Nonvascular Nervous System Complications in Pediatric Patients with COVID-19 Infection

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Abstract

Coronavirus disease (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 virus which primarily targets the lungs. However, the central nervous system (CNS) and peripheral nervous system involvement due to COVID-19, however, has been reported as early as the cases of respiratory system involvement. In addition, there have been many reports describing neuroimaging features of COVID-19, but data beyond case studies in the pediatric population are still limited, indicating limited CNS involvement. The CNS involvement and complications include, but are not limited to, encephalopathy, meningoencephalitis, ischemic stroke, venous sinus thrombosis, acute necrotizing encephalopathy, acute disseminated encephalomyelitis, posterior reversible encephalopathy syndrome, acute cerebellitis, acute hemorrhagic myelitis, and Guillain–Barré syndrome. In this manuscript, we will discuss the imaging characteristics of some of these entities with a known diagnosis of COVID-19.

Keywords
- COVID-19
- central nervous system
- peripheral nervous system

Introduction

Coronavirus disease (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) virus which primarily targets the lungs.

However, central nervous system (CNS) and peripheral nervous system (PNS) involvement due to COVID-19, however, has been reported as early as the cases of respiratory system involvement. In addition, there have been many reports describing neuroimaging features of COVID-19, but data beyond case studies in the pediatric population are still limited, indicating limited CNS involvement.

The CNS involvement and complications include, but are not limited to, encephalopathy,[1] meningoencephalitis,[2] ischemic stroke, venous sinus thrombosis,[3,4] acute necrotizing encephalopathy,[5] acute disseminated encephalomyelitis (ADEM),[6] posterior reversible encephalopathy syndrome (PRES),[7,8] acute cerebellitis,[9] acute hemorrhagic myelitis,[10] and Guillain–Barré syndrome (GBS).[11] In this manuscript, we will discuss imaging characteristics of some of these entities with a known diagnosis of COVID-19.

Neurological involvement from COVID-19 has been postulated by four potential mechanisms[12,13]:

1. Systemic inflammatory responses triggered by the viral infection either during acute infection or in the setting of multisystem inflammatory syndrome in children (MIS-C).
2. Vascular and prothrombotic effect of the viral infection.
3. An immune-mediated parainfectious or postinfectious autoimmune effect resulting from the viral infection.
4. A direct neurotropic or neuroinvasive effect of SARS-CoV-2 is believed to result from the olfactory pathway.

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Acute Disseminated Encephalomyelitis

ADEM is mediated by antigen-antibody complexes and is generally seen in children younger than 15 years, often within 2 weeks of an antigenic encounter either in the form of infection (in more than half of the cases, a respiratory infection) or vaccination.[14] Common clinical manifestations of ADEM include headache, seizures, fever, multiple neurological deficits, meningeal signs, and encephalopathy. In the absence of a diagnostic biomarker, the diagnosis of ADEM is based on typical clinical presentation and consensus criteria led by the International Pediatric Multiple Sclerosis Study Group (IPMSSG). The diagnosis is almost invariably supported by typical abnormal magnetic resonance imaging (MRI) findings and the exclusion of alternative diagnoses through additional testing.

On imaging, typical MRI lesions in ADEM are often multiple and bilateral (but rarely symmetrical) with a potential of involving both brain and spine. Spinal cord involvement typically presents as longitudinally extensive transverse myelitis. Both gray matter and white matter can be involved. ADEM lesions tend to be more rounded and larger, with indistinct margins, than other demyelinating conditions (e.g., multiple sclerosis) with greater involvement of the deep gray matter structures and brainstem. Although the corpus callosum may be involved in ADEM, the lesions are larger than seen in multiple sclerosis and tend not to involve the callososeptal interface.[14]

We report a 9-year-old presenting with fever and nausea, encephalopathy, convulsions, and hallucinations. The autoimmune encephalitis panel revealed no abnormalities. Although polymerase chain reaction (PCR) for COVID-19 was negative, at 14 days, COVID-19 IgG was positive. Brain MRI showed patchy and confluent regions of T2 prolongation involving the right cerebellar hemisphere and dorsal pons (►**Fig. 1A**), midbrain, sublenticular regions, subinsular white matter (►**Fig. 1B**), thalami, periatrial white matter, and right frontal subinsular white matter (►**Fig. 1C**). There was no mass effect, diffusion restriction, hemorrhage, or enhancement associated with the lesions. The patient recovered uneventfully following steroid therapy.

