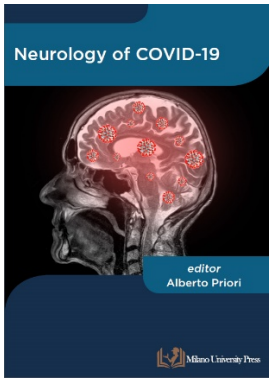

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Chapter 5. **Neuroimaging in COVID-19**

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Chapter 5. Neuroimaging in COVID-19

Marco Scarabello, Carla Uggetti, Luca Valvassori

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Human coronaviruses have neuroinvasive capacities and may be neurovirulent by two main mechanisms[1–3]: viral replication into glial or neuronal cells of the brain or autoimmune reaction with a misdirected host immune response[4]. Prior to the current pandemic there were reports of encephalitis-like syndromes caused by human coronaviruses[5]. Reports on central nervous system involvement during COVID-19 started early during the first wave[6] and large multicenter studies were subsequently carried out[7-17]. These studies showed a number of neuroradiological patterns, some of them similar to known disease entities or pathological conditions, with various frequencies and associated risk factors. The objective of this section is to highlight the different imaging features that must be recognized, the techniques to depict them and how to best interpret them with the current available knowledge.

Prevalence of abnormal neuroimaging findings

One of the earliest studies on neurological symptoms in patients with COVID-19[14] showed an estimated overall prevalence of 36.4% in hospitalized patients. Twenty-four percent of them had symptoms referred to the central nervous system. In another large retrospective cohort[8] 2,611 adults, 269 examinations were performed in 185 patients. MRI and CT examinations were performed and were available on 1.6% and 6.6% of patients, showing a low prevalence of neuroimaging studies in patients with COVID-19. Consecutive patients with neurological manifestations and brain magnetic resonance imaging (MRI) were selected among 16 French hospitals during 2020[7], excluding ischemic infarcts, cerebral venous thrombosis and previous chronic lesions. Among these 37 highly selected patients there were various patterns that can be strictly related to neuroradiological findings during COVID-19. Interestingly, there were 16/37 patients (43%) with unilateral fluid attenuation inversion recovery (FLAIR) and/

or diffusion hyperintensities in mesial temporal lobe; 11 (30%) showed non-confluent multifocal white matter hyperintense lesions on FLAIR/diffusion, with variable enhancement, associated with hemorrhagic lesions; 9 (24%) showed extensive and isolated white matter microhemorrhages; 4 (11%) showed extensive and confluent supratentorial white matter FLAIR hyperintensities; 2 (5%) showed FLAIR and diffusion ovoid hyperintense lesion located in the central part of the splenium of the corpus callosum; 2 (5%) showed non-confluent multifocal white matter hyperintense lesions on FLAIR/diffusion with variable enhancement; 2 (5%) showed acute necrotizing encephalopathy; 2 (5%) FLAIR or diffusion hyperintense lesions involving both middle cerebellar peduncles. The majority of the patients had one neuroimaging pattern (76%), with the rest multiple coexisting patterns. These patients underwent neuroimaging mainly because of alteration of consciousness (73%), pathologic wakefulness after sedation (41%), confusion (32%), and agitation (19%). From the available evidence it appears that neurological manifestations severe enough to warrant advanced neuroimaging are relatively uncommon and have a plethora of imaging patterns, some of them are more frequent than others and the majority are fairly unspecific, similar to other neuroradiological patterns related to various inflammatory, microvascular, and immune-mediated disorders.[18] Specific imaging patterns will be further discussed below.

Anosmia, usually associated to ageusia, is a frequent symptom in patients affected by COVID-19. MRI abnormalities of the olfactory bulb of these patients have been reported in several studies, with discordant results, also due to different technical approaches. A thinning and T2-hyperintensity of the olfactory bulbs can be sometimes detected with focused MRI studies.

