Case Report

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First Presentation of COVID-19 Infection with Cognitive Impairment due to Encephalitis, A Case Series

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Abstract

Coronavirus (COVID-19) is a worldwide epidemic. Although the main target of COVID-19 is the respiratory system, it is known that the virus can cause neurological complications. Previous studies have shown that its neurological manifestations are usually seen in critically ill patients. In this study, we introduced patients who developed COVID-induced encephalitis despite their good general condition and mild symptoms. The only symptoms of encephalitis in these patients were cognitive impairment, that persisted for more than 6 months. This disorder was confirmed by NUCOG test results in patients. While previous studies have shown that COVID-induced cognitive impairment improves over time. Therefore, it is recommended that the diagnosis and treatment of encephalitis be considered in patients with COVID-19 who have mild cognitive and behavioral symptoms.

Background

The novel coronavirus disease (COVID-19) is a global pandemic. Although the primary target of COVID-19 is the respiratory system, It is known that the virus can cause neurological complications . Neurological involvement ranging from headache and anosmia to more severe complications as encephalitis and stroke have been reported in many studies.

Kesehatan K et al. has reported the first case of encephalopathy in 2019. It was a patient with fever, cough, and altered mental status. In March 2020 the first case of meningoencephalitis associated with COVID-19 was described in a patient with fever, acute confusional state, and generalized tonic-colonic seizure.

Encephalitis and meningitis were reported in previous studies in Severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics. Alshebri MS et al. have summarized the reports of these patients in addition to those recognized during the recent COVID-19 pandemic . Patients with encephalopathy or encephalitis changes related to coronavirus infection were supposed to have a critically ill presentation. Furthermore, in earlier reports have suggested that patients with severe systemic manifestations of COVID -19 are more likely to develop neurological symptoms in comparison to patients with mild or moderate manifestations. During the other pandemics of respiratory pathogens, including H1N1 influenza, it was seen that neurological complications were negatively correlated with patients' prognosis . Cognitive impairmet is not are in the patients with viral infections, but it remains the unclear whether and how the COVID -19 infection may have cognitive presentations The Congnitive impairment due to COVID-19 related encephalitis has been increasingly reported and seems to have various clinical, laboratory, and imaging findings.

In this study, we reported 3 cases of COVID-19 related encephalitis, who presented with a good general condition, mild symptoms of COVID-19 infection, and cognitive impairment as the most significant presentation of the disease [1].

Case 1

The patient was a 68-year-old male, professor of mathematics, with a history of COVID-19 two weeks before the first visit to our outpatient clinic. He has had a mild fever, non-productive cough, and a positive SARS-CoV-2 polymerase chain reaction (PCR) test. He complained of difficulty in calculation, maintaining attention and equilibrium. His past medical history was negative for any relevant medical disorder, addiction or drug abuse. On physical examination, he had a disturbance in recent memory and concentration as well as disability in mathematical calculation. Other neurologic examinations didn't show any pathologic findings. Despite the patient's complaint of gait disturbance, neurologic examinations of gait and coordination could not reveal any abnormal findings. Serologic laboratory tests were unremarkable. Computed tomography (CT) scan of the brain and Electroencephalography (EEG) were normal [2].

Brain magnetic resonance imaging (MRI) with and without contrast was performed and showed bilateral symmetrical T2/FLAIR increasing signal intensity in internal and external capsule (lentiform fork sign), which were not enhanced in post-contrast T1 images. Diffusion-weighted MRI sequences showed symmetric confluent restricted areas with ADC-correlates

(Figure1-case 1). His cognitive impairment didn't improve after 6 months of follow-up (Table3).

Case 2

The patient was a 62-year-old female with a history of low-grade fever for 5 days and a positive PCR assay for SARS-CoV-2 three weeks before presenting in our outpatient clinic. At the time of admission, she complained of a persistent, unilateral, mild headache for 20 days. Her family has noticed a behavioral change with altered mental status without any problem in level of consciousness. In her past medical history, there were mild asthma and thalassemia minor. Except for folic acid (1 mg/day), she had not received any other medication. There was no history of addiction or drug abuse. On physical examination at the time of hospitalization, the patient was awakened but disoriented to time, place and person and could not follow commands. Anomia and sensory aphasia were present during the examination. Other neurologic examinations didn't show any pathologic findings. Routine serologic laboratory tests, vasculitis profile and screenings for neurotropic infections (inclusive brucellosis) were unremarkable.