Acute Hemorrhagic Leukoencephalitis

Acute hemorrhagic leukoencephalitis (AHLE) is a rare, severe, and rapidly progressive form of ADEM.[15] Like ADEM, AHLE is frequently preceded by viral infections, including coronaviruses. A preceding or concomitant infection, usually of the upper respiratory tract, has been described in approximately half of the reported cases.[16] While ADEM predominantly affects children and teenagers, AHLE is more commonly encountered in adults.[17] While imaging characteristics of AHLE and ADEM may be similar, including bilateral confluent white matter lesions, presence of hemorrhagic foci, and progression despite being on treatment favor AHLE,[16] there is a higher incidence of mass effect, restricted diffusion, and contrast enhancement described in AHLE than ADEM.[18] Cerebral leukoencephalopathy and microhemorrhages with progressive cystic and necrotic changes on MRI known as virus-associated necrotizing disseminated acute leukoencephalopathy have been described in critically ill COVID-19 adult patients with or without clinical features of ADEM or AHLE.[19] Similar findings have not yet been described in the pediatric population.

We describe a 5-year-old male who presented with headaches. Computed tomography (CT) scan of the head demonstrated multiple hyperdense lesions of varying sizes throughout the cerebrum and cerebellum with surrounding vasogenic edema and effacement of cerebrospinal fluid spaces along the foramen magnum. Some lesions had foci of relatively increased density suggestive of microhemorrhages and/or calcifications (►**Fig. 2A, B**). Subsequent MRI performed demonstrated susceptibility foci corresponding to hyperdense foci on CT consistent with hemorrhage (►**Fig. 2C**). Some lesions showed relatively decreased T2-hypointensity surrounded by extensive vasogenic edema with associated marked restricted diffusion contrast enhancement (►**Fig. 2D, F, G**). There was involvement of both cortex,

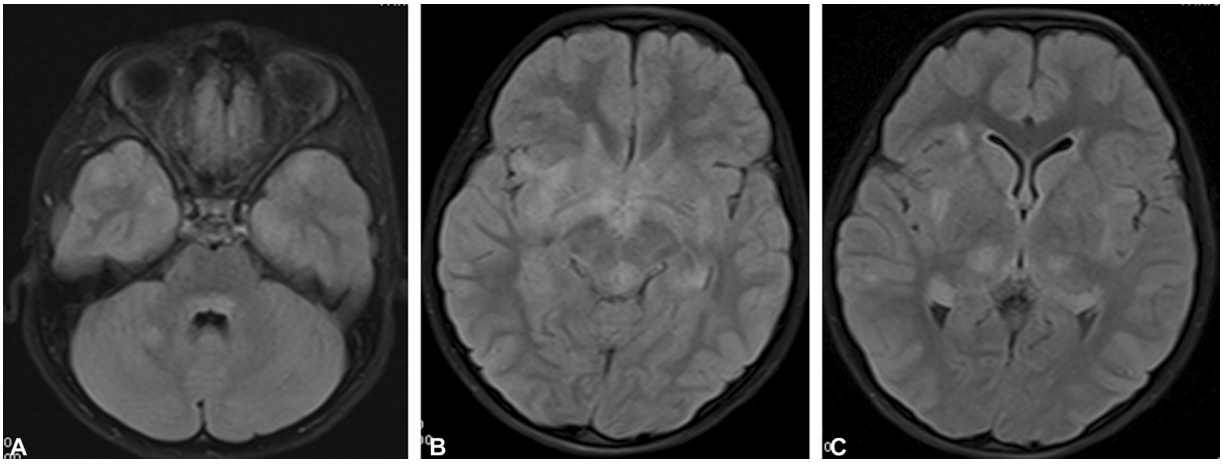

Fig. 1 9-year-old with ADEM. (**A**) Axial FLAIR images show focal and confluent regions of increased signal without mass effect in the right cerebellar hemisphere; (**B**) midbrain, sublenticular regions, and right subinsular white matter; and (**C**) bilateral thalami, right external capsule, and right subinsular white matter. FLAIR, Fluid-attenuated inversion recovery.