Macrovascular pathology

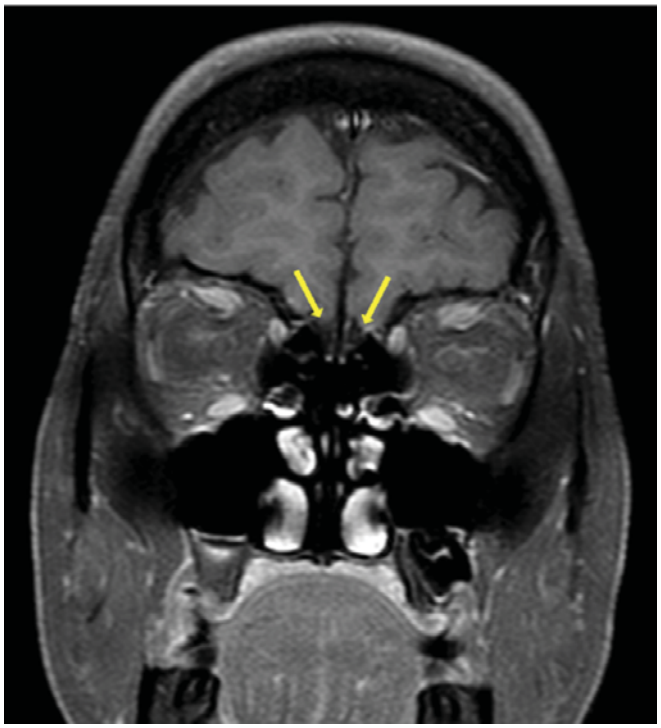
There have been various reports of ischemic and hemorragic stroke in patients with COVID-19. Klironomos et al.[8] reported 8.6% of patients having acute ischemic stroke and 6.3% having non-traumatic brain hemorrhage. One of the early studies[15] reported 4.6% incidence of acute ischemic stroke among patients hospitalized for COVID-19. Later studies[19,20] reported rates of acute ischemic stroke between 0.9% to 3.3%. It has been shown that COVID-19 increases stroke-related mortality[19]. Neuroimaging in acute stroke is fairly established[21] and presents no particular issue specific to COVID-19, except for the fact that a continuous flux of potentially COVID-19 positive patients through the CT scanner located in the emergency department may contribute to the delay of the first diagnostic step[22]. Brain hemorrhages have been reported, both as a presenting illness and as complications of anticoagulant therapy.

Table 5.1: Neuroimaging findings in COVID-19

	Description	Prevalence	Location	Imaging technique	Association
Macrovascular pathology	Ischemic stroke, lacunar stroke, cerebral venous thrombosis, brain parenchymal hemorrhage	0.9% to 8.6%	Brain hemisphere, basal ganglia, deep white matter	Noncontrast CT, CT angiography, MRI (DWI, FLAIR)	COVID-19 worsens the prognosis of ischemic stroke. Potential delay of diagnostic imaging due to patient isolation
White matter abnormalities	Nonconfluent white matter FLAIR hyperintensities	30% (selected patients)	Supratentorial WM, deep periventricular WM, splenium of corpus callosum, deep cerebellar WM, middle cerebellar peduncles	CT, MRI (FLAIR, DWI, T2-weighted)	Similar to an inflammatory demyelinating disease, such as acute disseminated enceph- alomyelitis or acute hemorrhagic leukoencephalitis
	Confluent white matter FLAIR hyperintensities	11% (selected patients)	Supratentorial WM	CT, MRI (FLAIR, DWI, T2-weighted)	Unclear pathogenesis. Severely ill patients, maybe post-hypoxic leukoencephalopathy or toxic-metabolic.
DWI abnormalities	b=1000 hyperintensities with low ADC values	Variable, low if ischemic stroke is excluded	Discrete foci in hemispheric WM, splenium of corpus callosum, globus pallidus	DWI, with ADC map	Hypoxic, toxic-metabolic, immune mediated injury patterns
SWI abnormalities	Round or ovoid foci of signal drop in GRE or SWI images, from punctate to a few millimiters	Variable, up to 74%	Splenium of the corpus callosum, juxtacortical U-fibers, and main white matter tracts	SWI, GRE	Found in more severe cases, and patients with worse prognosis
Pathological contrast-enhancement	Parenchymal or leptomeningeal contrast enhancement	Variable	Hemispheric WM, leptomeninges, cranial nerves, lumbar nerve roots	Post contrast T1-weighted, FLAIR images	Breakdown of the blood-brain barrier from various insults
Encephalitis-like abnormalities	FLAIR hyperintese lesions in gray and white matter, with variable diffusion restriction and contrast enhancement	Few case reports	Mesial temporal lobe, diffuse subcortical and deep WM	FLAIR, DWI, Post contrast T1-weighted, FLAIR	Similar to limbic enhcephalitis or ADEM

