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Case Report

Persistent disturbance of consciousness with bilateral globus pallidus and substantia nigra lesions in 2 patients with severe COVID-19 pneumonia

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ABSTRACT

With an increasing number of cases of Coronavirus disease 2019 (COVID-19), various neurological complications have been reported; however, some of these have not been fully elucidated. We herein report on 2 cases in which lesions at the bilateral globus pallidus and substantia nigra were observed. The patients were a 27-year-old male and a 61-year-old female. They underwent ventilation management due to COVID-19 pneumonia with hypoxemia. However, even after the sedative had weakened, the state of consciousness disturbance was found to have continued. Brain magnetic resonance imaging was performed for both patients. From the bilateral globus pallidus to the substantia nigra of both, the fluid attenuated inversion recovery images and T2-weighted images indicated high intensity, while the diffusion-weighted image resulted in high intensity and low apparent diffusion coefficient. Regarding the 61-year-old female patient, head computed tomography also indicated low density at the bilateral globus pallidus. The patients did not show any improvement in their neurological findings while hospitalized. Although COVID-19 associated with bilateral globus pallidus and substantia nigra lesions are rare, the neurological prognosis may be poor. We believe that attention should be paid to these imaging findings at the onset of consciousness disturbance.

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Introduction

As the number of cases of Coronavirus disease 2019 (COVID-19) has increased, it has been revealed that the disease is associated with various neurological complications. According to the review article by Moonis et al., the most common com-

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plications are acute infarcts and intracranial hemorrhages including microhemorrhages, along with leukoencephalopathy, global hypoxic injury, acute disseminated encephalomyelitis, cytotoxic lesions of the corpus callosum, olfactory valve involvement, cranial nerve enhancement, and Guillain-Barre syndrome [1]. Among these patients, various neuroimaging findings have been reported from computed tomography (CT) and magnetic resonance imaging (MRI) [1–4]; however, there are few reports on globus pallidus and substantia nigra lesions.

Case report 1

A 27-year-old male with no particular medical history. He visited his local doctor with diarrhea and fever and tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via a reverse transcription-polymerase chain reaction (RT-PCR) test, with a diagnosis of COVID-19. The SARS-CoV-2 delta variant was prevalent in Japan at this time. He was admitted to our hospital a few days later due to nausea, loss of appetite, and coughing with difficulty speaking.

His physical findings on admission were as follows: blood pressure of 122/79 mmHg, heart rate of 94 beats/min, respiratory rate of 20 times/min, arterial blood oxygen saturation of 94% (under administration of oxygen at 2 L/min), body temperature of 39 degrees, Glasgow Coma Scale of 15/15 (E4V5M6), and Body Mass Index of 35.4. The blood biochemistry findings were mildly low (white blood cell count, $2.7 \times 10^3/\mu\text{L}$; platelet count, $15.4 \times 10^4/\mu\text{L}$) and high (creatinine kinase, 641U/L; aspartate aminotransferase [AST], 43U/L; alanine aminotransferase [ALT], 68U/L; hemoglobin A1c, 6.4%). No other abnormalities were found via blood testing.

He developed pneumonia and his respiration gradually deteriorated even with the use of dexamethasone and tocilizumab. Endotracheal intubation was carried out for ventilation management. Treatment was also given for glucose tolerance abnormalities. One week after intubation, he had decreased blood pressure, developed pulmonary arterial thromboembolism, and septic shock was suspected. Additional treatment was performed. Prednisolone was also used for his organizing pneumonia.

Two weeks after intubation, the dose of sedatives was reduced, and extubation was performed. However, his consciousness disturbance continued. Although the patient could open his eyes on his own, he did not look us in the eyes and communication was impossible. Glasgow Coma Scale was 10/15 (E4V1M5). The patient was reintubated the next day because of unstable breathing due to an impaired consciousness.

No abnormal findings were found on head CT. Brain MRI was performed 9 days later. From the bilateral globus pallidus to the substantia nigra, the T1-weighted image (T1WI) indicated a mild low signal, the T2-weighted image (T2WI) indicated a high signal, the fluid attenuated inversion recovery (FLAIR) image indicated a high signal, the diffusion-weighted image (DWI) indicated a high signal, and apparent diffusion coefficient (ADC) had decreased. Although the left hippocampus also indicated a mild DWI high signal with decreased ADC, and a mild right-dominant FLAIR high signal was also found in the white matter, these involved no diffusional limitations (Fig. 1A-E). Magnetic resonance angiography (MRA)

revealed no abnormalities. Another 10 days later, follow-up MRI was performed. The abnormal signal area previously observed from the bilateral globus pallidus to the substantia nigra was obscured (Fig. 1F). A T2* weighted image indicated no abnormal low signals, while contrast imaging found no abnormal enhancing effects.

