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Posterior Reversible Encephalopathy Syndrome as a Rare Presentation of Coronavirus Disease 2019: A Case Report and Literature Review

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Background: The novel coronavirus (COVID-19) disease is a global pandemic of different severity ranging from a mild respiratory disease to a severe septic shock. The current evidence is suggestive of the neuroinvasive potential of this disease. However, there are limited reports regarding posterior reversible encephalopathy syndrome (PRES) as a neurological complication of COVID-19 in the literature.
Herein, we aimed to present a case of PRES in association with COVID-19 and review the current reports in this regard. <i>Case Report:</i> This report presents a case of PRES complicated with intracerebral hemorrhage in a 39-year-old male with COVID-19, presenting with sudden blood pressure crisis accompanied by seizure and confusional state. <i>Conclusion:</i> Although the main clinical symptoms of COVID-19 are confined to the
respiratory tract, the virus has the potential to target the brain, thereby inducing encephalitic syndrome, such as PRES.

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Introduction

The novel coronavirus disease (COVID-19) developed by severe acute respiratory syndrome coronavirus 2 primarily emerged in Wuhan, China, in December 2019, in a cluster of severe unknown pneumonia cases and then quickly disseminated across the world. This disease was acknowledged as a worldwide pandemic on March 11, 2020, by the World Health Organization with more than six million reported cases to date (1, 2).

The main clinical picture of this disease varies from mild acute respiratory symptoms to severe pneumonia with respiratory failure and septic shock. However, there is evidence indicating the potential effect of COVID-19 on the extrapulmonary organs, such as the gastrointestinal, cardiovascular, and nervous systems (3-6). More recently, there has been an increasing anecdotal report documenting the neuroinvasive potential of COVID-19. Ling Mao et al. were the first researchers who reviewed the neurological presentations of COVID-19, using a group of 214 patients with COVID-19. They introduced headache and hyposmia as the main conditions arising from central and peripheral nervous system involvement, respectively (7).

The literature review revealed only five reports regarding the development of posterior reversible encephalopathy syndrome (PRES) in COVID-19 patients. Regarding this, the present research was conducted to present a case of COVID-19 complicated with PRES to provide a more comprehensive review of the underlying mechanisms and consequences leading to central nervous system (CNS) complications.

Case Report

Case presentation

The patient was a healthy male aged 39 years with an unremarkable medical history referring to the Emergency Department of Bou Ali Hospital, Qazvin, Iran, with an acute confusional state following opium overdose. At presentation, the patient was cyanotic with a Glasgow Coma Scale score of 6. The vital signs revealed the body temperature of 35.5°C, blood pressure of 100/70 mmHg, respiratory rate of 8 breaths/min, pulse rate of 75 beats/min, and oxygen saturation of 80% while breathing ambient air.

The patient had chest breathing and pinpoint pupils. Additionally, the auscultation of the lung fields revealed bilateral coarse crackles. Therefore, he was resuscitated and intubated for airway protection. A naloxone infusion was commenced, and he later made a good recovery. The patient extubated himself and became oriented and alert, with a respiratory rate of 16 breaths/min.

Laboratory findings were significant for an elevated white cell count of 19,700, with the lymphocyte percentage of 5%, hemoglobin level of 17.4, and platelet count of 150,000. However, erythrocyte sedimentation rate and C-reactive protein level were within the normal range. The liver profile revealed the alanine transaminase, aspartate transaminase, and alkaline phosphatase levels of 214, 103, and 284 mg/dl, respectively. In addition, the urine toxicology screening was positive for opiates. Further evaluation revealed normal brain computed tomography (CT) findings. Moreover, the chest CT was compatible with COVID-19.

The patient was transferred to the department of infectious diseases. He was subjected to oral intravenous ceftriaxone (1 g twice a day) and hydroxychloroquine sulfate (200 mg twice a day). He also received an ancillary examination, and his throat swab sample was positive for COVID-19.

