


## Case report

## Cerebrospinal fluid confirmed COVID-19-associated encephalitis treated successfully

Yasmine Mohamed Kamal,<sup>1</sup> Yasmin Abdelmajid ,<sup>1</sup>  
Abubaker Abdul Rahman Al Madani<sup>2</sup>

<sup>1</sup>Neurology, Dubai Health Authority, Dubai, United Arab Emirates

<sup>2</sup>Neurology, Rashid Hospital, Dubai, United Arab Emirates

**Correspondence to**

Dr Yasmin Abdelmajid;  
yasminefarid92@hotmail.com

Accepted 6 September 2020

**SUMMARY**

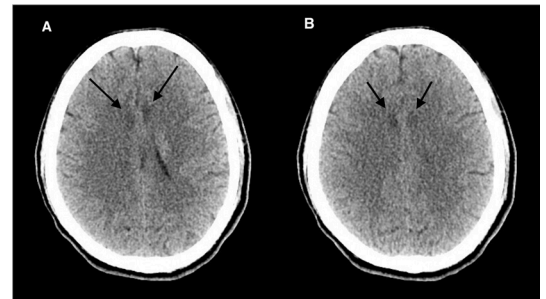
The COVID-19 pandemic that attracted global attention in December 2019 is well known for its clinical picture that is consistent with respiratory symptoms. Currently, the available medical literature describing the neurological complications of COVID-19 is gradually emerging. We hereby describe a case of a 31-year-old COVID-19-positive patient who was admitted on emergency basis. His clinical presentation was primarily neurological, rather than the COVID-19's classical respiratory manifestations. He presented with acute behavioural changes, severe confusion and drowsiness. The cerebrospinal fluid analysis was consistent with COVID-19 encephalitis, as well as the brain imaging. This experience confirms that neurological manifestations might be expected in COVID-19 infections, despite the absence of significant respiratory symptoms. Whenever certain red flags are raised, physicians who are involved in the management of COVID-19 should promptly consider the possibility of encephalitis. Early recognition of COVID-19 encephalitis and timely management may lead to a better outcome.

**BACKGROUND**

The COVID-19 virus, classified as SARS-CoV-2, emerged in Wuhan, China, and was initially identified as the new coronavirus disease. The WHO eventually named it as COVID-19 on 11 February 2020. Later on 5 June 2020, the WHO officially announced that COVID-19 has infected 6 535 354 individuals and claimed more than 387 155 lives worldwide.<sup>1</sup> COVID-19 is not the first coronavirus to infect humans. Other human coronaviruses (HCoV) include six other members designated as SARS-CoV, middle east respiratory syndrome-CoV, HCoV-HKU1, HCoV-NL63, HCoV-OC43 and HCoV-229E.<sup>2</sup>

As described in the literature, COVID-19 possesses neuroinvasive potentials, which makes the central nervous system (CNS) an important target. There are multiple proposed mechanisms of CNS involvement, including retrograde movement from the olfactory nerve, entry into CNS via circulating lymphocytes or entry via permeable blood-brain barrier.<sup>3</sup>

There are several neurological manifestations that have been described in patients with severe respiratory distress.<sup>4</sup> But this case is unique due to the fact that the patient's symptoms were mainly neurological in nature, that was preceded with

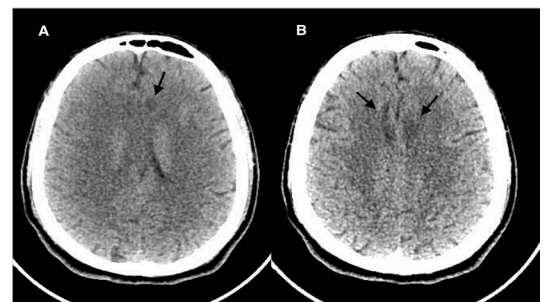


**Figure 1** (A, B) Initial CT of the brain without contrast axial image revealing bilateral symmetrical hypodensities in the bifrontal lobes.

a mild, self-limiting cough. What also enhances the uniqueness of this case is the presence of a very few reported cases of established encephalitis alongside an objective evidence of the virus itself in CNS.<sup>5,6</sup>

**CASE PRESENTATION**

On 10 May 2020, a 31-year-old previously healthy man, who happened to live in a particular area with uncontrolled COVID-19 spread in Dubai, started experiencing some mild, self-limiting cough symptoms without any episode of fever. This was not brought to medical attention and resolved spontaneously within 2 days. On 12 May 2020, he started to become physically and verbally aggressive, as stated by his acquaintances. On 14 May 2020, he presented to the emergency department in Rashid Hospital with an altered mental state and abnormal behaviour. The patient's acquaintances clearly stated that the patient does not suffer from