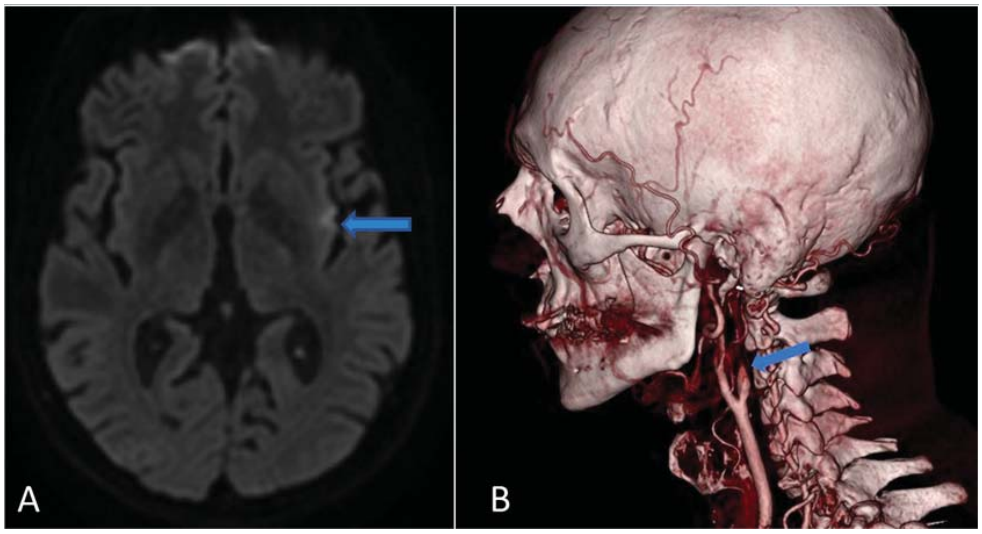
CT: computed tomography, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging, FLAIR: fluid-attenuated inversion recovery, SWI: susceptibility-weighted imaging, WM: white matter, ADEM : acute disseminated encephalomyelitis.

Figure 5.1: 52 yo female COVID-19 patient with anosmia



FLAIR coronal scan shows thinning and T2-hyperintensity in the bilateral olfactory bulbs (arrows)

Figure 5.2



A: FLAIR axial scan shows a small acute ischemic lesion (blue arrow) in the left insular cortex in a previously healthy 33 yo man. B: Sagittal contrast-enhanced CT of the epiaortic vessels shows dissection (blue arrow) of the cervical segment of the ipsilateral internal carotid.

