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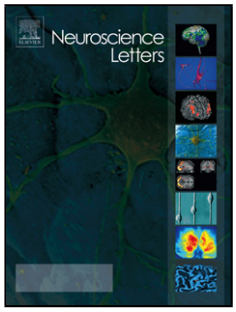

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Neuroimaging findings in COVID-19: A narrative review

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Highlights

- Brain imaging should be considered in the diagnostic work up of those COVID-19 patients who present with neurological symptoms.
- Vascular thrombosis, hemorrhagic patterns, cortical signal abnormalities, and neuroinflammatory features are the most common reported imaging abnormalities in these patients.

Since the appearance of the coronavirus disease 2019 (COVID-19) outbreak in late December in Wuhan (China), there has been an increasing number of publications regarding the potential neurotropism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While COVID-19 primarily affects the respiratory targets [1-3], neurological alteration and damage are not uncommon. Early studies from China have reported various neurological symptoms (including anosmia, headache, myalgia) and Central Nervous system (CNS) complications (cerebrovascular events, encephalopathy, and neuroinflammatory syndromes) in a large number of COVID-19 patients [4].

SARS-CoV-2 is similar in structure and pathogenesis to the other β–coronavirus family members, namely Severe Acute Respiratory Syndrome (SARS-CoV) and the Middle East Respiratory Syndrome (MERS). Similarity in structure and pathogenesis predicts similarity in clinical presentation and symptomatology. Prior experimental researches have established the neurotropism and neuroinvasiveness of coronavirus strains in previous SARS and MERS epidemics, even in the absence of pulmonary manifestations. SARS-CoV-2 has been suggested to have similar, but higher affinity for CNS targets [5].

Although it remains unsolved how coronavirus affects the human neuronal system, two main pathophysiological hypotheses seem to point the most likely explanations. One suggested mechanism is based on the direct viral invasion through hematological, transcribrial, and

neuronal retrograde dissemination pathways. The other possible mechanism is via hyperimmune-related reactions. Activation of inflammatory cells and cytokines precede cytokine storms, resulting in the activation of coagulation cascades, disseminated intravascular coagulation (DIC), and multiple end-organ failures, including CNS complications.

In this mini-review, we aim to summarize some of the most common imaging findings seen in patients with COVID-19. However, it is important to bear in mind that the exact relationship with SARS-CoV-2 has not yet been fully established. Indeed, while COVID-19 associated neurological features offer a possible causal or synergetic relationship between cerebral events and SARS-CoV-2 infection, coincidental events (rather than casual association) might explain some of these imaging results. In fact, due to high prevalence of the COVID-19 in communities, co-incidence of the infection with other diseases is an expected and highly likely phenomenon.

Radiologic findings

In our prior review on 20 studies consisting of 90 patients with neuro-COVID-19 symptoms (among 116 patients with coronavirus family infection)[6], 37 (41%) patients had normal imaging studies (brain CT or MRI). Amongst those who displayed abnormal neuroimaging findings (59%), vascular thrombosis, cortical signal abnormalities, hemorrhage, hemorrhagic posterior reversible encephalopathy syndrome (PRES), acute hemorrhagic necrotizing encephalopathy (ANE), meningitis/encephalitis, and acute disseminated encephalomyelitis (ADEM) were the most common reported abnormalities [6].

Similarly, in a recent observational study [7] on 73 patients who presented with neurological symptoms, 41.1% demonstrated normal brain MRI. The remainder 58.9% had various neuroimaging abnormalities, including acute ischemic infarcts (23.3%), cerebral venous thrombosis (1.4%), multiple microhemorrhages (11.3%), perfusion abnormalities (47.7%), multifocal white matter lesions (5.5%), basal ganglia lesions (5.5%), meningeal enhancement (4.8%), central pontine myelinolysis (4.1%), hypoxia-induced lesions (4.1%), restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum (CLOCC, 4.1%), PRES (2.7%), and neuritis (2.7%). The authors have also found that two imaging patterns of multifocal white matter lesions and basal ganglia abnormities (observed primarily in ICU patients with a more severe illness) were related more explicitly to SARS-CoV-2 infection itself rather than the disease complications.

In another multicenter observational study by Kermer *et al*. on 37 patients [8], the most frequent white matter abnormalities were described in three distinct patterns: signal abnormalities in the medial temporal lobe (43%), non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion associated with hemorrhages (30%), and white matter microhemorrhages

(24%). They stated medial temporal lobe signal abnormalities were similar to those found in viral or autoimmune encephalitis, whereby patterns 2 and 3 presented microhemorrhages. They also found that the presence of hemorrhage would worsen the prognosis in these patients.

Cerebrovascular events

Numerous publications have already ascertained the thrombo-inflammatory nature of SARS-Cov-2 infection [9, 10]. The elevated production of coagulopathy factors such as fibrinogen, platelet, D-dimer, and inflammatory cytokines (interleukin-6), along with capillary endothelial damage, predispose patients to thromboembolic events, leading to stroke, thrombosis, and hemorrhage. Therefore, it is not surprising that stroke-related imaging findings are among the most frequent abnormalities seen in patients with neuro-COVID symptoms. Findings such as territorial acute/subacute infarction, multiple ischemic foci, evidence of thrombus in large intra and extra-cranial vessels, cerebral venous thrombus complicated by hemorrhagic infarcts, and cortical/subcortical microhemorrhages have been reported frequently in various observational studies [6, 11].

