Corticosteroid Responsive Encephalopathy: Prolonged Coma in Patients Late in the Course of Dreadful Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Background: Responsible for the coronavirus disease 2019 pandemic that began in December 2019, severe acute respiratory syndrome coronavirus 2 mainly causes respiratory insult. Few cases were reported of extrapulmonary involvement, many of which were neurologic.

Case Summary: In this case report, we present two cases of prolonged coma after weaning off sedation in severe acute respiratory syndrome coronavirus 2 patients with rapid neurologic improvement shortly after high-dose corticosteroid regimen.

Conclusions: We thus hypothesize an inflammatory process being responsible for the prolonged coma. Inflammatory neurologic insult has been described with other coronaviruses. Further studies are needed to determine the extent and underlying mechanism of neurologic involvement in severe acute respiratory syndrome coronavirus 2 infections.

Key Words: coma; corticosteroids; encephalopathy; inflammation; severe acute respiratory syndrome coronavirus 2 infection

We present two cases of prolonged coma after withdrawal of sedation in patients recovered from dreadful severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection complicated with acute respiratory distress syndrome (ARDS). Both patients gave their informed consent to participate in this case report.

The first case was a 73-year-old woman (Table 1). She was admitted to ICU and intubated due to severe ARDS secondary to SARS-CoV-2 infection. She needed profound sedation (Richmond Agitation-Sedation Scale-5) for 13 days. She remained comatose after withdrawal of sedation, with a Glasgow Coma Scale (GCS) of 6/15 (spontaneous eye opening, without visual contact) and a mean Full Outline of UnResponsiveness (FOUR) score of 9/16. Brain MRI and electroencephalogram (EEG) were nonspecific. Lumbar puncture showed an isolated elevated protein level of 964 mg/L and oligoclonal band analysis showed a dysfunction of the blood-brain barrier with a type 4 profile (according to the oligoclonal band [OCB] classification) (1). Cerebrospinal fluid (CSF) meningoencephalitis polymerase chain reaction (PCR) panel, SARS-CoV-2 PCR, and fungal cultures returned negative. After excluding metabolic encephalopathy, structural abnormalities, and persistence of sedative drugs, we hypothesized an inflammatory encephalopathy secondary to the SARS-CoV-2 infection and initiated an empirical high-dose corticosteroid regimen (methylprednisolone 1 g/d for 3 d, followed by oral prednisone 1 mg/kg/d). In the next 2 days, we observed a rapid clinical improvement, reaching a GCS of 15/15 and a FOUR score of 13/16 (she remained intubated due to dysphagia) (Fig. 1).

The second case was a 73-year-old male (Table 1). He was intubated and sedated for 9 days due to severe ARDS secondary to SARS-CoV-2 infection. Eight days after withdrawal of all sedation, his GCS remained at 3/15 with a mean FOUR score of 8/16. Brain MRI did not show any signs of ischemia or hemorrhage. An EEG showed signs of diffuse encephalopathy. Lumbar puncture revealed an isolated elevated protein level of 907 mg/L and oligoclonal band analysis showed a dysfunction of the blood-brain barrier with a type 3 profile (according to the OCB classification) (1). CSF meningoencephalitis PCR panel, SARS-CoV-2 PCR, and fungal cultures returned negative. After excluding metabolic encephalopathy, structural abnormalities, and persistence of sedative drugs, we hypothesized an inflammatory encephalopathy secondary to the SARS-CoV-2 infection and initiated an empirical high-dose corticosteroid regimen (methylprednisolone 1 g/d for 3 d, followed by oral prednisone 1 mg/kg/d). In the next 2 days, we observed a rapid clinical improvement, reaching a GCS of 15/15 and a FOUR score of 13/16 (she remained intubated due to dysphagia) (Fig. 1).