Brain MRI showed diffuse cortical and subcortical hyperintensities with expansion to the left parieto-temporo-occipital lobes as well as to insular cortex without apparent restriction on DWI. In post gadolinium T1 images, gyriform cortical enhancements could be noticed (Figure 1- case 2). Due to the persistent confusional state with radiologic signs of encephalitis a lumbar puncture with Cerebrospinal fluid (CSF) analysis was performed (Table 1). CSF-PCR for SARS-CoV-2 was negative. An empiric antiviral and antibacterial (Vancomycin, Ceftriaxone and Aciclovir) treatment was begun and continued for 14 days [3,4].

EEG showed moderate diffused encephalopathy with intermittent right temporal slowing and continuous (left) lateralized delta activity. Due to fluctuations of behavioral and mental alterations and EEG abnormalities, a treatment with Levetiracetam (500 mg twice a day) was prescribed.

After 2 weeks, there was no new neurological finding. Brain MRS from left hemispheric (Temporal lobe) lesions showed a significant increase in choline peak with the reduction of N-acetyl aspartate (NAA) peak. Choline/NAA ratio was more than 2, suggesting the acute severe inflammatory process as encephalitis or infiltrative neoplastic lesion. The patient was undergoing LP again (CSF analysis is shown in (table 1)). Evaluation of malignant cytology of CSF was negative.

We followed up the patient for six months. The headache was improved, but cognitive impairment did not resolve considerably (Table 3).

Case 3

A 46-year-old healthy veterinarian male had a history of COVID-19 four weeks ago, presenting low-grade fever, myalgia, and a positive PCR assay for SARS-CoV-2. He was admitted to our hospital, complaining of recent memory disturbance and disruption to perform the daily activity (such as missing addresses) from 10 days ago until now. He also noticed blurred vision in left eye and left hemiparesis on the first day. History of drug abuse was negative. On physical examination at the time of hospitalization, he did not have any focal neurological deficits. Laboratory routine tests were unremarkable. Brain MRI showed bilateral multiple small white matter hyper intense lesions involving centrum semiovale, periventricular, sub and juxtacortical regions and corpus callosum. After injection of contrast, open ring and arch enhancable lesions in both temporal lobes and left parietal lobes were seen. These findings are primarily compatible with active demyelinating disease (Figure 1- case 3). In brain MRS from periventricular white matter lesion increased in choline peak and mild decrease in NAA peak with choline/NAA less than two are seen. Mostly suggestive for the inflammatory process.

He underwent a lumbar puncture; CSF analysis is shown in (table 1). We treated him with methylprednisolone 1 gram for 3 days. For more evaluation, cervical MRI and Visual Evoked Potentials (VEP) were done. According to negative Oligo-clonal-bands (OCBs) and IgG index in CSF, Normal VEP and normal cervical MRI, post COVID-19 encephalitis is the preferred diagnosis for this patient. In 6 month follow up cognitive impairment were slightly improved (Table 3).

A brief cognitive screen instrument, the Neuropsychiatry Unit Cognitive Assessment Tool (NUCOG) test was performed for patients to confirm cognitive impairment in follow-up. The NUCOG is a valid and reliable cognitive tool that is sensitive and specific for the detection of dementia. NUCOG can distinguish between dementia and psychiatric subtypes [5,6].

It was designed to be administered in approximately 20 minutes or less by trained clinicians. Administration of the NUCOG pro-vides a total score for a subject out of a possible 100, and scores out of 20 on five cognitive domains: attention, memory, executive, visuoconstructional function and language. Each of these domains is tested by a group of items that aim to ensure breadth of coverage while ensuring a balance between depth of coverage and time (Table 2).

