids, tocilizumab, and rituximab have been tried with variable outcomes [5]. A study by Narain et al. [14] revealed improved survival in COVID-19 patients. Hence, in our case series, we used IV tocilizumab 400 mg (4–8 mg/kg), and a short course of IV methylprednisolone (0.5–2 mg/kg). This resulted in drastic improvement in the patient's outlook, 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 follow-up [15]. In our case series, the patients had improved significantly at discharge and had no residual neurological damage on follow-up after 1 month. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530926).

Conclusion

COVID-19 can cause various neurological manifestations, and physicians must be wary of them. There are no disease-defining imaging findings on MRI of the brain and the yield of PCR analysis of CSF is low. Hence, physicians should rule out common causes of

encephalitis before reaching a diagnosis of COVID-19 encephalitis. Though data regarding long-term sequelae of COVID-19 encephalitis are limited, clinicians should ensure timely follow-up to detect any complications. Our study showed that complete recovery is possible with timely intervention. Though further studies are warranted to determine the effectiveness of the current proposed treatment for COVID-19 encephalitis, our study showed promising results for IV tocilizumab (4–8 mg/kg) and IV methylprednisolone (0.5–2 mg/kg) use in these patients.

Statement of Ethics

Ethical approval is not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Muhammad Hammad Sharif, Madeeha Khaleeque, Asad Ali Khan, Muhammad Hassan Jan, Atif Ahmed, Nida Latif, Abdul Qadir, Muhammad Hanif, and Amjid Iqbal performed conceptualization, writing – original draft, and writing – review and editing of the manuscript. Asad Ali Khan was involved in conceptualization, supervision, writing – original draft, and writing – review and editing of the manuscript.

Data Availability Statement

This manuscript has all the data relevant to this case report included. Further inquiries can be directed to the corresponding author.

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