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# TABLE 1. Summary of Relevant Patient History, Investigations, Treatment and Complications

|                                | Patient 1                                                                                                                                                                                                 | Patient 2                                                                                                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Sex, age**                   | Female, 73 yr old                                                                                                                                                                                      | Male, 73 yr old                                                                                                                                                                                      |
| **Relevant comorbidities**     | Rheumatoid arthritis (treated with baricitinib), hypertension, obesity, and previous smoker                                                                                                                                 | Myasthenia gravis, thromboembolic disease, atrial fibrillation, and prostate adenocarcinoma                                                                                                                |
| **Symptoms of SARS-CoV-2**     | Cough, fever, and hypoxemia                                                                                                                                                                              | Cough, fever, and dyspnea                                                                                                                                                                              |
| **Acute respiratory distress syndrome** | **Severe**                                                                                                                                                                                               | **Severe**                                                                                                                                                                                               |
| **Anosmia/ageusia**            | No                                                                                                                                                                                                        | No                                                                                                                                                                                                       |
| **ACEI/ARA**                   | Valsartan                                                                                                                                                                                               | No                                                                                                                                                                                                       |
| **Treatment received**         | **Antibiotherapy**  
Levofoxacin (days 1 and 2)  
Amoxicillin/clavulanic acid (days 3–10)  
Meropenem (days 11–18)                                                                                                                                  | Meropenem (days 1–15)  
Amoxicillin/clavulanic acid (days 15–17)  
Metronidazole (days 17–24)  
Vancomycin (day 7–14)  
Fluconazole (days 7–14)                                                                                                           |
|                                | **Anti-SARS-CoV-2-oriented**  
Atazanavir/ritonavir (7 d)  
Hydroxychloroquine (7 d)  
Tocilizumab (two doses)                                                                                                                                         | Lopinavir/ritonavir (7 d)  
Immunoglobulin (5 days; total, 2 g/kg)  
Coronavirus disease 2019 convalescent plasma (twice)                                                                                                           |
| **Sedation: molecule (duration)** | **Propofol** (mean, 300 mg/hr; days 1–10)  
Fentanyl (mean, 50 µg/hr; days 1–10)  
Midazolam (mean, 2 mg/hr; days 1–3)  
Cisatracurium (days 1–6)  
Dexmedetomidine (days 10–13)                                                                 | **Propofol** (mean, 300 mg/hr, days 1–10)  
Fentanyl (mean, 50 µg/hr; days 1–3)  
Midazolam (mean, 3–4 mg/hr; day 1)                                                                                                                   |
| **Complications during ICU stay** | **Acute kidney injury and invasive candidiasis with cutaneous manifestation**                                                                                                                     | **Acute kidney injury and sealed-off duodenal perforation**                                                                                                                                          |
| **Sequential Organ Failure Assessment score** | Minimum 5/24, maximum 12/24                                                                                                                                                                           | Minimum 3/24, maximum 8/24                                                                                                                                                                           |
| **Simplified Acute Physiology Score II** | 38 points                                                                                                                                                                                              | 24 points                                                                                                                                                                                             |
| **Neurologic investigations and results** | Biology: acute kidney injury and mild hypernatremia  
Brain CT scan: normal  
Brain MRI: normal  
EEG (twice): no irritative signs and signs of toxic-metabolic encephalopathy  
CSF analysis: opening pressure of 32 mm Hg, elevated protein (964 mg/L), oligoclonal band analysis: dysfunction of the blood-brain barrier with a type 3 profile (according to the OCB classification), meningoencephalitis panel negative (HSV-1, HSV-2, VZV, E. coli, H. influenzae, L. monocytogenes, N. meningitidis, S. agalactiae, S. pneumoniae, Enterovirus, C. neoformans/C. gattii, and SARS-CoV-2-PCR negative)  
ENMG: known and unchanged polyneuropathy                                                                                       | Biology: acute kidney injury  
Brain MRI: normal  
EEG: no irritative signs and signs of toxic-metabolic encephalopathy  
CSF analysis: elevated protein (907 mg/L); oligoclonal band analysis: dysfunction of the blood-brain barrier with a type 3 profile (according to the OCB classification), meningoencephalitis panel negative (HSV-1, HSV-2, VZV, Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Enterovirus, and Cryptococcus neoformans/Cryptococcus gattii), and SARS-CoV-2-PCR negative  
ENMG: known and unchanged polyneuropathy                                                                                                           |