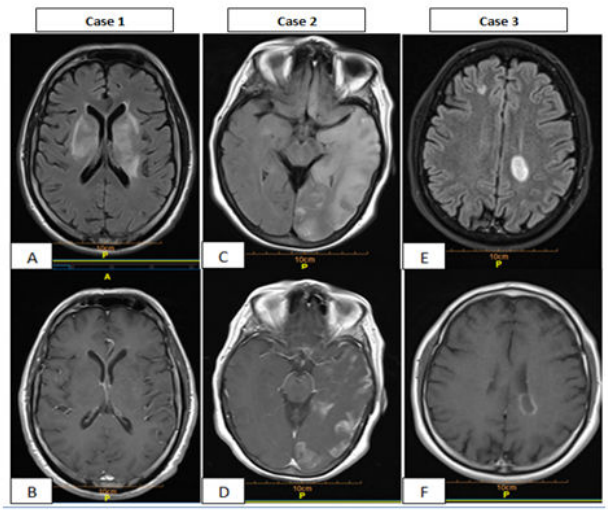

Figure1: Brain MRI of 3 cases with and without contrast; Fig 1-A, B: symmetrical T2/FLAIR increase signal intensity. Fig 1-C, D:

diffuse cortical and subcortical high signal change and gyral enhancement. Fig 1-E, F: bilateral multiple small white matter hyper intense lesions.

Table1: Three patients with cognitive impairment as the first presentation of post-COVID encephalitis, in brief.

	Case 1	Case 2	Case 3
Gender-age	**M-68**	**F-62**	**M- 46**
COVID PCR	**14 days**	**5 days**	**30 days**
Chief complaint	Calculation and concentration and recent memory disturbance	headache and impaired content of consciousness	short term memory disturbance and missing addresses
Physical examination	NL	Disoriented, couldn't follow commands, Anomia and sensory aphasia	NL
CSF Analysis	-	First LP: Glu: 57 mg/dl Pr: 64 mg/dl RBC: 0 cell/cmm WBC: 60 cell/cmm (N: 20%, L: 80%)	Glu: 70 mg/dl Pr: 43 mg/dl RBC: 200 cell/cmm WBC: 6 cell/cmm *smear, culture, HSV-1, HSV-2, COVID PCR were all negative.
		LP after 14 days treatment: Glu: 62 mg/dl Pr: 53 mg/dl RBC: 25 cell/cmm WBC: 10 cell/cmm *smear, culture, HSV-1, HSV-2, COVID PCR, and cytology were all negative.	*OCB: negative IgG Index: negative
Brain MRI	symmetrical T2/ FLAIR increase signal intensity at internal and external capsule suggestive of metabolic encephalopathy and encephalitis	diffuse cortical and subcortical high signal change in left parietotemporoo ccipital lobes and insular cortex gyral enhancement suggestive for encephalitis	bilateral multiple small white matter hyperintense lesions in both temporal lobes and left parietal lobes compatible with active demyelinating disease
Other Para clinic	Metabolic and routine lab data is normal	MRS: Choline/NAA ratio was more than 2 compatibles with encephalitis or infiltrative neoplastic lesion	MRS: Choline/NAA less than two are seen suggestive for the inflammatory process Cervical MRI: Normal

Table2: Items in the five domains of the NUCOG

Attention	Visuoconstructional	Memory	Executive	Language
Orientation-time & place	Drawing reproduction	Verbal registration	Motor sequencing	Verbal comprehension
Digit span forward& reverse	Praxis-limb & orobuccal	Verbal recall	Categorical fluency	Verbal repetition
Overlearned sequence	Left/right orientation	Spatial recall	Abstract thinking	Writing-spontaneous & to command
	Neglect-visual somatosensory	Long-term autobiographical recall	Managing interference	Reading
	Calculation			Word-finding

Table3: The result of patients' NUCOG test in follow-up.

