Spectrum of neuroimaging mimics in children with COVID-19 infection

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has affected over 200 million people globally (including over 30 million people in the United States), with children comprising 12.9% of reported cases in the United States. In children, COVID-19 infection appears to be associated with mild respiratory symptoms; however, serious neurological complications may occur in conjunction with multisystem inflammatory syndrome. A wide spectrum of neurological diseases have been observed in children with COVID-19 infection including encephalitis, acute necrotizing encephalopathy, acute disseminated encephalomyelitis, cytotoxic lesion of the callosal splenium, posterior reversible encephalopathy syndrome, venous sinus thrombosis, vasculitis and infarction, Guillain–Barré syndrome, transverse myelitis, and myositis. This review describes the characteristic magnetic resonance neuroimaging features of these diseases and their differentiations from other imaging mimics. In addition, we review the possible pathophysiology underlying the association between these diseases and COVID-19-infection. As new SARS-CoV-2 variants emerge and COVID-19 infection continues to spread worldwide, pediatricians, radiologists, and first-line care givers should be aware of possible neurological diseases associated with COVID-19 infection when these reported neuroimaging patterns are observed in children during this pandemic.

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was declared by the World Health Organization as a pandemic on March 11, 2020 [1]. As of August 20, 2021, the pandemic has affected over 200 million people globally (over 30 million people in the United States), with children comprising 12.9% of reported cases in the United States [2]. Although pulmonary disease is the predominant manifestation of COVID-19, neurological abnormalities, including self-reported neurological symptoms and clinically captured neurological signs or syndrome, have been reported in approximately 36%–82% of all COVID-19 cases [3,4]. In children, COVID-19 infection is often asymptomatic or associated with mild respiratory symptoms [5]. An early study

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reported a rare incidence of neurological complications in children, and even neuroimaging had a low yield in children with COVID-19 [6]. However, as the disease continues to spread, with increasing number in children, an immune-mediated syndrome called pediatric multisystem inflammatory syndrome in children (MIS-C) has been described, representing a relatively rare but severe hyperinflammatory illness temporally associated with SARS-CoV-2 infection [7]. Patients with MIS-C have neurological complications; a systemic review reported that approximately 22%–55% of children with MIS-C had neurological involvement, with a wide range of manifestations [8]. Reports of severe neurological involvement in children with COVID-19 have emerged including two large series published by Lindan et al. [9] and LaRovere el al [10]. Numerous case reports have indicated the presence of acute encephalopathy or encephalitis [11–24], acute necrotizing encephalopathy (ANE) [25,26], acute disseminated encephalomyelitis (ADEM) [20,26–32], cytotoxic lesions in the callosal splenium [26,33–37], posterior reversible encephalopathy syndrome (PRES) [26,38], cerebral venous thrombosis [39,40], vasculitis and acute infarction [20,21,41–47], and Guillain–Barré syndrome (GBS) [20,21,26,48–58] and its variant Miller-Fisher syndrome (MFS) [59–62], transverse myelitis [9,50,63–65], and myositis [50,63–65]. These neurological complications were reported to occur in acute or sub-acute phase as primary neurological disorders and in delayed phase as complications of MIS-C that typically occurs weeks after the COVID-19 infection [9,20]. ADEM and myelitis were observed throughout all phases; encephalitis, GBS/MFS, thrombo-ischemic diseases were observed in acute or sub-acute phase; and splenial lesions and myositis of the neck and face were predominantly seen in the delayed phase [9,20].

Magnetic resonance imaging (MRI) has been the mainstays of diagnostic neuroimaging. MRI is safe to children, without exposure to ionizing radiation or iodinated contrast medium. Fluid-attenuated inversion recovery (FLAIR) imaging is a T2-weighted turbo spin-echo sequence that suppresses the signal of cerebrospinal fluid within the sulci, ventricles, and cisterns. Diffusion-weighted imaging (DWI) is a technique measuring water diffusivity in the brain. DWI has proved to associate with disease severity or detect lesions earlier than conventional MRI in many conditions, including infarction, infection, and demyelination [66]. Arterial spin-labeling (ASL) is a noninvasive MR method that uses arterial water as an endogenous tracer for perfusion imaging. This review focuses on the MRI of neurological diseases in children with COVID-19 infection.

