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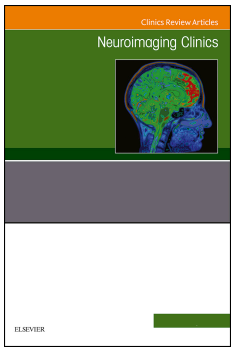

Acute Neurological Complications of COVID-19

Sanders Chang, Michael Schecht, Rajan Jain, Puneet Belani

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Sanders Chang[1], Michael Schecht[1], Rajan Jain[2,3], Puneet Belani[1,4].

[1]Department of Diagnostic, Molecular and Interventional Radiology, Icahn School of Medicine at Mount Sinai

[2]Department of Radiology, NYU Grossman School of Medicine

[3]Department of Neurosurgery, NYU Grossman School of Medicine

[4]Department of Neurosurgery, Icahn School of Medicine at Mount Sinai

Sanders Chang, MD

1176 5th Ave.MC Level.

New York, NY 10029

Email: sanders.chang@mountsinai.org

Phone: 408-839-7369

Michael Schecht, MD

1176 5th Ave. MC Level.

New York, NY 10029

Email: Michael.Schecht@mountsinai.org

Phone: 212-241-8333

Rajan Jain, MD

660 1st Avenue, 1st Floor

New York, NY 10016

Email: Rajan.Jain@nyulangone.org

Phone: 212-263-6246

Puneet Belani, MD(Corresponding Author)

1176 5th Ave.MC Level.

New York, NY 10029

Email: puneet.belani@mountsinai.org

Phone: 914-406-0657

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Keywords

COVID, COVID-19, SARS-COV-2 virus, stroke, large vessel occlusion, venous sinus thrombosis, ADEM, leukoencephalopathy, posterior reversible encephalopathy syndrome, PRES, anosmia, multi-system inflammatory syndrome

Key Points

- A myriad of neurological manifestations can be seen in a significant number of COVID-19 patients. This chapter will focus on the acute findings
- Acute/sub-acute stroke is the most common neuroimaging finding seen in patients with COVID-19. Other vascular findings include dural venous sinus thrombosis, arterial dissection, and vasculitis
- Intracerebral hemorrhage may manifest as a large hemorrhage or microhemorrhages, the latter being more predominant in the hemispheres or corpus callosum
- Leukoencephalopathies may manifest as PRES
- Neuropathies may be multiple or single, ranging from anosmia, facial nerve palsy, to Guillain-Barré syndrome
- Multi-system inflammatory syndrome can be seen in the pediatric population

Abstract

The coronavirus 19 (COVID-19) pandemic has impacted many lives globally. Neurological manifestations have been observed among individuals at various stages and severity of the disease, the most common being stroke. Prompt identification of these neurological diagnoses can affect patient management and prognosis. This chapter will discuss the acute neuroradiological features typical of COVID-19, including cerebrovascular disease, intracerebral hemorrhage, leukoencephalopathy, and sensory neuropathies.

Introduction

The coronavirus 19 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has affected hundreds of millions people globally and led to several million deaths as of September 2021 [1]. In addition to respiratory sequelae (e.g., interstitial pneumonia, acute respiratory distress syndrome), neurologic manifestations have been observed with COVID-19, including encephalopathy, acute cerebrovascular disease, and sensory abnormalities [2, 3]. The frequency of neurologic symptoms has been observed in up to 36.4% of COVID-19 patients and is more common in patients with severe stages of infection [4].

Recognizing the neuroradiological features associated with COVID-19 is crucial as they have implications on diagnosis and management. This chapter reviews the various acute neuroradiological patterns that have been observed with SARS-CoV-2 infections (Table 1).

Stroke

Stroke has been observed in 1-3% of all hospitalized patients with COVID-19 [5, 6]. From a meta-analysis of published articles detailing MRI neuroimaging findings during the peak of the pandemic, acute and subacute strokes were the most common neuro-radiological abnormality [7]. Development of strokes bears important implications in the clinical course of the COVID-19 patient. Their detection signifies poor prognosis with reported rates of mortality up to 50% [8]. Severe disability has been seen in COVID-19 survivors with ischemic strokes upon discharge, significantly greater than those with non-COVID-19 related ischemic strokes [9]. Moreover,

studies have shown that COVID-19 represents a significant independent risk factor in stroke development among hospitalized patients, even greater than traditional comorbidities such as cardiovascular disease and obesity [10, 11].