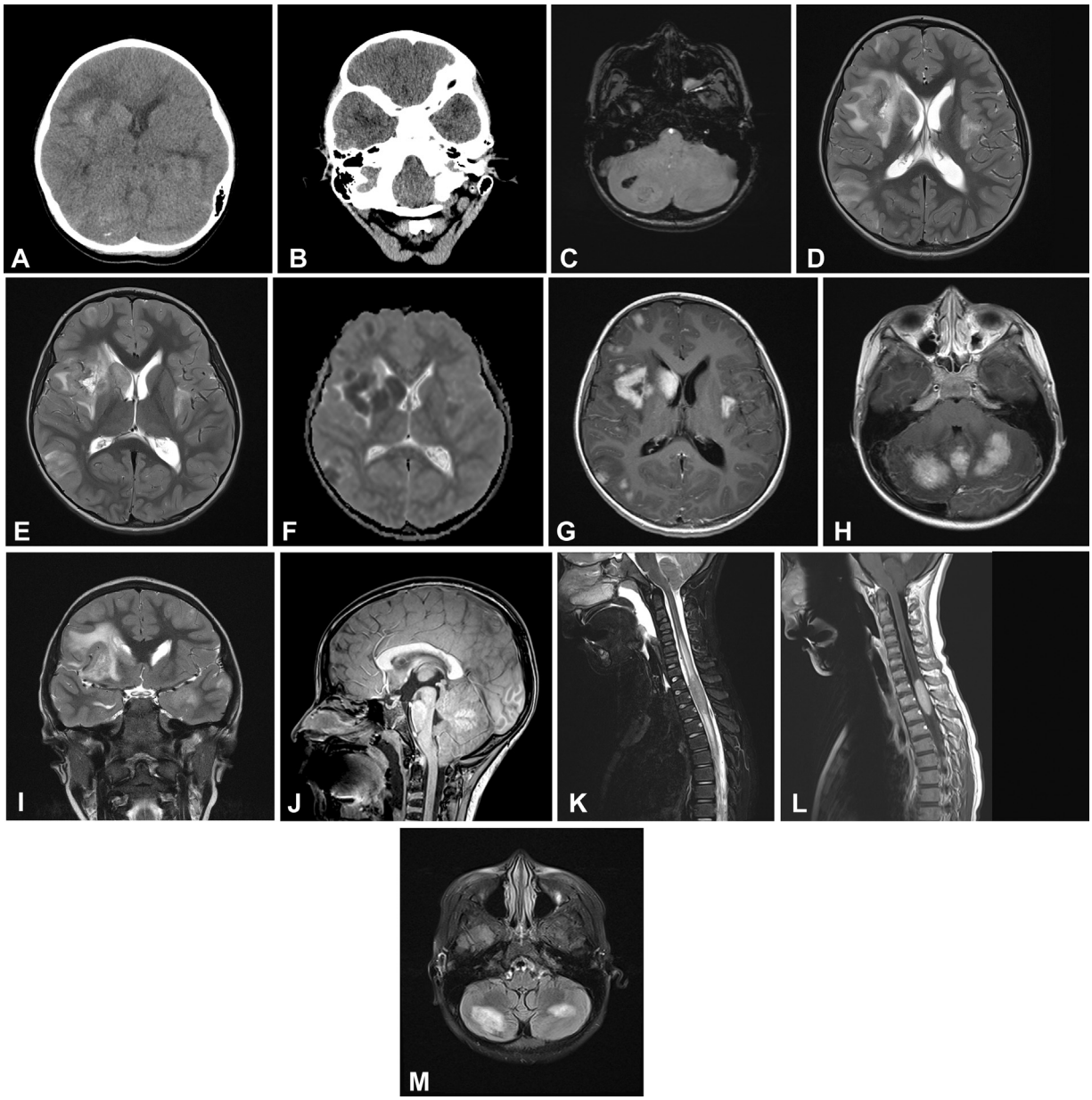

Fig. 2 5-year-old with AHLE. (**A**) Axial noncontrast CT shows confluent hypodense lesions in the cerebrum and cerebellum. There is focal increased density of the right frontal lobe. Punctate focus of increased density is seen of the right cerebellar hemisphere, likely related to hemorrhage. (**B**) Axial noncontrast CT shows effacement of the basal cisterns at the level of the foramen magnum. (**C**) Axial susceptibility weighted image shows a focus of hypointensity consistent with hemorrhage, corresponding to the increased density seen on CT. (**D, E**) Axial T2-weighted images show vasogenic edema of the bilateral cerebral hemispheres and right caudate head. Foci of relative T2-hypointensity are present within the regions of vasogenic edema. (**F**) Axial ADC image shows multiple foci of diffusion restriction involving the deep gray matter structures and cerebral cortex. (**G, H**) Gadolinium enhanced axial T1-weighted images shows multiple foci of enhancement within the infratentorial and supratentorial brain corresponding to the regions of relative T2 hypointensity and diffusion restriction. (**I**) Coronal T2-weighted image shows edema involving the intracranial optic nerves. (**J**) Sagittal T1-weighted image shows effacement of the basal cisterns at the level of the foramen magnum with dilatation of the cerebral aqueduct and inferior recesses of the third ventricle. (**K**) Sagittal T2-weighted and (**L**) sagittal gadolinium enhanced T1-weighted images of the upper spinal cord show an oval lesion similar to those seen intracranially associated with marked enhancement and adjacent extensive vasogenic edema. ADC, apparent diffusion coefficient; AHLE, acute hemorrhagic leukoencephalitis; CT, computed tomography.

subcortical white matter and deep gray matter structures (►**Fig. 2E**). Optic chiasm, intracranial optic nerves and optic tracts were also involved (►**Fig. 2I**). There was mild hydrocephalus characterized by dilatation of the inferior recesses of the third ventricle and widening of the cerebral aqueduct (►**Fig. 2J**). Similar T2 hypointense expansible cord lesions with extensive vasogenic edema were