The precise pathophysiology of white matter microhemorrhages in COVID-19 patients remains unclear. It has been suggested that they might be related to diffuse endothelial dysfunction, secondary to the direct viral invasion of the endothelial cells (via ACE-2 receptors) and the subsequent endothelial inflammation.

Guillain-Barre syndrome (GBS)

GBS has been reported as a significant parainfectious peripheral neurological sequelae of SARS-CoV-*2* infection, similar to other coronavirus strains. These patients generally have normal MRI studies of the central nervous system, although post-contrast enhancement in the cervical and lumbar nerve roots has been reported frequently [7]. COVID-19 associated GBS mainly develops within a few days to weeks of established viral infection. This temporal relationship reflects a post-infective immune-mediated process as the primarily responsible mechanism. In a review by Caress *et al*.[12] on 37 cases of GBS associated with COVID-19, the mean time interval between COVID-19 symptoms and GBS onset was 11 days. Brain imaging had been performed in fewer than half of patients (14/37), which displayed cranial nerve abnormalities only in 28% of them. Furthermore, spine imaging was obtained in 15 cases, with 40% showing abnormal features, including root enhancement, radiculitis, leptomeningeal enhancement, and myelopathy.

Perfusion abnormalities

MRI perfusion abnormalities are observed in a large number of individuals presenting with COVID-19 associated neurologic signs. These abnormalities might be related to hypoxic-ischemic events and seizures, or present as an isolated finding [7]. In Helms *et al.* study, bilateral

frontotemporal hypoperfusion, leptomeningeal enhancement, and stroke-related abnormalities were the most conspicuous neuroimaging findings in COVID-19 patients presenting with a severe illness [13].

Acute inflammatory/infectious CNS syndromes

A range of COVID-19 associated inflammatory features is identified on radiological exams, including post-infectious ADEM, acute hemorrhagic leukoencephalitis, myelitis, and autoimmune encephalitis. As mentioned earlier, virus-induced vasculopathy and coagulopathy, direct invasion of CNS, hyperinflammatory reactions and post-infective autoantibodies might partly explain these findings. In terms of radiologic findings, unilateral FLAIR hyperintensity and/or diffusion restriction in the medial temporal lobe have been frequently reported in these patients, similar to changes with autoimmune limbic encephalitis [11]. Similar imaging results have been featured in the concept of meningitis/encephalitis in a few case series [6, 14].

PRES, multifocal white matter abnormalities, basal ganglia lesions, and leptomeningeal enhancement have also been named as relevant neuroimaging manifestations in COVID-19 [11, 15]. Again the vasculitis-like phenomenon and inflammatory cascades, secondary to COVID-19-induced CNS damages, are the likely responsible mechanism for these findings [16].

COVID-19 in brain PET:

Nuclear medicine operations are not routinely employed in COVID-19 patients [17]. However, it is assumed that molecular imaging with FDG PET-CT is potentially able to add valuable data regarding the pathophysiological basis of the disease [18, 19]. In this era, a few reports have described metabolic abnormalities in patients presenting with neuro-COVID-19 manifestations. In a case series by Delorme *et al.* [20] brain FDG PET-CT was performed in four COVID-19 patients with possible immune encephalitis. PET displayed a consistent pattern of metabolic abnormalities in all patients: hypometabolism in the prefrontal or orbito-frontal cortices and hypermetabolism in the cerebellar vermis. None of these patients had specific MRI features nor significant cerebrospinal fluid (CSF) abnormalities. Regarding the PET-CT findings and the negative CSF SARS-CoV-2 PCR results, the authors suggested a parainfectious cytokine storm or immune-mediated process rather than a direct neuroinvasion mechanism.

Other case reports have issued similar findings. Grimaldi *et al.* [21], demonstrated diffuse cortical hypometabolism, associated with putaminal and cerebellum hypermetabolism in autoimmune encephalitis concomitant with SARS-CoV-2 infection. In another case study, anosmia of COVID-19 was evaluated using FDG PET-CT. They found hypometabolism of the left orbitofrontal cortex in a COVID-19 patient, representing with persistent isolated anosmia [22]. These findings, along

with normal morphological data on MRI, might suggest reduced neuronal activity and functional alterations in neuro-COVID-19 patients. However, further studies (specifically using BOLD functional MRI) are still needed in this regard before we draw a definite conclusion.

Summary:

Brain imaging should be considered in the diagnostic work up of those COVID-19 patients who present with neurological symptoms. In this regard, radiologists and clinicians should be familiar with the spectrum of neuroimaging findings in COVID-19 to detect and understand the disease process, and to evaluate its progression during the course of treatment. Yet, further studies are still warranted regarding the long-term neurological sequel and prognostic implications in COVID-19.

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