Research article

# Neurological complications associated with coronavirus disease-2019 (COVID-19): MRI features

Neven Moustafa Hazzaa [*]

*Radiology Department, Queens Hospital, Barking, Havering and Redbridge University Hospitals NHS Trust, RM7 0AG, London, United Kingdom*

A B S T R A C T

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is an RNA virus, which is a strain of Severe Acute Respiratory Syndrome-related CoronaVirus (SARSr-CoV), of Coronavirus family. On 31 December 2019, a cluster of cases of unknown pneumonia in Wuhan-China was reported to the World Health Organization (WHO) that subsequently spreading as coronavirus disease 2019-(COVID-19) pandemic worldwide. On 12 January 2020, novel SARS-COV-2 was declared the cause of COVID-19 from the initial analysis of the virus genetic sequences obtained from lower respiratory tract specimen of 41 patients admitted to a designated hospital in Wuhan. The classical COVID-19 presentation is respiratory symptoms. Neuroradiological findings were reported. Our aim is to document neurological complication of COVID-19. We observed confirmed 23 COVID-19 patients presented with severe neurological symptoms. Brain-MRI showed predominately; cerebrovascular thromboembolism-related acute infarcts, autoimmune-meningoencephalitis, Acute disseminated encephalomyelitis (ADEM)-like white matter lesions.

*Conclusion:* Different neurological presentations are associated with COVID-19, necessitating further studies to clarify the mechanism of its CNS involvement.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA virus. It is one of the strains of SARS-related coronavirus (SARSr-CoV), a species of the coronavirus family. It is the 3rd viral strain following Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-1 in the coronavirus family, which results in severe clinical respiratory disease. The genetic resemblance between SARS-CoV-2 and SARS-CoV-1 is 79.5% [1, 2, 3]. SARS-CoV-2 initially caused a pneumonia epidemic in Wuhan, China, and subsequently spreading as COVID-19 global-pandemic [3, 4].

COVID-19 is primarily affects the respiratory system. The elderly population and people with underlying health conditions (UHC) are more susceptible to severe infections [5, 6]. However, there are growing indications that COVID-19 can cause neurological damage [7, 8]. Coronaviruses have been found to cause central nervous system (CNS) demyelination in humans and animals [9].

10% of COVID-19 patients had non-specific neurological symptoms including headache, dizziness, loss of consciousness, and seizures, and they were more likely to have cranial nerve complications, with olfactory and gustatory dysfunction occurring in around 85% and 88 percent of patients, respectively. Cerebrovascular dysfunction was identified as the only neurological manifestation in 3% of patients. SARS-CoV-2 has also been linked to acute meningitis and encephalitis, as shown by T2 hyperintensities in the mesial temporal lobe on MRI. Acute Necrotizing Encephalopathy has also been reported, along with cases of Guillain-Barré syndrome, which may be the first manifestations of COVID-19. 2.3% of COVID-19 patients reported neuropathic pain, most likely due to peripheral neuropathy, while 10.7% of cases displayed evidence of skeletal muscle damage with elevated blood creatine phosphokinase level (CPK). These presentations appear in critically ill patients with severe respiratory failure, in patients without a history of respiratory symptoms, and in healthy young people. Future research should look into the incidence and factors that influence the severity of these complications [10].

## 2. Cases report

### 2.1. Materials and methods

The study was conducted during the 2 waves of COVID-19-pandemic from March 2020 to January 2021 and included only laboratory-

confirmed COVID-19 patients with neurological complications. Ethical approval was sought for this study and approval was granted by the health research authority (HRA) and Health and Care Research Wales (HCRW). Patients consents were waived on the basis described in the application form, protocol, supporting documentation and any clarifications received by HRA. We analyzed only anonymized data.

The patients' electronic medical records including clinico-laboratory, microbiological, and radiological findings were retrospectively collected and subsequently analyzed from Cyberlab, Electronic patient-reported outcomes (ePRO), and picture archiving and communication system (PACS). The obtained laboratory parameters included lymphocyte, neutrophil and red blood cell counts, as well as the hemoglobin, C-reactive protein, acute kidney injury (AKI), alkaline phosphatase and D-Dimer levels. Head Computed tomography (CT) and magnetic resonance imaging (MRI) for all patients and any available radiographs or CT chest scans were evaluated. Testing for COVID-19 was performed via naso-pharyngeal swab for the identification of SARS-CoV-2 RNA by RT-PCR.

