Case Report

Encephalopathy in the Setting of COVID-19: A Case Report

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ABSTRACT: We present an interesting case of encephalopathy in a patient diagnosed with COVID19 pneumonia describing the clinical course and recovery. We hope this unique presentation can contribute to the ever-growing evidence and literature on COVID-19 encephalopathy.

KEYWORDS: *COVID-19, Encephalopathy, Encephalopathy in COVID-19.*

Introduction

Since its outbreak in early 2020, COVID-19 continues to be a major health concern in most parts of the world.

During the course of the pandemic, it has been established that COVID-19 also can cause multi-organ involvement including a wide range of neurologic manifestations [1].

Viral respiratory infections, in general, have a frequent association with encephalopathy and COVID-19 has often been associated with encephalopathy in as many as 31.8% of patients [1,2].

The outcomes of viral encephalopathy are usually grave and are accompanied by various complications such as seizures, vertigo, ataxia, dysarthria, dysphagia and dysphonia [3,4,5].

Similarly, patients developing COVID-19 encephalopathy have a risk of developing acute as well as long term neurological sequelae that must be identified early provided with prompt neurological rehabilitation [6].

We present an interesting case of encephalopathy in a patient diagnosed with COVID-19 pneumonia describing the clinical course and recovery.

We hope this unique presentation can contribute to the ever-growing evidence and literature on COVID-19 encephalopathy.

Case Report

A 48-year-old female, with a past medical history of hypothyroidism, presented for evaluation of a 3-day history of fever, cough, and breathlessness.

She was identified as a COVID-19 suspect as per standard COVID-19 protocols and admitted to the ward with an opening saturation of 90% on room air and a respiratory rate of 22 cycles per minute.

Physical examination was remarkable for reduced air entry on auscultation of bilateral lung fields.

The diagnosis of COVID-19 was confirmed by the presence of SARS-CoV-2 viral nucleic acid in a nasopharyngeal swab specimen detected by the real-time polymerase chain reaction (RT-PCR) test.

The patient further underwent a full COVID-19 workup which included chest HRCT thorax, routine serum and hematological investigations, inflammatory markers, and special tests.

The HRCT thorax showed patchy multifocal areas of ground-glass opacities scattered bilaterally in peripheral and subpleural portions of lung parenchyma.

Routine serum and hematologic workup were as in Table 1.

Low flow oxygen support and oral Favipiravir was started along with standard supportive care for COVID-19.

The patient's condition worsened over three days with increased oxygen requirement and was shifted to the intensive care unit in view of tachypnoea.

During the course in the intensive care unit, the patient was provided high flow oxygen support for three days and was started on injectable Remdesivir on compassionate grounds for six days.

Owing to the raised interleukin-6 levels and parameters indicating an imminent cytokine storm, a single dose of injectable Tocilizumab in a dose of 400mg was given intravenously on the seventh day of illness (fourth day of admission).

The patient's oxygen requirement decreased after 6 days of intensive care and was gradually weaned-off oxygen support in two days.

However, the patient suddenly had seizures a few hours before she was to be shifted to the wards.

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The initial presentation was that of partial seizures followed by secondary generalization.

Antiepileptic Leviteracetam was started immediately and helped terminate the seizure but on the following day, the patient presented with status epilepticus.

The patient was intubated in view of altered sensorium and low GCS.

An infusion of midazolam was started for the status epilepticus, after which her seizures terminated.

Examination of the neurological system was suggestive of sluggishly reacting with preserved motor and sensory reflexes.

A full workup for correctable causes of seizures was unremarkable.

Lumbar puncture demonstrated CSF proteins of 46 mg/dl, glucose of 200mg/dl and no cells. CSF culture both bacterial and fungal demonstrated no growth.

A panel for screening out other viral, bacterial and fungal infections in CSF such as *Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae,* Cytomegalovirus (CMV), Enterovirus (EV), Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), Human parechovirus (HPeV), Varicella zoster virus (VZV), *Cryptococcus neoformans/gattii* was done and no organisms were detected.

Thus, steering our diagnosis towards encephalopathy and making encephalitis less likely.

However, the testing facility for CSF-COVID-19 was not available and hence the presence of COVID-19 in CSF could not be ruled out.

Further workup included an EEG and MRI that were done after appropriate neurological opinion.

The MRI was suggestive of areas of diffusion restriction with T2, FLAIR hyperintense signal in cortical sulci of bilateral cerebral, cerebellar hemispheres, bilateral thalami and hippocampi which was suggestive of encephalopathy.

The initial EEG had left temporo-occipital spike and wave discharges of 1Hz with secondary generalization (Figure 1).

The midazolam infusion was tapered as the patient was not convulsive and the patient's mental status was reassessed.

The patient moved limbs in response to command but had eye opening on painful stimulus.