On the third day, the patient suddenly developed three episodes of generalized tonic-clonic seizure with profound postictal confusion. In addition, he had increased blood pressure (180/130 mmHg). Nonetheless, the other vital signs were within the normal range. As a result, a neurologic consultation was requested. On neurological examination, the patient was confused and disoriented to time and place. No gaze deviation was observed. Additionally, left-sided hemiparesis and plantar reflex were notable.

Initial diagnosis and assessment

An initial diagnosis of acute cerebrovascular accident was made considering a sudden loss of

consciousness, neurological deficit, seizure, and elevated blood pressure. The brain CT scan revealed bilateral posterior parieto-occipital hypoattenuation in the cortex and subcortical white matter, which extended to the frontal lobes, as well as a cortical hemorrhage in the right parietal lobe (figures 1 and 2). Further workup included the T2-weighted FLAIR magnetic resonance imaging (MRI) of the brain demonstrating bilateral posterior parietooccipital hyper-intense signals in the cortex and subcortical white matter, extending to the frontal lobes consistent with posterior reversible leukoencephalopathy syndrome. There was also evidence of the presence of a heterogeneous hypersignal lesion in the right parietal lobe compatible with acute hemorrhage (figures 3-5). However, the brain MR venography was unremarkable.

Management and treatment

The patient was relocated to the intensive care unit (ICU). Labetalol infusion was started at a dose of 1 mg/min with the close monitoring of blood pressure and pulse rate. Meanwhile, phenytoin infusion was started at a dose of 50 mg/min. Due to uncontrolled seizures, intravenous sodium valproate was added at a dose of 1500 mg (bolus), followed by 400 mg, three times a day. The therapeutic measures for the management of COVID-19 were also continued.

Patient Outcome

During the study period, the patient still remained in the ICU. The seizures had been controlled, and his vital signs were stable. The patient was awake and oriented. However, the leftside hemiparesis was still persistent.

Discussion

The novel coronavirus disease has been considered a global pandemic since March 11, 2020. As the virus is mainly attached to the cellular receptor angiotensin-converting enzyme 2 receptors located in the nasal epithelium and lower respiratory airways, the typical symptoms are roughly confined to the respiratory tracts. However, beyond the typical syndrome, the patients might encounter an arrav of neurological complications. The main mechanism of the neuropathogenesis of COVID-19 is still poorly understood. However, there is evidence revealing the tendency of this virus to permeate the epithelium barrier and enter the bloodstream or lymph and subsequently affect the CNS. Additionally, this virus may enter the CNS through neuronal dissemination via olfactory bulb or cranial peripheral nerves (6-10).