The results are presented as descriptive statistics in the form of counts and percentages.

## 2.2. Results

We identified 23 patients (17 males and 6 females, age range: 28–89 years, median age: 70 years). Patients were classified into 2 groups based on the severity of critical illness necessitating admission to intensive care units with mechanical ventilation therapy (MVT) (Group-A) or without MVT (Group-B). The 5 patients (22%) in group-A were 4 males and 1 female (mean age: 60). There were 18 patients (78%) in Group-B, including 13 males and 5 females (mean age: 72).

### 2.2.1. Clinicolaboratory presentations in all patients' groups

Some patients (P) were initially presented with cough (9-P, 39%), shortness of breath (8-P, 35%), and fever (5-P, 22%). 6 patients (26%) had decreased $O_2$ saturation with acute respiratory distress syndrome (ARDS), (with 3-P in Group-A). The commonest neurological symptoms were confusion (18-P, 78%) and focal neurological deficit (17-P, 74%). Other symptoms included coma (6-P, 26%), cognitive difficulty (2-P, 9%) and fall (4-P, 17%) (Figure 1 A).

Most of the patients had underlying health conditions (19-P, 83%), with 16-P (70%) had ≥2 coexisting conditions (3-P in Group-A and 13-P in Group-B), most commonly hypertension (10-P, 43%), hyper-cholsetrolemia (8-P, 35%) diabetes mellitus (6P, 26%), chronic kidney disease (6-P, 26%), Heart disease (6P, 26%), and CNS disease (6P, 26%) (Figure 1 B).

Blood test was performed for all patients. Elevated C-reactive protein (21-P, 91%), lymphocytopenia (19-P, 83%), low hemoglobin (17-P, 74%), acute kidney injury - AKI (12-P, 52%), neutrophilia (13-P, 57%) were the most common findings. In addition to low red blood cell count (13-P, 57%), elevated alkaline phosphatase (12-P, 52%) and high D-Dimer (P-9, 39%) were common features. All 5 patients in Group-A had the same findings (Figure 1 C).

### 2.2.2. Clinico-radiological findings in each patient group

#### 2.2.2.1. Group-A.
A total of 5 patients received MVT after clinical deterioration into coma. 4 patients failed to wake up after sedation cessation and 1 patient was non-responsive following status epilepticus.

