



# Acutely altered mental status as the main clinical presentation of multiple strokes in critically ill patients with COVID-19

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## Abstract

**Background and aims** Cerebral infarction in COVID-19 patients might be associated with a hypercoagulable state related to a systemic inflammatory response. Its diagnosis might be challenging. We present two critically ill patients with COVID-19 who presented acutely altered mental status as the main manifestation of multiple strokes.

**Methods** Clinical presentation and diagnostic work-up of the patients.

**Results** Two patients in their sixties were hospitalized with a bilateral pneumonia COVID-19. They developed respiratory failure and were admitted to ICU for mechanical ventilation and intense medical treatment. They were started on low-molecular-weight heparin since admission. Their laboratory results showed lymphopenia and increased levels of C-reactive protein and D-dimer. Case 1 developed hypofibrinogenemia and presented several cutaneous lesions with biopsy features of thrombotic vasculopathy. Case 2 was performed a CT pulmonary angiogram at ICU showing a bilateral pulmonary embolism. When waking up, both patients were conscious but with a remarkable global altered mental status without focal neurological deficits. A brain MRI revealed multiple acute bilateral ischemic lesions with areas of hemorrhagic transformation in both patients (case 1: affecting the left frontal and temporal lobes and both occipital lobes; case 2: affecting both frontal and left occipital lobes). Cardioembolic source and acquired antiphospholipid syndrome were ruled out. COVID-19-associated coagulopathy was suspected as the possible main etiology of the strokes.

**Conclusion** Acutely altered mental status might be the main manifestation of multiple brain infarctions in critically ill COVID-19 patients. It should be specially considered in those with suspected COVID-19-associated coagulopathy. Full-dose anticoagulation and clinical-radiological monitoring might reduce their neurological consequences.

**Keywords** COVID-19 · Acutely altered mental status · Multiple strokes

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Carolina Díaz-Pérez and Carmen Ramos contributed equally to this work.

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## Introduction

The COVID-19 caused by the novel coronavirus SARS-CoV-2 usually manifests with fever, cough, and dyspnea, with characteristic bilateral areas of ground-glass opacity on chest CT images. Some patients progress to an inflammatory phase that might require mechanical ventilation and admission to the intensive care unit (ICU) [1].

In severe forms of the disease, several neurological manifestations have been described, mostly affecting the central nervous system [2]. Cerebral infarction may be associated in these patients with a hypercoagulable state due to a systemic inflammatory response [3–5].

It is not unusual for critically ill patients to develop brain ischemic lesions with symptoms not clearly identified as a focal neurological deficit. We present two critically ill

COVID-19 patients who presented acutely altered mental status as the main manifestation of multiple strokes.

## Results

### Case 1

A 61-year-old-man presented with a bilateral pneumonia COVID-19 with fever, cough, and dyspnea. He was admitted to the Internal Medicine Service on hydroxychloroquine, lopinavir/ritonavir, and low-molecular-weight heparin (LMWH) 60 mg q.d.

He developed respiratory failure and the laboratory results showed lymphopenia (300 cells/ $\mu$ l [normal 1000–4000]) and increased levels of C-reactive protein (32.2 mg/dl [normal < 0.50]), ferritin (538 ng/ml [normal 30–400]), fibrinogen (631 mg/dl [normal 150–400]), and D-dimer (124.86  $\mu$ g/ml [normal 0.15–0.50]). He was admitted to the ICU for mechanical ventilation, receiving systemic corticosteroids and tocilizumab. A remarkable complication was hypofibrinogenemia (73 mg/dl) with prolonged prothrombin time (18.6 s [normal 0–13.9]) and slight thrombocytopenia (99,000 cells/ $\mu$ l [normal 150,000–400,000]), consistent with disseminated intravascular coagulation according to the International Society on Thrombosis and Haemostasis criteria [6].

After clinical and analytical improvement, he was discharged back to the Internal Medicine Service. Neurological examination revealed drowsiness, inattention, disorientation, and slow speech with no focal neurologic deficits. The symptoms fluctuated and psychomotor agitation

partially responded to quetiapine. The electroencephalogram pattern was suggestive of moderate diffuse encephalopathy.

