ACS Chemical Neuroscience

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Viewpoint

Brain Imaging in COVID-19

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Cite This: https://doi.org/10.1021/acschemneuro.1c00467

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ABSTRACT: Considering the neurological and neuropsychiatric manifestations of coronavirus disease 2019 (COVID-19), its early diagnosis is crucial. This Viewpoint aims to highlight these manifestations through multimodal neuroimaging studies reflecting neurochemical and structural impairment.

KEYWORDS: *COVID-19, neuroimaging, neurochemical impairment, structural impairment, neuropsychiatric manifestation, neurological manifestation*

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) presents devastating pulmonary manifestations, including pneumonia, cough, fever, and myalgia. Its common neurological manifestations include anosmia, cerebrovascular disease, and encephalopathy. Evidence further suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects various brain regions linking the brain stem, eyes, mouth, and nose. Magnetic resonance imaging (MRI), computed tomography (CT), and MR spectroscopy (MRS) of the brain are used for the evaluation of metabolic and structural abnormalities involving enlarged volumes of various brain regions, such as olfactory cortices, hippocampus, and cingulate gyrus.[1] Concerning the cases of neurological and neuropsychiatric abnormalities in the COVID-19 survivors, the viral footprint in the brain is well established. The knowledge of clinicoradiological manifestations should be considered of upmost priority which can be used for patient care and better understanding of the disease. The suggested pathways, described by the researchers, of SARS-CoV-2 entry in the brain are (i) *cytokine storm*, the unexpected massive influx of proinflammatory cytokines that likely disrupt the blood−brain barrier (BBB) leading to the structural and functional abnormality of the brain; (ii) *endothelial dysfunction*, endothelial cell damage and endotheliitis that potentially cause BBB injury and cerebral vascular thrombosis, resulting in cerebral microhemorrhages or brain edema; and (iii) *hypoxia*, elderly group with comorbidities, such as chronic hypertension and diabetes mellitus, that demonstrate neurological complications. Severe hypoxic brain damage further impairs small vessels, leading to periventricular neuronal demyelination or white matter microhemorrhages and widespread small vessel thrombosis.

2. BRAIN IMAGINING-BASED FEATURES

For the prognosis and diagnosis of COVID-19-induced neurological manifestations, the application of noninvasive neuroimaging techniques is paramount as described below.

CT provides images of internal organs, bones, and blood vessels. CT scans of patients with COVID-19 have revealed intracerebral hemorrhage (ICH) in the right hemisphere with intraventricular loss of gray−white matter differentiation in the left occipital and temporal lobes. The literature also mentions the high proportion of hemorrhagic events, white matter abnormalities, and ischemic infarction in patients with severe COVID-19.[2]

MRI is a unique noninvasive technique used to monitor structural details of the brain. MRI-based findings in COVID-19 patients include atrophy and gliosis involving the left temporo-parietal lobe, i.e., hemorrhagic rim enhancing lesions within the medial temporal lobes of the patients.[2] Data from patients with/without ICH lesions suggest that hemorrhagic complications are frequently associated with those under intensive care. Axial diffusion and gradient-echo sequences in these patients reveal acute infarcts and microhemorrhages (Figure 1).

Fluid-Attenuated Inversion Recovery (FLAIR). According to the literature, FLAIR images from patients with COVID-19 demonstrate hyperintense signal changes in the right mesial temporal lobe and slight hippocampal atrophy; extensive patchy areas of abnormal signal involving bilateral frontoparietal white matter; cortical FLAIR signal abnormality in frontal, parietal, occipital, and temporal lobes; and multiple areas of restricted diffusion associated with edema. Susceptibility-weighted imaging has revealed extensive superimposed hemorrhages in the parietooccipital region. Such images further exhibit nonconfluent multifocal white matter hyperintense lesions along with variable intensification. Such hemorrhages indicate clinical implications as they are often associated with severe respiratory conditions.

Diffusion-Weighted Imaging (DWI). DWI indicates hyperintensity along the walls of the temporal horn of the

Received: July 14, 2021
Accepted: July 26, 2021

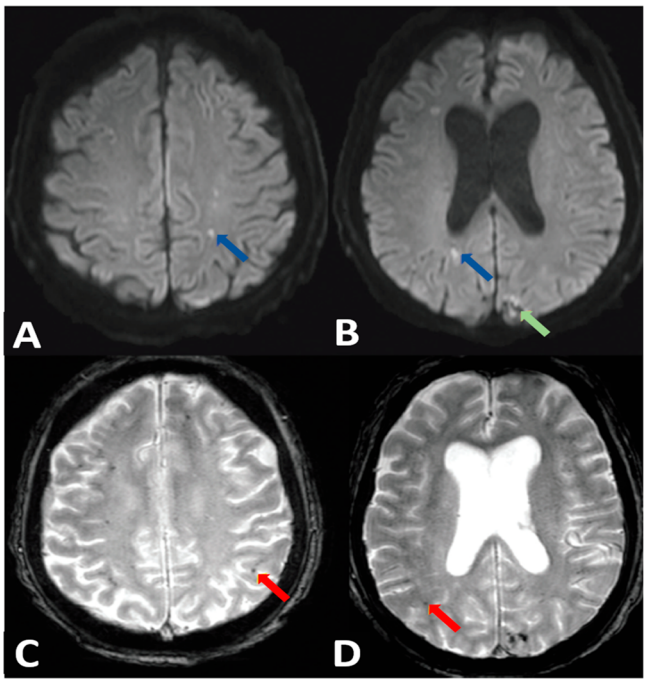

Figure 1. MRI images from 61-year-old man with COVID-19: (A, B) acute infarcts within the bilateral cerebral white matter (blue arrows) and left occipital hemorrhagic infarct (green arrow) (images obtained using axial diffusion sequence); (C, D) innumerable microhemorrhages throughout the bilateral cerebral hemispheres (red arrows) (images obtained using gradient-echo sequences). Copyright permission was obtained to reproduce Figure 1 from the publisher.[3]

right lateral ventricle and acute ischemic stroke with the foci of hyperintensity scattered within the left carotid territory associated with neurological symptoms, such as headache and transient generalized seizure.