Chest radiographs and CT scans showed bilateral pulmonary opacities for all Group-A patients. CT and MRI Head for 3 patients showed multiple bilateral non-territorial T2/FLAIR white matter hyperintense lesions with diffusion restriction on DWI and ADC maps, extending to the corpus callosum in 2 of these patients (Figure 2). MRI Head of further 1 patient showed bilateral subdural collection (Figure 3 a, b, c, d). The MRI Head of the remaining 1 patient in Group-A showed cortical and subcortical T2/FLAIR hyperintensities in the right precentral gyrus and both tempro-
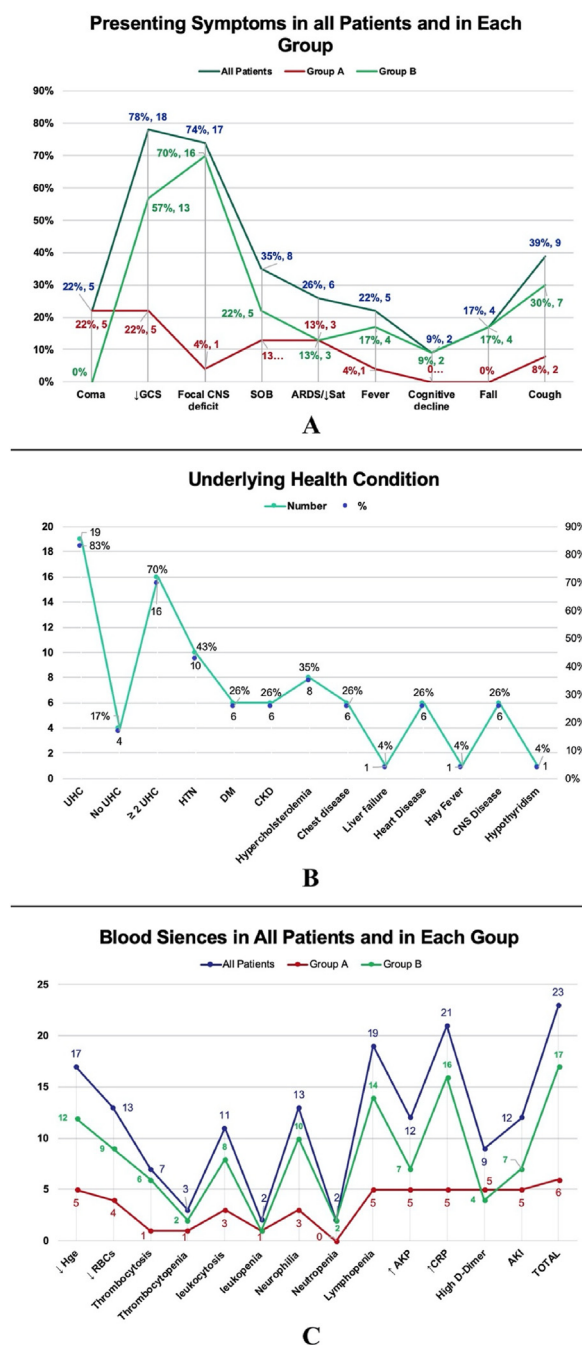


**Figure 1.** A: Figure-1 "A" provides the number and percentage of patients of each Presenting symptoms in all patients (in deep green), in Group A (in red) and in Group B (in light green). B: Figure-1 "B" provides the number (in green) and percentage (in blue) of patients with underlying health condition (UHC) in all groups. C: Figure-1 "C" provides the number of patients of each blood Indices in all patients and in each patient's group in all patients (in Blue), in Group A (in red) and in Group B (in green).

occital lobes, involving hippocampi and insula on both sides, with right focal gyral hemorrhagic changes. Bilateral occipital white matter oedema and thalamic pulvinar signal changes were also seen (Figure 4). The imaging findings for Group-A are summarized in table-1.