Pupils were reacting normally with normal motor and sensory reflexes.

A repeat EEG was done to reassess the seizure activity and poor GCS that was suggestive of diffuse slowing.

After 3 days of mechanical ventilation, the patient was weaned off the ventilator.

However, due to a poor GCS, a tracheostomy was done.

The patient gradually improved in the following 2 weeks and began responding to verbal commands with an improved GCS of E4M5VT.

The patient was given a T-piece trial on which she maintained her saturation and tracheostomy tube was removed after 48 days of admission.

The patient further improved clinically and hemodynamic parameters were stable and was shifted to the wards after 50 days of ICU stay.

During the course of admission in the wards, functional endoscopic evaluation of vocal was done to assess swallowing and was suggestive of left vocal cord palsy with minimal pooling in valleculae and pyriform fossa.

The patient was advised swallowing exercises to be continued.

The patient's GCS further improved to E4M6V5 and appropriate neurological rehabilitation was provided along with speech, swallowing and physical therapy till day 85 of admission.

On day 88 from the admission patient was discharged with minimal difficulty in articulation of speech and swallowing.

The patient was advised to follow up for neurological rehabilitation and physical therapy after 15 days of discharge.

On follow up, the patients EEG and MRI brain were repeated.

The EEG was suggestive of inter-ictal EEG suggestive of mild generalized background slowing.

The follow-up MRI brain reported resolving cortical changes.

A written informed consent was obtained from the patient regarding the publication of these data.

Table 1. Reports of the patient.

	On admission	Onset of encephalopathy requiring intensive care (Day 6 of admission)	Post-COVID encephalopathy while requiring mechanical ventilation (Day 8 of admission)	On discharge
WBC (4-10x10^3/µL)	3.4	5.7	8.3	4.1
Platelets (150-400 x10^3/µL)	165	135	100	196
N/L ratio	2.2/0.9=2.44	4.83/0.34=14.2	6.6/1.1=6	2.98/0.5=5.96
PF ratio (Normal >300)	81	-	133	476
Ferritin (10-291 ng/ml)	47.7	-	-	-
LDH (0-500 U/l)	566.3	-	-	-
D-dimer (ng/ml)	150	-	-	-
CRP (mg/l)	60.93	-	-	-
PCT (0-0.5ng/ml)	0.12	0.24	0.19	1.8
IL-6 (pg/ml)	144.8	-	-	-
RT-PCR	positive	POSITIVE	NEGATIVE	Negative
Creatinine (mg/dl)	0.5	0.5	0.6	0.4
Sodium (mg/dl)	138	140	146	137

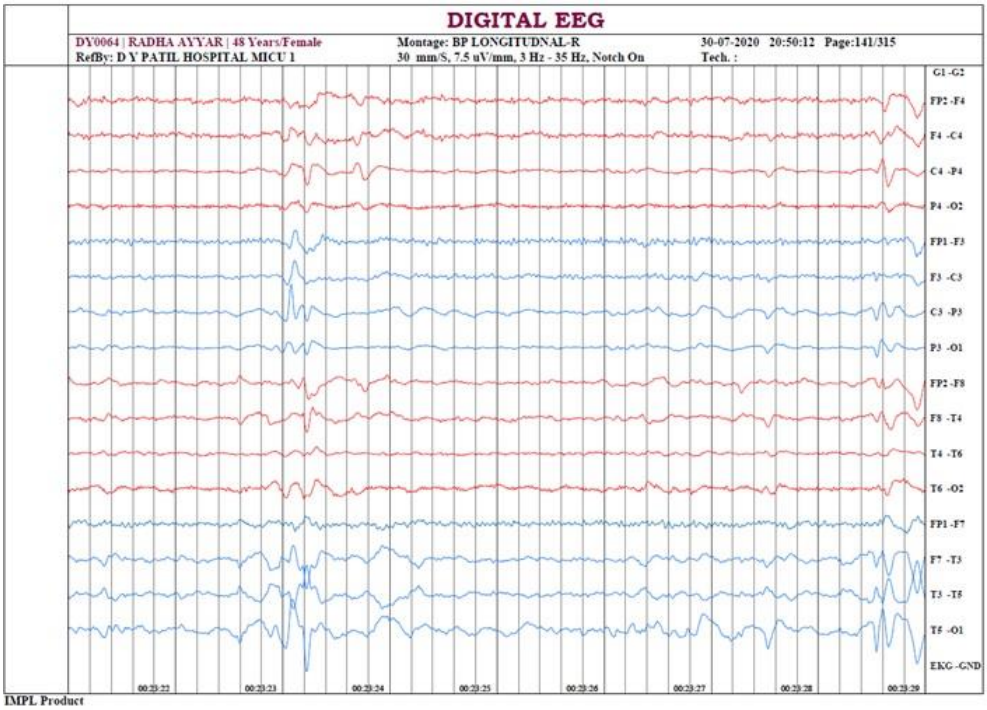

Figure 1. EEG suggestive of left temporo-occipital spike and wave discharges of 1 Hz with secondary generalization.