				Onset of PRES	6 ·		`		
	Age (years)	Gender	РМН	from hospitalization (days)	Symptoms of PRES	Need for intubation	Brain CT	Brain MRI	Prognosis
Yildiz Kaya et al. (13)	38	Male	Non- mentioned	5 days of ICU admission	Acute confusional state, vision loss, and hypertension crisis	No	Not performed	Bilateral, especially left occipital, frontal cortical white matter and splenium of corpus callosum T2 FLAIR hyperintensities and diffusion restriction in DW imaging	Complete clinical recovery on the 10 th day, imaging on the 24 th day
A. M. Francesci (14)	48	Male	Negative	17 days	Acute confusional state with blood pressure variability	Yes	Focal bilateral subcortical vasogenic/cytot oxic edema in the posterior parieto-occipital regions with a small right-sided hemorrhage	Vasogenic edema in the posterior parieto- occipital regions with subacute blood products and evidence of extensive petechial hemorrhages diffusely distributed throughout the corpus callosum	Gradual improveme nt of mental status over a week (the discharge was not mentioned.)
	67	Female	Hypertensio n, diabetes mellitus, coronary artery disease, gout, asthma	Primary presentation	Altered mental status and hypertension crisis		Edema in the bilateral parieto- occipital regions with associated mass effect and cortical sulcal effacement	Multiple areas of restricted diffusion with associated edema, mostly in the posterior parieto-occipital lobes but also in the right frontal lobe, basal ganglia, and cerebellar hemispheres and evidence of superimposed hemorrhages in the parieto-occipital region in SW along with abnormal enhancement	Gradual recovery and finally was discharged
Louis Kishfy (15)	67	Female	Diabetes and hypertension	25 days	Confusional state and hypertension crisis	Yes	Characteristic convexal subarachnoid hemorrhage	Scattered foci of T2 hyperintensity involving the subcortical white matter of both occipital lobes and both posterior temporal lobe with the effacement of the adjacent sulci and evidence of convexal subarachnoid hemorrhage	Slowly improveme nt to baseline and finally discharged on day 33
	58	Male	Hyperlipide mia	26 days	Confusional state and hypertension crisis	Yes	Not performed	Hyperintense foci involving the subcortical white matter of the right occipital lobe and the left cerebellar hemisphere with effacement of the adjacent local sulci in T2 FLAIR and characteristic petechial hemorrhage	Extubated on day 30 and, at the time of the report, kept in the hospital with a slowly improving mental status
Our patient	39	Male	Negative	3 days	Confusional state and seizure and hypertension crisis	Yes	Bilateral posterior parieto- occipital hypo- attenuation in the cortex and subcortical white matter extending to the frontal lobes and a cortical hemorrhage in the right parietal lobe	Bilateral posterior parieto-occipital hyper-intense signals in the cortex and subcortical white matter extending to the frontal lobes in T2 FLAIR	Still in the ICU, control of seizures, alert and oriented state, but with persistent left hemiparesis

It should be noted that information regarding different neurological presentations of COVID-19 is completely descriptive. The first report of COVID-19-related encephalopathy was recorded in a 74-year-old male who had a past medical history of chronic obstructive pulmonary disease (COPD), presented with a progressive fever and productive cough, and was first diagnosed with COPD exacerbation. However, over 24 h, he profound confusional developed а state. Regarding the unexplained encephalopathy and the outbreak of the novel emerging virus, the suspicion of COVID-19 was proposed, which was eventually confirmed by polymerase chain reaction assay (11).

Later, there was a report on the first case of hemorrhagic necrotizing encephalopathy caused by COVID-19. The patient was an elderly woman who presented with an acute febrile confusional state. The results of the brain MRI revealed the presence of hemorrhagic rim-enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions, which was compatible with hemorrhagic necrotizing encephalopathy. As the patient had a 3-day history of flu-like symptoms, the diagnostic test for COVID-19 was performed, which was positive (12).

Yildiz Kaya et al. reported the case of a 38-yearold man with COVID-19 suddenly developing an acute agitated confusional state, accompanied by vision loss and hypertension crisis. His neurological examination was normal, except for apathy and severely impaired visual acuity (hand motion perception). With the suspicion of acute cerebrovascular accident, he underwent brain MRI revealing bilateral occipital and frontal subcortical signal changes in T2/FLAIR and diffusion restriction in diffusion-weighted MRI. With a diagnosis of PRES, corticosteroid therapy was started leading to the complete recovery of the clinical symptoms on day 10 and the regression of MRI abnormalities on day 24 (13).

Similarly, Franceschi reported two cases of COVID-19 complicated with PRES. One of the cases was a man with 48 years of age who developed a sudden confusional state upon hospitalization. The brain CT scan showed bilateral subcortical focal vasogenic/cytotoxic edema in the posterior parieto-occipital areas, as well as a small hemorrhage on the right side. The other patient was a woman aged 67 years with a past medical history of diabetes mellitus, hypertension, gout, coronary artery disease, and asthma, referring to the emergency department with an acute confusional state and hypertension crisis. The brain CT scan results were indicative of edema in the bilateral parieto-occipital areas with cortical sulcal effacement as the associated mass effect. Furthermore, the brain MRI showed restricted diffusion in multiple areas and its associated edema. With a diagnosis of PRES, the cases underwent supportive therapy, such as blood pressure control. Both of the cases survived and had a normal mental status after the recovery of COVID-19 symptoms (14).