Certain neuroradiological characteristics are linked to COVID-19-related strokes. These features include multi-territorial involvement, involvement of atypical vessels, and large vessel occlusions.

Stroke Distribution

Strokes in COVID-19 patients more commonly involve the anterior circulation compared to the posterior circulation [12-14]. Multi-vascular distribution is a common feature, observed in up to 40% of cases [12]. This rate is higher than that observed in the pre-pandemic era (10.7%) [15]. The high prevalence of multi-territorial strokes is consistent with the induced prothrombotic environment and increased embolic risk associated with the SARS-COV-2 virus, and had been reported in the previous 2003 outbreak of SARS-COV-1 virus infection [16]. Infection severity is also likely correlated with risk for multi-territorial strokes. In one study, multi-territorial strokes were significantly more frequent among hospitalized patients with severe infection compared to outpatients with less severe infections (56.4% versus 33.3%) [17].

Large vessel occlusions

Large vessel occlusions (LVOs) have been observed in up to around 60% of COVID-19 patients with ischemic infarctions [18, 19]. In comparison, arterial occlusions have historically been observed up to 46% of ischemic strokes in the pre-pandemic era [20]. In one study, proximal large vessel occlusions were significantly more common among COVID-19 compared to historical controls [6]. The relatively high prevalence of LVOs among COVID-19 related acute ischemic strokes suggests the prothrombotic nature of the SARS-COV-2 virus.

LVOs in COVID-19 patients most commonly involve the anterior circulation, particularly the MCA and internal carotid artery (Figure 1) [12, 13]. Other locations include the posterior cerebral artery (PCA), basilar artery, vertebral artery, and common carotid arteries [12, 21, 22]. Significant thrombotic burden and occlusions of otherwise uncommonly affected vessels have also been observed in the subclavian artery [12] and the pericallosal artery [23]. Occlusions can appear in tandem, which was seen in up to 40% of patients in one case series [12].

Strokes in Younger Patients

Younger age onset of strokes has been observed in COVID-19 patients. In one study, 73.3% of patients with large vessel occlusions were younger than 50 years old [12]. Median age of stroke-onset in COVID-19 patients was found to be significantly lower than that of patients without COVID-19 (median age of 63 versus 70) [6]. In addition, the mean age of COVID-19 patients with emergency large vessel occlusions was also significantly less than that of patients without COVID-19 (mean age of 59 versus 74) [24].

Certain clinical factors are shared among younger patients with COVID-19 and stroke, such as the absence of traditional risk factors for stroke (e.g., diabetes, hypertension, hyperlipidemia, and coronary artery disease) [12], and minimal to absent respiratory symptoms during the initial stage of the disease course [25]. In one study, a significantly higher number of patients younger than 50 years old experienced an ischemic stroke in the absence of any prior respiratory symptoms (50.0%, $p = 0.014$) [26].

Pathophysiology of stroke

The mechanism behind the development of strokes in COVID-19 patients is presumed to be multifactorial. Interaction between the SARS-COV-2 virus with endothelial angiotensin converting enzyme 2 (ACE-2) receptors is thought to result in direct endothelial damage, predisposing to occlusive events [27]. Indirectly, a proinflammatory state induced by a misdirected immune response to the SARS-COV-2 virus can result in propagation of thrombosis and plaque rupture. Inflammatory infiltrates have been found within the intima of surgically removed thrombosis on pathology, consistent with endotheliitis [28].

It is unclear whether arterial thrombosis is a de novo phenomenon or related to worsening of pre-existing atheromatous plaque. A substantial number of COVID-19-related strokes have been observed in patients with prior atherosclerotic disease [22, 27, 28]. However, patients without any significant medical history, especially those younger than the observed population, have presented with strokes and large vessel occlusions. Direct endothelial damage may be the primary mechanism behind occlusive events in these patients. In addition, acute extracranial

events, such as pulmonary embolism or cardiac arrests, may be triggers for strokes. In one meta-analysis, younger COVID-19 patients (<50 years) had a higher frequency of elevated cardiac troponin, suggesting that acute myocardial injury is a possible risk factor for the development of strokes [26].