Case	1	2	3
ATTENTION	20-Dec	20-Jan	18/20
VISUOCONSTRACTION	17.5/20	20-Apr	20/20
MEMORY	11.5/20	3.5/20	16/20
EXECUTIVE FUNCTION	20-Dec	20-Jan	20/20
LANGUAGE	20/20	20-Mar	20/20
Total score	73/100	12.5/100	94/100

Discussion

Earlier reports of patients with COVID-19 infections have focused on respiratory symptoms. However, increasing reports of neurological complications in patients with COVID-19 infection showed that these complications should be addressed in all patients with suspicious neurologic symptoms.

In this case series, we reported three patients; as we have explained, these patients had mild manifestations of the COVID-19 infection and developed cognitive impairment that did not improve completely over time. Although cognitive impairments can be mild after recovery of COVID-19, the only manifestation of encephalitis was cognitive impairment. This cognitive impairment interfered with the daily functioning of our patients.

Neurological manifestations of COVID-19 infection are not rare, especially large vessel stroke, Guillain-Barre syndrome and meningoencephalitis are reported in previous studies.

A spectrum of MRI findings has been described in patients with COVID-19-related encephalopathy, including leptomeningeal enhancement, ischemic strokes, and cortical Fluid-attenuated inversion recovery (FLAIR) signals.

Eric M. Liotta et al. showed that the most frequent neurologic manifestations of COVID-19 were myalgia's (44.8%), headaches (37.7%), encephalopathy (31.8%), dizziness (29.7%), dysgeusia (15.9%), and anosmia (11.4%). Movement disorders, motor and sensory deficits, ataxia, and seizures were uncommon (0.2 to 1.4% of patients each.

At first, it was thought that the virus would interfere with the sense of smell by attacking the receptors of the angiotensin-converting enzyme (ACE), but subsequent studies have shown that the virus can cause CNS infection. In more detail, the target receptor for these coronaviruses is the ACE 2 receptor present in the glial cells of the brain and the spinal cord. There are generally three mechanisms by which this virus enters the brain: (a) retrograde transfer via cribriform plate, (b) damage to the blood-brain barrier, and (c) transfer from peripheral nerve terminal to CNS via synapse connected route. Following CNS invasion, neurological damage can occur via the following mechanisms: (a) immune-mediated damage in the setting of cytokine storm and (b) neuronal damage in the setting of significant hypoxia due to severe pneumonia and acute respiratory distress syndrome (ARDS) .

The first case of meningitis/encephalitis associated with SARS-Coronavirus-2 was reported in march 2020 by Takeshi Moriguchia et al., A 24-year-old man with a Glasgow coma scale (GCS) of 6 (E4 V1 M1) with noticeable neck stiffness. Although the specific SARSCoV-2 RNA was not detected in the nasopharyngeal swab, it was detected in CSF. MRI demonstrated the abnormal findings of medial temporal lobe, including hippocampus suggesting encephalitis, hippocampal sclerosis or post convulsive encephalitis. This patient diagnosed with severe encephalitis . Since then, the clinicians and the researches worldwide have been observing more and more neurological manifestations of COVID-19 and various cases were reported about encephalitis caused by COVID-19 infection [7,8].

In a systematic review by Yusak M.T. Siahaan et al., 33 cases of COVID-19 induced encephalitis have been investigated. They reported that the most prominent symptoms of the central nervous system in a patient with encephalitis were disorientation/confusion (72.72%), loss of consciousness (54.54%), and seizures (27.27%).

Two case series involving CSF analysis data from 12 patients reported that the CSF had no white blood cells and the PCR assay for SARS-CoV-2 was negative in all the patients. In the most previous studies performed on patients' CSF and autopsies, we did not find the virus itself in their CSF. This can show us; these complications were not caused by a direct attack of the virus on the central nervous system; instead, these complications can be caused by para infectious syndromes.

In the study by Yusak M.T. Siahaan et al., also the clinical, laboratory, and imaging findings supported the hypothesis that the process of cytokine-immune mediated inflammation was the cause of cerebral damage in COVID-19-associated encephalitis, rather than direct invasion.