#### 2.2.2.2. Group-B.
The commonest presentations were focal neurological deficit (16-P, 70%) and altered level of consciousness (13-P, 57%) (Figure 1 A).
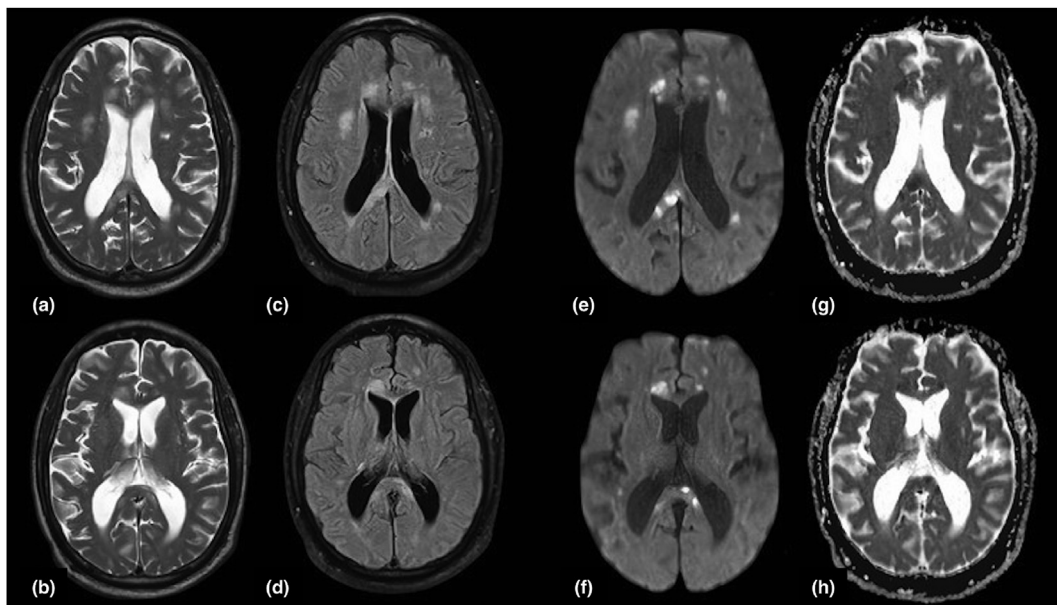
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**Figure 2.** Provides representative images from a single patient, illustrating the multiple T2/FLAIR white matter hyperintense foci extending to the corpus callosum showing restricted diffusion on DWI. MRI images demonstrate multiple T2 (a,b) FLAIR (c, d) white matter hyperintense foci extending to the corpus callosum showing restricted diffusion on DWI (e, f) and ADC map (g, h).
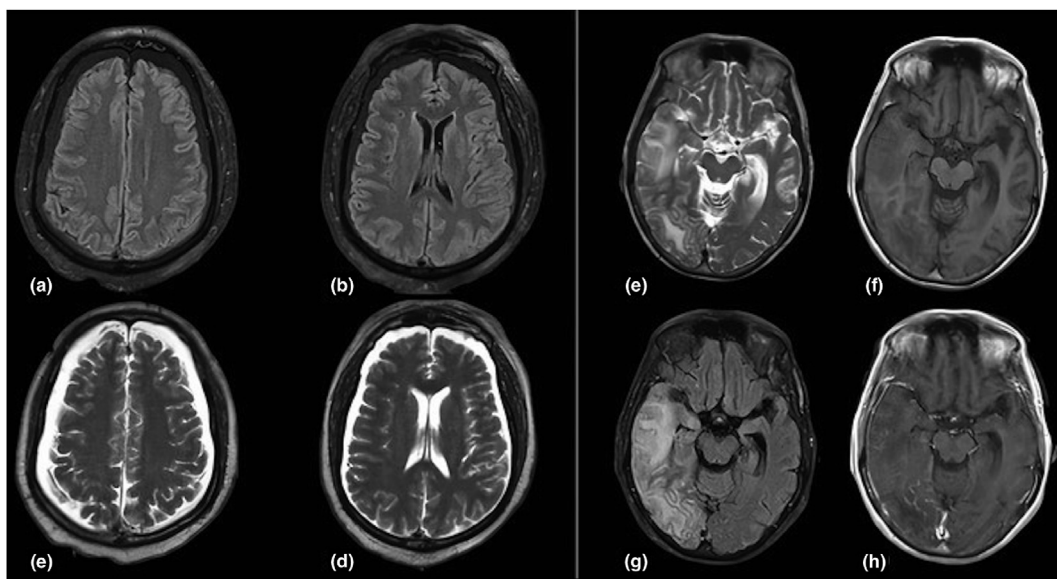


**Figure 3.** Provides representative MRI images from 2 patients, illustrating the bilateral subdural collection (a–d) in one patient in Group-A as well as right hemispheric T2/FLAIR hyperintensities with mild leptomeningeal enhancement (e–h) in another patient in Group-B. MRI images demonstrate bihemispheric subdural collection with slight meningeal thickening in T2WI (c, d), FLAIR (a, b). No contrast was administrated. MRI images in other patients demonstrating T2 (e) FLAIR (g) hyperintensities within the right occipitotemporal lobes, showing mild leptomeningeal enhancement (f, h).

Chest radiographs and CT scans were obtained for 8 patients which showed bilateral pulmonary opacities. All 18 patients of group-B underwent head CT and MRI. Acute thromboembolic events were detected in 15 patients; 11 of these patients had acute territorial cortical infarcts. Deep grey matter acute ischemia was visualized in 4 patients, which was observed in the thalamus (2 patients) within the corresponding posterior cerebral artery (PCA) territory or in the basal ganglia (2-P) within the MCA territory with evidence of common carotid artery (CCA) thrombosis extending to MCA/M1-segment on CT angiography (CTA) images (Figure 5). Thrombolysis (5-P, 29%), and thrombectomy (2-P, 12%) were acquired.