also present (►**Fig. 2K, L**). The patient was placed on steroids, and a biopsy of the right frontal lesion was performed. Histopathology revealed foci of lymphohistiocytic perivascular inflammation leading to a diagnosis of ADEM. Multiple hemorrhagic lesions throughout the cerebrum and cerebellum led to the eventual diagnosis of AHLE. Follow-up MRI obtained 18 months after the initial presentation demonstrated resolution of

enhancing lesions with the persistence of areas of T2 prolongation involving the cerebellar hemispheres, likely related to gliosis (►**Fig. 2M**).

ADEM has been described both following COVID-19 infection and vaccination in both children and adults.[18,20–22] In a multinational multicollaborative study by Lindan et Al,[23] ADEM-like changes were the most common finding seen in their cohort. Parsons et al[6] described one of the first cases of ADEM after COVID-19 infection in a 51-year-old woman who made a good recovery. In a handful of reported pediatric ADEM cases, variable imaging findings and usually good clinical outcomes have been reported. It is crucial to note that the diagnosis in most cases was made based on suggested imaging findings and not strictly based upon the IPMSSG criteria. Siracusa et al[24] described a 5-year-old girl with a callosal splenial lesion and a focal left parietal lesion that demonstrated diffusion restriction. The lesions subsided following therapy with steroids. However, the imaging findings were not necessarily characteristic of ADEM. Mclendon et al[25] described a case of a 17-month-old boy with imaging findings of extensive supratentorial white matter prolongation without associated restricted diffusion or spinal cord involvement. The patient was treated with intravenous immune globulin and high-dose steroids, and a neurological exam at 2-month follow-up was normal. de Miranda Henriques-Souza et al[20] described a 12-year-old girl with extensive supratentorial white matter involvement and spinal cord involvement, characterized by T2 prolongation and diffusion restriction within the brain and T2-prolongation and expansion within the spinal cord. The patient made a partial recovery after steroid therapy.