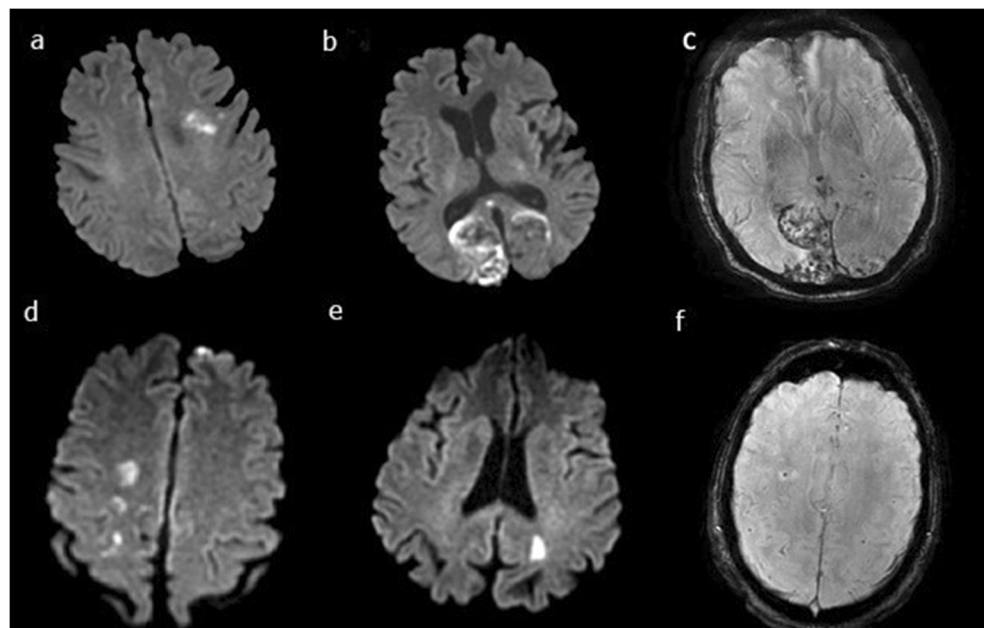
A brain MRI was performed demonstrating multiple ischemic lesions affecting the left frontal and temporal lobes and both occipital lobes with extensive areas of hemorrhagic transformation (Fig. 1a–c). Cardioembolic source was ruled out and acquired antiphospholipid syndrome study was normal. He developed several cutaneous lesions with biopsy features of thrombotic vasculopathy. These findings, together with the analytic disturbances, pointed to COVID-19-associated coagulopathy as the main etiology suspected for the strokes.

### Case 2

A 65-year-old man with hypertension and diabetes mellitus presented with a bilateral pneumonia COVID-19 with fever and dyspnea, mild respiratory compromise, and analytic disturbances (lymphopenia of 790 cells/ $\mu$ l [normal 1000–4000], D-dimer 0.55  $\mu$ g/ml [normal 0.15–0.50], C-reactive protein 10.2 mg/dl [normal < 0.50], lactate dehydrogenase 338 U/l [normal 135–225]). He was admitted to the Internal Medicine Service on hydroxychloroquine, lopinavir/ritonavir, and LMWH 80 mg b.i.d.

He developed respiratory failure with analytical deterioration (lymphopenia of 410 cells/ $\mu$ l, D-dimer 21.4  $\mu$ g/ml, lactate dehydrogenase 820 U/l). He was admitted to ICU for mechanical ventilation, receiving high doses of methylprednisolone and tocilizumab. Due to persistent high D-dimer levels, a CT pulmonary angiogram was performed showing a bilateral pulmonary embolism. He was discharged back to the Internal Medicine Service 2 weeks later, remaining respiratory stable with analytical improvement.