Subarachnoid bleeding due to fall, that could be a result of an altered level of consciousness, was observed in 1 patient.

Furthermore, the MRI Head for another patient in Group-B showed areas of cortical/subcortical T2/FLAIR hyperintense signals in the right temporooccipital lobes (Figure 3 e, f, h) and extensive white matter signal changes with mild leptomeningeal enhancement on post-contrast images. The cerebrospinal fluid (CSF) analysis was negative for coronavirus for this patient so autoimmune encephalitis was diagnosed.

The remaining patient in Group-B, showed areas of cortical/subcortical and white matter signal changes in both cerebral hemispheres associated with areas of restricted diffusion and nodular leptomeningeal
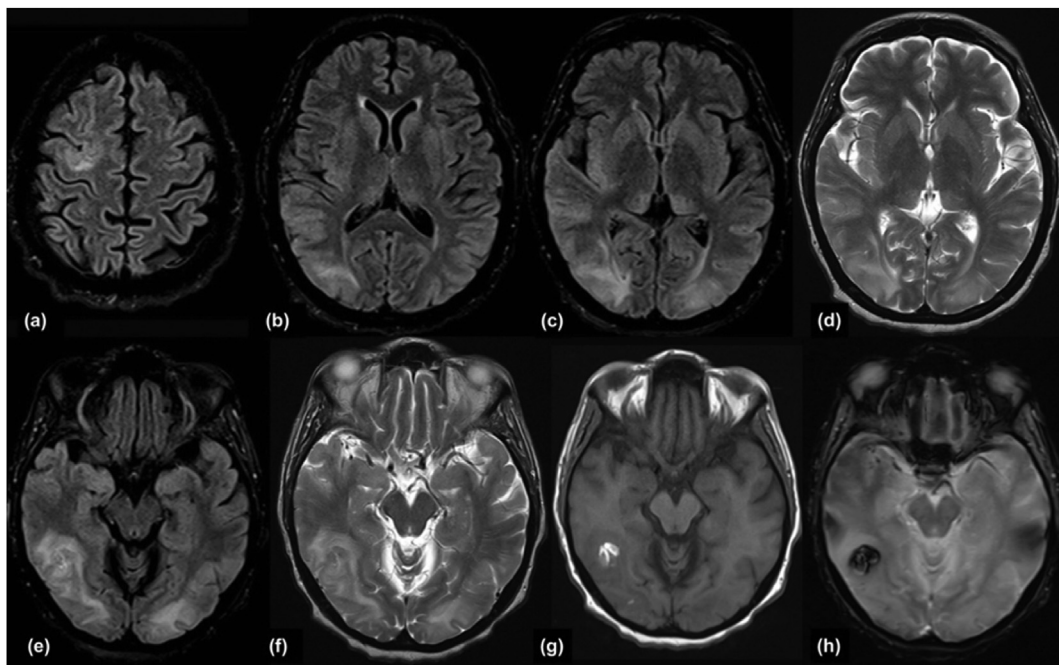
**Figure 4.** Provides representative images from a single patient in Group-A, illustrating the MRI findings of COVID-19-associated acute hemorrhagic necrotizing encephalopathy. MRI images demonstrate T2 (d, f) FLAIR (a, b, c, e) cortical and subcortical hyperintense signals in both cerebral hemispheres associated with tempro-occipital white matter edema. These changes involve the right precentral gyrus, both hippocampi and insulae as well as the thalamic pulvinar and the basal ganglia on both sides. T1WI (g) shows right focal gyral areas of T1 shortening in the right temporal lobe and corresponding susceptibility artifacts on T2* sequence (h) in keeping with hemorrhagic changes.
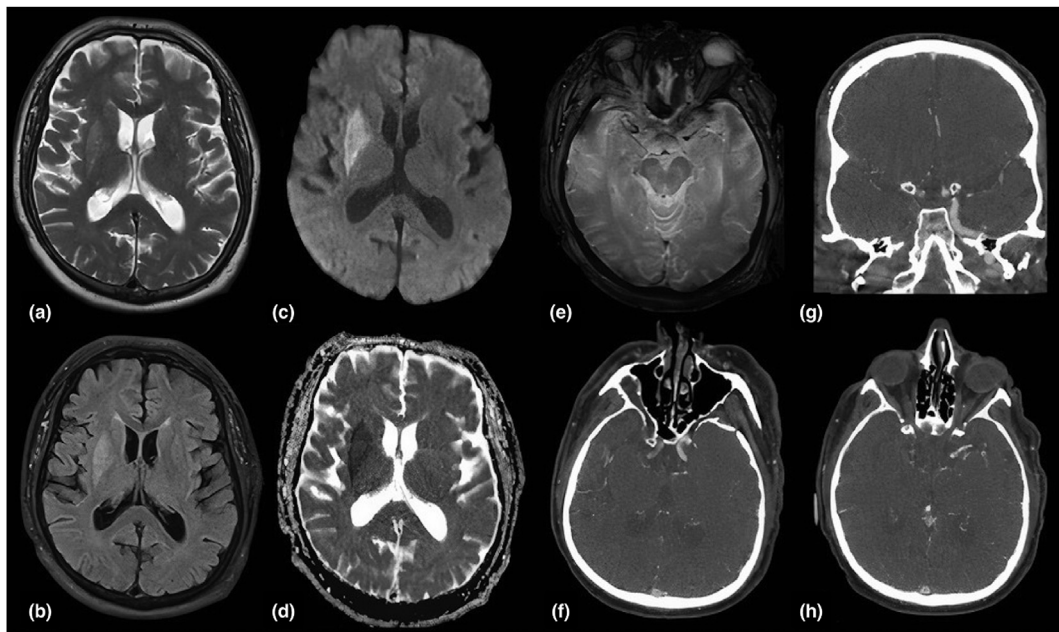