Pathophysiology

SARS-CoV-2 is believed to enter the central nervous system (CNS) through three pathways: direct entry through cells possessing angiotensin-converting enzyme 2 receptor (ACE2),
such as neurons, astrocytes, and oligodendrocytes; trans-neuronal spread; and hematogenous dissemination across a defective blood–brain barrier [67–69] (Fig. 1). In the brain, a high ACE2 concentration is found in the motor cortex, posterior cingulate cortex, middle temporal gyrus, brainstem, circumventricular organs, thalamus, and olfactory bulb [69]. Transneuronal spread of SARS-CoV-2 into the CNS may occur through the olfactory pathway and the trigeminal nerve [69–71]. When blood vessels are affected, endothelial injury, an uncontrolled immune response elicited by pulmonary or systemic infection, and breakdown of the blood–brain barrier may result in vasculitis and thrombosis with subsequent occlusion [69]. Moreover, endothelial dysfunction and disordered autoregulation may contribute to PRES [38,72]. Triggered by viral infection and other conditions, the uncontrolled response may develop into a “cytokine storm” that is characterized by elevated circulating cytokines, immune-cell hyperactivation, stimulation of the complement and coagulation cascade, and later secondary organ dysfunction [73]. To reach the CNS, the virus may infect the vascular endothelium and cross the blood–brain barrier or infect leukocytes that pass through the blood–brain barrier to reach the brain tissue through the “Trojan horse mechanism” [69]. The entry of the virus into the brain is followed by both direct damage by the virus and indirect injury by the cytokine storm [68,74,75], with resultant injuries responsible for neurological diseases such as encephalitis, ADEM, ANE, transverse myelitis in the spinal cord, MFS involving the cranial nerves, and GBS affecting the peripheral nervous system. Hypercoagulation, which is associated with viruses and cytokine storm, may contribute to venous sinus thrombosis [75,76].

**MR neuroimaging**

**Encephalitis**

Encephalitis is an acute inflammation of the brain parenchyma caused mainly by viral infections [77]. Clinical presentations include fever, headache, conscious disturbance, seizure, and behavioral change. Numerous cases of COVID-19 associated encephalitis have been reported [9,11–24]. Electron microscopic evidence of SARS-CoV-2 inclusions has been found in the cerebellum in a child with acute COVID-19 infection [9].

MR imaging (MRI) reveals poorly delineated areas of T2-hyperintensity in the cortical gray matter and subcortical white matter, accompanied by gyral swelling and hemorrhage (Fig. 2). Deep gray nuclei are sometimes involved. Contrast enhancement is variable. In addition to the herpes virus family, many other viruses such as influenza viruses, adenovirus, respiratory syncytial virus, parainfluenza virus, and Japanese encephalitis virus, have been associated with childhood encephalitis. The topography of involvement is
related to causative agents [78,79], and the involved areas typically do not match the major vascular distribution. For example, deep gray nucleus lesions are documented in encephalitis associated with the Epstein-Barr virus, West Nile virus, influenza virus, and Japanese encephalitis. In the early stage of the disease, DWI may indicate restricted diffusion in affected areas. Patients with lesions showing restricted diffusion had poor clinical outcomes [80]. However, in mild encephalopathy with a reversible splenial lesion (MERS), the T2-hyperintensity and restricted diffusion of the splenial lesion resolve completely or near completely on follow-up imaging within days to weeks and affected children usually have good outcomes [81]. Perfusion imaging (ASL imaging) may show elevated cerebral blood flow, suggestive of seizure activity [82]. In addition, diffuse hypoperfusion of the brain indicates poor clinical outcomes.