White matter abnormalities

Kremer et al.[7] reported a prevalence of 30% (CI 15-45%) of non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion-weighted images with variable enhancement associated with hemorrhagic lesions among patients with severe COVID-19, and 11% of extensive and confluent supratentorial white matter FLAIR hyperintensities, making white matter one of the main structures to be analyzed in severe COVID-19 with brain lesions. White matter changes can be in the form of symmetrical, periventricular lesions[8] located posteriorly in the occipital and parietal lobes[15] or even affect middle cerebellar peduncles. Ventricle size changes and dynamic evolution of white matter lesions has also been reported, with improvement in a small percentage of cases (14%)[23]. White matter can also been affected by COVID-19-related diffuse posthypoxic leukoencephalopathy[24]. Isolated lesions of the corpus callosum have been reported[7] as well as lesions located on the midline in the splenium of the corpus callosum, which is a typical locations for toxic-metabolic damage[25-27].

Diffusion abnormalities

Klironomos et al.[8] reported 5/41 patients with acute ischemic infarcts and 5/41 with acute lacunar infarcts. One patient from their series presented with restricted diffusion in the splenium of corpus callosum. One patient had restricted diffusion in the globus pallidus. Kremer et al.[7], who decided to exclude patients with macrovascular pathology, reported diffusion weighted imaging (DWI) abnormalities in the form of non-confluent white matter abnormalities (with corresponding FLAIR hyperintensities) both supra- and infratentorially, along with restricted diffusion in the middle cerebellar peduncles. If we exclude DWI changes due to acute ischemic/cytotoxic damage from macrovascular or lacunar infarcts which are common in adult and elderly patients and not strictly related to COVID-19 effects, there are patterns resembling acute disseminated encephalomyelitis (ADEM)[28], hypoxic damage (bilateral globus pallidus), toxic-metabolic damage (splenium of corpus callosum), which could be a consequence of microvascular damage, hypoxic ischemia during severe COVID-19 pneumonia, and immune-mediated white matter lesions.

Susceptibility weighted imaging abnormalities

Susceptibility weighted imaging (SWI) abnormalities were reported as the most frequent finding in patient with central nervous system involvement by Klironomos et al.[8] being found in 74% of them (29/39). Interestingly, the shape of susceptibility foci were reported as round or ovoid, the latter probably due to microscopic thrombi along small medullary veins with subsequent

microbleeds[29]. They were more frequently located in the splenium of the corpus callosum, juxtacortical U-fibers, and main white matter tracts. Fifty-nine percent of patients had SWI abnormalities in the corpus callosum. Low signal intensity foci were also reported in subarachnoid and intraventricular location, as well as cortical superficial siderosis. There were reports of susceptibility changes in patients with severe COVID-19 on mechanical ventilation/oxygenation[30-32], the pathophysiology of which is the subject of ongoing research, with some advocating possible COVID-19-mediated microvascular damage and thrombosis and others focusing on secondary effects induced by the severe illness and hypoxic-ischemic environment[29,33]. Generally, patients whose neuroimaging findings included susceptibility changes had worse clinical conditions, worse prognosis, longer duration of mechanical ventilation and worse laboratory profiles (high peak D-dimer, lower nadir platelet count, higher international normalized ratio)[29].

Perfusion abnormalities

Among the largest cohort of patients with abnormal neuroimaging findings there were reports describing no significant perfusion abnormalities[8] using dynamic susceptibility contrast (DSC) technique (19/39 patients), with relative cerebral blood flow (rCBF) within normal range, but also studies highliting a significant proportion of patients with perfusion-weighted abnormalities[34-38]. Chougar et al.[34] performed three-dimensional pseudocontinuous arterial spin labeling (pCASL) on 46/73 patients in their neuroimaging cohort, with roughly half of them belonging to the intensive care unit (ICU) subgroup. Twenty-two patients out of 46 had perfusion abnormalities, 9 were seizure related, 4 secondary to ischemic lesions and 10 were isolated. The proportion of patients with pCASL abnormal values were higher in the ICU group and more of the latter had isolated perfusion abnormalities. Lambrecq et al. analyzed clinical, biological, brain MRI and electroencephalographic findings in patients with neurological symptoms during COVID-19. Half of the foty patients who underwent perfusion weighted imaging showed abnormal results: 19/20 of them had hypoperfusion, especially in frontal and temporal lobes and a minority of them showed hyperperfusion (4/20). Hypoperfusion seemed to represent an important feature in the radar chart of what they described as COVID-19–related encephalopathy. Other studies reported a similar proportion of perfusion abnormalities, with the temporal lobes often affected[36-38].