Dural vein thrombosis

Dural vein thrombosis is a relatively rare presentation among COVID-19 patients: in one large study, the prevalence was only 0.02% (Figure 2) [29]. When present, sinus vein thrombosis tends to involve multiple sites, most commonly the superior sagittal sinus, transverse and sigmoid sinuses [30–32]. Other sites include the cortical veins, vein of Galen, and internal cerebral veins [33]. Complications from the venous thrombosis may also be seen, such as surrounding parenchymal hemorrhage, cerebral edema, and hemorrhagic venous infarcts [31, 34].

Given the low number of cases, the relationship between the development of dural vein thrombosis and SARS-COV-2 virus has yet to be elucidated. In many case series, dural venous thrombosis and its associated complications were seen in patients with predisposing risk factors, such as hypertension, diabetes, obesity, OCP use, and hormonal therapy for cancer. However, sinus thrombosis can present in patients without prior risk factors or inciting events [35]. Its pathogenesis is likely tied to the prothrombogenic state associated with COVID-19.

Arterial dissection

Arterial dissections are rarely observed among COVID-19 patients, typically occurring in the extracranial carotid and vertebral arteries, and often bilaterally [18, 36–38]. One report noted extension of the dissection from the distal cervical part to the petrous segment of the internal carotid arteries [37]. Patients were also noted to lack typical risk factors for dissection, such as connective tissue disorders, or inciting events, such as trauma (Figure 3).

Although the mechanism remains unclear, endothelial damage propagated by the cytokine storm as well as direct infection by the SARS-COV-2 virus likely play a role. Dissections at other sites, such as the aorta and coronary arteries, have been observed in the context of COVID-19 and likely follow a similar pathogenesis [39, 40].

Vasculitis and Focal Cerebral Arteriopathy

Acute vasculitis is a rare neuroradiologic manifestation observed in COVID-19 patients. Typical imaging features include long segment vessel wall enhancement of multiple arteries. In one case of a 64-year-old, vasculitis was observed in both MCAs, ACAs, vertebral arteries, and the basilar artery and was associated with multi-territorial infarcts [41].

In pediatric COVID-19 patients, several cases of focal cerebral arteriopathy of childhood-inflammatory type have been reported [42, 43]. Imaging findings include focal stenosis and irregular narrowing of a large vessel, such as the M1 segment, with associated wall thickening and concentric contrast enhancement. In lieu of typical cardiovascular factors and pre-existing disease, focal cerebral arteriopathy may represent a possible mechanism for which strokes can

develop in children. One case of stroke has been observed in a COVID-19 patient as young as 5 years old [44].

Intracerebral Hemorrhage

Intracranial hemorrhage is a neurological complication seen in approximately 0.2% of COVID-19 patients [29]. It has been observed in up to 42% of patients with abnormal neuroradiological findings [14]. Typical imaging features of intracranial hemorrhage include massive intraparenchymal hemorrhage, usually with extension into the subarachnoid and intraventricular spaces, multifocal intraparenchymal hemorrhages, and microhemorrhages [8,23,31,32,45]. Diffuse edema is often associated with foci of hemorrhage [23, 31], and may contribute to significant mass effect with increased risk of brain herniation [46]. Rarely, acute parenchymal hematomas can involve the bilateral basal ganglia [47]. The mechanism behind this distribution of hemorrhage is hypothesized to be disrupted drainage of the basal ganglia secondary to occlusion of the great cerebral vein.

Intracranial hemorrhage may result spontaneously, which typically occurs in critically ill patients with severe infections and multi-organ failure [23, 31]. Hemorrhage can also result secondarily from other pathologic processes, such as hemorrhagic transformation of ischemic strokes [8, 17, 18, 46], rupture of dissecting aneurysms [48] and pseudoaneurysms [49], hemorrhagic infarction associated with venous sinus thrombosis [33, 34], reversible cerebral vasoconstriction syndrome [50], posterior reversible encephalopathy syndrome (PRES) [51, 52] and iatrogenic causes.