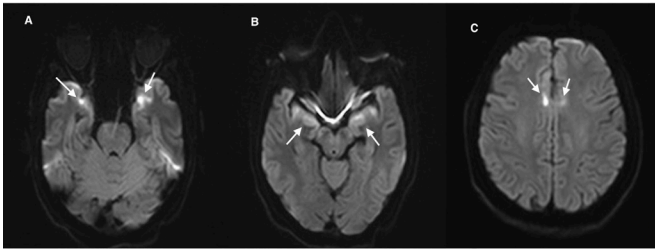


**Figure 2** (A, B) Repeated CT of the brain without contrast axial image after 24 hours still revealing hypodensities in the bifrontal lobes.



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**To cite:** Kamal YM, Abdelmajid Y, Al Madani AAR. *BMJ Case Rep* 2020;**13**:e237378. doi:10.1136/bcr-2020-237378



**Figure 3** (A, B) MRI of the brain diffusion-weighted images axial image revealing rather symmetrical diffusion restriction in the anteromedial temporal lobes bilaterally, and (C) areas of diffusion restriction in the parasagittal frontal lobes bilaterally.

any comorbidities and denied any history of alcohol intake or substance abuse.

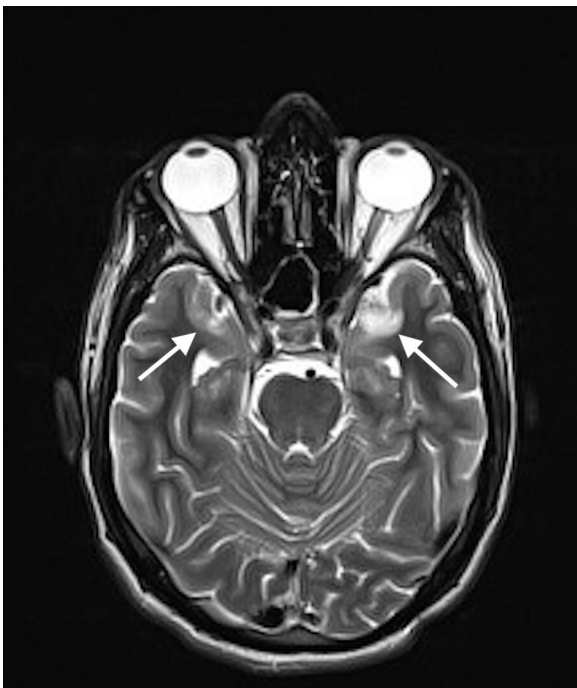
The patient was afebrile. His heart rate was 76/min, blood pressure was 120/80 mm Hg, respiratory rate was 12/min and oxygen saturation on room air was 100%. Neurological examination revealed acute confusion state associated with severe agitation and fluctuations in the level of consciousness. Cranial nerves examination was unremarkable. The motor examination including tone, power in upper and lower limbs, and deep tendon reflexes was normal as well. Coordination was difficult to assess at this point. No neck stiffness or other meningeal signs were evident.

Chest examination, including inspection, auscultation, percussion and palpation, revealed no abnormalities. Abdominal examination revealed a soft abdomen and present bowel sounds, without any evidence of tenderness or organomegaly.