Major differential diagnoses of encephalitis include acute ischemic infarction, autoimmune encephalitis, status epilepticus, and toxic or inherited metabolic diseases. Acute ischemic infarction usually assumes vascular distribution and is associated with the sudden onset of illness. Autoimmune encephalitis may cause abnormalities in the limbic system but may be indistinguishable in patients with herpes simplex encephalitis. Status epilepticus is usually unilateral and characterized by transient postictal edema. Toxic or inherited metabolic diseases can be differentiated by their symmetric involvement in the basal ganglia and characteristic biochemical study results.

**Acute necrotizing encephalopathy**

Acute necrotizing encephalopathy (ANE) is a rapidly progressive encephalopathy with bilateral thalamotegmental involvement that predominantly affects infants and young children in Far East countries (Japan, Taiwan, and Korea) [83]. It is believed that this disease is most likely immune-mediated or metabolic [84], although influenza A virus, mycoplasma, herpes simplex virus, and human herpes virus-6 have been reported as common causative agents. Clinical manifestations include fever, seizures, rapid neurological deterioration, and altered consciousness levels. The affected infants and children usually have high mortality rates and severe neurologic sequelae. ANE has rarely been reported in children with COVID-19 infection [25,26].

The neuroimaging hallmark of ANE is T2-hyperintensity in the bilateral thalami, as well as in the midbrain tegmentum and pons [83] (Fig. 3). In some cases, the deep cerebral white matter and cerebellum are involved. In the first few days, decreased diffusivity may be observed in the affected regions of the brain stem, cerebellum, and thalami [85]. The affected areas may rapidly cavitate, likely because of tissue necrosis, and become hemorrhagic, followed by ring enhancement around the hemorrhagic areas.

Before reaching the diagnosis of ANE, a wide range of disorders affecting the bilateral thalami should be considered. Hypoxic–ischemic encephalopathy may involve deep gray nuclei bilaterally, but it is usually accompanied by a

![Fig. 3 (A) Axial FLAIR and (B) coronal T2-weighted images show hyperintensities in the bilateral thalamus and bilateral frontal deep white matter. (C) Axial T1-weighted image reveals hyperintensities, suggesting hemorrhages in the thalami. (D) Axial diffusion-weighted image showing decreased diffusion in the bilateral thalamic lesions surrounding the hemorrhages. (E) Axial postcontrast T1-weighted image reveals no contrast enhancement of the abnormalities.](image-url)
circulatory or hypoxic episode and an appropriate clinical course. Certain encephalitis, such as Japanese encephalitis, may also involve the deep gray matter symmetrically. However, thalamic involvement in Japanese encephalitis is not necessarily symmetrical, and brain stem involvement is uncommon. ADEM is usually associated with cerebral white matter lesions in addition to thalamic lesions. The asymmetrical involvement and the response to steroid therapy in patients with ADEM may help in differentiation. Venous infarction is prone to hemorrhage. The confirmation of the patency of internal cerebral veins and the straight sinus using contrast-enhanced MRI and MRV may help exclude this disease. Osmotic demyelination syndrome tends to symmetrically involve the external capsule, caudate nucleus, and putamen. Toxic encephalopathy and inherited metabolic diseases more commonly involve the caudate nucleus and putamen. In addition, clinical and laboratory findings in ANE are different from the features of these diseases.

**Acute disseminated encephalomyelitis**

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated, monophasic demyelinating disease affecting the white matter and typically occurs following a viral illness or immunization. Affected patients may present with widespread neurological dysfunctions including fever, malaise, myalgia, seizure, and impaired consciousness. Numerous case reports and series have reported ADEM in children with COVID-19 [9,20,26–32].

The characteristic imaging findings are multifocal punctate to floculent T2-hyperintensities over subcortical and deep white matter regions (Fig. 4). Deep gray nuclei, and less frequently the brainstem and cerebellum, are also involved but the callososseptal interface is usually spared. The distribution of the abnormalities is usually bilateral but asymmetric. Contrast enhancement of the lesions, in punctate, ring, or peripheral shape can be seen. Decreased diffusion is uncommon, but when present, it may suggest a poor prognosis [86,87].