The study by Julie helms et al. showed that 63% of patients who enter the ICU because of COVID-19 infection involve the nervous system in the form of encephalopathy. Considering the high incidence of COVID-19 delirium and/or neurological symptoms, the risk of long-term neurocognitive sequelae, and neuropsychiatric disorders in survivors . A systematic review conducted by Ghannam et al. showed that 23% of the patients had complications of encephalopathy or encephalitis

Since encephalitis caused by COVID-19 can be a Para infection syndrome, it is better to note that it can cause the different symptoms. (Table 4) compares the number of case reports published in the field of COVID-19 encephalitis, and as you can see, encephalitis in these patients had different manifestations with a mild to severe spectrum.

In a nationwide surveillance study to investigate the spectrum of neurological and psychiatric complications of COVID-19 across the UK, altered mental status including encephalopathy or encephalitis and primary psychiatric diagnoses, was the second most common neuropsychiatric complication, often occurring in younger patients. Seven of the 153 cases notified to the registry presented with encephalitis [9,10].

In one cross-sectional study by Marcel S. Woo et al., 18 young patients were evaluated for cognitive impairment after recovery from COVID-19 infection. Notably, 14 (78%) patients reported sustained mild congnitive decficits. While short-term memory, attention and the concentration were particularly affected by COVID-19, screening results did not correlate with hospitalization, treatment, viremia, or acute inflammation. Moreover, we detected subtle cognitive deficits that did not restrain most patients in daily life and were only unmasked by our specific screening, including deficits in short-term memory, attention and concentration.

Table4: Different manifestations of COVID-19 encephalitis in previous case reports.

Study	Symptom & Sign	MRI finding	CSF Finding
Asim Haider et al. case report(24)	A 66-year-old male with multiple new-onset seizures followed by persistent confusion/ bizarre behavior like staring/ he did not have any focal neurological deficits or neck rigidity.	Small acute/ subacute lacunar infarcts and a patchy area of T2 bright signals in the cortical and periventricular regions.	COVID-19 PCR is negative WBC : 3 cell/cmm RBC : 299cell/cmm GLU : 86 mg/dl PROT : 77mg/dl

Eric Freire-Álvarez et al. case report (25)	A 39-year-old-man with mental disorientation and inconsistent language disorder. Neurological examination revealed a tendency to drowsiness, minimal stiff neck and paraphasia	Hyper intensity at the cortical and subcortical right frontal regions, right thalamus and mammillary body, bilateral temporal lobes and cerebral peduncles, with no leptomeningeal enhancement	COVID-19 PCR is negative WBC : 20 cell/cmm RBC : 0 cell/cmm GLU : 48 mg/dl PROT : 198mg/dl
Yasmine Mohamed Kamal et al. Case report (17)	a 31-year-old man with altered mental state and abnormal behavior. Neurological examination revealed acute confusion state associated with severe agitation and fluctuations in the level of consciousness.	High signal intensity in the temporal lobe cortex bilaterally. Involvement of the parasagittal frontal lobes bilaterally bright signals on T2-flair and T2-weighted images with corresponding diffusion restriction	COVID-19 PCR is positive WBC < 5 cell/cmm RBC : 150 cell/cmm GLU : 60 mg/dl PROT : 45 mg/dl

According to all the above, Different clinical, laboratory and MRI findings in terms of extent and severity, the severity of encephalitis can correspond to the severity of systemic involvement. This means that patients with more severe systemic involvement present with more severe manifestations of encephalitis. In our patients, despite the mild symptoms of COVID-19 infection, MRI findings indicated encephalitis and only the manifestation of brain involvement was cognitive impairment. This cognitive impairment in our patients caused daily dysfunction that remained persistent.

Conclusion

In addition to respiratory manifestations, COVID-19 can cause neurological disorders. Its neurological manifestations are usually seen in critically ill patients. On the other hand, mild cognitive impairments can occur during the recovery period of COVID-19 infection, but the disorder often resolves on its own. In this study, we introduced patients with mild COVID-19 symptoms who were in good general condition. They developed COVID-induced encephalitis. The only symptoms of encephalitis in these patients were cognitive impairment, that has remained persistent over time. Therefore, it is recommended that the diagnosis and treatment of encephalitis be considered in patients with COVID-19 who have mild cognitive and behavioral symptoms.

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