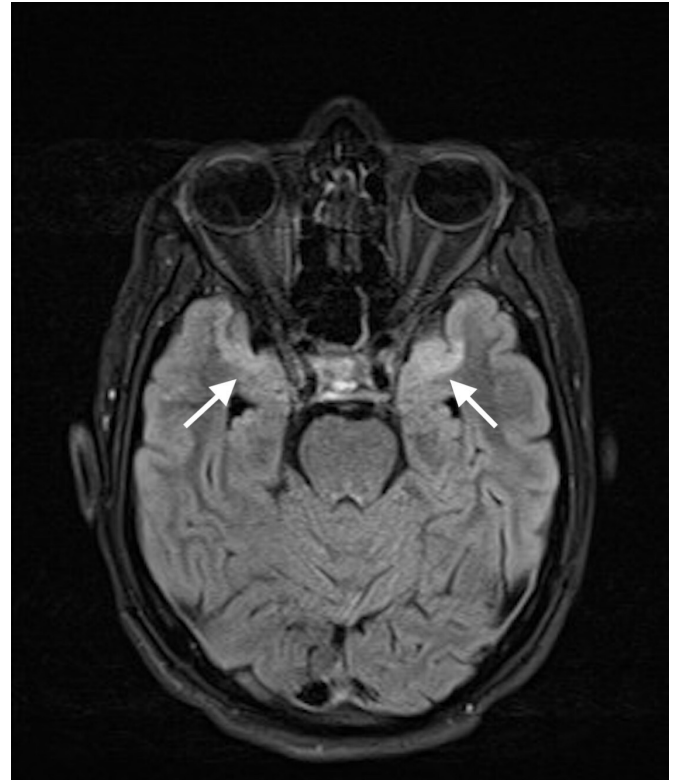
## INVESTIGATIONS

### Imaging

- ▶ **Brain CT without contrast** revealed multiple hypodensities in the external capsules bilaterally, the insular cortex and the



**Figure 4** MRI of the brain T2-weighted axial image revealing hyperintense signals in the temporal lobe cortex bilaterally.



**Figure 5** MRI of the brain T2-fluid attenuated inversion recovery axial image revealing hyperintense, rather symmetrical, signals in the anteromedial temporal lobes bilaterally.

deep periventricular white matter of the frontal lobes bilaterally (figure 1). Another brain CT was performed 48 hours after the initial one, but did not reveal any significant interval changes (figure 2).

- ▶ **Chest X-ray** was unremarkable.
- ▶ **Pulmonary CT** showed normal attenuation in both lungs without any appreciable air space consolidations, pneumothorax or pleural effusion. No evidence of ground glass opacities.
- ▶ **Pulmonary CT angiogram** shows good flow of contrast of the main pulmonary trunk, right and left main pulmonary arteries, as well as the lobar, segmental and subsegmental branches without any appreciable filling defects. No evidence of pulmonary embolism.
- ▶ **Abdominal CT** was normal
- ▶ **Brain MRI with contrast**, performed after 2 weeks to comply with our hospital's protocol that only allows COVID-19-negative patient to get in contact with the MRI machine, revealed abnormal signal intensity in the temporal lobe cortex bilaterally in a rather symmetrical fashion. In addition, the involvement of the parasagittal frontal lobes bilaterally was evident as well, displaying bright signals on T2-fluid attenuated inversion recovery and T2-weighted images with corresponding diffusion restriction. These findings are suggestive of encephalitis (figures 3–5).

### Electrophysiological studies

- ▶ **Electroencephalogram** did not display any significant epileptic discharges. That could possibly be due to the masking effect of lorazepam that was given to the patient to manage his agitation.

**DIFFERENTIAL DIAGNOSIS**

Living in an area where there is a higher infection rate of COVID-19 is a red flag by itself. Given the presenting symptoms, COVID-19 encephalitis should be considered, as well as acute metabolic disorders, such as renal and hepatic encephalopathies. Our patient had an initially elevated bilirubin level; however, the alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase were within normal limits (table 1). Hepatitis C antibodies and hepatitis B surface antigen were negative, and abdominal CT scan was normal too. The elevated bilirubin normalised within 2 weeks, indicating that this elevation was non-specific. Acute cerebrovascular accident or toxic insults should also be wisely ruled out. Nevertheless,

viral, bacterial, parasitic, mycobacterial and fungal encephalitis should be excluded. COVID-19 encephalitis should be also considered in the differential diagnoses, particularly nowadays. Such life-threatening conditions need proper screening for all the above mentioned to avoid uninvited complications.

**TREATMENT**

The patient was admitted in an isolated high dependency care unit. Primary care was initiated, including nasogastric tube and Foley’s catheter insertion, oxygen supplementation by nasal cannula, as well as intravenous fluids for the purpose of hydration.

The following treatment plan was decided on and was immediately started, and it included chloroquine 150 mg two times per day for 2 weeks, along with two tablets of lopinavir–ritonavir two times per day for 2 weeks. Seven hundred and fifty milligrams of intravenous acyclovir sodium, three times per day, was started empirically before the cerebrospinal fluid (CSF) results were obtained, addressing the possibility of herpes simplex virus (HSV) I and II encephalitis. The decision to continue the acyclovir for a further duration of 2 weeks was made, despite of the absence of evidence of HSV in the CSF, based on the fact that the patient was gradually improving, and there might be possibility of a false negative herpes simplex PCR CSF test.

Levetiracetam 1 g two times per day was started empirically, tackling the suspicion of non-convulsive seizure as a possible cause for the altered level of consciousness. In addition, 2 mg of intravenous lorazepam and 2.5 mg of intramuscular haloperidol two times per day were given as required, whenever needed.