ADEM should be differentiated from other diseases, with an imaging appearance of multifocal white matter–gray matter lesions. Multiple sclerosis has a predilection for periventricular white matter (callososseptal interface) and involves subcortical U-fibers, but it usually spares the gray matter. Vasculitis usually involves the cortical and subcortical regions of the brain and deep gray nuclei. PRES typically affects the bilateral parasagittal cortex and subcortical white matter regions (watershed zones) more commonly in the posterior circulation.

**Cytotoxic lesions of the callosal splenium**

Cytotoxic lesions of the callosal splenium have been reported in children with seizure- and drug-related conditions, viral encephalitis, and metabolic derangements [37,88]. Affected children presented with cognitive impairment, seizures, hallucinations, and delirium. Splenial lesion has been reported in children with COVID-19 infection [9,10,26,33–37] and were predominantly observed in patients with MIS-C [9,36].

MRI reveals an ovoid homogeneous T2-hyperintense lesion centered in the splenium of the corpus callosum (Fig. 5). The lesion typically exhibited restricted diffusion and showed no enhancement [88].

**Posterior reversible encephalopathy syndrome**

Posterior reversible encephalopathy syndrome (PRES) is described as a potentially reversible syndrome predominantly affecting the parieto-occipital regions, likely resulting from failed cerebrovascular autoregulation, vasospasm, or vascular endothelial damage [89]. It is most commonly associated with hypertension, eclampsia, and immunosuppressive treatment.
Other associated conditions include hemolytic-uremic syndrome, thrombocytopenia purpura, autoimmune diseases, endocrine disorders, stimulant drugs, and excess mineralocorticoids. Neurological symptoms vary from seizure, headache, altered mental status, and visual disturbances. In children with COVID-19 infection, PRES is rarely reported [26,38].

MRI reveals T2-hyperintensities in the bilateral parasagittal cortex and white matter (vascular watershed zones), with a predilection for the parieto-occipital regions in 90% of affected patients [89] (Fig. 6). Atypical PRES may show abnormalities in the basal ganglia, brainstem or cerebellum. Diffusion-weighted imaging is negative in the majority of cases, but restricted diffusion is reported in approximately 20% of cases.

Fig. 6 Posterior reversible encephalopathy syndrome in an 11-year-3-month-old boy presenting with fever, headache, seizure, and conscious disturbance. (A) Axial and (B) coronal FLAIR images show cortical and subcortical hyperintensities in the bilateral anterior and posterior watershed zones, and the cerebellar regions. (C) Axial arterial-spin labeling perfusion image shows increased perfusion in the parasagittal frontal and occipital regions. (D) Axial diffusion-weighted image is unremarkable. (E) Axial post-contrast T1-weighted image shows no contrast enhancement in the affected regions.
Contrast enhancement is variable and patchy contrast enhancement may be noted in the cortical–subcortical regions when the blood–brain barrier breaks down. Perfusion imaging can show both increased and decreased perfusion in the affected areas.

PRES can be distinguished from acute ischemic infarction, which is usually unilateral and more commonly involves the middle cerebral artery (MCA) distribution with restricted diffusion. Status epilepticus can mimic PRES but is often unilateral. Hypoglycemia resembles PRES on imaging by its parieto-occipital predominance; differentiation relies on clinical history and laboratory findings. Thrombosis of the superior sagittal sinus can be diagnosed with a blood clot occluding the sinus and is more often complicated by hemorrhages. Thrombotic microangiopathies more often show diffuse cerebral edema and microhemorrhages.

**Venous sinus thrombosis**

Cerebral venous sinus thrombosis (CVST) is defined as the thrombotic occlusion of a venous sinus, or cortical and/or deep veins [90,91]. Accompanied by increased intracranial pressure, headache is frequent in CVST, but the most common manifestations in newborns are seizures and altered mental status. CVST has been an infrequent neurological manifestation in children with COVID-19 infection [39,40].