Thereafter, there was no marked improvement in his consciousness disturbance or neurological findings. The patient was transferred to another hospital on day 53.

Case report 2

A 61-year-old woman with hypertension, a history of smoking, and a heavy drinker tested positive for SARS-CoV-2 via RT-PCR, a few days after having a meal with others and was diagnosed with COVID-19. The SARS-CoV-2 alpha variant was prevalent in Japan at this time. She had a fever the next day and was admitted to a nearby hospital. She had pneumonia and her respiratory condition was worsened despite having been administered dexamethasone. She was transferred to our hospital a week later.

Her physical findings on admission were as follows: blood pressure of 164/104 mmHg, heart rate of 104 beats/min, respiratory rate of 30 times/min, arterial blood oxygen saturation of 96% (under administration of oxygen at 10 L/min), body temperature of 37.2 degrees, Glasgow Coma Scale of 15/15 (E4V5M6), and Body Mass Index of 24.4.

The blood biochemistry findings were high (AST, 39 U/L; ALT, 40 U/L; lactate dehydrogenase, 417 U/L; γ -glutamyltranspeptidase, 102 U/L; hemoglobin A1c, 6.5%; and C-reactive protein, 8.81 mg/dl). No other abnormalities were found via blood testing.

Endotracheal intubation was performed the same day for ventilation management. Treatment was also given for glucose tolerance abnormalities. Her disease was complicated by bacteremia and pulmonary suppuration, so metronidazole was also administered for 16 days. Dialysis was started due to renal failure.

Two weeks after intubation, the dose of sedatives was reduced but her consciousness disturbance continued. Although the patient could open her eyes on her own, communication was impossible. Glasgow Coma Scale was 6/15 (E4VTM1).

Head CT revealed a low absorption area in the bilateral globus pallidus (Fig. 2A). Brain MRI indicated a T2WI high signal, a FLAIR image high signal, a DWI high signal, and decreased ADC from the bilateral globus pallidus to the substantia nigra. In addition, areas with mild high signals on T2WI, a FLAIR image, and DWI were observed at the right temporal lobe, bilateral subcortical frontal lobes, and outside the right putamen, without a decrease in ADC. (Fig. 2 B-E)

Thereafter, there was no marked improvement in the patient's consciousness disturbance or neurological findings. The patient was transferred to another hospital on day 48.

Discussion

There are a few reports on lesions at the globus pallidus and substantia nigra related to COVID-19 [3-7]. According to