In a recent systematic literature review by Manzano et al,[25] some of the clinical and imaging features of ADEM seen following COVID infection and vaccination are similar to those following other infections and vaccinations. However, some noticeable differences include (1) higher propensity to involve adult population, (2) more severe antecedent infection, (3) myelin oligodendrocyte glycoprotein antibody seropositive was rare (can be seen in 35–65% of pediatric ADEM cases), and (4) higher morbidity and mortality particularly in adult patients.

Although ADEM or AHLE are rare in pediatric neuro-COVID-19 infections, these entities should still be considered in the differential diagnosis of typical lesions seen in patients with encephalopathy with or suspicion of COVID-19 infection. Again it is essential to remember that ADEM is an imaging diagnosis of exclusion.

Posterior Reversible Encephalopathy Syndrome

PRES is characterized by neurological symptoms and imaging findings attributable to vasogenic edema.[27] Both clinical and imaging findings are generally reversible. However, approximately 40% of patients with PRES require care in the intensive care unit due to complications such as status epilepticus, cerebral ischemia, intracranial hemorrhage, or intracranial hypertension.[28] Although the etiology of PRES is not definitively understood, there are two leading hypotheses. One is loss of cerebral vascular autoregulation due to an acute increase in the arterial blood pressure, leading to vascular leakage and vasogenic edema.[29] The second theory

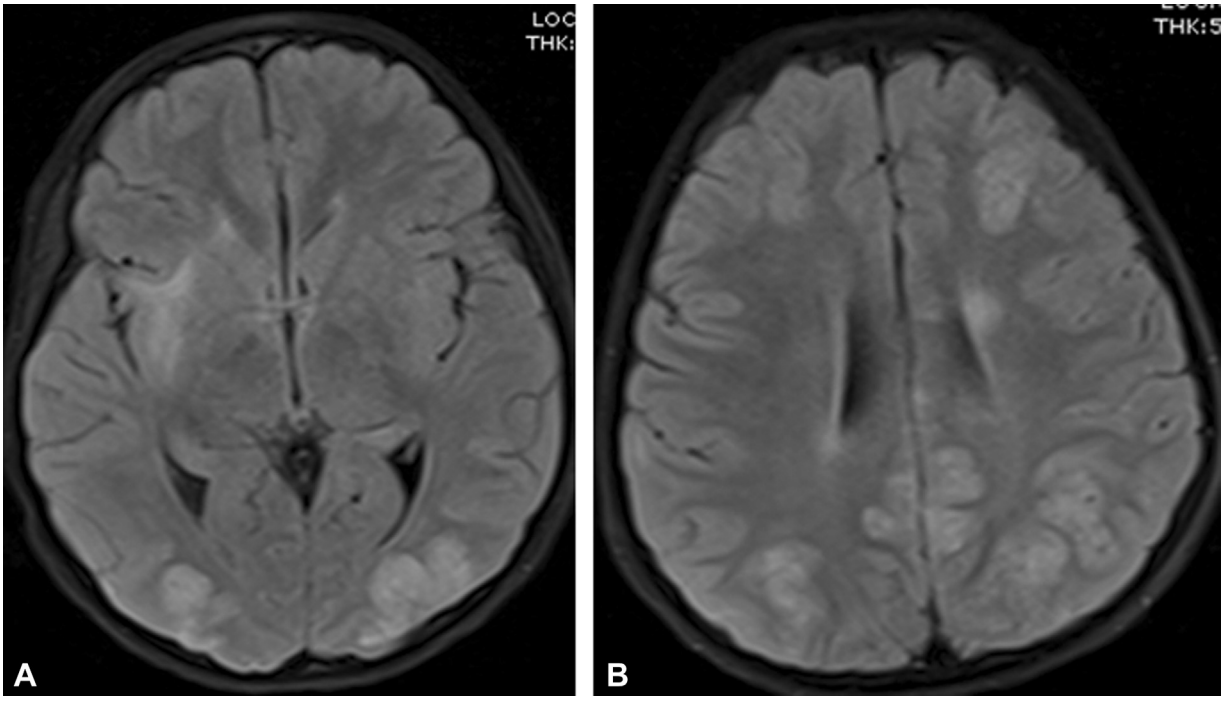

Fig. 3 9-year-old with PRES. (**A, B**) Axial FLAIR images show multiple, confluent foci of T2 prolongation involving the cerebral cortex with involvement of the right subinsular white matter. There is preferential involvement of the posterior cerebrum. FLAIR, fluid-attenuated inversion recovery; PRES, posterior reversible encephalopathy syndrome.