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Discussion

Various presentations have been described for patients diagnosed with COVID-19 infection.

Encephalopathy as one of the sequelae of COVID-19 has been documented and it poses a clinical challenge to differentiate from metabolic causes of encephalopathy and encephalitis.

Usually, the presence of fever, focal neurologic signs, cerebrospinal fluid (CSF) pleocytosis, neuroimaging, and electroencephalogram (EEG) findings along with presence of virus in the CSF suggest encephalitis, however only a few cases have reported a presence of COVID-19 virus in CSF [7].

A definitive diagnosis of encephalopathy and distinguishing it from encephalitis is dependent on virus isolation.

In COVID-19 this is difficult because SARS-CoV-2 is transient in CSF and its titer in CSF can be extremely low [8].

In our case there was no testing facility available for CSF for COVID-19.

The occurrence of encephalopathy and encephalitis has been observed with other viral infections such as Herpes simplex virus, Dengue virus, Japanese B virus, Varicella virus, enterovirus etc. [3,5,9].

Various mechanisms of encephalopathy/ encephalitis have been studied in other viral infections which include metabolic derangement, cytokine storm, vasogenic brain edema, Reye-like syndrome, hemorrhagic shock and encephalopathy syndrome and acute necrotizing encephalopathy.

In some cases, with severity, the cases were complicated by multiple organ dysfunction and disseminated intravascular coagulation (DIC).

Some cases were found to have localized edema of the cerebral cortex and have been termed acute encephalopathy with febrile convulsive status epilepticus.

These include hemi-convulsion and hemiplegia with frontal lobe predominance.

The pathogenesis is unclear but there is increasing evidence of excitotoxicity and neuronal death [3].

Overall, the presence of fever, seizures and altered sensorium in this patient with COVID-19 with initial hypoxia and ongoing sepsis, with EEG and MRI suggestive of encephalopathy leads us to a near definitive diagnosis.

However, because of lack of CSF evidence, the etiology of encephalopathy can be attributed to multiple factors.

Various mechanisms have been postulated with respect to encephalopathy in COVID-19.

The key receptor for host intracellular invasion (ACE2) is expressed in neurons and glia.

This is the site of invasion by SARS-CoV [10].

It has also been observed that in the absence of SARS-CoV-2 infiltration of CNS, cytokines can elicit neuropsychiatric symptoms.

This is hypothesized to be a consequence of neuroinflammatory responses and/or blood-brain-interface (BBI) with compromised integrity which leads to migration of peripheral immune cells into the CNS causing a disruption of neurotransmission [11,12].

Another mechanism for encephalopathy in COVID-19 is hypoxic encephalopathy, in a study by Chen T, 161 patients diagnosed with COVID-19 were evaluated of which 20% showed evidence of hypoxic encephalopathy [13].

Various drugs have been implicated in worsening encephalitis and encephalopathy in cases with viral infections.

These include salicylates, other NSAIDs and theophylline [3].

An additional mechanism implicated in COVID-19 infection is that the virus may have similar antigenic determinants as that in the human neuronal cells.

Especially with myelin autoantigens which may result in postinfectious encephalomyelitis in patients with COVID-19 infection [14].

It has also been noted that individuals with comorbidities are predisposed with hypoxic/ metabolic changes which might be responsible for encephalopathy in patients with COVID-19 [15].

Encephalopathies and encephalitis in COVID-19 have been managed by injectable Remdesivir, IVIG, plasma exchange, high doses of dexamethasone along with antibiotics [16].

In our case we used empirical treatment for management of viral encephalitis by using injectable acyclovir.

Our patient had already received injectable Remdesivir, Tocilizumab and Methylprednisolone.

Higher antibiotics viz. injectable Meropenem and Teicoplanin were administered to our patient.

Reports suggest that patients with COVID-19 encephalopathy often required intensive care and mechanical ventilation.

Patients have also been treated with repeated plasmapheresis with some regaining full consciousness following treatment.

In general, COVID-19 patients with neurological complications in the intensive care setting have poor outcomes but some reports have indicated that the patients improve following ICU management [15].

Conclusion

Encephalopathies in the setting of viral infections are associated with neuropsychiatric manifestations and are often seen with poor functional outcomes and greater mortality in hospitalized patients [1,3].

This emphasizes the need for early diagnosis with better and aggressive management in patients with COVID-19, thus improving the outcomes, as was observed in our patient.

Further modalities for treatment need to be explored for early recovery of patients with encephalopathy in the setting of COVID-19.

Conflict of interests

None to declare.

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