In addition, Louis Kishfy presented two cases of PRES due to COVID-19. The first patient was a 58-year-old man who developed a sudden acute confusional state on the 26th day of hospitalization. The brain CT showed scattered T2-hyperintense foci affecting the subcortical white matter of both occipital and posterior temporal lobes with the effacement of the adjacent sulci. The second patient was a female aged 67 years with a past medical history of and diabetes hypertension who developed acute confusional state on the 25th day of hospitalization. The brain CT scan was suggestive of hyperintense foci affecting the subcortical white matter of the right occipital lobe and the left cerebellar hemisphere with the effacement of the adjacent local sulci. At the time of the report, the patients still remained in the ICU (15).

In our case, the initial presentation was an acute confusional state, which was attributed to the opium overdose. However, similar to previous reports, the second clinical scenario of impaired consciousness was not clearly explained by the metabolic and toxic etiologies, which raised the suspicion of underlying COVID-19 disease. Additionally, the diagnosis of PRES was established based on the clinical and radiographic features of the clinical event on the 3rd day. Table 1 summarizes the clinical course of COVID-19 patients in association with PRES.

In a study performed by Tim Coolen et al., evaluating a case series of 19 non-survivors of severe COVID-19, postmortem brain MRI showed hemorrhagic and PRES-related brain lesions. Furthermore, in the mentioned study, the autopsies revealed the evidence of hemorrhagic and PRESrelated changes in four cases. Accordingly, it was hypothesized that the virus has the potential to induce endothelial disturbances (16).

It should be noted that PRES is a reversible neurological entity characterized by seizure, headache, visual symptoms, impaired consciousness, and other focal neurological findings with an acute rise in diastolic blood pressure. The most widely accepted mechanism of PRES is the impaired autoregulation of cerebral blood flow combined with some components of endothelial dysfunction (17). Although the hallmark of the disease is the reversibility of the symptoms, the severe manifestations of PRES might be associated with intracranial hemorrhage, subarachnoid hemorrhage, and ischemic infarct leading to permanent neurological impairment or even death as occurred in our case (18). The development of PRES in COVID-19 patients is affected by different clinical conditions. However, to the best of our knowledge, there are limited reports on the association of COVID-19 with PRES in the literature.

The pathogenesis of post-infectious encephalopathy is not poorly understood. However, the endothelium engagement by the virus seems to be underlying mechanism increasing the the the blood-brain barrier permeability of and susceptibility to blood pressure variations and impairing the homeostatic regulation of blood flow to the brain. Additionally, the hemorrhage could be the result of coagulopathy over the course of the disease (19).

Based on a report, the association of PRES with COVID-19 could not be clearly established. However, regarding the increasing number of patients with COVID-19 and its emerging neurological complications, much attention should be taken in the management of this disease. The present report indicated the diverse neurological of COVID-19, presentations highlighting the importance of neurological assessment in the affected patients.

Conclusion

The COVID-19 is a global pandemic due to its high transmission rate. Current evidence suggests the neuroinvasive potential of COVID-19. The present study involved the report of the first case of COVID-19 associated with PRES.

Summary points

- The COVID-19 has the potential to affect the central nervous system.
- Regarding the increasing number of COVID-19 patients worldwide, much attention should be paid to the neurological assessment of the affected patients.
- Posterior reversible encephalopathy syndrome might be associated with COVID-19 disease.

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None.

Conflict of interest

The authors declare that they have no conflict of interest. Furthermore, no funding was used for the implementation of the present research.

Ethical considerations

Informed consent was obtained from the patient for publication, and the study was approved by the Local Ethics Committee.

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