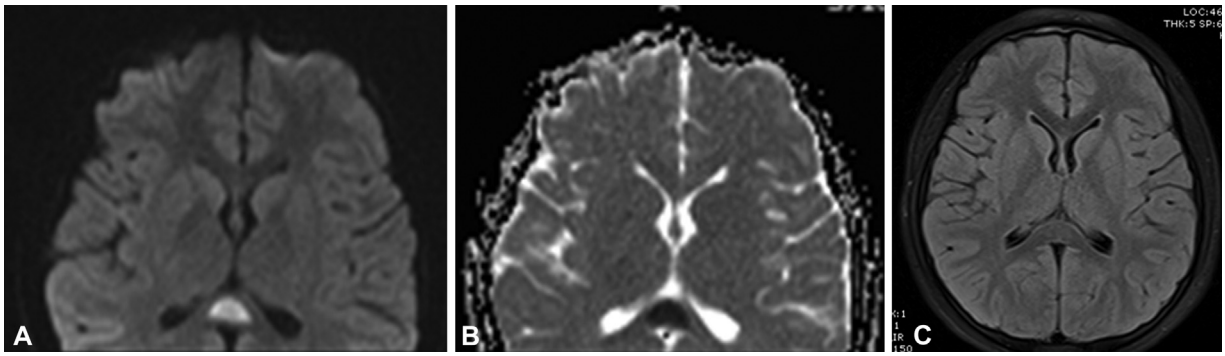

Fig. 4 11-year-old with transient splenial lesion. (**A**) Axial DWI and (**B**) axial ADC images show a well-defined focus of diffusion restriction involving the mid-portion of the splenium of the corpus callosum. Axial FLAIR image (**C**) shows corresponding hyperintensity involving the splenium of the corpus callosum. ADC, apparent diffusion coefficient; DWI, diffusion-weighted images; FLAIR, fluid-attenuated inversion recovery.

is related to the circulating endogenous and exogenous toxins causing endothelial dysfunction.[30] These theories are employed to explain the epidemiology of PRES in the patients with acute arterial hypertension, and patients who are immunosuppressed (e.g., solid organ or bone marrow transplant recipients who are on immunosuppression) comprise the great majority of the cases. Since the beginning of COVID-19 pandemic, multiple reports have described imaging findings consistent with PRES in all age groups.[7,31,32] Many of the COVID-19 patients who developed PRES did not have hypertension making the endothelial damage theory the more likely working mechanism. It is likely that the cytokine storm syndrome is responsible for the endothelial damage leading to PRES in COVID-19 patients.[33]

We include a 9-year old male who presented with convulsions and facial droop. MRI showed cortical and subcortical T2 prolongation involving predominantly the posterior parts of the brain. However, there was the involvement of the