Pathophysiology of hemorrhage

The pathophysiology for the development of intracranial hemorrhage is multifactorial. COVID-19 is associated with coagulopathies, such as thrombocytopenia and disseminated intravascular coagulation, which increase the risk for hemorrhage [53]. More directly, SARS-COV-2 virus is known to bind to the ACE-2 receptor in order to enter host cells. ACE-2 receptors are expressed on various organs, including cerebrovascular endothelial cells, and are integral components of the renin-angiotensin pathway. SARS-COV-2-induced downregulation of ACE-2 receptors can result in dysregulation of blood pressure control and lead to blood pressure spikes, potentially causing arterial wall rupture and hemorrhage in the brain [45]. Alternatively, the mechanism of diffuse thrombotic microangiopathy has been proposed [54]. Diffuse thrombosis and vascular endothelial damage can lead to breakdown of the blood-brain barrier, facilitating the development of microhemorrhages which eventually coalesce into large intraparenchymal hematomas.

Iatrogenic causes most likely play a role in the pathogenesis of intracranial hemorrhage. Anticoagulation therapy has been determined to be the cause of a substantial number of cases of intracranial hemorrhage in COVID-19 patients [18, 55]. In one study, the majority of parenchymal hemorrhages were attributed to anticoagulation (60%), whereas a minority of cases were related to indeterminate mechanisms (30%) [55]. Other case series indicated that all patients with observed hemorrhagic transformation of ischemic strokes were on anticoagulation therapy [18, 46]. Characteristic imaging features can help distinguish coagulopathic intracranial hemorrhages from other etiologies. The presence of a “fluid-blood” level, represented by a

meniscus separating dependent hyperattenuating blood products from lighter hypoattenuating serous fluid, is a highly specific finding for anticoagulation or antiplatelet therapy in COVID-19 patients [54, 56].

High prevalence of intracranial hemorrhage has been reported in COVID-19 patients on extracorporeal membrane oxygenation (ECMO) therapy. In one case series, up to 41.7% of COVID-19 patients on veno-venous ECMO therapy had subarachnoid, intraparenchymal, or intraventricular hemorrhage [57]. ECMO therapy is associated with derangements of hematologic and coagulation pathways, resulting from continuous contact between the patient's blood and extracorporeal circuit [58]. These factors, possibly compounded by the coagulopathic environment associated with the SARS-COV-2 virus, promote the development of hemorrhagic complications.

Microhemorrhages

Microhemorrhages make up approximately 11.1% of abnormal neuroimaging findings in COVID-19 patients [7]. Distribution patterns are various and include cortical, juxtacortical, subcortical, deep white matter, perivenular, and corpus callosal involvement [7, 22, 32]. Microhemorrhages attributable to COVID-19 can be made by deduction through the exclusion of other etiologies, such as hypertensive coagulopathy, diffuse axonal injury, or cerebral amyloid angiopathy, based on atypical distribution patterns and absence of clinical factors, such as hypertension or trauma [14].

Corpus callosum involvement, particularly the splenium, is a commonly reported finding in multiple case series of COVID-19 patients [51, 55, 59]. Microhemorrhages in the corpus callosum have been previously described in other patient populations, such as in delayed post-hypoxic leukoencephalopathy from acute respiratory distress syndrome [60, 61], high-altitude cerebral edema [62], and in critical illness-associated microbleeds [63], in which there is additional involvement of the juxtacortical white matter with sparing of the deep and periventricular white matter. The underlying mechanism is multifactorial, related to hypoxic-induced injury to the blood-brain barrier as well as impaired cerebral venous return from increased intracranial pressures. COVID-19-related microhemorrhages likely follow similar mechanisms; however, the pervasive use of mechanical ventilation among COVID-19 patients represents a confounding factor. Increased intrathoracic pressures related to ventilator use can reduce cerebral venous return in critically ill patients, which may better explain the development of microhemorrhages than direct effects from the SARS-COV-2 virus [55].

