Extensive cerebellar involvement and cognitive impairment in COVID-19-associated acute necrotizing encephalopathy

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Abstract: Neurological complications of the newly appeared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are increasingly recognized. Here, we report a case of a young male presenting with a clinical and neuroimaging scenario of an acute necrotizing encephalopathy related to the coronavirus disease 2019 (COVID-19). This case is notable by its distinct pattern of magnetic resonance imaging findings of an extensive involvement of the cerebellum, and emergence of cognitive and behavioral impairment.

Keywords: acute necrotizing encephalopathy, cerebellum, COVID-19, SARS-CoV-2

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Introduction
Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic provoked by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a wide array of neurological manifestations, ranging from headache, dizziness, and seizures, to encephalopathy, meningitis/encephalitis, and stroke have already been reported. In addition to this, several cases of acute necrotizing encephalopathy have been recently evidenced. However, the possible clinical and neuroimaging signs of the COVID-19-related acute necrotizing encephalopathy remain underexplored.

Here, we extend the spectrum of clinical and neuroimaging findings of the acute necrotizing encephalopathy by presenting a case of a young patient who developed acute necrotizing encephalopathy with a widespread involvement of the cerebellum in conjunction with cognitive and behavioral impairment.

Case report
A 44-year-old man complaining of fever, shortness of breath, and cough was admitted to our emergency department. His previous medical history was unremarkable. The chest X-ray revealed bilateral interstitial pneumonia. The initial blood test results were indicative of a viral infection, that is, increased white blood cell count (10,150/μl), mild absolute lymphopenia (967/μl), and elevated C-reactive protein (63 mg/ml). Real-time polymerase chain reaction (RT-PCR) assay from naso- and oropharyngeal swabs were positive for SARS-CoV-2 infection. According to the national guidelines on COVID-19 management, treatment with azithromycin 500 mg qd, hydroxychloroquine 400 mg bid, and lopinavir/ritonavir 200 mg/50 mg bid was started.

After 1 week of hospitalization, the patient developed symptoms of an acute neurological dysfunction suggestive of an encephalopathy: severe headache, followed by altered mental status (confusion, disorientation, amnesia). On neurological examination, the patient had a decreased level of consciousness: Glasgow coma scale 13 (E3/V4/M6), nuchal rigidity, and positive bilateral Kernig sign. A clinical suspicion of meningitis/encephalitis was raised. Head computed tomography (CT) did not reveal any hypo- or hyperattenuating brain lesions (Figure 1A). On the simultaneously performed chest CT, multiple, bilateral ground glass opacities and consolidation with a peripheral and extensive cerebellar involvement and cognitive impairment in COVID-19-associated acute necrotizing encephalopathy

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predominantly posterior lung distribution were identified (Figure 1B). The patient was referred to the intensive care unit (ICU), where he underwent an initial lumbar puncture (LP) that showed slightly elevated chloride levels and the presence of red blood cells in the cerebrospinal fluid (CSF) (Table 1). Intravenous infusion with methylprednisolone (1000 mg/day) was started. Due to progressive respiratory deterioration and hypoxemia (pulse oximetry <80%) the patient was intubated and ventilated mechanically for 3 days. He was continuously sedated with propofol, achieving a score of −3 on the Richmond Agitation-Sedation Scale. After 3 days, the dose of methylprednisolone was reduced to 500 mg/day.