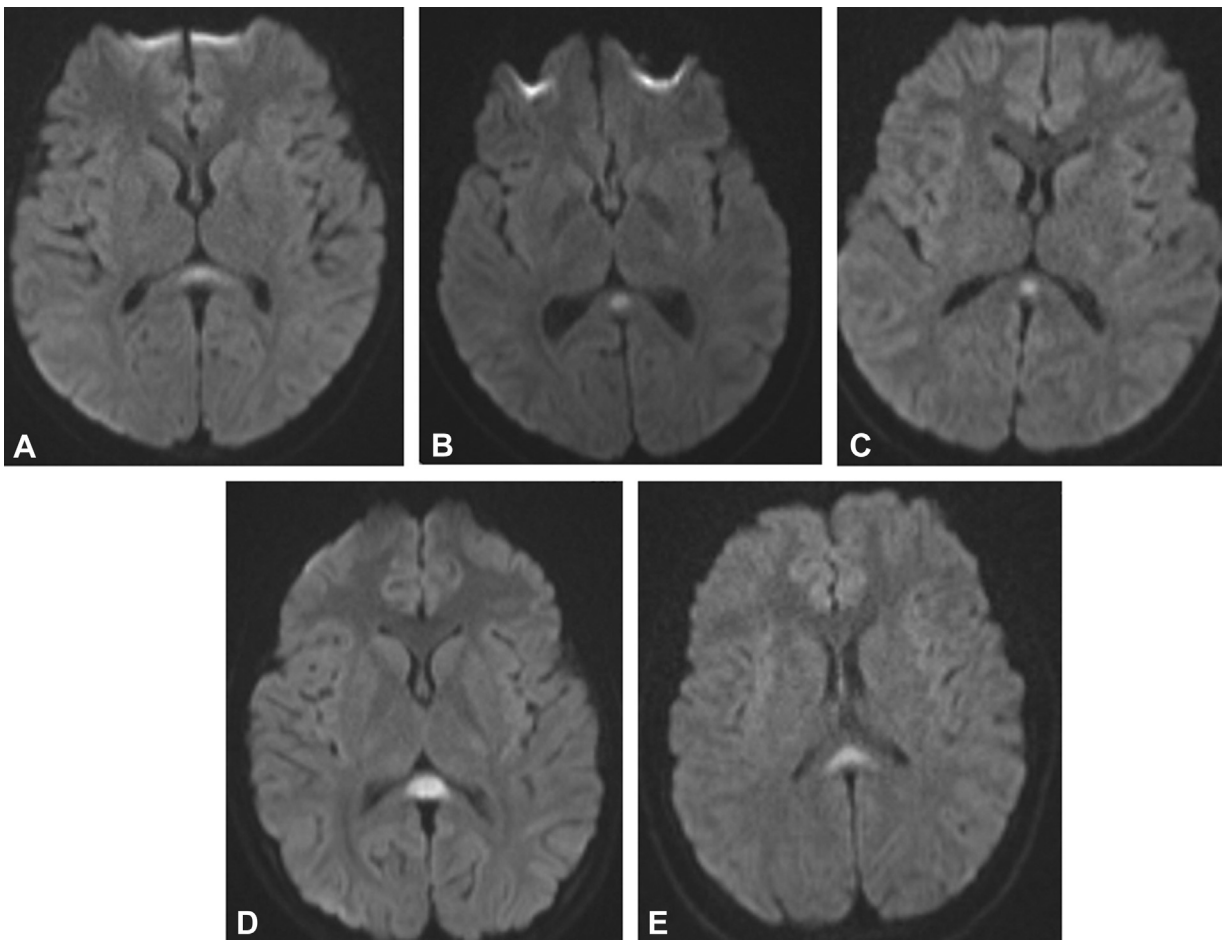

Fig. 5 (**A–E**) Axial diffusion weighted images of five different patients demonstrating transient splenial lesions.

left frontal lobe as well (►**Fig. 3A, B**). There was no corresponding diffusion restriction or enhancement. The patient did not have arterial hypertension or immunosuppression and made a full recovery.

Reversible Splenial Lesion

Reversible splenial lesions represent cytotoxic lesions of the corpus callosum that usually resolve with the resolution of the underlying trigger mechanisms. The differential diagnosis of the reversible (transient) lesion of the splenium of the corpus callosum is extensive.[34] In children, it is more commonly associated with seizure (acute seizure activity, status epilepticus, antiepileptic medication), viral infections (influenza being most common), and electrolyte imbalances. In neuro-COVID-19, the involvement of the splenium of the corpus callosum is indistinguishable from other causes of the reversible splenial lesions. Generally, there is isolated diffusion restriction involving the midportion of the splenium of the corpus callosum with or without corresponding T2 prolongation. This is presumed to represent transient intramyelinic edema arising from cytokine storm resulting from diffuse systemic inflammation.[12] There is no mass effect, hemorrhage, or associated enhancement. The lesions generally resolve within days on diffusion-weighted images (DWI) after initiation of therapy or improvement of symptoms.[12,35–38] Transient or reversible splenial lesion is also the most common imaging finding described in kids with MIS-C associated with COVID-19.[22] ADEM-like imaging appearance, diffuse cranial nerve enhancement, and cases of GB syndrome have also been described in the setting of MIS-C.

