



BRIEF COMMUNICATION

Orbitofrontal involvement in a neuroCOVID-19 patient

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Abstract

Neurological manifestations of coronavirus disease 19 (COVID-19) such as encephalitis and seizures have been reported increasingly, but our understanding of COVID-19-related brain injury is still limited. Herein we describe prefrontal involvement in a patient with COVID-19 who presented prior anosmia, raising the question of a potential trans-olfactory bulb brain invasion.

1 | INTRODUCTION

Several coronavirus disease 19 (COVID-19)-related cerebral manifestations have been reported since the start of the pandemic.¹⁻⁶ The pathophysiological mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) brain injury are still unknown and debated, with the exception of cerebrovascular complications, probably related to a

hypercoagulable state, as shown by the high rate of thrombotic events in patients with COVID-19.⁶⁻⁹ Many authors have suggested that the virus enters the central nervous system (CNS) through olfactory neurons,¹⁰ as SARS-CoV-1 invades the brains of mice brain in experimental models.¹¹ This mode of entry could also explain the frequency of anosmia observed during the onset of COVID-19.¹ However, after several months of a worldwide COVID-19 pandemic, there is no substantial evidence for the presence of SARS-CoV-2 in the brain, with the exception of two patients with SARS-CoV-2 RNA detected in their cerebrospinal fluid (CSF).^{3,12}

If we assume that SARS-CoV-2 invades the brain through the olfactory pathway, the orbital prefrontal cortex, adjacent to the olfactory bulb, should be the first region of the brain affected. This hypothesis is supported by brain 18fluoro-2-deoxy-D-glucose (18FDG) positron emission tomography computed tomography (PET-CT) that showed hypometabolism within the orbitofrontal cortex in a COVID-19 patient with isolated anosmia.¹³ In addition, another recent study found that 88.9% of electroencephalography (EEG) studies performed in COVID-19 patients for suspected encephalopathy and/or seizure-like events revealed epileptiform discharges, mostly within the frontal lobes.¹⁴ Herein we report a case of status epilepticus as the first manifestation of COVID-19. Right frontal lobe involvement was demonstrated by both magnetic resonance imaging (MRI) and EEG.

2 | CASE DESCRIPTION

A 69-year-old man was admitted to the intensive care unit (ICU) for status epilepticus requiring endotracheal

intubation, preceded by a 5-day history of cough, fever, and anosmia. SARS-CoV-2 was detected by reverse transcription-polymerase chain-reaction (RT-PCR) in a tracheal aspirate. Medical history was significant for diabetes mellitus, hypertension, and a single seizure, which had occurred 1 year earlier, related to hyperglycemia and uncontrolled diabetes. Upon admission to our ICU, the patient was treated with intravenous levetiracetam. Brain CT (computerized tomography) was unremarkable, and EEG showed repetitive 1 Hz rhythmic bursts over the right frontal region, suggestive of a nonconvulsive status epilepticus (Figure 1). Cerebrospinal fluid (CSF) examination was unremarkable, showing 1 leukocyte per cubic millimeter, 18 red blood cells per cubic millimeter, and protein and glucose levels, respectively, at 0.66 g/L and 10.5 mmol/L (blood glucose at 20 mmol/L). RT-PCR assay of the CSF was negative for SARS-CoV-2. All other tests for infectious agents and autoimmune disease were negative in serum and CSF (Table S1). Brain MRI revealed hyperintensity of the right orbital prefrontal cortex adjacent to the olfactory bulb, which seemed to spread toward the right mesial prefrontal cortex and to the right