COVID-19-Related Leukoencephalopathies

Leukoencephalopathies have been observed in up to 27% of abnormal neuroimaging findings among COVID-19 patients [14]. These include white matter abnormalities that are similar imaging patterns described in the literature associated with other infectious diseases,typically associated with PRES, acute disseminated encephalomyelitis (ADEM) and acute hemorrhagic leukoencephalitis (AHLE). There are several pathologic findings described in COVID-19-related leukoencephalopathy which may relate to the different imaging patterns. However, the definite mechanisms are as yet incompletely understood [64].

PRES

PRES manifestations are typically seen as reversible confluent white matter changes in the posterior cerebrum. These appear as striking areas of hypoattenuation on noncontrast CT, correlating with findings of T2/FLAIR signal abnormality on MRI. The distribution is typically in the areas associated with PRES, predominantly the subcortical white matter of the posterior temporal and occipital lobes [51, 65, 66]. Corresponding high diffusivity is seen in these regions. Areas of hemorrhage are also described, including small parenchymal hemorrhages visible on CT as well as microhemorrhages best visualized on GRE/SWI (Figure 4) [52, 67, 68]. The pathologic mechanism is thought to be related to direct binding of the virus to surface ACE-2 receptors on neurovascular endothelial cells, leading to break down of the blood brain barrier [55]. Blood pressure dysregulation due to ACE-2 dysfunction is also a possibility [52]. Interestingly, the PRES-like findings of COVID-19 may be associated with lower blood pressure elevations than seen in other PRES etiologies [67, 68].

Acute Leukoencephalopathy

A range of ADEM-type lesions have been described secondary to COVID-19 [64, 69, 70]. Findings generally include multifocal areas of white matter restricted diffusion (Figure 5) with associated T2/FLAIR hyperintensity. These predominate in the posterior white matter, in a similar distribution to PRES-like findings. However, the less confluent distribution of these lesions helps to make the distinction between these pathologies. Of note, however, the degree of

central restricted diffusion is greater in COVID-19 lesions when compared to findings of ADEM seen secondary to other viral infections. Lesions are also reported in the corpus callosum, basal ganglia, brain stem, and cerebellum [59, 69]. Enhancement may be associated with these lesions, as well as multiple microhemorrhages visualized on GRE/SWI imaging [71]. Upon follow up imaging after the acute episode, lesions may demonstrate more confluence on T2/FLAIR as well as development of cavitation and volume loss [72].

More severe manifestations have also been described with imaging findings similar to AHLE. A case report of a patient with severe acute respiratory syndrome and altered mental status described more central expansile T2/FLAIR hyperintensity involving the basal ganglia and thalami. There was more frank evidence of hemorrhage than seen in less severe ADEM like cases. Predominantly peripheral enhancement was also seen [73].

The underlying pathologic mechanism shares some similarity to the PRES-like syndrome, including suspected ACE-2 related endothelial dysfunction. Cytokine storms with elevated bloodstream cytokines and interleukins may also play a central role [72]. On pathology, a range of lesions are identified, including those which share features of ADEM and AHLE [64]. It may be that acute leukoencephalopathy in the setting of COVID-19 represents a spectrum of disorders rather than one entity.

Neuropathies

Anosmia/Dysgeusia

Sudden onset and persistent alterations of taste and smell have been frequently reported in the setting of COVID-19 respiratory illness. In fact, loss of smell is reported as a helpful symptom in initial diagnosis of COVID-19. Several case reports and case series describe abnormal imaging findings in the anterior cranial fossa/olfactory bulbs seen in the early stages of infection (Figure 6). An initial case report described T2/FLAIR signal abnormality in the gyrus rectus and olfactory bulbs at 3 days following presentation. At 28 days, the cortical edema had resolved and atrophy was demonstrated in the olfactory bulbs [74]. A follow-up case series identified intrinsic T1 hyperintensity and possible enhancement in the olfactory bulbs in 5 patients. Earlier work has shown CNS involvement via olfactory bulb invasion in experimental mouse models. This phenomenon has also been described in other viral infections as well [75]. More recent case series evaluating patients with persistent anosmia at least one month after presentation described variable findings of volume loss, morphologic change, and signal abnormality [76]. The pathologic mechanism is not yet completely understood. One possibility is injury of olfactory epithelial cells bearing ACE-2 receptors. Direct nerve invasion with retrograde tracking along the olfactory pathway has also been suggested, as seen in HSV infections, however it remains unproven [76].