**Fig. 1** **a, b** Case 1. Multiple ischemic lesions visible on DWI sequences (brain MRI) affecting the left frontal and temporal lobes and both occipital lobes. **c** Case 1. Extensive areas of hemorrhagic transformation on SWI sequences (brain MRI) affecting both occipital lobes. **d, e** Case 2. Acute bilateral ischemic lesions affecting both frontal and left occipital lobes on DWI sequences. **f** Case 2. Several microhemorrhagic foci affecting both frontal and left occipital lobes on SWI sequences



When waking up in the ICU, he was conscious without focal neurological deficits but with remarkable global altered mental status, fluctuating inattention, disorientation, inconsistent speech, and psychomotor agitation that required risperidone.

Systemic, infectious, and toxic-metabolic conditions were excluded. An electroencephalogram showed moderate encephalopathy and a brain MRI revealed acute bilateral ischemic lesions affecting both frontal and left occipital lobes, with several microhemorrhagic foci (Fig. 1d–f). Cardioembolic source and acquired antiphospholipid syndrome were ruled out. COVID-19-associated coagulopathy was suspected as the possible main etiology of the strokes, supported by the pulmonary embolism as another thrombotic complication.

## Discussion

A high frequency of cerebrovascular events is being reported in COVID-19 patients, with a prevalence of around 5% [7]. Owing to the recency of the pandemic, the available evidence of this association is based on small series and must be regarded cautiously. The strokes are frequently labeled as cryptogenic, but diagnostic investigations could not be completed in some COVID-19 patients and that may contribute to this high rate. Different mechanisms of stroke appear to be directly related to COVID-19 and are being progressively reported [4]. This includes a hypercoagulable state possibly linked to the viral invasion of the vascular endothelium, which may trigger activation of the complement system leading to thrombotic and inflammatory cascades [3, 4]. Up to 20–55% of COVID-19 hospitalized patients may present this coagulopathy [3], but those with concomitant stroke show more significant disturbances (mostly higher D-dimer levels), suggesting that this state may underlie much of stroke in this disease [5]. Furthermore, some critically ill COVID-19 patients exhibit a coagulopathy consistent with disseminated intravascular coagulation [5], as in case 1.

To our knowledge, acute confusional state and encephalopathy have been described in COVID-19 patients related to the systemic condition, without a primary neurological cause [2, 8]. Although the most common findings in stroke are focal neurological deficits, ischemic lesions in those patients might be due to multifocal and distal vessel occlusions which could more frequently manifest as an altered mental status [9]. Additionally, this could be especially relevant in younger patients without previous comorbidities, less prone to present altered mental status during an acute disease, as in the cases we report.

In view of the above and supported by our evidence, we consider important to rule out cerebrovascular entities by performing periodic neurological examinations preceded by transient withdrawal of sedatives in those intubated COVID-

19 patients with suspicion of COVID-19-associated coagulopathy. We suggest performing a brain MRI in patients with acutely altered mental status on examination and in those who cannot be clinically evaluated [8].

Full-dose anticoagulation would probably be indicated and could prevent complications in these patients, being necessary more studies to confirm this supposition [10].

## Conclusions

In conclusion, acutely altered mental status might be the main manifestation of multiple brain infarctions in critically ill COVID-19 patients and should be specially considered in those with suspected COVID-19-associated coagulopathy. Full-dose anticoagulation and clinical-radiological monitoring might reduce neurological consequences in them.

**Author contribution** Carolina Díaz-Pérez, MD, designed and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content. Carmen Ramos, MD, designed and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content. Alberto López-Cruz, MD, had a major role in the acquisition of data. José Muñoz Olmedo, MD, had major role in the acquisition of data. Jimena Lázaro González, MD, had a major role in the acquisition of data. Enrique de Vega-Ríos, MD, had a major role in the acquisition of data. Carmen González-Ávila, MD, had a major role in the acquisition of data. Carlos Hervás, MD, had a major role in the acquisition of data. Santiago Trillo, MD, PhD, interpreted the data and revised the manuscript for intellectual content. José Vivancos, MD, PhD, interpreted the data and revised the manuscript for intellectual content.

## Compliance with ethical standards

Due to the fact that it is a case report, it was not presented to the institutional Review Board or other ethics committee. Verbal informed consent was obtained from the patient's relatives to the submission of the case report.

**Conflict of interest** The authors declare that they have no conflict of interest.

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