Stroke

BRIEF REPORT

Large and Small Cerebral Vessel Involvement in Severe COVID-19

Detailed Clinical Workup of a Case Series

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BACKGROUND AND PURPOSE: Case series indicating cerebrovascular disorders in coronavirus disease 2019 (COVID-19) have been published. Comprehensive workups, including clinical characteristics, laboratory, electroencephalography, neuroimaging, and cerebrospinal fluid findings, are needed to understand the mechanisms.

METHODS: We evaluated 32 consecutive critically ill patients with COVID-19 treated at a tertiary care center from March 9 to April 3, 2020, for concomitant severe central nervous system involvement. Patients identified underwent computed tomography, magnetic resonance imaging, electroencephalography, cerebrospinal fluid analysis, and autopsy in case of death.

RESULTS: Of 32 critically ill patients with COVID-19, 8 (25%) had severe central nervous system involvement. Two presented with lacunar ischemic stroke in the early phase and 6 with prolonged impaired consciousness after termination of analgosedation. In all but one with delayed wake-up, neuroimaging or autopsy showed multiple cerebral microbleeds, in 3 with additional subarachnoid hemorrhage and in 2 with additional small ischemic lesions. In 3 patients, intracranial vessel wall sequence magnetic resonance imaging was performed for the first time to our knowledge. All showed contrast enhancement of vessel walls in large cerebral arteries, suggesting vascular wall pathologies with an inflammatory component. Reverse transcription-polymerase chain reactions for SARS-CoV-2 in cerebrospinal fluid were all negative. No intrathecal SARS-CoV-2-specific IgG synthesis was detectable.

CONCLUSIONS: Different mechanisms of cerebrovascular disorders might be involved in COVID-19. Acute ischemic stroke might occur early. In a later phase, microinfarctions and vessel wall contrast enhancement occur, indicating small and large cerebral vessels involvement. Central nervous system disorders associated with COVID-19 may lead to long-term disabilities. Mechanisms should be urgently investigated to develop neuroprotective strategies.

Key Words: central nervous system ■ cerebrospinal fluid ■ cerebrovascular disorders ■ coronavirus disease ■ neuroimaging

Individual coronavirus disease 2019 (COVID-19) case descriptions with acute ischemic stroke have been published.[1–3] Comprehensive workups of as many cases as possible are needed to understand a potential Neuro-COVID-19 disease. Below 8 cases of severe COVID-19 pneumonia with subsequent neurological complications are presented.

METHODS

Data that support the findings of this study are available from the corresponding author upon reasonable request. From March 9 to April 3, 2020, we analyzed 8 consecutive patients with severe COVID-19 and concomitant severe central nervous system (CNS) involvement treated at the Intensive Care Unit, University Hospital Zurich, and Graubuenden Cantonal

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Nonstandard Abbreviations and Acronyms

ACE-2	angiotensin-converting enzyme 2
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
IL-6	interleukin-6
MRI	magnetic resonance imaging
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Hospital. The study was approved by the local ethics committee. Written consent was given by legal representatives, as all patients were incapable of judgment.

Severe cerebral dysfunctions triggering comprehensive diagnostic workup were impaired consciousness (negative or delayed wake-up attempt after the termination of analgosedation with persistent coma or stupor for >3 days and midazolam serum levels below detection limit), focal neurological deficits, and seizure/status epilepticus. For information on neuroimaging, electroencephalography recordings, blood serum, and cerebrospinal fluid (CSF) analyzes, please see Expanded Material & Methods in the Data Supplement.[4–6]

Descriptive statistics and frequency analysis are calculated to describe study sample characteristics. Mean, SD and median, range are used where appropriate.

RESULTS

Eight (25%) of 32 critically ill patients with COVID-19 (age [SD] 67.6 [6.8] years, 7 male) presented with severe CNS involvement including negative/delayed wake-up attempt with persistent coma or stupor, myoclonic movements, hemiparesis, and dysarthria. Two patients died. Patient characteristics are given in Table I in the Data Supplement. Two patients presented with primary focal neurological deficits due to ischemic stroke with single lacunar ischemic lesions in the initial computed tomography. Follow-up magnetic resonance imaging (MRI) scans showed additional small ischemic lesions in different vascular territories, indicating cerebral small vessel disease. All but one patient presented with impaired consciousness after termination of analgosedation. In all but 2, MRI showed multiple cerebral microbleeds, in 3 with additional subarachnoid hemorrhage (Figure 1). Computed tomography or magnetic resonance (MR) angiographies performed in 7 patients showed no signs of vasculitis. Three patients showed contrast enhancement of large- to middle-sized cerebral arteries in vessel wall imaging indicating large cerebral vessel involvement (Figure 2).

Laboratory findings and results from stroke workup are given in Tables II and III in the Data Supplement, respectively. All CSF samples were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and showed no signs of inflammatory syndrome. While SARS-CoV-2-specific IgG was detected in all sera, no intrathecal SARS-CoV-2-specific IgG synthesis was detectable. In 2 patients, metagenomic virus sequencing of CSF was negative. All patients showed similar, unspecific electroencephalography patterns with background slowing and anterior rhythmic delta activity, consistent with metabolic encephalopathy.