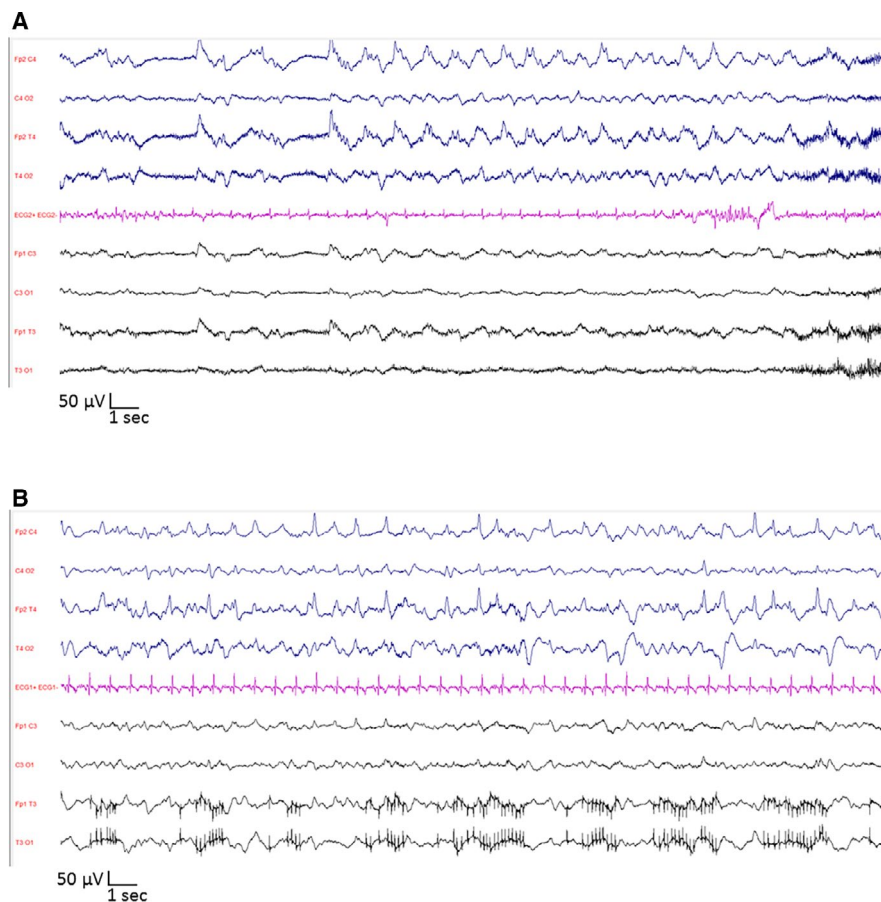


FIGURE 1 ELECTROENCEPHALOGRAPHY (EEG) findings. Samples of a scalp EEG recording, in a bipolar montage, showing (A) repetitive 1 Hz rhythmic bursts predominating on the right frontal lobe, suggestive of a nonconvulsive status epilepticus and (B) 2 days later, lateralized periodic discharges (LPDs) on the right frontal lobe