**Figure 5.** Provides representative images from a single patient, illustrating the MRI findings of right MCA/LCA territory infarct within the right basal ganglia due to thrombosis of the ipsilateral ICA/MCA. MRI images demonstrate T2 (a) FLAIR (b) hyperintensities within the right corpus straitum showing restricted diffusion on DWI (c) and ADC map (d). CT angiography (g, f, h) demonstrated thrombosis of the right ICA and the M1 segment within no visualization of the distal right MCA.

enhancement. CSF analysis showed abundant white blood cells in this patient was diagnosed with para-infectious meningoencephalitis (Figure 6). The imaging findings for Group-B are summarized in Table 1.

### 2.2.3. Patients outcome in each group

7 patients (30%) died (2-P in Group-A, 5-P in Group-B), and 5 patients are still inpatients under ongoing care (1 in Group-A and 4 in Group-B).

11 patients (48%) were discharged from the hospital (2 in Group-A, 9 in Group-B), who were receiving treatment in outpatient clinics.

### 3. Discussion

COVID-19 is caused by the SARS-CoV-2 virus, which primarily affects the respiratory system. However, there are growing evidence that the
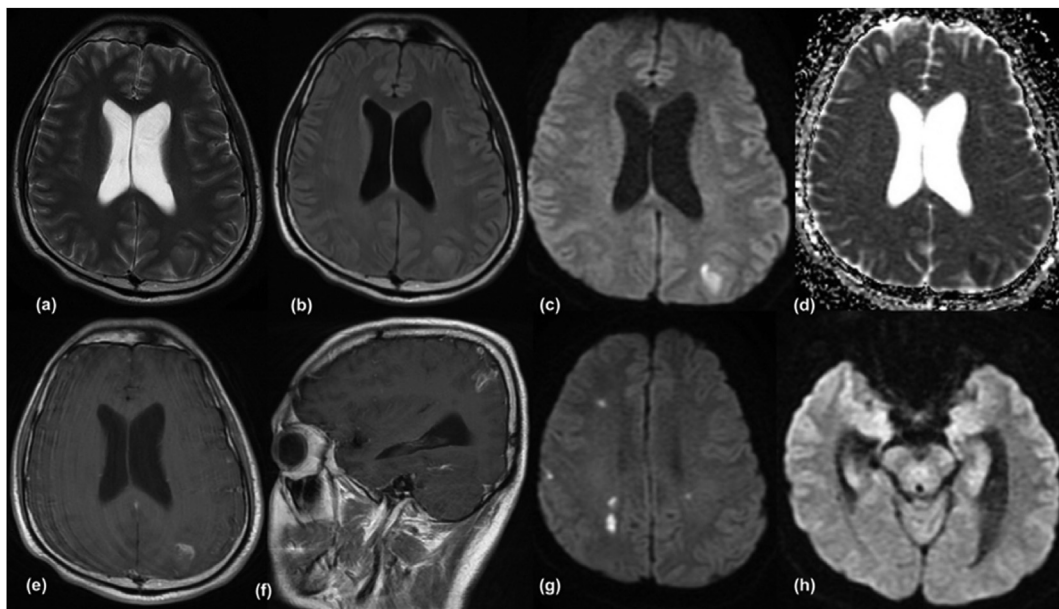
**Figure 6.** Provides representative images from a single patient in Group-B, illustrating the MRI findings of COVID-19 related para-infectious meningoencephalitis. MRI images demonstrate T2 (a) FLAIR (b) cortical and subcortical hyperintense signals within the left superior parietal lobule showing related restricted diffusion on DWI (c) and ADC map (d). Post contrast Axial (e) and coronal (g) T1WI images show corresponding nodular enhancement. DWI (g) shows further areas of restricted diffusions in both corona radiata, more on the right side, as well as the cortex of the right inferior parietal lobule. Cortical signal changes are best demonstrated on DWI sequence (h).

**Table 1.** Summarizes the imaging findings of cases in each patient group.

| Row Labels | Group A. Number | Group B. Number |
|---|---|---|
| Post-viral immune-mediated-ADEM | 3 | 0 |
| Meningitis with bilateral subdural hygroma. | 1 | 0 |
| Acute haemorrhagic necrotizing encephalopathy | 1 | 0 |