Brain autopsy of one patient showed microbleeds in the pontine tegmentum and microinfarcts in the basal ganglia. Around the rostral surface of the cerebellum extensive, subarachnoid hemorrhage was found. Adjacent cerebral tissue showed multiple fresh microinfarcts and parenchymal hemorrhages.

At time of submission, all surviving patients were still hospitalized but showed significant neurological recovery (3 with mild cognitive deficits, one with persistent myoclonic movements).

DISCUSSION

In the Wuhan series, 27 of 88 patients hospitalized with severe COVID-19 infection (30.7%) had CNS symptoms.[7] Thirteen of them (48.1%) suffered from impaired consciousness. Most of our patients presented with prolonged impaired consciousness, 2 of them with acute ischemic stroke early after disease onset. Few series of patients with large vessel stroke have been described.[1–3] Severe COVID-19 mostly develops in patients with cardiovascular risk factors and is characterized by a pronounced proinflammatory early phase,[8] both increasing stroke risk.

Extraordinary findings in our series were detected later in the illness course. In all but one patient with delayed wake-up, neuroimaging or autopsy showed multiple cerebral microbleeds, in 2 with additional small ischemic lesions, indicating CNS small vessel disease. Different factors might explain the involvement of small cerebral vessels. All but one patient had hypertension. Cerebral microbleeds might be unspecific in the present patient population with cardiovascular risk factors. Hypertension-type microbleed distribution, however, was present in only one patient. None had a history of cerebral amyloid angiopathy. All had a hypercoagulable state with increased fibrinogen and D-dimer levels, which might lead to thrombotic microangiopathy, but only one fulfilled the disseminated intravascular coagulation disorder criteria.[9]

In 3 patients with severe COVID-19, intracranial vessel wall MRIs were performed, for the first time to our knowledge. MR vessel wall imaging showed contrast enhancement of vessel walls in large- and middle-sized cerebral arteries, suggesting inflammatory vascular wall pathologies. However, MRI vessel wall contrast enhancement is nonspecific for vasculitis involving cerebral vessels. None of our patients showed inflammatory CSF or characteristic autoantibodies indicating systemic vasculitis. Vessel

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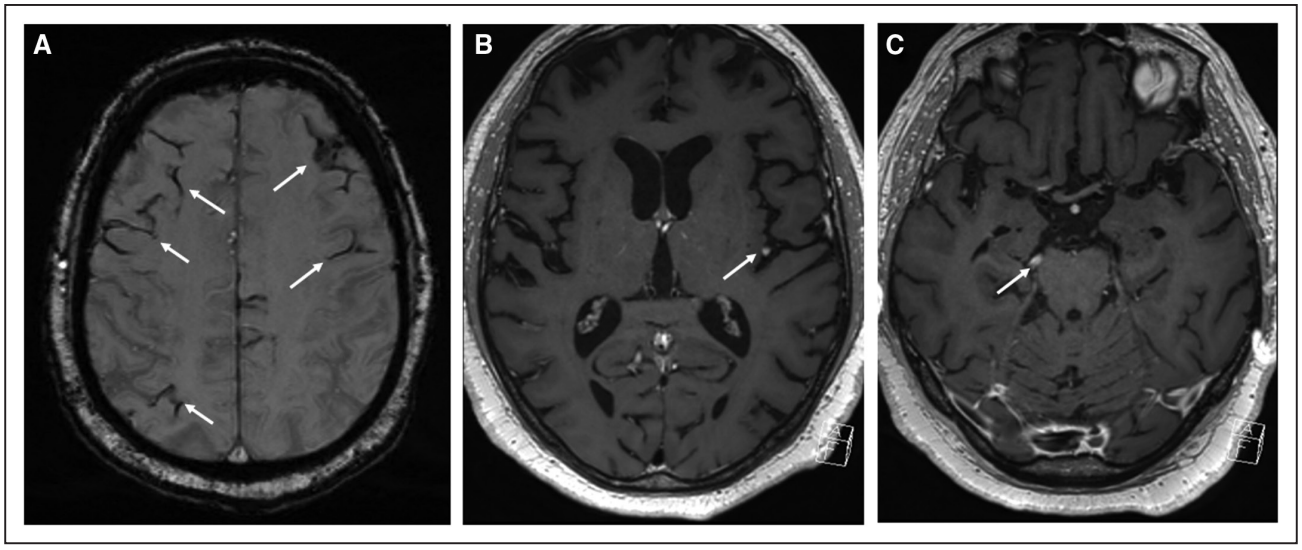

Figure 1. Magnetic resonance imaging (MRI) findings in patient 2.
Susceptibility-weighted imaging (SWI) shows subarachnoid hemorrhage (**A**). Intracranial vessel wall imaging (VWI) demonstrates vessel wall contrast enhancement of the left middle cerebral artery (MCA; **B**) and right posterior cerebral artery (PCA; **C**).