After clinical improvement and recovery of spontaneous respiration, the patient was examined

Table 1. CSF cell and metabolite dynamics.

| Parameters | 1st LP (day 1)a | 2nd LP (day 4)a | 3rd LP (day 11)a | Reference values |
|------------|-----------------|-----------------|------------------|------------------|
| Appearance | Clear           | Clear           | Clear            | −                |
| Protein [g/l] | 0.30           | 0.28            | 0.33             | <0.5             |
| Glucose [mmol/l] | 3.70           | 3.40            | 5.20             | 3.5–6.2          |
| Chloride [mmol/l] | 123            | 104             | 106              | 97–115           |
| Cell count [/µl] | 4              | 11              | 5                | <5               |
| Lymphocytes (%) | 100            | 90              | 100              | 40–80%           |
| Erythrocytes | 2–3            | 40–50           | 20–25            | Absent           |

aDay after the onset of neurological symptoms. CSF, cerebrospinal fluid; LP, lumbar puncture.
repeatedly for neurological status, which revealed bilateral limb ataxia with left limbs being more affected, bulbar palsy (mainly dysphonia and dysphagia), decreased gag reflex, and no nystagmus. On the next day, 1.5T brain magnetic resonance imaging (MRI) showed bilateral, symmetrically distributed lesions within the infra- and supratentorial structures with the predominant involvement of both cerebellar hemispheres and vermis (Figure 2A–F). The lesions were characterized by a hyperintense signal on fluid-attenuated inversion recovery and diffusion-weighted images (restricted diffusion), hypo-hyperintense signal on T1-weighted images, and hypointense signal on susceptibility weighted images (hemorrhage). The restricted diffusion indicative of a cytotoxic edema was confirmed by a hypointense signal on the apparent diffusion coefficient maps. There was a faint contrast enhancement on T1-weighted post-contrast images. Extracerebellar lesions with similar imaging appearance were also identified in both thalami (Figure 2G–L). The pattern described was compatible with an acute necrotizing encephalopathy related to SARS-CoV-2 infection.

A second LP performed on the 4th day after the onset of neurological symptoms showed a slight pleocytosis and the presence of red blood cells. RT-PCR for SARS-CoV-2 in the CSF was negative. PCR for other viruses, that is, herpes simplex virus 1 and 2, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6, was also negative, as was CSF culture for bacteria and fungi. The third LP was normal, other than the presence of red blood cells. Serum and CSF levels of interleukin-6 (IL-6) could not be quantified due to the unavailability of corresponding assays in our hospital.

Over the next 2 weeks, the patient’s cerebellar and bulbar syndromes slowly improved, but at the same time cognitive and behavioral impairment emerged. Cognitive impairment was characterized by reduced visuospatial ability, verbal fluency, and attention. Behavioral impairment was characterized by episodes of sudden screaming, self-hits to the chest, poor judgment and insight, and disinhibition (i.e., urinating in the room, inappropriate naked body postures, etc.). The neuropsychological examination showed mild cognitive dysfunction (Montreal Cognitive Assessment score: 23), moderate depression (Beck Depression Inventory score: 19), and no anxiety (Hamilton Anxiety Rating Scale score: 9).

To control the behavioral manifestations risperidone 1 mg bid was prescribed. A second MRI performed 2 weeks after the first revealed partial regression of the cerebellar lesions. The patient

Figure 2. Brain MRI. Widespread bilateral cerebellar and thalamic lesions [arrows] showing a hyperintense signal on axial fluid-attenuated inversion recovery images [A, G], restricted diffusion [cytotoxic edema] on diffusion-weighted images [B, H], and apparent diffusion coefficient maps [C, I], hemorrhages on susceptibility-weighted images [D, J], hypo-hyperintense signal on T1-weighted pre-contrast images [E, K], and contrast enhancement on T1-weighted post-contrast images [F, L].

MRI, magnetic resonance imaging.
was kept on gradually tapered methylprednisolone until discharge. After obtaining a negative oropharyngeal swab result for SARS-CoV-2, the patient was discharged with a slight disability (modified Rankin Scale score: 1–2) and minor behavioral symptoms.