| Cerebrovascular disease- Acute territorial infarcts | 0 | 15 |
| Subarachnoid bleed | 0 | 1 |
| Para-infectious process with meningoencephalitis and autoimmune encephalitis | 0 | 2 |
| **Grand Total** | **5** | **18** |

neurological manifestation of COVID-19 are common; [11]. The cause and pathophysiology are still under debate. As the genomic sequence is similar between SARS-CoV-1 and SARS-CoV-2 [12], they share angiotensin-converting-enzyme 2 (ACE2) as their receptor in various organs, including the lungs, heart, kidneys, gut, nervous system, vascular system, and skeletal muscles. This may explain why both viruses might interact with the same brain ACE2 receptor. Both viruses may also spread via the olfactory tract from infected nasal cells to the brain, causing inflammatory and demyelinating reactions [8]. A CNS immune response as a result of a "cytokine storm" can also cause neural damage [13]. Some studies have suggested that SARS-CoV-2-infected patients may have a predisposition to thromboembolic events [14, 15].

In our case series, we identified 23 confirmed COVID-19 patients with neurological complications detected on MRI and CT scans. SARS-CoV-2 infection was confirmed by RT-PCR. The neurological presentations include headache, dizziness, anosmia, myalgia, seizures, focal neurological deficit and loss of consciousness. CNS manifestations associated with COVID-19 can be classified as a direct viral effect, immune-mediated para-infectious or post-infectious process as well as, systemic-related neurological consequences of COVID-19. Peripheral nervous system and muscle disease including Guillain-Barré syndrome have also been reported in previous studies [18].

### 3.1. Group-A

3 patients had MRI Head showing multiple, bilateral T2WI/FLAIR white matter hyperintense lesions extending to the corpus callosum with restricted diffusion on DWI and ADC maps. CSF analysis was normal. Although the clinical findings were indicative of COVID-19-associated CNS changes, other possible causes were proposed considering the lack of laboratory tests that confirm CNS infection. The MRI appearances reasonably indicated a viral etiology, particularly demyelinating disease or post-viral immune-mediated-ADEM [9].