**Delay from withdrawal of sedation to corticosteroid initiation**  
| Patient 1 | 11 d                                                                                                                                                                                                | Patient 2 | 8 d                                                                                                                                 |
| Delay from withdrawal of sedation to MRI | 7 d                                                                                                                                                                                                 | 3 d                                                                                       |

ACEI = angiotensin converting enzyme inhibitor, ARA = angiotensin 2 receptor antagonist, CSF = cerebrospinal fluid, EEG = electroencephalogram, ENMG = electroneuromyography, HSV = herpes simplex virus, OCB = oligoclonal band, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SARS-CoV-2-PCR = severe acute respiratory syndrome coronavirus 2 polymerase chain reaction.
A secondary inflammatory insult following SARS-CoV-2 infection was suspected to be responsible for the prolonged coma in our patients, as metabolic, toxic, and active infectious etiologies were ruled out.

Previous studies have shown a neurotropism for many coronaviruses (2). SARS-CoV-2, responsible for the coronavirus disease 2019 pandemic that emerged in China in December 2019, has also been associated with neurologic complications. Neuroinvasive capabilities of SARS-CoV-2 and the exact mechanism of CNS invasion remain unclear, with two major hypothesis: hematogenous and through the olfactory bulb (2, 3). Neurologic involvement could be directly due to viral replication or secondary to the development of an autoimmune-triggered response. SARS-CoV-2 has been shown to use its surface glycoproteins to bind to angiotensin-converting enzyme 2 receptors on target cells, which are found especially on cell membranes of respiratory epithelium and type II alveolar cells and vascular endothelium. A recent anatomopathological study of three SARS-CoV-2-infected samples showed proof of direct endothelial cell invasion, resulting in diffuse endothelial inflammation, with signs of lymphocytic-induced endotheliitis in several organs (lung, heart, kidneys, and liver) (4).

Clinical involvement of this neurologic invasion remains poorly documented. A retrospective study of 99 patients in Wuhan, China, showed only 8% had headaches and 9% had acute delirium (5). A systematic review suggested that headache was the most frequent symptom. A French study identified neurologic insult in 58 patients admitted to the ICU for SARS-CoV-2-induced ARDS. Among them,
14% already had neurologic symptoms at admission and up to 67% after sedation. Symptoms included acute delirium in 65% of patients, psychomotor agitation in 69%, corticospinal signs in 67%, and executive dysfunction in 36%. EEGs carried out on eight patients showed nonspecific changes and in only one patient was a diffuse bilateral frontal slowing consistent with encephalopathy described. Lumbar punctures in seven patients showed no pleocytosis. High CSF protein levels were found in only one patient. SARS-CoV-2 reverse transcriptase PCR was negative in all tested CSF samples. As opposed to our two patients, these cohort studies did not report any case of delayed awakening (6).

Previous case reports described patients with cerebral hemorrhage potentially caused by SARS-CoV-2 infection or other types of encephalitis. The cause of the insult was thought to be directly from the virus itself, and investigations (namely, MRI or EEG) were abnormal, as opposed to our two patients (7).

A recent review of neurologic complications observed with SARS-CoV-2 confirmed that headache was a frequent complaint, probably due to cytokines and chemokines triggering nociceptive sensory neurons. Between 5.1% and 88% of patients with SARS-CoV-2 report anosmia and ageusia. Encephalopathy might present with delirium, confusion, or coma, possibly due to cytokine storm (8).

No case of postinfectious prolonged coma in patients infected with SARS-CoV-2 has been described to date to the best of our knowledge. In our two patients, as iatrogenic factors (namely, sedative accumulation) and structural or electrical abnormalities were reasonably excluded (with the limitation that we did not have access to continuous EEG monitoring at our center), we hypothesized that this coma might be due to cerebral inflammation secondary to cytokine storm or directly due to SARS-CoV-2 infection. When considering the remarkable evolution after potent anti-inflammatory treatment, we hypothesized that these prolonged comas were related to postviral CNS inflammation. More studies are needed to understand the physiology of late CNS presentations in SARS-CoV-2 infections. High-dose corticosteroids should be considered in such cases after exclusion of other possible origins.

Drs. Montaut and Madigan contributed equally to the redaction of this case report.

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