Enoxaparin 40 mg subcutaneously once a day and pantoprazole 40 mg daily were prescribed for deep venous thrombosis prophylaxis and gastrointestinal prophylaxis, respectively. For supplementation, 10 mL of calcium–magnesium–D<sub>3</sub>–zinc (OSTEOCARE) 150 mg–75 mg–75 unit–3 mg/5 mL syrup was given as well.

After 1 week of his admission, the patient’s level of consciousness improved dramatically, despite his fluctuating confusion and agitation. The same management plan was resumed, except an increment in the enoxaparin dose to 70 mg subcutaneously two times per day was made, as a result of the patient’s elevated D-dimer levels of 2.6 mg/dL (table 2).

The patient eventually became fully conscious and well coherent, with a complete resolution of his psychosis and agitation. After 2 weeks, he was successfully able to resume his normal life routine.

**OUTCOME AND FOLLOW-UP**

Fifteen days after admission, COVID-19 RNA PCR test was performed again on samples from both the nasopharynx and the CSF (table 3). Both results turned out to be negative. In addition, the bilirubin level improved as well.

The patient was safely discharged from the hospital on 5 June 2020, retaining his normal baseline condition. On discharge, he was only prescribed vitamin C and zinc supplements. He did not require further anticoagulation as his D-dimer fell back to its normal limits and his pulmonary angiogram was unremarkable.

**Table 1** Laboratory investigations performed on admission

Complete blood count	WBC: 5400 cells/cmm RBC: 4.48 million cells/cmm Haemoglobin: 130 g/L Hematocrit: 38.8% Platelets: 2 99 000 cells/cmm
Urea and electrolytes	Sodium: 138 mmol/L Potassium: 3.9 mmol/L Urea: 18 mg/dL
Creatinine	0.7 mg/dL
Nasopharyngeal swab	SARS-CoV-2 RNA PCR for N gene, E gene, RDRP/ORF1ab: positive (detected)
CSF appearance	Clear and colourless
CSF cytology and microbiology	WBC: <5 cells/cmm RBC: 150 cells/cmm Gram stain: no organism is seen Culture: no growth Tuberculous PCR direct detection: <i>Mycobacterium tuberculosis</i> not detected
CSF virology	SARS-CoV-2 RNA PCR (N gene, E gene, RDRP/ORF1ab): positive (detected) Herpes simplex virus I & II DNA PCR: negative Varicella zoster virus DNA PCR: negative Human herpes virus 6 DNA PCR: negative Human herpes virus 7 DNA PCR: negative Enterovirus RNA PCR: negative
CSF analysis	CSF protein: 45 mg/dL CSF glucose: 60 mg/dL CSF chloride: 119 mg/dL
D-dimer	0.42 µg/mL FEU
Bilirubin	Direct: 0.9 mg/dL Indirect: 2.1 mg/dL Total: 3.2 mg/dL
Liver function tests	Alkaline phosphatase: 73 U/L SGPT (ALT): 14 U/L AST: 33 U/L GGT: 11 U/L Total protein: 8.4 g/dL Albumin: 4.8 g/dL Globulin: 3.6 g/dL
Hepatitis B surface antigen	Non-reactive
Hepatitis C antibodies	Non-reactive
HIV 1&2 antigen and antibody	Non-reactive
HbA1c	5.4%
Serum glucose (random)	88 mg/dL
Vasculitis work-up	Thrombophilia screening, lupus anticoagulant, rheumatoid factor, anti-nuclear antibodies, extractable nuclear antigen profile, and anti-cardiolipin IgG and IgM are normal

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; FEU, fibrinogen equivalent unit; GGT, gamma-glutamyl transferase; RBC, red blood cell; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell.

**Table 2** Laboratory investigations performed 1 week after admission

Bilirubin	Total: 3.0 mg/dL
D-dimer	2.65 µg/mL FEU

FEU, fibrinogen equivalent unit.