The MRI appearance of a thrombus parallels that of a hematoma (Fig. 7). During the acute stage (1–5 days), the clot containing intracellular deoxyhemoglobin displays T1-isointensity to mild hyperintensity and T2-hypointensity. In the subacute stage (5–20 days) when the clot is oxidized to produce methemoglobin, the clot shows T1-hyperintensity, T2-hypointensity (intracellular methemoglobin), and T2-hyperintensity (extracellular methemoglobin after the lysis of red blood cell) [90]. Postcontrast T1-weighted imaging in an orientation perpendicular to the venous structure shows the clot as a nonenhancing filling defect (empty delta sign). Because rapidly moving blood reveals hypointensity in a venous sinus (flow void), diagnosing CVT may be challenging in that both patent veins and a clot may show similar signal intensities. The use of T2* sequences, such as GRE and SWI, helps depict thrombosed blood vessels by showing the exaggeration of the hypointensity (T2* blooming) in clots. Coronal two-dimensional time-of-flight MRV can depict the absence of venous flow in the cross-sectional vein. Contrast-enhanced MRV is highly sensitive for identifying the clot as the empty delta sign [92].

Indirect imaging findings of CVST include parenchymal edema and venous congestion, revealing T2-hyperintensity and swelling, in territories drained by the occluded vein or sinus [91]. Accompanied hemorrhages occur in 35%–40% of patients. Venous ischemia is indicated by restricted diffusion. In long-standing thrombosis, thickening and contrast

![Fig. 7 Cerebral venous thrombosis complicating with hemorrhagic venous infarctions in a 13-year-old girl with acute lymphoblastic leukemia on chemotherapy. (A) Axial T1-weighted image shows abnormal hyperintensity within the superior sagittal sinus. Associated hemorrhagic venous infarctions, demonstrating areas of mixed high and low intensities, are found in the bilateral parasagittal frontal and parietal regions drained by the thrombosed sinus. (B) Sagittal T2-weighted and (C) coronal T2-weighted images show abnormal high and low signal intensities within the superior sagittal sinus and in the venous infarctions. (D) Axial postcontrast T1-weighted image shows the “empty delta” sign, representing a filling defect (nonenhancing clot) in the superior sagittal sinus. (E) MRV in coronal projection reveals a lack of flow in the major venous sinuses, except the right transverse and sigmoid sinuses.](image-url)
enhancement of the falx or tentorium are observed due to collateral circulation [90]. Several conditions need to be differentiated from CVST on imaging. Anatomic variations, including hypoplastic sinus (frequently transverse sinus), sinus fenestration, sinus septations, and partial sinus absence, may mimic CVST. Arachnoid granulations appear as ovoid projections within a sinus whereas clots are more likely elongated.

Vasculitis and infarction

Vasculitis is the inflammation of blood vessels caused by infection, collagen vascular disease, immune-mediated reaction, drug abuse, or neoplasms. In children with either ischemic or hemorrhagic strokes, cerebral vasculitis should be considered [93]. Vasculitis may accompany intracranial infections and up to one-third of children with stroke have postvaricella angiopathy occurring weeks to months after uncomplicated chickenpox [94]. Vasculitis and associated infarction are frequent reported in children with COVID-19 infection [10,20,21,41–47].

Neuroimaging findings of vasculitis include the segmental narrowing of the vessel with a “beads-on-a-string” appearance, irregularities of the vessel wall, vasospasm, dissection, and occlusion (Fig. 8). Parenchymal findings are swelling and T2-hyperintensities in the cortex, subcortical white matter, and the basal ganglia. Postcontrast T1-weighted imaging may reveal wall thickening and contrast enhancement of the affected vessel wall. Decreased diffusion has been reported in acute infarction. Infarctions show progressive decrease in mass effect and increasing contrast enhancement during the second week (subacute stage) [95].

In children, the differential diagnosis of vasculitis includes vasospasm and reversible cerebral vasoconstriction syndrome (RCVS). Vasospasm usually involves the major cerebral vessels. The affected patients may have a history of trauma or subarachnoid hemorrhage. RCVS can be indistinguishable from vasculitis without performing vessel wall imaging.

