

# Persistent cognitive impairment as a rare manifestation of mild COVID-19 infection – 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 Neuropsychiatry Unit Cognitive Assessment Tool (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.

**Keywords:** COVID-19, SARS-CoV-2, encephalitis, cognitive impairment

## BACKGROUND

The novel coronavirus disease (COVID-19) is a global pandemic [1]. Although the primary target of COVID-19 is the respiratory system, It is known that the virus can cause neurological complications [2]. Neurological involvement ranging from headache and anosmia to more severe complications as encephalitis and stroke have been reported in many studies [3].

Kesehatan K et al. have reported the first case of encephalopathy in 2019. It was a patient with fever, cough and altered mental status [4]. 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-clonic seizure [5].

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) epi-

demics. Alshebri MS et al. have summarized the reports of these patients in addition to those recognized during the recent COVID-19 pandemic [3]. Patients with encephalopathy or encephalitis changes related to coronavirus infection were supposed to have a critically ill presentation [5]. Furthermore, 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 [6]. During other pandemics of respiratory pathogens, including H1N1 influenza, it was seen that neurological complications were negatively correlated with patients' prognosis [7]. Cognitive impairment is not rare in patients with viral infections [8-10], but it remains unclear whether and how the COVID-19 infection may have cognitive presentations [11]. Cognitive impairment due to COVID-19 related encephalitis has been increasingly reported and seems to have various clinical, laboratory and imaging findings [12].

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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.

### Case 1

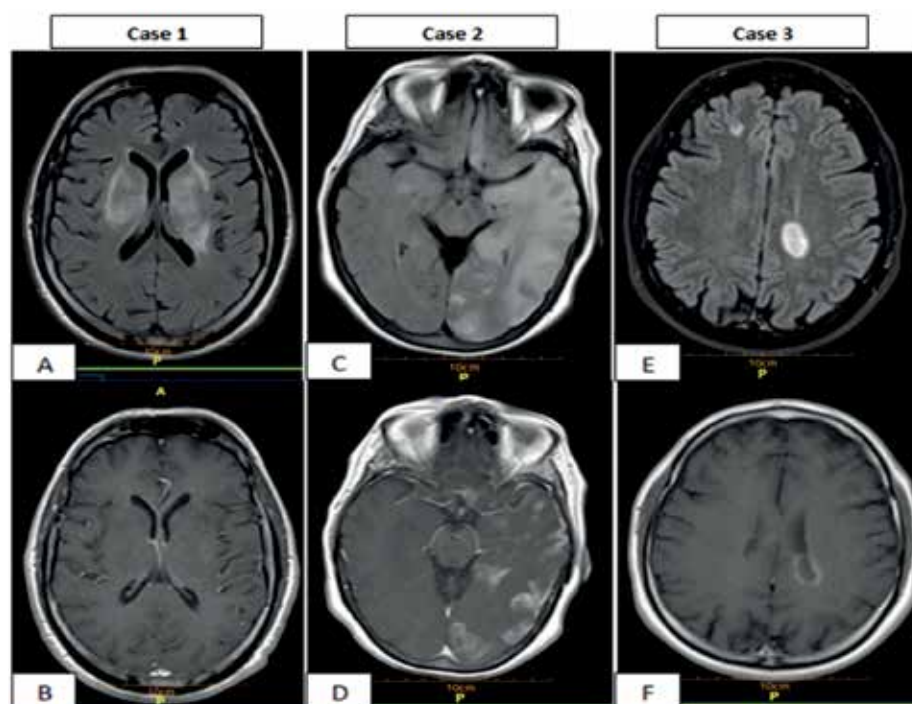
The patient was a 68-year-old male, professor of mathematics, with a history of COVID-19 two weeks before the first visit to our outpatient clinic. He has had a mild fever, non-productive cough, and a positive SARS-CoV-2 polymerase chain reaction (PCR) test. He complained of difficulty in calculation, 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.

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 (Figure 1- case 1). The patient's cognitive function was assessed after 6 months with a NUCOG test, which was still impaired (Figure 2).

### 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.



**FIGURE 1.** Brain MRI of 3 cases with and without contrast; Figure 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

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 (Glucose: 57 mg/dl, Protein: 64 mg/dl, RBC: 0 cell/cmm, WBC: 60 cell/cmm). 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.

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.

The patient's cognitive function was assessed after 6 months with a NUCOG test. Cognitive impairment did not resolve considerably (Chart 1).