wall contrast enhancement may be interpreted as unspecific endothelial dysfunction. Autopsy results of one patient, however, showed systemic endothelial damage and endotheliitis affecting several organs. This suggests that cerebral vessels might also be affected. Infectious and immune-mediated vasculitis may cause CNS vessel disease, and a certain type of vasculitis involving cerebral vessels might also be induced by COVID-19. An autopsy study in patients with severe COVID-19 revealed lymphocytic endotheliitis in multiple organs.[10] The ACE-2 (angiotensin-converting enzyme 2), as the main host cell receptor of SARS-CoV-2, is also expressed in the endothelium of the brain.[11] It might be that the endothelium is directly affected by the virus or that the virus induces a parainfectious immune-mediated endotheliitis. However, in the only postmortem analysis, we did not find any histopathologic sign of infectious cerebral vasculitis or perivascular inflammatory cell infiltration. Another mechanism might be that the cerebral vessels are affected by the inflammatory state in the peripheral blood. Increased levels of cytokines play an important role in the immunopathology of COVID-19.[8] In our patients, serum IL (interleukin)-6 was elevated in all but one. Cytokines or inflammation-induced metabolic changes leaking from peripheral blood to the CNS micromilieu might lead to disturbances of the blood-brain barrier and dysfunction of the brain tissue.

The study has several limitations. Only 8 patients were studied. The actual onset of CNS symptoms might have remained undetected in patients under analgosedation.

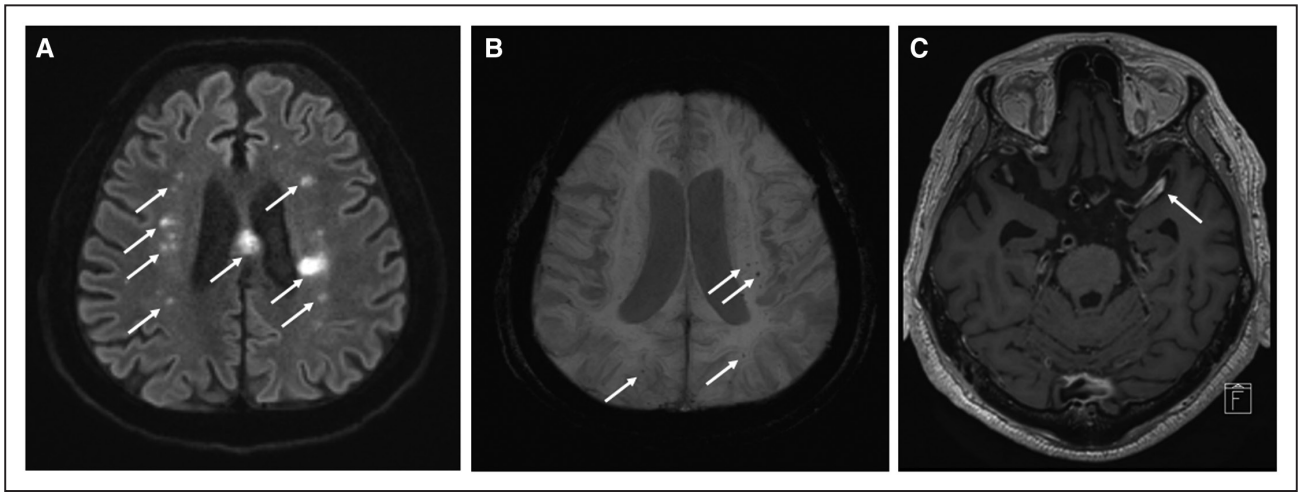

Figure 2. Magnetic resonance imaging (MRI) findings in patient 6.
Diffusion-weighted imaging (DWI) shows multiple subacute ischemic lesions in different territories (**A**) and ubiquitous microbleeds in susceptibility-weighted imaging (SWI; **B**). Intracranial vessel wall imaging (VWI) demonstrates vessel wall contrast enhancement of the left middle cerebral artery (MCA; **C**).

CSF analysis might not have coincided with the occurrence of cerebral complications. Therefore, inflammatory CSF signs might have been missed. Furthermore, reverse transcription-polymerase chain reaction assay for SARS-CoV-2 in the CSF are not validated regarding sensitivity and timing of lumbar puncture.

CONCLUSIONS

Severe cerebrovascular disorders are common in patients with severe COVID-19. Besides early primary stroke, in a later phase, microbleeds, microinfarctions, and vessel wall contrast enhancement occur, indicating small and large cerebral vessel involvement. This calls for implementation of standardized diagnostic protocols for MRI, electroencephalography, and CSF analysis in clinical practice and further research to clarify whether SARS-CoV-2 directly affects endothelial cells of brain vessels.

ARTICLE INFORMATION

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Supplemental Materials

Expanded Materials and Methods
Tables I–III
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