Pathological contrast-enhancement

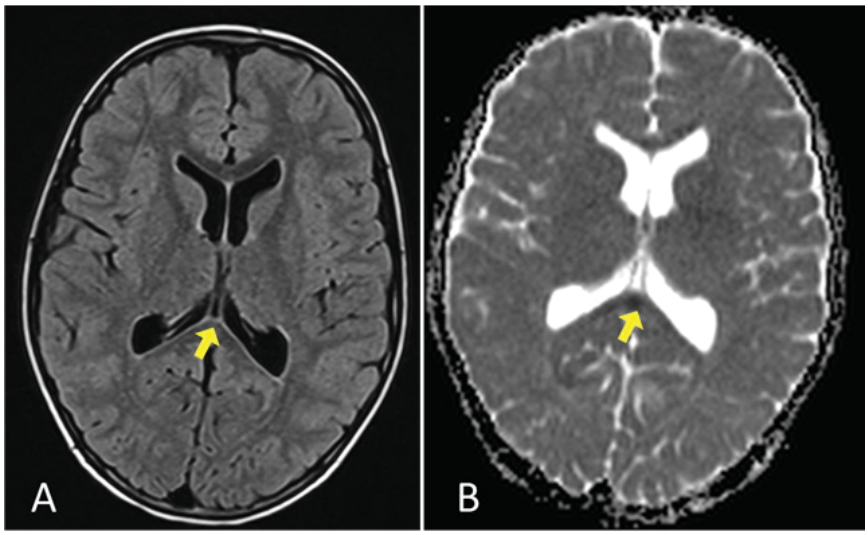
Enhancement in brain MRI after administration of gadolinium-based contrast agents reflects disruption or abnormal permeability of the blood-brain barrier. Several different mechanisms can lead to such effects and therefore there were different reports of contrast-enhancing (CE) lesions associated with pathological CE. Kremer et al.[7] reported variable CE in non-confluent white matter lesions, with superimposed hemorrhagic changes. Klironomos et al.[8] reported pathological CE after ischemic, hemorrhagic and hypoxic insults in three patients, which are expected from the breakdown of the blood brain barrier. Interestingly, they reported subtle leptomeningeal enhancement, most visible on contrast-enhanced T2-weighted FLAIR and they demonstrated progression of the enhancement in one patient at follow-up although there was clinical improvement. Two patients in their series exhibited cranial nerve enhancement (bilateral facial nerve CE and vestibular nerve respectively) and two others showed pathological CE along the roots of the cauda equina. The studies by Kandemirli[10] and Chougar[34] also showed variable leptomeningeal and perivascular white matter pathological CE in a small proportion of patients.

Encephalitis and encephalitis-like abnormalities

There were several reports of encephalitis and encephalitis-like syndromes in patients with COVID-19. Moriguchi et al.[39] reported a case of a 24-years old man who was found unconscious and had generalized seizures and neck stiffness at admission to the hospital. Cerebrospinal fluid analysis found SARS-CoV-2 RNA. Brain MRI showed signs of ventriculitis along the right temporal horn, restricted diffusion and high FLAIR signal in the right hippocampus. Hayashi et al.[27] reported a case of mild encephalitis/encephalopathy with a reversible splenial lesion.