### 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 was normal (Glucose: 70 mg/dl, Protein: 43 mg/dl,

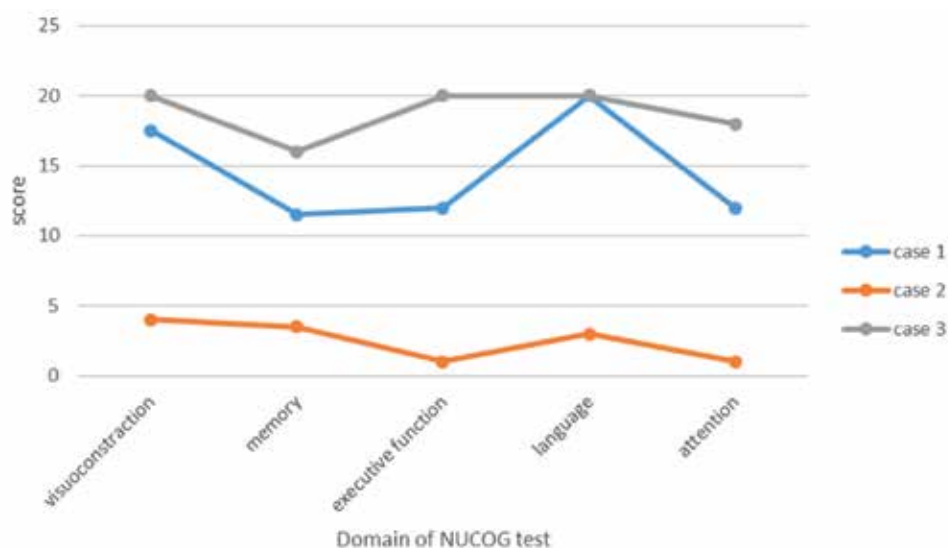
RBC: 200 cell/cmm, WBC: 6 cell/cmm). CSF-PCR for SARS-CoV-2, Herpes simplex virus (HSV) type 1 and 2 were negative. We treated him with methylprednisolone 1 gram for 3 days. For more evaluation, cervical MRI and Visual Evoked Potentials (VEP) were done. According to negative Oligo-clonal-bands (OCBs) and IgG index in CSF, Normal VEP and normal cervical MRI, post COVID-19 encephalitis is the preferred diagnosis for this patient. The patient's cognitive function was assessed after 6 months with a NUCOG test, which was still impaired (Chart 1).

## DISCUSSION

There are increasing reports of late neurological and neuropsychiatric complications in patients with COVID-19 infection [2]. Here we reported rare presentations of COVID-19 with early onset of neuropsychiatric disorders in three patients without previously known systemic or respiratory infections. The psychiatric symptoms were also lasting for several weeks without obvious improvement after recovery of COVID-19 acute infection. Although mild cognitive decline was reported frequently after of COVID-19 infection, to our knowledge, severe cognitive impairment inferring normal functioning of daily life, which was observed in our patients, is a very rare condition. In all three patients, COVID-19 was presenting with mild systemic symptoms, normal level of consciousness and obvious cognitive impairments as the only manifestation of CNS involvement (e.g. encephalitis).

Eric M. Liotta et al. showed that the most frequent neurological 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 ). 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) high signals [14]. The pathophysiologic explanation of CNS involvement in COVID-19 infection is still not clear. The virus may use the angiotensin-converting enzyme (ACE) receptor as the mediator for invasion and trafficking into CNS [15]. But neurological damage can also occur through an immune-mediated cytokine storm or significant hypoxia due to severe pneumonia and acute respiratory distress syndrome (ARDS) [16].

In the first report of a patient with severe COVID-19 related encephalitis the specific SARS-CoV-2 RNA could not be detected in the nasopharyngeal swab, but in CSF [5]. Since then, clinicians and researchers worldwide have been observing more



**FIGURE 2.** The result of NUCOG test after 6 months of disease recovery

and more COVID-19 related encephalitis. Yusak M.T. Siahaan et al., have reported 33 cases of COVID-19 related encephalitis in which disorientation and confusion (72.72%), loss of consciousness (54.54%), and seizures (27.27%) were found to be the most observed clinical conditions [12].

In two case series involving CSF analysis data from 12 COVID-19 patients pleocytosis was not found in the CSF of patients with encephalitis. The PCR assay for SARS-CoV-2 was also negative in all patients [14-17]. These findings, are in line with previous reports and support the hypothesis that CNS involvement and encephalitis of COVID-19 may be due to a para-infectious immune mediated condition instead of a direct invasion of virus [12].

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, 7 of the 153 cases notified to the registry presented with encephalitis [17]. In this report we observed obvious and persistent cognitive dysfunction without severe systemic complications. According to recent reports of neurologic complications of COVID-19 infection, there was a general postulation that major cognitive decline was consequent of severe systemic infection. Encephalopathy was the most frequent neurologic complication ( up to 63% ) in patients who entered the ICU due to COVID-19 infection [18]. On the other hand more than 20 % of these patients experienced long

term cognitive disorders [15]. Our patients developed cognitive decline earlier than expected, which was also persistent, despite mild course of the other clinical features of COVID-19 infection.

Patterns of cognitive decline due to COVID-related encephalopathy may vary in different populations. Marcel S. Woo et al., reported 18 young with cognitive impairment after recovery from COVID-19 infection. Similar to our findings, 14 (78%) patients reported sustained mild cognitive deficits. While short-term memory, attention, and concentration were particularly affected, screening results did not correlate with hospitalization, treatment, viremia or acute inflammation [19].

This finding that cognitive decline may occur in patients with mild COVID-infection, in the early phases as well as after resolution of systemic and respiratory inflammation, shows the possibility of a neurogenic inflammatory effect of this virus. Future controlled studies are required to investigate the magnitude of different immunologic processes in pathogenesis of such etiology.

## CONCLUSION

Mild cognitive impairments can occur during each phase of the COVID-19 infection even in patients with mild infection and good general condition. Cognitive decline with mild systemic symptoms may be the only presentation of the disease. Cognitive and behavioral symptoms may persist after recovery and need distinct attention and clinical follow up.

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