Other Cranial Neuropathies

Other cranial neuropathies have been observed in COVID-19, such as palsy of the facial nerve [77–79] and abducens nerve [77]. These manifestations can occur as the initial symptom or

develop more subacutely, usually up to 2 weeks from the initial onset of COVID-19 symptoms. Patients typically present with mild to no respiratory or constitutional symptoms.

Characteristic imaging features include STIR hyperintensity with gadolinium enhancements of the affected cranial nerve. Diffusion restriction may also be observed [77]. In facial nerve palsies, enhancement of the facial nerve may actually be normal and reflect anatomy, such as the circumneural venous plexus [77]. However, presence of asymmetric enhancement and correlation with clinical symptoms can increase confidence that the enhancement is actually pathological.

As with olfactory neuropathies, the pathogenesis of these other cranial neuropathies is not well understood, but may be similar to that of neurotropic viruses, such as HSV and VZV, in which direct viral invasion of the nerve can lead to axonal spread and subsequent inflammation and demyelination [80]. Immune-mediated injury of the nerve from proinflammatory cytokines may additionally play a role [77].

Conclusion

COVID-19 infections are associated with a myriad of acute neuroradiological features, many of which necessitate careful and prompt diagnoses. Cerebrovascular disease is a predominant complication of COVID-19 infection, attributing to the prothrombotic environment engendered by the SARS-COV-2 virus. Acute and subacute strokes, the most common neuroradiological

findings, share typical features, including multi-territorial distributions, involvement of atypical vessels, and prevalence among younger patients. Appearances of intracerebral hemorrhages are more variable, although predilection for the cerebral hemispheres and corpus callosum are salient features. COVID-19-related leukoencephalopathies share similar imaging patterns with white matter diseases observed in other infections, such as PRES, ADEM, and AHLE. Acute cranial nerve neuropathies, such as anosmia and dysgeusia, can present with pathological enhancement and nerve atrophy. Radiologists and clinicians alike should be aware of the typical neuroimaging features of COVID-19 infections as these findings can play a significant role in patient management and treatment outcomes.

Clinics Care Points

Figure Legends

Figure 1. 33-year-old female with ongoing COVID-19 infection experienced sudden onset left hemiparesis and sensory loss. Axial CTA image of the neck (1a) and sagittal MIP (1b) demonstrated a large noncalcified thrombus (arrows) in the proximal right ICA causing moderate stenosis. Subsequent MRI DWI (1c) demonstrated a large acute infarct involving the right MCA territory (star).

Figure 2. 40-year-old male presented with severe headache in the setting of a recent COVID-19 diagnosis. MR venogram coronal MIP image (2a) showed thrombosis of the left transverse and sigmoid sinuses (circle). MRI DWI (2b) showed hyperintenseacute venous infarct in the right temporal lobe (arrow) corresponding to the region of the venous thrombosis.

Figure 3.34-year-old female with no significant past medical history and no recent trauma presented with acute onset of left facial droop, dysarthria, right gaze deviation, and left hemiparesis/hemisensory loss. Sagittal view from a CTA of the head and neck (3a) and lateral view from a catheter angiogram arterial phase injection of the right ICA (3b) demonstrated an acute dissection in the right ICA shortly after its origin (arrows). Axial DWI (3c) showed an acute right ganglionic infarct. COVID-19 PCR was positive.

Figure 4. 64-year-old male with ongoing COVID-19 pneumonia requiring intubation developed rhythmic jerking and status epilepticus. MRI FLAIR sequence (4a) demonstrated extensive symmetric cerebral edema with a parieto-occipital dominance (star) and scattered small foci of recent hemorrhage on the GRE sequence (4b). Findings were consistent with a posterior reversible syndrome-like leukoencephalopathy with hemorrhage.

Figure 5. 60-year-old female with morbid obesity, hypertension, and asthma admitted with COVID-19 with hospital course complicated by acute renal failure requiring hemodialysis, respiratory failure, and flaccid quadriparesis. Brain MRI axial diffusion sequence showed restricted diffusion in the centrum semiovale bilaterally. Findings likely reflect a combination of hypoxia and critical illness-related encephalopathy.

Figure 6. 37-year-old male patient suffered from anosmia following COVID-19 infection with loss of smell worse on the right side. Coronal T2-weighted (6a) and FLAIR (6b) MR images 6-months post-infection showed atrophy and hyperintensity of the olfactory bulbs bilaterally (arrows), worse on the right side.

Table 1: Neuroimaging Findings in Acute COVID-19 Infection

Clinical Syndrome	Imaging Findings (CT or MRI)	Proposed Pathogenesis
Stroke	■ Anterior circulation more common ■ Multi-territorial involvement ■ Large vessel occlusions, especially in uncommonly affected vessels: subclavian artery and pericallosal gyrus) ■ Higher prevalence among younger patients and those without traditional risk factors for stroke	■ Endothelial cell dysfunction via immune-mediated cytokine storm or direct viral interactions ■ Indirect propagation of thrombosis and plaque rupture from immune response to the virus
Dural Vein Thrombosis	■ Multifocal involvement: superior sagittal sinus, transverse and sigmoid sinuses, and internal jugular vein ■ Associated parenchymal hemorrhage, cerebral edema, venous infarcts	■ Indirect propagation of thrombosis and plaque rupture from immune response to the virus

Arterial Dissection	■ Extracranial carotid and vertebral arteries, commonly bilateral ■ Absence of typical risk factors such as connective tissue disorders or trauma	■ Endothelial cell dysfunction via immune-mediated cytokine storm or direct viral interactions
Vasculitis	■ Long segment vessel wall enhancement of multiple arteries ■ Focal Cerebral Arteriopathy: pediatric patient with focal stenosis, irregular narrowing, concentric contrast enhancement of a large vessel	■ Endothelial cell dysfunction via immune-mediated cytokine storm or direct viral interactions
Intraparenchymal Hemorrhage	■ Unifocal or multifocal involvement with extension into subarachnoid and intraventricular spaces ■ Associated diffuse edema and mass effect ■ Microhemorrhages: cortical, juxtacortical, deep WM, perivenular, and corpus callosal	■ Dysregulation of blood pressure control through virus-related downregulation of ACE-2 receptors ■ Endothelial cell dysfunction via immune-mediated cytokine storm or

	involvement	direct viral interactions ■ Iatrogenic: anticoagulation, ECMO, mechanical ventilation ■ Hypoxic-induced injury to the blood-brain barrier
Posterior Reversible Encephalopathy Syndrome (PRES)	■ CT hypoattenuation, T2/FLAIR signal abnormality, and diffusion restriction in the subcortical WM of posterior temporal and occipital lobes ■ Associated parenchymal hemorrhages and microhemorrhages	■ Endothelial cell dysfunction via immune-mediated cytokine storm or direct viral interaction ■ Dysregulation of blood pressure control through virus-related downregulation of ACE-2 receptors
Leukoencephalopat	■ Multifocal WM lesions with	■ Endothelial cell

hy	diffusion restriction and T2/FLAIR hyperintensity, predominantly in the posterior WM. Central restricted diffusion greater for COVID-19 lesions ■ Associated enhancement and microhemorrhages ■ Severe: central expansile T2/FLAIR hyperintensity in the basal ganglia and thalami	dysfunction via immune-mediated cytokine storm or direct viral interactions
Cranial neuropathy ■ Ansomia/Dysgeusia ■ Facial and abducens nerve palsy	■ Anosmia/Dysgeusia: T2/FLAIR signal abnormality in the gyrus rectus and olfactory bulbs ■ Facial and abducens nerve palsy: affected cranial nerves demonstrating STIR hyperintensity, gadolinium enhancement, and diffusion restriction	■ Autoimmune-mediated

CT=computed tomography; MRI=magnetic resonance imaging; WM=white matter; ACE-2=angiotensin converting enzyme 2;

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