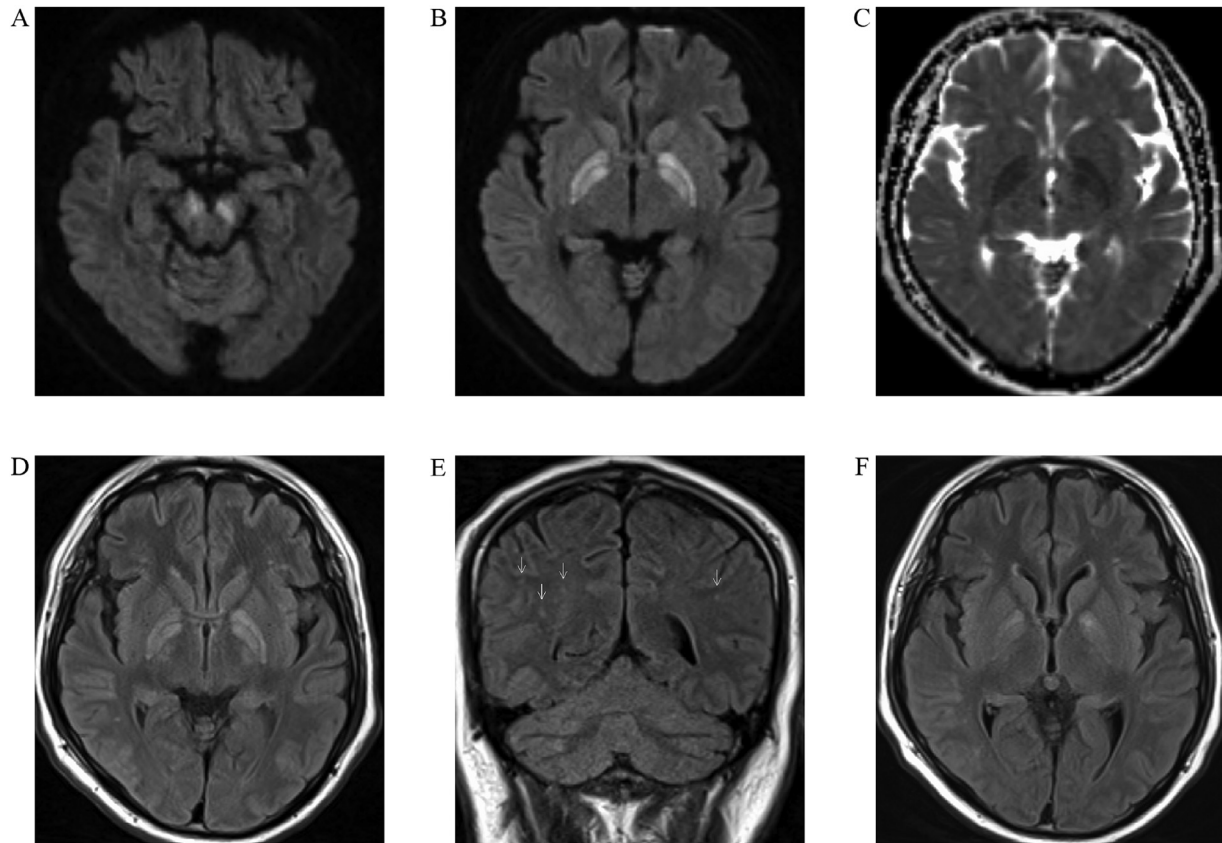


Fig. 1 – (A-C) DWI and ADC on the MRI axial plane indicated a high signal area from the bilateral globus pallidus to the substantia nigra with diffusion limitations. (D) FLAIR image on the MRI axial plane indicates high signals at the globus pallidus. (E) FLAIR image on the MRI coronal plane indicates high signals at the cerebral white matter (white arrows). (F) FLAIR image on the follow-up MRI axial plane 10 days later indicates that the abnormal high signal area is slightly obscured.

Chougar et al., among the 43 cases with acute central nervous system symptoms due to COVID-19 with abnormalities found via MRI, 4 cases had basal ganglia lesions, of which 1 case was a globus pallidus lesion, 2 were substantia nigra lesions, and 1 was found in the upper part of the striatonigral pathways [4].

Reports describing the disease course indicate that many cases with a bilateral globus pallidus and substantia nigra lesions are noted following prolonged consciousness after ventilation management due to severe COVID-19 pneumonia [4-7]. The onset and course are similar to our cases.

Regarding the MRI findings, a T2 extended region, high signal, and decreased ADC on the DWI at the bilateral globus pallidus and substantia nigra were also reported, which are similar to our findings [3-7]. It possibly indicates necrosis of the globus pallidus and substantia nigra.

The abnormal signals at the bilateral globus pallidus may lead to a differential diagnosis of carbon monoxide poisoning, drug intoxication, and metabolic disorders [8]. However, our cases had no carbon monoxide poisoning, history of drug use, or hepatic dysfunction.

Kulick-Soper et al. pointed out that the bilateral globus pallidus and substantia nigra lesions related to COVID-19 may be caused by hypoxic ischemic changes due to severe hypox-

emia [5]. Sawlani et al. have also reported a case of hypoxic-ischemic encephalopathy that had abnormal signals at the globus pallidus and substantia nigra [3]. However, since this case had undergone cardiac arrest, we believe that the effect thereof should also be considered. Brun et al. states a possible cause may be demyelination or small vessel CNS vasculitis [6].

Hypoxic ischemic lesions indicate various images according to brain maturity, duration, and severity of insult, along with the type and timing of imaging studies, with the globus pallidus also damaged by hypoxia [9,10]. Our 2 cases also developed hypoxemia requiring intubation and ventilation management due to severe pneumonia, which might have affected their condition. Case 1 was in shock possibly caused by sepsis over the course of his disease, which may also relate to the bilateral globus pallidus and substantia nigra lesions.

Our 2 cases had localized white matter lesions. With COVID-19, symmetrical lesions of the subcortical and deep white matter have been reported, which are suspected to be hypoxic ischemic lesions [11,12]. While our cases may have similar pathologies, they are not completely the same due to their asymmetry.