Guillain–Barré syndrome and Miller–Fisher syndrome

Guillain–Barré syndrome (GBS) is a rare, potentially life-threatening immune-mediated disease characterized by rapidly progressive, symmetrical weakness of the extremities and sensory disturbances [96]. Miller–Fisher syndrome (MFS) is a rare subset of GBS, commonly associated with cranial nerve involvement. The classical feature of GBS is acute, progressive ascending limb weakness, whereas MFS is characterized by acute ophthalmoplegia, ataxia, and areflexia [97]. Numerous cases of GBS [10,20,21,26,48–58] and multiple reports of MFS [59–62] have been reported in children with COVID-19 infection.

In children with MFS or cranial neuritis, the affected nerve is thickened and prominently enhances (Fig. 9). On sagittal and axial MRI, slight thickening of the spinal root with avid contrast enhancement [96] is observed in children with GBS, with an initial preponderance of the anterior nerve roots (Fig. 10). Progression to the enhancement of the entire cauda equina ensues within several days.
Contrast enhancement of the cranial nerves may be seen in inflammatory diseases such as meningoencephalitis, Lyme disease, Bell’s palsy, sarcoidosis, Tolosa-Hunt syndrome, multiple sclerosis, and postradiation neuritis, and neoplastic diseases like leukemia, lymphoma, and metastasis. The affected nerves in neoplastic diseases tend to be more irregular and thickened.

Transverse myelitis

Transverse myelitis is an inflammatory condition of the spinal cord with rapidly progressive neurological dysfunction, resulting in bilateral motor, sensory, and autonomic dysfunction [98]. Multiple cases of myelitis have been reported in children with COVID-19 infection [9,50,63–65].

MRI in the sagittal section reveals expansion of the spinal cord with intramedullary T2-hyperintensity usually spanning two or more spinal segments (Fig. 11). The imaging differential diagnosis of myelitis includes multiple sclerosis, neuromyelitis optica, infarction, and neoplasm. In multiple sclerosis, the abnormality is usually peripheral, involves less than half of the cross-sectional area, and spans less than two spinal segments. Nearly all patients with multiple sclerosis have associated intracranial abnormalities. Neuromyelitis optica is characterized by optic nerve contrast enhancement and extensive cord involvement spanning ≥3 spinal segments. Spinal cord infarction involves the ventral or central cord with...
Neoplasms invariably present with cord expansion, extensive edema and diffuse/nodular contrast enhancement.

**Myositis**

Myositis is an inflammatory change in muscles, especially skeletal muscles. The clinical presentation is characterized by pain, tenderness, swelling, or weakness. Myositis has been reported in children with COVID-19 infection [9,21,99,100] and was predominantly observed in patients with MIS-C [9].

MRI indicates hyperintensity on T2-weighted images and/or diffuse contrast enhancement on fat-saturated T1-weighted images within the affected paraspinal muscles [100].

**Conclusion**

COVID-19 infection appears to be associated with a wide spectrum of neurologic diseases in children. We have discussed the proposed pathophysiology and the neuroimaging features of diseases reported in children with COVID-19 infection. Differential diagnoses of these diseases with other imaging mimics were also discussed. At the time of writing, the highly contagious SARS-CoV-2 B.1.617.2 (or the delta) variant has emerged and is spreading rapidly in many countries [101]. Because the risk of infection in children is expected to increase with this delta variant, clinicians must be prepared for a higher prevalence of neurological abnormalities. Pediatricians, radiologists, and first-line caregivers should be familiar with the neuroimaging patterns of COVID-19 because these patterns can be the first sign of COVID-19 infection when faced with children having neurologic abnormalities in this era.

**Conflicts of interest**

The authors declare no conflicts of interest.

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**Fig. 11** Myelitis in a 16-year-old boy presenting with numbness and weakness of the lower extremities. (A) Sagittal and (B) axial T2-weighted images show mild spinal cord expansion and intramedullary hyperintensity in the dorsal spinal cord at the C3–C4 level.

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