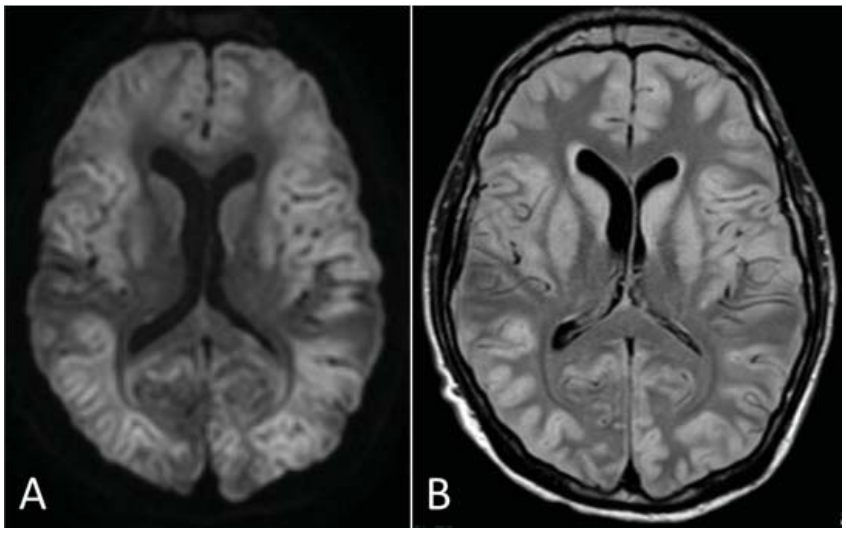
Grimaldi et al.[40] showed a peculiar case of a man presented with subacute cerebellar syndrome and myoclonus several days after general infectious symptoms began. Of note, brain MRI findings were normal and brain ^{18}F-FDG PET showed diffuse cortical hypometabolism associated with putaminal and cerebellum hypermetabolism. Autoimmune limbic encephalitis was also described and reviewed by the group led by Pizzanelli[41], with the usual brain MRI signature. Acute disseminated encephalomyelitis has also been reported, with the pattern of abnormal neuroimaging findings, in adults and children[42,43]. Finally, in critically ill COVID-19 patients severe hypoxic, toxic and metabolic encephalopathies may be found.

Figure 5.3



FLAIR scan (A) and Diffusion weighted image (DWI) show an alteration in the central aspect of the splenium of corpus callosum, consistent with the diagnosis of mild encephalopathy with a reversible splenial lesion (MERS).

Figure 5.4



Diffusion weighted (A) and FLAIR (B) images show widespread gyral T2 hyperintensity, swelling and restricted diffusion, consistent with extensive anoxic suffering in a 40 yo male patient with severe respiratory failure due to COVID-19.

Practical implications in neuroimaging of COVID-19 neuropathology

Many retrospective studies and case reports have been published on neuroimaging during COVID-19. Some patterns have emerged and there is evidence that more severe disease and the need for mechanical ventilation are risk factors for a positive brain MRI. Most of the findings are not specific to COVID-19 and are in fact common to other disease entities and etiologies. The majority of the findings are still being analyzed form the pathophysiological point of view to ascertain the cause, mechanism and possible treatment. From the neuroradiological perspective, since COVID-19 can have epidemic waves and variable disease course, it is important to note that SARS-CoV-2 positive patients can present with acute neurological emergencies unrelated to the viral illness and time-dependent imaging needs to be performed accordingly. This review can provide the necessary references to guide in the differential diagnosis of central nervous system pathology in patients with COVID-19.

Take-home message

- The majority of patients with COVID-19 showed abnormal findings at CT and MRI caused by concurrent macrovascular pathology, mainly ischemic stroke.
- Highly selective studies have shown a few neuroimaging patterns directly or indirectly related to the viral illness itself.
- The most prevalent abnormalities were non-confluent and confluent white matter FLAIR hyperintensities with variable enhancement, leptomeningeal enhancement, small SWI susceptibility foci.
- The neuroimaging patterns resemble known immune-mediated, toxic, hypoxic or severe illness-related abnormalities.
- The prevalence of abnormal CT and MRI findings increases with the severity of COVID-19.

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