The closely related SARS-CoV-1 virus has been associated with neurological diseases such as encephalitis, and multiple sclerosis [16].

The MRI Head of further 1 patient in Group-A who was manifested with status epilepticus, showed cortical and subcortical T2/FLAIR hyperintensities in the right precentral gyrus and both tempro-occital lobes, involving hippocampi and insulae on both sides, with right focal gyral hemorrhagic changes. Bilateral occipital white matter oedema and thalamic pulvinar signal changes were also seen. No abnormal enhancement could be seen in post-contrast images. CSF was normal in this patient. Therefore, COVID-19-associated acute hemorrhagic necrotizing encephalopathy, probably as a result of a cytokine storm was considered in this case [7, 18].

Expected MRI findings associated with hypoxic-ischemic injury were not evident in our patients.

The brain MRI of the remaining 1 patient in Group-A showed bilateral subdural collection after 10 days from the initial unremarkable-MRI. Appearances were suggestive of meningitis complicated by bilateral subdural hygroma.

### 3.2. Group-B

i Stroke: 15 patients showed MRI findings of acute territorial cortical infarcts. CTAs were performed for 6 patients, 5 of these showed filling defects within the ipsilateral ICA/MCA and 1 patient within the basilar artery consistent with thromboembolism. The closely related SARS-CoV-1 virus has been associated with neurological diseases such as ischemic stroke caused by viral vasculopathy [16, 17]. Sepsis

may result in a predisposition to cerebral stroke, and increasing evidence suggests that COVID-19 tends to cause cerebrovascular thromboembolism due to excessive inflammation, associated ARDS-induced hypoxia and immobilization [8, 18]. Additional possible cause includes vascular angiopathies with the resultant stimulation of inflammatory and thrombotic processes, that is reflected by the thrombocytopenia with increased level of D-dimer and C-reactive protein in severe COVID-19 patients [18].

ii Para-infectious process: The MRI of 2 patients in Group-B showed cortical and subcortical signal changes on FLAIR/T2WI associated with leptomeningeal enhancement. These changes show no diffusion restriction and present in the right cerebral hemisphere in one patient and scattered in both cerebral hemispheres with areas of white matter restricted diffusion in the second patient. A case study reported COVID-19 patients with viral encephalitis, and autopsy reports showed brain edema and partial neuronal degeneration [8]. The closely related SARS-CoV-1 virus was associated with neurological diseases such as polyneuropathy and encephalitis [16]. In most cases of SARS, autopsy studies demonstrated cerebral, meningeal, vascular, and ischemic changes with neuronal demyelination and intra-neuronal SARS-CoV [8, 17]. In our cases, the CSF analysis was negative for COVID-19 in both patients and showed abundant white blood cells in the second patient. Therefore, probable autoimmune meningoencephalitis was considered for the first patient and para-infectious meningoencephalitis for the second patient [18].

iii Trauma: One patient in Group-B showed subarachnoid hemorrhage due to fall. We believe that confusion associated with COVID-19 infection may have led to head trauma.

Although coronaviruses are commonly known for causing respiratory diseases, there is growing evidence suggesting neurotropism [17]. Previous brain necropsy studies with induced SARS-CoV infection confirmed neuronal apoptosis, direct neuronal viral infection, and ischemic-injury [17]. The direct confirmation of COVID-19 as the cause of intracranial changes on the MRI of our patients is hard to establish due to the absence of autopsy workup.

Our study has several important limitations including the incomplete reporting of clinic-laboratory findings. Our patient size was small due to the difficulty in patient recruitment during the pandemic period.

In conclusion, COVID-19 can cause CNS complications with an increased risk of para or post-infectious processes; as autoimmune or viral encephalitis, acute necrotizing encephalopathy related to a cytokine storm, ADEM, or cerebrovascular disease. This case series suggests that COVID-19 may result in a predisposition to neurological complications, necessitating further studies to clarify the mechanism of its CNS effect. Careful clinical scrutinization and public advice of its CNS manifestation are also needed for early detection and subsequent management in order to decrease its resulting debilitating neurological and socioeconomic sequelae.

## Declarations

### Author contribution statement

Neven Moustafa Hazzaa: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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