Diffusion Tensor Imaging (DTI). DTI maps have shown that patients recovered from COVID-19 are more likely to have enlarged hippocampi, olfactory cortices, Heschl's gyrus, cingulate gyrus, insulas, and Rolandic operculum. These patients presented statistically significant higher bilateral gray matter volumes indicating disruption in microstructures.

MRS studies reflect metabolite abnormalities. In one study, multivoxel MRS imaging was performed in three distinct patients with COVID-19 having white matter disorder and recent cardiac arrest with mild white matter abnormality and without any abnormality. The patient with white matter abnormality presented the abnormality of choline and *N*-acetyl-aspartate concentrations. The patient with white matter disorder showed more pronounced alterations reflecting neuroinflammation.[1]

3. CLINICAL MANIFESTATIONS

Patients with severe COVID-19 potentially demonstrate cytokine storm syndrome that triggers ischemic strokes. Other anomalies include ICH, hypoxic−ischemic encephalopathy, and ischemic stroke. White matter in the subcortical region of the brain protects nerve fibers from injury. White matter abnormalities are reportedly the most persistent neuroimaging pattern observed in these patients. The abnormalities are presented as converging hyperintensities on T2/FLAIR of MRI along with unnatural restricted diffusion and hypointensities on CT and T1W imaging in deep white matter, subcortical and middle cerebellar peduncles, corpus callosum, and corticospinal tracts, causing nonspecific neurological signs. COVID-19-associated coagulopathy often presents cerebral venous thrombosis and large vessel occlusion.

COVID-19 and Psychiatric Disorder. COVID-19-associated systemic and neuroinflammatory changes are linked to substantial increase in the brain neuroglial reactivity, proinflammatory molecules, and altered neurochemical profile. Environmental stress caused by social restrictions, pandemic fears, and intensive therapy also promotes neuropsychiatric pathologies, including bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and major depressive disorder. Notably, many patients with COVID-19 present psychosis without any psychiatric history. Patients with headache, dysgeusia, and anosmia and those requiring oxygen therapy scored low in attention, memory, and executive function tests in contrast to asymptomatic patients. Patients presenting clinical hypoxia and headache scored less in the global cognitive index, indicating cognitive dysfunction.

When assisted with psychiatric and neuropsychological evaluations, noninvasive neuroimaging techniques, including MRI and MRS, efficiently detect COVID-19-associated neurological alterations and establish a correlation between these alterations.

Abnormal metabolite concentration is observed in various neurological disorders. In this context, MRS is potentially beneficial for analyzing any neurochemical alterations, such as in glutamate, glutamine, γ-aminobutyric acid, and glutathione. Reportedly, glutathione and its precursors *N*-acetyl-cysteine and α-lipoic acid likely constitute a novel treatment approach for addressing respiratory distress cytokine storm syndrome in patients with COVID-19 pneumonia.

4. IMPORTANCE OF NEUROIMAGING STUDIES

Studies involving asymptomatic patients with minimal/no pulmonary damage have indicated that the neurological impact of COVID-19 is not factored due to the pulmonary illness.[4] Even in patients without respiratory manifestations, the neuroimaging findings have revealed T2 hyperintense signal abnormalities and intracerebral hemorrhage resulting in confusion, amnesia, and hemiparesis.[4] These clinical manifestations are predominantly reported in patients with multiple vascular risk factors and those with severe COVID-19.

Development of profound neurologic symptoms is reported in patients with COVID-19. These can be associated with severe as well as fatal complications such as encephalitis or ischemic stroke.[5]

Neuroradiological findings also reveal that clinical diversities arising during the course of COVID-19 are associated with the severity of the viral infection. Abnormalities in the cranial nerves are exclusively confined to mild infection, whereas hemorrhages are commonly associated with severe infection. Patients with severe COVID-19 display extreme forms of abnormalities.

The comparative analysis of brain images before and after COVID-19 infection shows significant deleterious effects of the infection on the olfactory and gustatory cortical systems. Such patients reputedly illustrate severe effects on gray matter volume and thickness, suggesting neuronal damage. Hence, extensive reliable longitudinal data are required for better comprehension of COVID-19 and its neurological manifestations.

https://doi.org/10.1021/acschemneuro.1c00467
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX

5. CONCLUSION

In patients with COVID-19, brain imaging efficiently detects neurological impairment. Considering future implications, longitudinal cohort studies involving MRI, MRS, and neuropsychological evaluation are planned. Upcoming cohort studies will investigate depleted antioxidant GSH level and its role in the major causes of the excessive inflammatory response linked to severe COVID-19 induced neurological/neuropsychiatric outcome.

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Notes

The authors declare no competing financial interest.

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https://doi.org/10.1021/acschemneuro.1c00467
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX