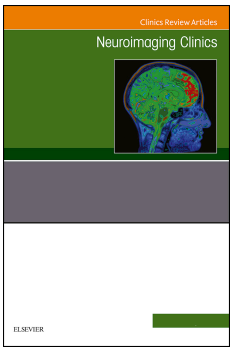
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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COVID-19: Subacute to Chronic Neuroimaging Findings

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KEY WORDS

COVID-19

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Post-Covid Syndrome

SYNOPSIS

A range of neurological disorders are associated with COVID-19 infection. In this article clinical syndromes typically occurring in the subacute to chronic phase of illness and their neuroimaging findings are described with discussion of their COVID-19 specific features and prognosis. Proposed pathogenic mechanisms of these neuroimaging findings and challenges in determining etiology are reviewed.

KEY POINTS

- A range of neuroimaging findings are associated with COVID-19 in the subacute to chronic phase of illness including leukoencephalopathy, microhemorrhages, hypoxic-ischemic injury, and PRES.
- Post-infectious immune-mediated syndromes such as ADEM and GBS may be associated with COVID-19 typically in the subacute phase.

- Neuroimaging findings of leukoencephalopathy and ADEM are relatively poor prognostic markers in COVID-19 patients.
- COVID-19-related PRES and ADEM are more commonly associated with intraparenchymal hemorrhage or microhemorrhage than non-COVID-19-related PRES or ADEM, which may be secondary to underlying coagulopathies or vascular endothelial dysfunction.
- Prognosis of COVID-19-related and non-COVID-19-related PRES and GBS is similar.
- A range of neurologic and psychiatric symptoms are associated with post-COVID syndrome and the role of imaging in diagnosis and prognosis remains unclear.

COVID-19: Subacute to Chronic Neuroimaging Findings

INTRODUCTION

In December of 2019, a novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China causing an illness known as Coronavirus disease 2019 (COVID-19).[1] The virus spread worldwide in 2020 creating a global pandemic. As of August 31, 2021, the World Health Organization (WHO) tallied 216,867,420 cases and 4,507,837 deaths worldwide.[2]

While COVID-19 primarily manifests as a respiratory illness, neurologic involvement is well documented.[3,4] Initial papers reported neurological complications in 36% (78/214) of COVID-19 patients including dizziness (16.8%), headache (13.1%) and impaired consciousness (7.5%), all relatively non-specific.[5] In a later large prospective study, neurological disorders were diagnosed in 13.5% of hospitalized COVID-19 patients and were associated with increased risk of in-hospital mortality and decreased likelihood of discharge home.[6]

PATHOGENESIS OF NEUROLOGICAL INVOLVEMENT BY COVID-19

Multiple theories are proposed for SARS-CoV-2 involvement in the CNS. The systemic immune response to SARS-CoV-2 results in an inflammatory state that can progress to an exaggerated, uncontrolled response known as “cytokine storm” mediated by pro-inflammatory cytokines, which induce endothelial cell dysfunction, vascular damage, and activation of the coagulation cascade resulting in hypercoagulability.[7–9]

Endothelial cell dysfunction may also occur by direct viral interactions with the vascular endothelium via the angiotensin converting enzyme-2 (ACE-2) receptor.[10] The ACE-2 receptor is the obligate receptor for the spike protein of the SARS-CoV-2 virus. This ubiquitous receptor is found throughout the body, including within endothelial cells of arteries and veins and within glial cells and brainstem nuclei.[11] SARS-CoV-2 particles have been found in brain capillary endothelium and adjacent neuronal cells supporting a hematogenous route of neurotropic viral entry into the CNS.[12]

Direct invasion of the CNS by SARS-CoV-2 via neuronal retrograde spread from nasal mucosa to the olfactory bulb has been proposed and is supported by symptoms of anosmia and several autopsy series showing positive SARS-CoV-2 polymerase chain reaction (PCR) signals in the olfactory bulb.[13–17] Lastly, the virus may

infect circulating immune cells, which then act as Trojan horses carrying the virus across the blood-brain-barrier (BBB) facilitating CNS disease.[13] Cerebrospinal fluid (CSF)-confirmed SARS-CoV-2 associated with viral encephalitis has been reported,[18] but more commonly CSF and autopsy samples test negative suggesting that direct CNS involvement by SARS-CoV-2 is unlikely.[6]

NEUROIMAGING FEATURES IN SUBACUTE TO CHRONIC COVID-19

Regardless of time course since COVID-19 onset, most neuroimaging studies in COVID-19 patients show normal or non-specific findings.[19,20] One study that imaged 242 patients in the acute to subacute phase of illness (< 2 weeks) showed that most common imaging finding was nonspecific white matter (WM) microangiopathy (55.4%).[20] Early reports on the neuroimaging findings in subacute and chronic COVID-19 infection centered on patients requiring mechanical ventilation in the intensive care unit (ICU) with delayed awakening after sedation. In one study, 44% (12/27) of COVID-19 ICU patients with neurologic symptoms had positive magnetic resonance imaging (MRI) scans, most showing abnormal cortical or WM signal; the remainder of examinations were normal.[19]

Early literature during the acute crisis of a worldwide pandemic was rapidly published often with incomplete data. Radiologists used clinical information and pattern recognition of well-described radiological entities to assign a diagnostic label or infer pathophysiology of the COVID-19 associated neuroimaging features, which is both valuable and subject to diagnostic error. Heterogeneity of imaging protocols and treatments in ICU settings also made it difficult to compare imaging findings. Despite these challenges, some common neuroimaging features have emerged in the ICU setting and the subacute to chronic phases of COVID-19 (Table 1). Neuroimaging findings including leukoencephalopathy, microhemorrhages, posterior reversible encephalopathy syndrome (PRES), and hypoxic-ischemic injury are reported and may be the result of an immune response or complications from prolonged illness and treatments. Post-infectious autoimmune manifestations are also reported after the acute COVID-19 infection including acute disseminated encephalomyelitis (ADEM) and Guillain-Barré syndrome (GBS).[9] Despite overlap between imaging findings particularly in the ICU setting, recognizing more typical features of each disorder can help the radiologist suggest the most likely diagnosis with implications on treatment and prognosis.

Leukoencephalopathy with or without microhemorrhage

WM changes with or without microhemorrhages can occur in critically ill COVID-19 patients requiring mechanical ventilation and long ICU stays, and are typically detected by imaging later in their hospitalization course.[19,21,22] One study reporting on 35 patients with cerebral leukoencephalopathy and/or microbleeds found patients with these findings had longer hospitalizations, required longer ventilator support, were more severely thrombocytopenic, and had higher D-dimer values.[22]

MRI findings typically show abnormal symmetric and confluent T2-hyperintensity extending from the precentral gyrus through the centrum semiovale and corona radiata, with relative sparing of subcortical and callosal WM that may be more conspicuous on diffusion weighted imaging (DWI) (Figure 1).[21,22] Associated microhemorrhages vary from a few to innumerable, are predominantly punctate, and involve the subcortical WM and/or corpus collosum, particularly the splenium (Figure 2). While inconsistently reported or obtained, CSF samples are typically negative for SARS-CoV-2 PCR assay.[19,21]

Previous studies published before the pandemic have documented diffuse leukoencephalopathy with or without microhemorrhages along the corticomedullary junction and in the corpus callosum in critically ill ICU patients.[23,24] Intriguingly, studies of mountain climbers with high-altitude cerebral edema also show similar patterns of WM edema, albeit reversible, with callosal involvement followed by accrual of microhemorrhages in the subcortical WM and corpus callosum on follow-up MRI.[25]

Despite these apparently divergent narratives of disease, hypoxemia is a common factor, suggesting a similar etiology either related to hypoxemia itself or hypoxic-induced hydrostatic or chemical changes leading to breakdown of the BBB with subsequent microhemorrhages.[23,24] BBB disruption from endothelial damage due to interactions of SARS-CoV-2 spike proteins with capillary endothelial cells or an exaggerated immune response may also occur,[1,26] since cytokine release and tissue damage are enhanced in hypoxic conditions.[13]

Another potential explanation for diffuse leukoencephalopathy is a delayed post-hypoxic leukoencephalopathy (DPHL) that can develop in ICU patients, and has been reported in intubated patients with subacute COVID-19.[21,27] DPHL typically follows a biphasic course with a period of recovery after hypoxic-ischemic injury follow by neurologic deterioration with leukoencephalopathy on MRI (Figure 3).[28,29]

Posterior Reversible Encephalopathy Syndrome

PRES is a neurological disorder presenting with headaches, seizures, and neurological deficits.[30] Neuroimaging of "classical" PRES shows relatively symmetric subcortical vasogenic edema in a parietal-occipital distribution that reverses on follow-up imaging; however, atypical patterns can involve the frontotemporal lobes, basal ganglia, thalamus, and infratentorial brain.[31] Typical risk factors for PRES include hypertension, renal failure, immunosuppressive agents, cytotoxic drugs, (pre)eclampsia, and sepsis.

PRES has been reported in COVID-19 patients often co-existing with similar risk factors and respiratory distress requiring intensive care (Figure 4).[32–34] In a retrospective study on COVID-19 patients with neuroimaging (n=278), the prevalence of PRES was 1.1%.[32] The onset of PRES varies, but the majority of cases occur > 2 weeks after hospitalization for COVID-19.[34]

The cause of COVID-19-related PRES is unclear, but likely involves endothelial cell dysfunction.[33] In a post-mortem MRI virtual autopsy study on COVID-19 patients, findings included subcortical micro- and macro-bleeds and cortico-subcortical edema reminiscent of PRES for which viral-induced endothelial damage either by direct infection or by a systemic cytokine storm were postulated.[35]

Many reported cases of COVID-19-related PRES show evidence of subcortical or callosal micro- and/or macro-hemorrhages on MRI susceptibility weighted sequences (Figure 5).[32–34,36,37] Classical PRES is associated with hemorrhages in only about 15-30% of patients suggesting that hemorrhage may be more common in COVID-19-related PRES.[31,38] Coagulopathy from cytokine storm and antithrombotic therapy in combination with endothelial cell dysfunction may increase the risk of developing hemorrhage in COVID-19-related PRES necessitating early cessation or reversal of antithrombotic therapy.[33] Approximately 70-90% of patients with PRES have clinical recovery with resolution of vasogenic edema on neuroimaging.[34] To date, the literature does not suggest that COVID-19-related PRES has a worse prognosis, but further studies are needed to substantiate this claim. Imaging resolution of vasogenic edema and the parieto-occipital distribution can help differentiate PRES from other leukoencephalopathies associated with COVID-19.

Hypoxic-Ischemic Injury

Hypoxic-ischemic brain injury is usually due to an acute event such as cardiac arrest or profound hypotension[39] and can be seen as a presenting or delayed complication of COVID-19 infection. In one large study,

hypoxic-ischemic injury was more common after hospital admission for COVID-19 and among critically ill patients with respiratory distress, sepsis, acute renal failure, hypoxia, and hypotension.[6]

In milder cases of hypoperfusion or hypo-oxygenation, diffuse hypoxic-ischemic injury shows cortical diffusion restriction on MRI in a border zone distribution (Figure 6).[40] After a moderate-to-severe hypoxic-ischemic insult, bilateral, symmetrical diffuse abnormal signal in the entire cerebral cortex, cerebellum, hippocampus, basal ganglia, and thalamus may be observed.[24,40] Overall, the prognosis is poor with a high mortality and severe neurological or cognitive deficits in survivors of prolonged and profound hypoxia.[39]

Neuroinflammatory Syndromes

Acute Disseminated Encephalomyelitis and Acute Hemorrhagic Leukoencephalitis

ADEM is a rare immune-mediated demyelinating disorder with delayed neurological deficits including encephalopathy.[41] ADEM is typically a monophasic illness thought to be secondary to cross-reactivity in immunity to viral antigens and is more common in children and adolescents.[41]

ADEM and its severe variant, acute hemorrhagic leukoencephalitis (AHLE), have been reported after COVID-19 infection, with 80% of cases occurring in adult patients.[42] One study reported a mean interval between onset of COVID-19 and ADEM symptoms of 24.7 days (range 0-214 days).[42]

On neuroimaging, classic ADEM typically shows T2-hyperintense lesions of varying sizes in the bilateral supratentorial or infratentorial WM with variable involvement of the deep gray matter, thalami and brainstem.[41] Lesions often demonstrate ring or arc contrast enhancement along the leading edge of inflammation. In COVID-19-related ADEM, the deep WM was most frequently involved, followed by the corpus collosum and subcortical WM; contrast enhancement was reported in 89% of cases (Figure 7).[42] Deep gray matter was less frequently involved compared to classic ADEM. In about 1/3 of classic ADEM cases, there is spinal cord involvement, which was also noted in COVID-19-related cases.[43,44] One study reported that 42% of patients (18/43) with COVID-19-related ADEM and AHLE had evidence of intracranial hemorrhage on neuroimaging, which is significantly higher than that seen with classic ADEM.[44] Like COVID-19-related PRES, COVID-19-related ADEM may be more susceptible to hemorrhagic changes due to underlying coagulopathies or endothelial dysfunction.

Of note, almost two-thirds of COVID-19 patients who developed ADEM or AHLE needed intensive care for the antecedent infection.[44] Unlike classic ADEM, the morbidity associated with COVID-19-related ADEM and AHLE was high even with standard treatments and mortality ranged from 10-32% suggesting it is a relatively poor prognostic marker.[42,44]

Guillain-Barré Syndrome

An association of GBS with SARS-CoV-2 infection is recognized with the overall prevalence of GBS in the COVID-19 population (~15/100,000) exceeding the general population (~2/100,000).[45] GBS includes a spectrum of immune-mediated polyneuropathies with multiple subtypes triggered by multiple different viral and bacterial infections.[46]

A systematic review of 73 patients with COVID-19 and GBS from 52 publications reported that most cases resembled the classic acute inflammatory demyelinating polyradiculopathy (AIDP) subtype.[47] In nearly all patients (n=68), symptoms of GBS developed after COVID-19 symptoms (median=14 days). A subsequent systematic review reporting on 109 patients similarly found that COVID-19-related GBS most commonly presents as the AIDP subtype, often with facial palsy.[48] Another large systematic review and meta-analysis reported patients with COVID-19 (n=136,746) had increased odds for demyelinating GBS subtypes (OR 3.27, 95%CI:1.32-8.09) with olfactory or cranial nerve involvement in 41.4% and 42.8%, respectively.[45]

Brain and spinal MRI in COVID-19-related GBS can show cranial nerve enhancement, brainstem leptomeningeal enhancement, or spinal nerve root or cord leptomeningeal enhancement (Figure 8).[47] CSF SARS-CoV-2 PCR assay is typically negative and most patients (>70%) have a good prognosis after treatment with intravenous immunoglobulin comparable to non-infected contemporary or historical GBS controls.[45,47]

The CSF results, response to treatment, and approximate two-week latency between COVID-19 symptoms and onset of GBS all suggest a post-infectious autoimmune-mediated mechanism. However, further studies are needed to determine the association and pathophysiological mechanism of GBS in COVID-19 patients.[46,48] The causal association between COVID-19 and GBS is controversial. Retrospective epidemiological data and a prospective cohort study from the United Kingdom (UK) did not support any significant causal association between COVID-19 and GBS.[49]

COVID-19 NEUROLOGIC INVOLVEMENT IN CHILDREN AND ADOLESCENTS

Children and adolescents are mostly spared severe COVID-19 infection; however, when they are hospitalized, one multicenter cohort estimated 22% (365/1695) have neurological involvement.[50] Another recent large study found that among hospitalized children and adolescents (n=1334), neurological or psychiatric manifestations are common (3.8 cases per 100) with most patients presenting after their acute COVID-19 illness had resolved.[51]

Neurologic symptoms in these young patients are often attributed to a para-infectious or post-infectious immune-mediated disorder such as ADEM. Nevertheless, some patients also present with a novel inflammatory process termed multisystem inflammatory syndrome in children (MIS-C).[51] The most common neurologic symptom in patients with MIS-C is encephalopathy typically occurring weeks after SARS-CoV-2 infection. In one study, two-thirds of MIS-C patients with neurologic symptoms (17/23) had abnormal brain imaging most commonly showing reversible splenial lesions in the corpus collosum.[51] Splenial lesions in this patient population appear as ovoid, T2-hyperintense foci with variable restricted diffusion sometimes extending into adjacent WM.[52]

Patients with MIS-C were more likely to require supportive care in the ICU than pediatric patients with other COVID-19-related neurological diseases; however, early outcomes were similar with death being uncommon and disability in approximately one-third.[51] Future studies are needed to determine long-term neurocognitive outcomes in children.

POST-COVID SYNDROME: "LONG HAULERS"

There is increasing evidence of distinct, chronic manifestations of COVID-19 infection that affect multiple organ systems.[53] Chronic or long-term COVID-19 symptoms have been referred to as post-acute sequelae of SARS-COV-2 (PASC) , post-COVID syndrome, or long COVID. People suffering with chronic COVID-19 symptoms are sometimes called "long haulers." An exact medical definition of post-COVID syndrome is evolving. Recent literature suggests a couple of definitions: a) subacute or ongoing COVID-19 infection including symptoms or abnormalities 4-12 weeks beyond acute COVID-19 infection and/or b) chronic or post-COVID syndrome in which symptoms or abnormalities persist beyond 12 weeks of acute COVID-19 infection not attributable to another diagnosis.[53]

Post-COVID syndrome symptoms include fatigue, "brain fog" (cognitive impairment), headache, numbness/tingling, dysgeusia, anosmia, and myalgias.[53–55] Neuropsychiatric symptoms have also been reported in up to 30-40% of COVID-19 survivors including anxiety, depression, sleep disturbances, and post-traumatic stress disorder, which is similar to that reported with other coronaviruses.[53,55,56] Chronic neuropsychiatric sequelae have also been reported with other less common types of viral encephalitis.[57]

A study of 62,354 COVID-19 survivors showed a significantly higher likelihood of a new psychiatric diagnosis compared to controls, including anxiety and mood disorders, sleep disturbances, and dementia in the elderly.[58] In a retrospective cohort study of 236,379 COVID-19 survivors, the incidence of a neurologic or psychiatric diagnosis 6 months following the acute infection was 33.6% with 12.8% receiving such a diagnosis for the first time.[59] For patients with severe COVID-19 infection prompting ICU admission, risks were greater with 46.4% receiving a neurologic or psychiatric diagnosis 6 months following the acute infection and 25.8% receiving such a diagnosis for the first time.[59] In another study of 18 patients with mild to moderate COVID-19 infection nearly three months following recovery, over 75% had problems with memory, attention, and concentration suggesting that even with milder infections, long-term cognitive deficits are a potential sequela.[60]

Confounding the post-COVID syndrome discussion is that many of the known complications of COVID-19 infection such as stroke, hypoxic-ischemic injury, and leukoencephalopathy leave surviving patients with long-term neurological deficits that may manifest as lingering symptoms.[53] It remains puzzling that post-COVID syndrome affects patients across the entire spectrum of disease severity from the relatively asymptomatic to ICU patients. One study involving over 4000 COVID-19 survivors reported that age > 70, more than five symptoms during the acute illness, presence of comorbidities, and female sex were associated with higher risk of development of post-COVID syndrome.[61]

Potential pathophysiologic mechanisms of post-COVID syndrome are similar to those proposed for COVID-19 CNS involvement.[53] Stefano et al. also postulated that cerebral hypoxia causes neuronal cell metabolic derangement and mitochondrial dysfunction leading to cognitive impairment.[62] Others proposed that post-COVID syndrome symptoms overlap with those of myalgic encephalomyelitis/chronic fatigue syndrome such that there may commonality in terms of pathophysiology.[54]

There is also imaging evidence of limbic structural brain changes in patients with cognitive decline after milder COVID-19 infection not requiring hospitalization. A longitudinal imaging study utilized the UK Biobank to

compare brain MRIs from individuals before and after COVID-19 infection to well-matched controls and demonstrated a greater reduction in gray matter thickness in the orbitofrontal cortex and parahippocampal gyrus, as well as greater changes in mean diffusivity in areas functionally connected to the olfactory cortex.[63]

As of this writing, it is not clear how long the symptoms reported with post-COVID syndrome will last, nor is it clear what role imaging may play in diagnosis or prognosis. Advanced neuroimaging such as diffusion tensor imaging (DTI), cerebral fluorodeoxyglucose (FDG)-positron emission tomography (PET), and perfusion imaging may lead to better understanding of how COVID-19 impacts neuroconnectivity and function.[64–67]

CHALLENGES AND LIMITATIONS

Early in the COVID-19 pandemic, neuroimaging was performed on only the sickest patients because of the contagious nature of SARS-CoV-2. Safety concerns around transportation to imaging suites and the repeated use of imaging equipment coupled with the inherent challenges of scanning patients on mechanical ventilation limits the complete understanding of the prevalence of subacute to chronic neuroimaging findings in COVID-19 patients. One potential alternative for critically ill patients in the ICU setting is the use of a low-field (0.064-T) portable MRI at bedside (Figure 9).[68] One study obtained neuroimaging in 20 patients with COVID-19 on ventilation using portable, low-field MRI at bedside and observed positive neuroimaging findings in 40% of patients.[68] Imaging critically ill SARS-CoV-2 patients with encephalopathy is challenging but should be considered given the potential to inform treatment planning and prognosis.

Determining the etiology or causality of chronic CNS complications in Covid-19 infection is challenging given the novel nature of the disease, emergence of novel variants, a complex clinical course particularly in ICU patients, and polypharmacy from different treatment regimens. There remains a critical, unmet need for histopathology, CSF-specific markers, and autopsy studies to establish with greater certainty the pathophysiology and long-term consequences of SARS-CoV-2 on the CNS. Collaborative and thoughtful future research efforts by radiologists will lead to greater understanding of the role of neuroimaging in evaluating COVID-19 CNS complications.

SUMMARY

COVID-19 is associated with subacute to chronic neurological disorders related to immune system activation resulting in coagulopathy and cytokine storm with endothelial cell dysfunction that may lead to leukoencephalopathy, microhemorrhages, and PRES. Immune system activation may also manifest as autoimmune disorders such as ADEM and GBS. Comorbidities such as hypertension play a role in development of PRES and complications from critical illness and prolonged ICU stays contribute to hypoxic-ischemic injury and leukoencephalopathy. Evidence for direct viral invasion of the CNS is minimal, but it may play a role in olfactory symptoms. Future imaging studies utilizing databases and advanced neuroimaging may help to establish the long-term consequences of SARS-CoV-2 on the CNS.

Clinics Care Points

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Table 1: Neuroimaging Findings in Subacute to Chronic COVID-19 Infection

Clinical Syndrome	**Imaging Findings (CT or MRI)**	**Proposed Pathogenesis**
Leukoencephalopathy with or without microhemorrhages	▪ Symmetric, confluent T2-hyperintensity in cerebral WM with increased conspicuity on DWI extending from precentral gyrus through cerebral WM along corticospinal tracts sparing subcortical and callosal WM ▪ Associated *microhemorrhages* usually punctate in subcortical WM and corpus collosum (splenium most common)	▪ Hypoxemia ▪ Endothelial cell dysfunction via immune-mediated cytokine storm or direct viral interactions
Posterior Reversible Encephalopathy Syndrome (PRES)	▪ Symmetric subcortical WM vasogenic edema in parietal-occipital distribution ▪ COVID-19-related PRES more commonly associated with micro- and/or macro-hemorrhages	▪ Endothelial cell dysfunction via immune-mediated cytokine storm or direct viral interaction ▪ Co-morbidities and treatment-related complications
Hypoxic-Ischemic Injury	▪ Mild: Cortical diffusion restriction in border zone distribution ▪ Moderate to severe: Restricted diffusion of entire cerebral cortex, hippocampus, basal ganglia, and/or thalamus	Hypoxia from cardiac arrest or profound hypotension
▪ Acute Disseminated Encephalomyelitis (ADEM) ▪ Acute Hemorrhagic Leukoencephalitis (AHLE)	▪ T2-hyperintense lesions in deep WM > corpus collosum and subcortical WM with arc enhancement along leading edge ▪ Lesions may be larger in AHLE ▪ AHLE and COVID-19-related ADEM more likely to have hemorrhagic foci; deep GM involvement is less common	Autoimmune-mediated

	▪ +/- spinal cord involvement	
Guillain Barré Syndrome	▪ Spinal nerve root and spinal leptomeningeal enhancement ▪ Cranial nerve and brainstem leptomeningeal enhancement	Autoimmune-mediated
Multisystem Inflammatory Syndrome in Children (MIS-C)	▪ *Reversible* discrete, ovoid, T2-hyperintense foci with variable diffusion restriction in splenium of corpus callosum most common	Post-infectious immune dysregulation

CT=computed tomography; MRI=magnetic resonance imaging; WM=white matter; DWI=diffusion weighted imaging; GM=gray matter

FIGURE LEGENDS

Figure 1. Leukoencephalopathy in a 67-year-old patient with chronic COVID-19 and encephalopathy. Multiple axial diffusion-weighted images through the brain show symmetric and confluent hyperintensity extending along the corticospinal tracts through the centrum semiovale, corona radiata, and posterior limb of the internal capsule (white arrow) with relative sparing of subcortical white matter.

Figure 2. Leukoencephalopathy with microhemorrhages in two COVID-19 patients with encephalopathy and chronic (> 3 weeks) ICU stays on mechanical ventilation. Axial T2-weighted images (A) in an elderly patient show diffuse white matter hyperintensity with hypointense microhemorrhages along the corticomedullary junction bilaterally. Axial susceptibility weighted images (B) in a different elderly patient showing punctate foci of susceptibility compatible with microhemorrhages along the corticomedullary junction and within the genu and splenium of the corpus collosum.

Figure 3. Delayed post-hypoxic leukoencephalopathy (DPHL) in a 71-year-old ICU patient with COVID-19. Initial MRI early in hospitalization prior to intubation with axial DWI (A), axial ADC (B), and axial T2-weighted (C) images showing punctate foci of diffusion restriction compatible with acute infarcts in the centrum semiovale with otherwise normal appearing white matter. Follow-up MRI during the 5th week of hospitalization after prolonged intubation with an axial T2-weighted image (D) shows diffuse, symmetric abnormal T2-hyperintensity bilaterally in the centrum semiovale consistent with DPHL.

Figure 4. Posterior reversible encephalopathy syndrome in a 67-year-old patient with subacute COVID-19 infection, hypertension and diabetes. Axial non-contrast CT (A) demonstrates bilateral, symmetric parieto-occipital hypodensities, and axial FLAIR MRI images show relatively symmetric subcortical white matter hyperintensities in the parieto-occipital (B and C) and frontal (D) white matter.

Figure 5. Posterior reversible encephalopathy syndrome in an ICU patient with subacute to chronic COVID-19 infection and labile hypertension. MRI of the brain shows symmetric abnormal T2-hyperintensity in the parieto-

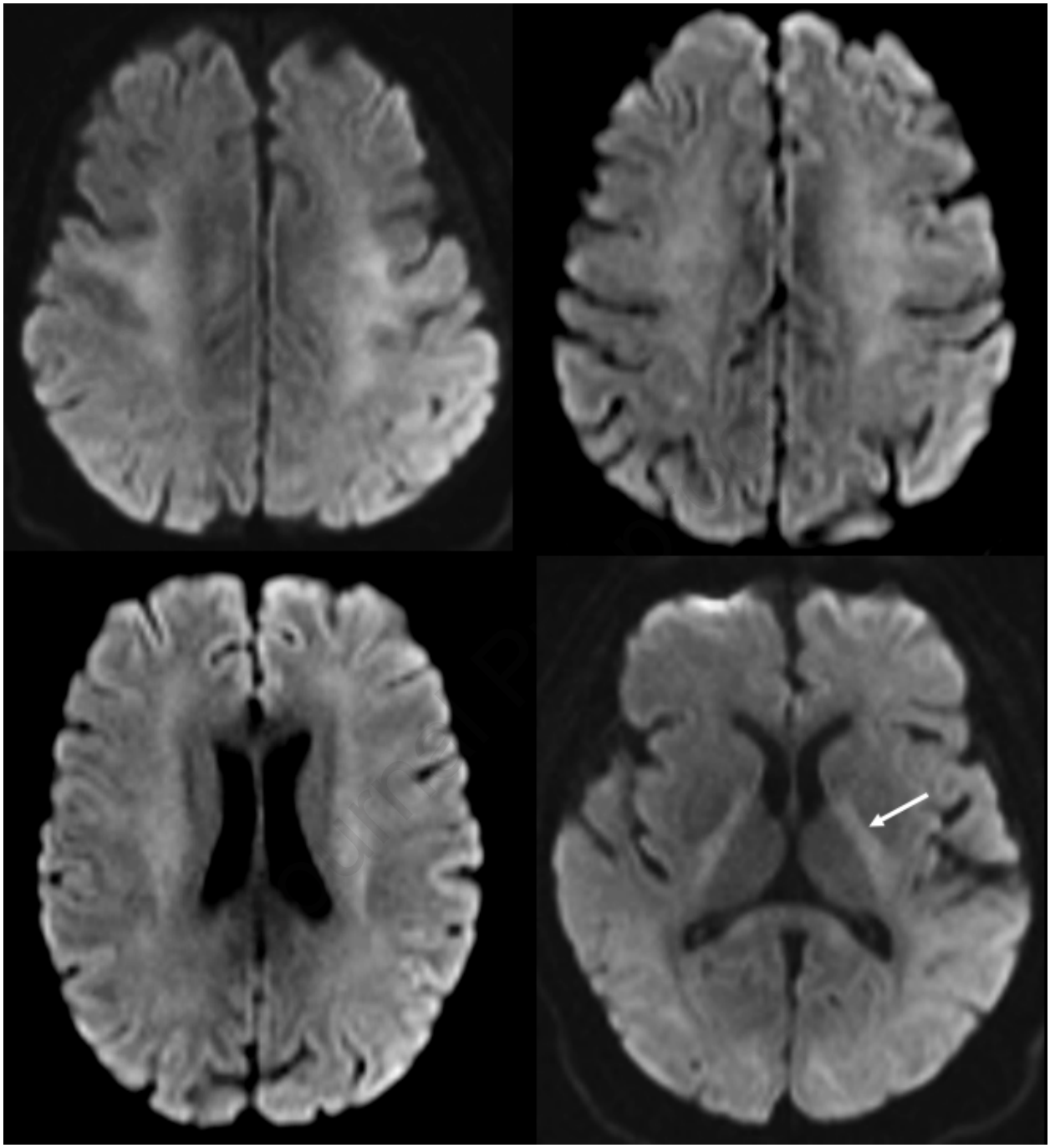
occipital subcortical white matter on axial (A) and coronal (B) FLAIR images with associated punctate susceptibility consistent with microhemorrhage on an axial SWI (black arrow, C). Axial DWI (D) and ADC image (E) show reduced diffusivity in the same region. On sagittal T1-weighted imaging (F), there is associated parieto-occipital gyral hyperintensity that may reflect cortical laminar necrosis.

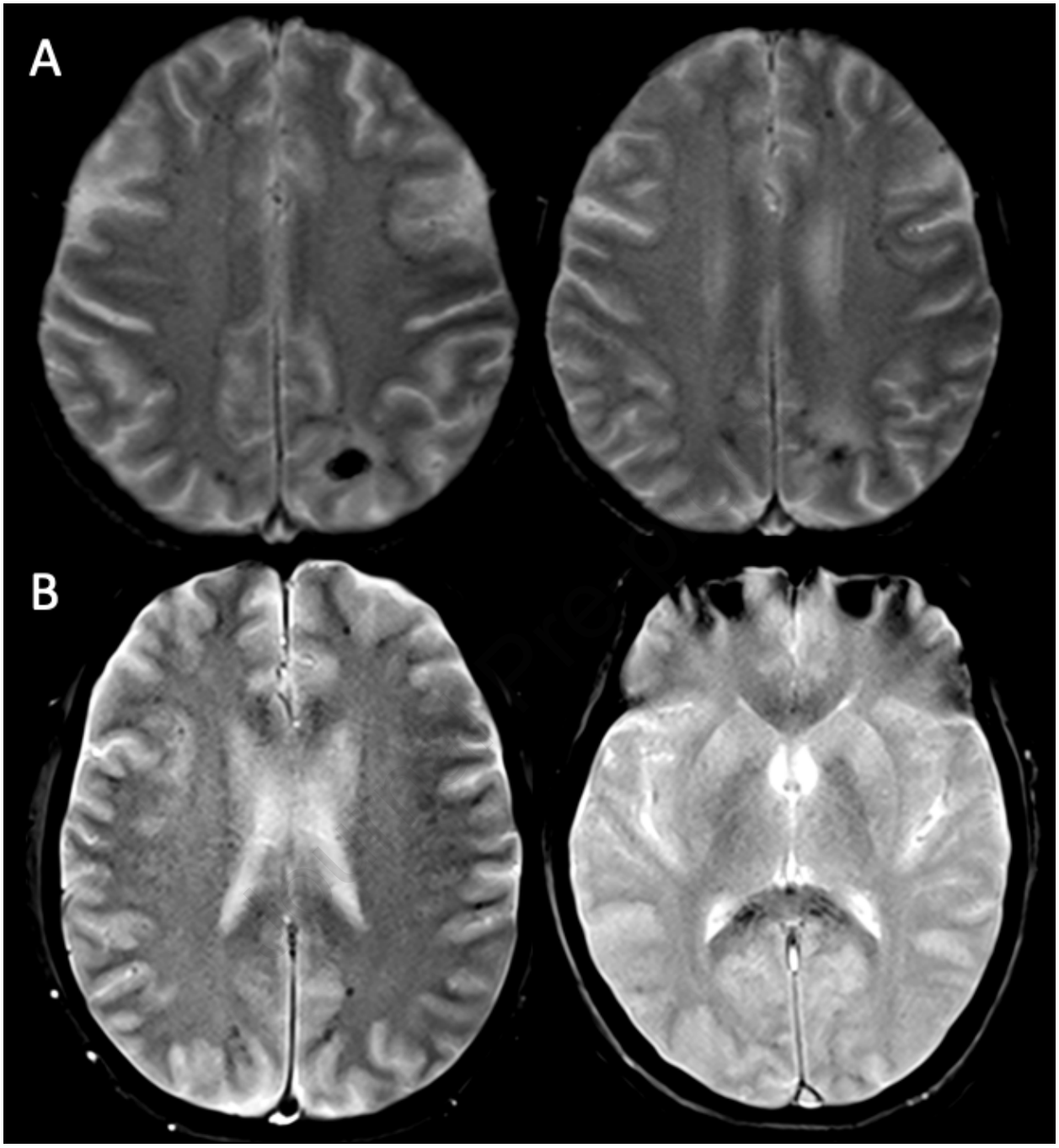
Figure 6. Hypoxic-ischemic injury in an elderly COVID-19 patient. Multiple axial diffusion-weighted images through the brain show bilateral, symmetric-appearing areas of restricted diffusion compatible with acute infarcts in a border zone distribution suggestive of hypoperfusion.

Figure 7. Acute disseminated encephalomyelitis in an elderly patient with COVID-19 and subacute encephalopathy. Non-contrast MRI of the brain with axial FLAIR (A) and T2-weighted (B and C) images show ovoid and ring-like hyperintense lesions in the periventricular white matter and left brachium pontis most compatible with demyelinating lesions, with several posterior lesions demonstrating restricted diffusion on axial DWI (D).

Figure 8. Acute motor and sensory axonal neuropathy (AMSAN) subtype of Guillain-Barré syndrome in a 63-year-old female who recovered from COVID-19 respiratory illness 3 weeks prior and then developed facial palsy, difficulty swallowing, and ascending numbness. MRI of the brain with axial post-gadolinium FLAIR (A) and post-gadolinium T1-weighted (B and C) images through the skull base show abnormal enhancement of the mastoid (arrows, A and B) canalicular, labyrinthine, and tympanic segments (arrows, C) of the facial nerves bilaterally. Coronal T1-weighted post-gadolinium images show abnormal enhancement along the bilateral olfactory (arrows, D), V2 (arrows, E) and V3 (arrows, F) segments of the trigeminal nerves.

Figure 9. Ultralow field (0.064 Tesla) portable MRI in an ICU patient with COVID-19. Axial T2-weighted image shows areas of bilateral infarction. Portable MRI was used as a triage tool in the height of the pandemic particularly in chronically intubated patients.

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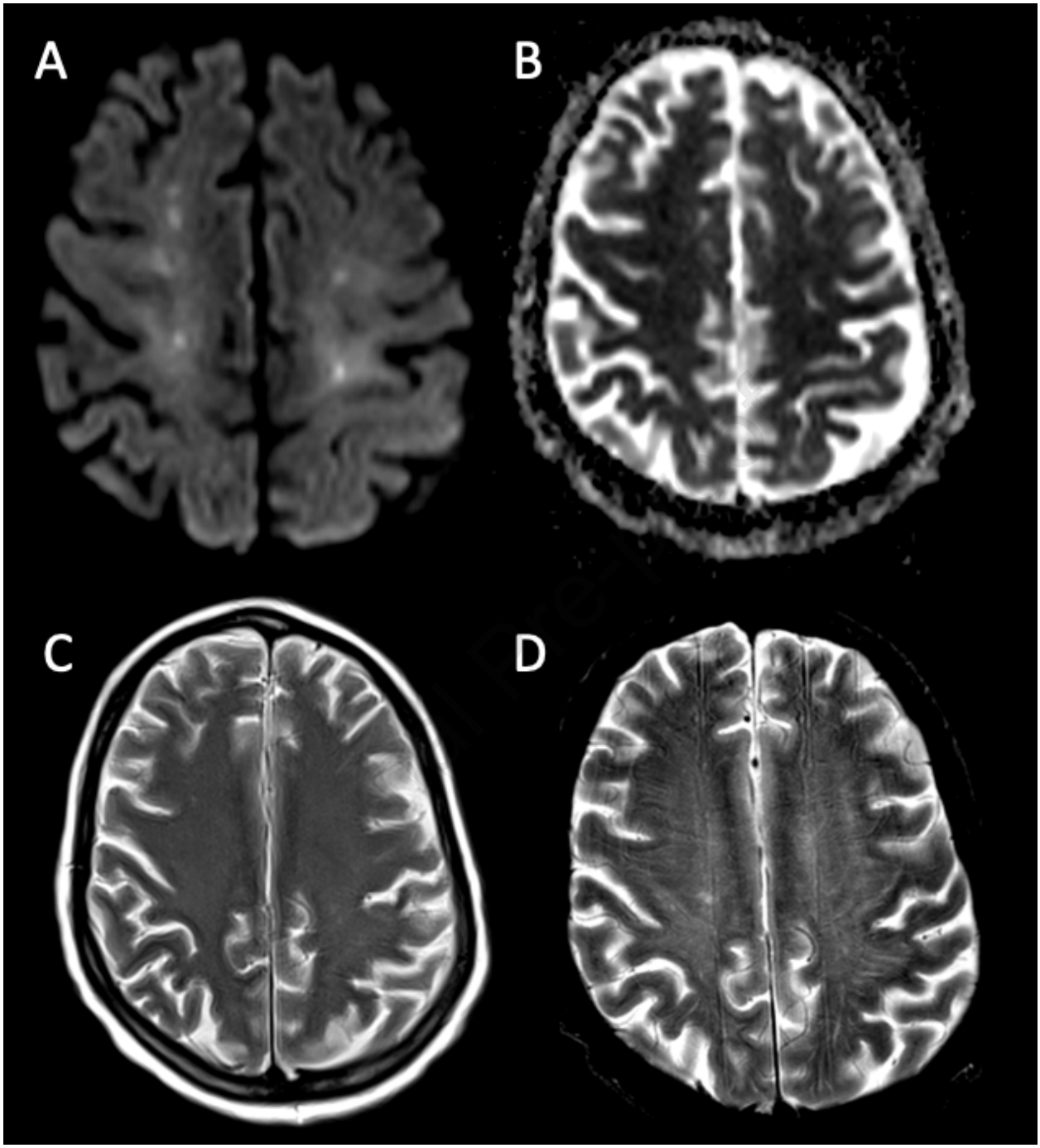
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