**Discussion**

Previously, several cases of acute necrotizing encephalopathy due to SARS-CoV-2 have been recognized. Clinically, acute necrotizing encephalopathy is characterized by seizures, altered mental status, and focal neurological deficits. The neuroimaging features of acute necrotizing encephalopathy are the presence of multiple and symmetrically distributed lesions (sometimes with hemorrhages) within the thalamus, basal ganglia, brainstem, and subcortical white matter. The presumed first case of acute necrotizing encephalopathy in a female patient with lesions within the bilateral thalami and medial temporal lobes was reported by Poyiadji *et al.* Additionally, similar cases with brainstem involvement and aplastic anemia, with extrapulmonary complications (myocarditis), and with detected SARS-CoV-2 in the CSF were later described. Cytokine storm triggered by the SARS-CoV-2 is thought to account for the emergence of acute necrotizing encephalopathy. The anti-inflammatory effect of the steroids might be responsible for the neurological and neuroimaging improvement observed in our patient.

The spectrum of COVID-19-associated neurological complications also includes immune-mediated para- and post-infectious disorders that might present with a clinical and neuroimaging profile similar to acute necrotizing encephalopathy. Acute hemorrhagic leukoencephalitis (or Weston-Hurst syndrome) is one of the entities to be taken into account in the differential diagnosis. Acute hemorrhagic leukoencephalitis is a rare and severe variant of the acute disseminated encephalomyelitis, characterized by multifocal and symmetrical brain lesions within the brain hemispheres, basal ganglia, brainstem, and cerebellum. These lesions are associated with hemorrhages and demyelination, and are caused by an excessive immunological response triggered by the molecular mimicry between human myelin and viral antigens. Recently, a case of COVID-19-associated acute hemorrhagic leukoencephalitis presenting with hemorrhagic lesions within the basal ganglia and sparing the thalamus was described. Interestingly, these lesions had a concentric pattern of demyelination on brain MRI, that is, alternation of areas of hyperintensity and isointensity. Also, several other cases of COVID-19-associated acute disseminated encephalomyelitis with hemorrhages were reported by Paterson *et al.* The patients described presented multiple lesions with petechial hemorrhages in various brain regions, but mainly in the subcortical white matter and without thalamic involvement.

As both acute necrotizing encephalopathy and acute hemorrhagic leukoencephalitis share many similarities, their definite diagnosis might be challenging. Nevertheless, some hints might be helpful for their distinction. First, thalamic involvement occurs constantly in acute necrotizing encephalopathy, and is infrequent in acute hemorrhagic leukoencephalitis. Second, CSF lacks inflammatory cell invasion in acute necrotizing encephalopathy, but is dominated by a neutrophilic pleocytosis in acute hemorrhagic leukoencephalitis. Additionally, applying the diagnostic criteria of the acute necrotizing encephalopathy proposed by Neilson might help in distinguishing these pathologies. In our case, the presence of bilateral thalamic lesions along with cerebellar lesions and a non-inflammatory CSF are in favor of an acute necrotizing encephalopathy.

Overall, our case is unique in its presentation of the COVID-19-related acute necrotizing encephalopathy due to a peculiar constellation of widespread cerebellar involvement and cognitive/behavioral disturbances, and thus is a valuable addition to current neurological practice.

**Conclusion**

Acute necrotizing encephalopathy with a predominant involvement of the cerebellum and cognitive impairment might be one of the neurological manifestations of COVID-19. Due to its high mortality and disability rate, the spectrum of the clinical and neuroimaging presentation of COVID-19-related acute necrotizing encephalopathy requires further research and more in-depth description. The clinical suspicion of acute necrotizing encephalopathy should be raised in every patient with altered mental status and signs of focal neurological damage.
Author contributions
DC and SAG: data collection, analysis and interpretation, drafting and revising the manuscript. IC and EZ: data collection, analysis and interpretation, revising the manuscript. NG and VC: data collection and interpretation, revising the manuscript. DE, DM and MC: interpretation of the data, revising the manuscript.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethics statement
The present study was approved by the local Ethics Committee of the Institute of Emergency Medicine (notification no. 81 from 02.07.2020) and is in accordance with the Declaration of Helsinki. The patient signed the written consent to publish the medical data and images.

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