**Table 3** Laboratory investigations performed 2 weeks after admission

Nasopharyngeal swab	SARS-CoV-2 RNA PCR (N gene, E gene, RDRP/ORF1ab): negative (not detected)
CSF appearance	Clear and colourless
CSF cytology and microbiology	WBC: <5 cells/cmm RBC: 50 cells/cmm Gram stain: No organism is seen Bacterial, fungal and AFB cultures: no growth
CSF virology	SARS-CoV-2 RNA PCR (N gene, E gene, RDRP/ORF1ab): negative (not detected) Herpes simplex virus I & II DNA PCR: negative Varicella zoster virus DNA PCR: negative Human herpes virus 6 DNA PCR: negative Human herpes virus 7 DNA PCR: negative Enterovirus RNA PCR: negative
CSF analysis	CSF protein: 55 mg/dL CSF glucose: 67 mg/dL CSF chloride: 119 mg/dL
D-dimer	0.65 µg/mL FEU
Bilirubin	Total: 1.1 mg/dL

AFB, acid-fast bacillus; CSF, cerebrospinal fluid; FEU, fibrinogen equivalent unit; RBC, red blood cell; WBC, white blood cell.

A telephonic follow-up consultation was held with the patient, where he confirmed that he remains unquestionably in a good condition.

## DISCUSSION

SARS-CoV-2 is acknowledged to affect the nervous system and induce polyneuropathy, encephalitis and acute ischaemic strokes.<sup>7,8</sup> The mechanism by which coronavirus affects the CNS is not yet fully understood. It is sensible to agree that the mechanism of neuroinvasion could be either the traditional viral entry into CNS via circulating lymphocytes, or its entry via a permeable blood–brain barrier.<sup>3</sup>

One would debate that the acuteness of our patient's neurological symptoms, as displayed in the symptomatology, brain imaging, as well as the elevated D-dimer, might suggest a viral influence on the vascular network of the CNS.

Nevertheless, the possible mechanism of injury of the brain's vascular endothelium could be some disruption in the vascular structures, eventually leading to clotting and infarction.<sup>9–11</sup> This, however, was not suggested in the presented case. A detailed look at the MRI of the brain (figures 3–5) study reveals an abnormal distribution that is symmetrical bilaterally, affecting mainly the frontal and temporal lobes. This picture highly suggests a viral pathology rather than a vascular insult.

As explained earlier, the behavioural changes, acute psychosis, acute confusional state and drowsiness were the initial and main presenting symptoms in a patient with COVID-19 without major respiratory symptoms, except for the self-limiting episode of mild cough that resolved spontaneously, prior to his presentation, without medical interference. The early suspicion of COVID-19 encephalitis and performing the appropriate CSF studies was the key to establishing the correct diagnosis and timely management.

Despite the absence of CSF pleocytosis, the suspicion of CNS encephalitis should still be considered. Upadhyayula suggested that viral meningoencephalitis may occur frequently in the lack of CSF pleocytosis.<sup>12</sup> In addition, Erdem *et al* also suggested that the suspicion of CNS infections should not be underestimated despite the lack of CSF pleocytosis.<sup>13</sup> There are also several

## Patient's perspective

When the doctors explained to me what happened and how COVID-19 affected my brain, I got terrified! I knew about the COVID-19 pandemic, but I couldn't believe this happened to me! I am very blessed and grateful that I have received the necessary medical care and recovered completely from the COVID-19 infection. I, at some point, thought I lost my life. No words can express how I currently feel.

## Learning points

- ▶ A red flag of the possibility of COVID-19 encephalitis should be raised whenever patients present with abnormal behaviour, acute psychosis, confusion state or drowsiness.
- ▶ Prompt and specific investigations to diagnose this condition should not be hindered in absence of the more common respiratory COVID-19 symptoms such as anosmia, dysgeusia, flu-like symptoms, headache, and sensory or motor deficits.
- ▶ Early diagnosis and management of such cases is important to avoid further undesired complications.

published case series that described patients without CSF pleocytosis in relation to bacterial meningitis, herpes simplex encephalitis and enteroviral meningitis.<sup>14–16</sup>

Patients with meningoencephalitis associated with COVID-19 may not present with the commonly known flu-like illness, as with the presented patient.<sup>17</sup>

We conclude that early establishment of the diagnosis and the immediate commencement of a management plan may contribute to a better outcome.

**Acknowledgements** We would like to thank Dr Raheel Ahmed for his assistance in direct patient care, as well as Dr Maria Khan, for the final review of the article.

**Contributors** The contributors of this work include YMK for direct medical care and writing the structure of the article; YA for direct patient care, editing the article and the submission process; and AAAAM for direct patient care, as well as being the most responsible physician. We would also like to express our gratitude for the Infectious Disease team, the Psychiatry team and the nursing team in Rashid Hospital for helping us provide the complete medical care that the patient needs. Last but not least, we are thankful to the patient for consenting to publish his case.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## ORCID iD

Yasmin Abdelmajid <http://orcid.org/0000-0003-1920-7602>

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