From the clinical course of our 2 cases, abnormal blood glucose levels, renal failure, and encephalopathy associated with

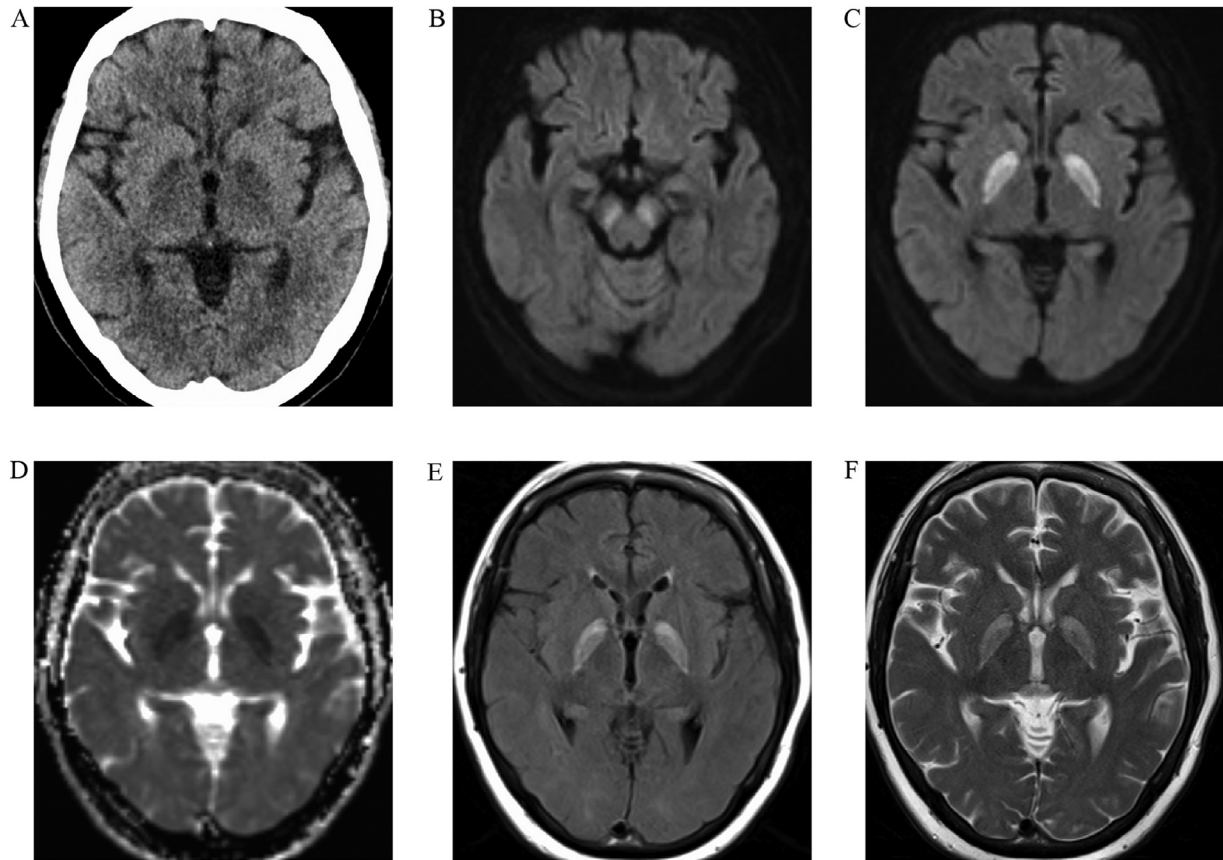


Fig. 2 – (A) CT of axial plane indicates a low density area from the globus pallidus to the substantia nigra. (B-D) DWI on the MRI axial plane indicated a high signal area from the bilateral globus pallidus to the substantia nigra with diffusion limitations. (E) FLAIR on the MRI axial plane indicates a high signal area from the globus pallidus to the substantia nigra. (F) T2WI on the MRI axial plane indicates a high signal area from the bilateral globus pallidus to the substantia nigra.

medronidazole were thought to be possible causes of the central nerve lesions in the basal ganglia region; however, no typical imaging findings were found for them.

Previous studies have also reported cases with improvement in consciousness disorder although they suffered from movement disorders and parkinsonism [4,7]. However, our 2 cases saw no improvement in their consciousness disturbance while they were hospitalized. In order to elucidate the pathology and neurological prognosis, we believe that accumulation of cases and further study is necessary going forward.

Conclusion

We experienced 2 cases of persistent consciousness disturbance with bilateral globus pallidus and substantia nigra lesions in patients with severe COVID-19 pneumonia. Although rare, because central nervous system complications related to COVID-19 may be suspected and the neurological prognosis may be poor, attention should be paid to these imaging findings at the onset of consciousness disturbance.

Patients consent

Informed written consent was obtained from the patient for publication of the Case Report and all imaging studies. Consent form on record.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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