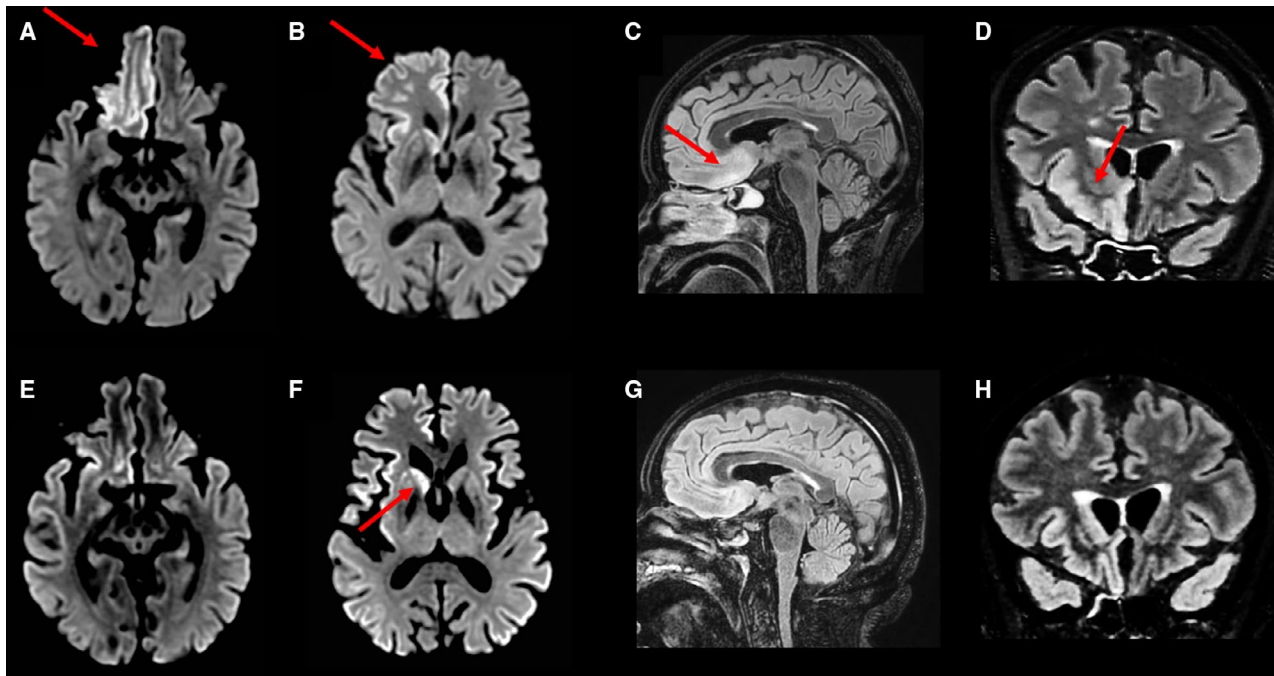


FIGURE 2 Brain magnetic resonance imaging (MRI). Upper panel: Brain MRI on admission: A and B, Axial diffusion-weighted imaging (DWI) showing right orbitofrontal cortex and caudate nucleus hyperintensity (tip of the red arrow). C, Sagittal fluid-attenuated inversion recovery (T2/FLAIR) showing right orbitofrontal cortico-subcortical hyperintensity toward the caudate nucleus (tip of the red arrow). D, Coronal T2/FLAIR showing an orbitofrontal hyperintensity (tip of the red arrow). Lower panel: Brain MRI on day 15: E and F, Axial DWI showing decrease of the hyperintensity within the right orbitofrontal cortex but persistence on the right caudate nucleus (tip of the red arrow). G, Sagittal and H, coronal T2/FLAIR showing decrease of the hyperintensity within the right orbitofrontal cortex

caudate nucleus (Figure 2A–D). No gadolinium enhancement was observed. After a multidisciplinary discussion, treatment with intravenous immunoglobulins at 2 g/kg was administered. EEG showed persistent short-interval (0.7–1.2 seconds) lateralized periodic discharges (LPDs) over the right frontal lobe on day 2. The patient improved after 1 week, allowing for weaning from mechanical ventilation, but he presented signs of frontal lobe syndrome including verbal perseverations and imitation behavior, and was drowsy for several days after extubation. MRI performed on day 15 showed the persistence of a marked hyperintensity of the right caudate nucleus and a significant decrease of the hyperintensity of the prefrontal cortex (Figure 2E–H). MRI performed on day 30 was normal. We concluded that initial MRI hyperintensities were partly due to peri-ictal diffusion abnormalities. We hypothesize that this particular form of orbitofrontal status epilepticus may have been triggered by the passage of SARS-CoV-2 through the olfactory pathway.

3 | DISCUSSION

This case of orbital and mesial prefrontal involvement of COVID-19 provides insight into the early steps of SARS-CoV-2 brain invasion, and reinforces the broadly

suspected hypothesis of neuroinvasion directly through olfactory epithelium, but many questions still remain unanswered.

First, if we assume that electrophysiological and radiological abnormalities result from direct viral injury to neurons, the expected consequences would be neuronal death and necrosis, classically reported in acute necrotizing encephalitis related to herpes simplex virus type 1. In this case, the virus would invade the CNS through retrograde axonal transport after olfactory bulb invasion, and then spread toward cortical and/or deep gray matter structures. In our patient, clinical and radiological features improved, making direct viral damage unlikely. Moreover, CSF was negative for SARS-CoV-2. However, because no brain biopsy was performed due to the patient's clinical improvement, we cannot exclude that this process occurred.

Second, post-infectious encephalitis could be hypothesized. The radiological pattern observed in our case was strictly different from that observed in acute disseminated encephalomyelitis,^{15,16} but immune-mediated encephalitis cannot be ruled out, even if an extensive work-up was inconclusive. In addition, the patient received intravenous immunoglobulins, with clinical and radiological recovery, but evidence for a causal relationship between treatment and improvement is weak, and there is little of evidence for efficacy of intravenous immunoglobulins in COVID-19.

Third, another possibility is sepsis-associated encephalopathy, due to blood-brain barrier (BBB) dysfunction related to systemic infection.¹⁷ Viral infection of olfactory epithelium, could lead to release of regional cytokines, which, in turn, could cause involvement of the contiguous orbitofrontal cortex, through local BBB leakage, with migration of leukocytes and activation of microglial cells.

Finally, this patient with significant vascular risk factors could have had previous unknown right frontal vascular disease that produced seizures in the setting of an intercurrent infection, but normal brain MRI on day 30 excluded this hypothesis.

To conclude, whether COVID-19-related CNS dysfunction results from direct viral injury, indirect consequences of immune-mediated disease, systemic effects of infection, or local effects of the virus is still a matter of debate and these hypotheses are not mutually exclusive. However, the recent reports of frontal hypometabolism on PET-CT, frontal EEG abnormalities during COVID-19, and our case description are strong arguments in favor of a “SARS-CoV-2-related-frontal involvement,” whether direct or indirect.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare in relationship with this manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHORS CONTRIBUTIONS

LLG, JD, SD, and NW wrote the manuscript. AC, DG, VN BR, and DB critically reviewed the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

In accordance with the ethical standards of our hospital's Institutional Review Board (Committee for the Protection of Human Subjects) and current French law, informed consent for demographic, physiological, and hospital-outcome data analyses was not obtained because this case report did not modify existing diagnostic or therapeutic strategies. Nonetheless, patients and/or relatives were informed about the anonymous data collection and told that they could decline inclusion. This database

is registered at the Commission Nationale de l'Informatique et des Libertés (CNIL, registration no. 1950673).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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