We present an 11-year-old female who had a fever, neck pain, and fatigue. Inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were elevated. Although PCR was negative, COVID-19 IgG was elevated. There was lung involvement on chest CT (not shown). The patient developed a headache, which prompted a brain MRI. DWI (►**Fig. 4A**) and apparent diffusion coefficient map (►**Fig. 4B**) showed the typical reversible splenial lesion of the corpus callosum. There was subtle T2 prolongation on fluid-attenuated inversion recovery (►**Fig. 4C**). A follow-up examination performed 3 days later showed resolution of the lesion on DWI (not shown).

While classically described as an ovoid lesion, the involvement may be more variable in the setting of COVID-19, such as linear (►**Fig. 5A**, 11-year-old male), round (►**Fig. 5B**, 12-year-old male), punctate (►**Fig. 5C**, 11-year-old female), oval (►**Fig. 5D**, 12-year-old male), or V-shaped (►**Fig. 5E**, 15-year-old male).

Guillain–Barré Syndrome

GBS is an acute, generalized polyradiculoneuropathy preceded by an infection such as *Campylobacter jejuni*, Epstein–Barr virus, influenza, or cytomegalovirus in two-thirds of cases.[39,40] GBS has been described following influenza vaccinations.[39] GBS was reported early in the COVID-19 pandemic,[37] initially in adults and subsequently in children.[42] Following the development of the COVID-19 vaccines, GBS was described following vaccinations, similar to influenza vaccinations.[43]

Imaging findings of GBS seen following COVID-19 infection in children are indistinguishable from GBS developing following other etiologies and include thickening and abnormal contrast enhancement of the cauda equina nerve roots. We present a 6-year-old male with COVID-19 disease whose COVID-19 infection was confirmed by PCR testing. The patient developed typical symptoms of GBS characterized by inability to walk, rapid loss in muscle tone, and difficulty breathing, requiring intubation and, subsequently, a tracheostomy. Brain MRI performed was normal. Spinal MRI revealed normal-appearing spinal cord. Gadolinium-enhanced MRI of the lumbar spine showed the characteristic enhancement of the cauda equina nerve roots. (►**Fig. 6A, B**).

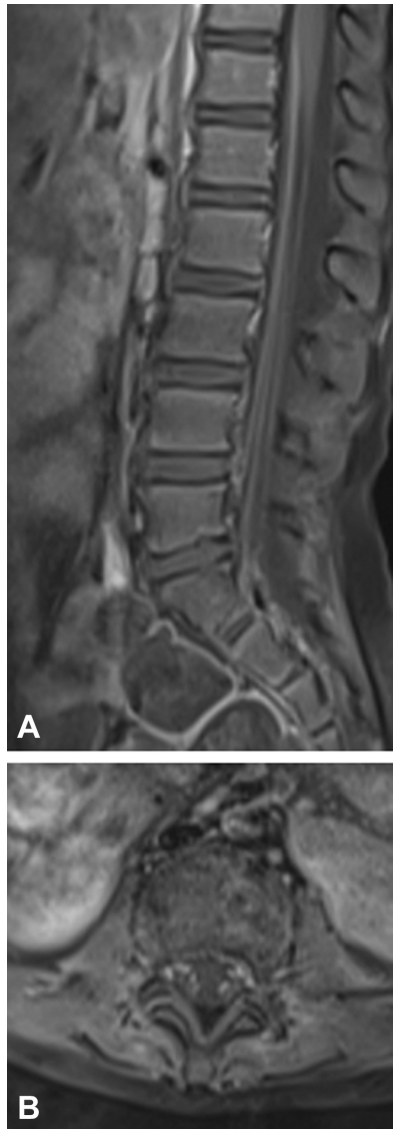

Fig. 6 6-year-old with Guillain–Barré syndrome. (**A**) Sagittal and (**B**) axial gadolinium-enhanced T1-weighted images of the lumbar spine show intense, homogenous enhancement of the cauda equina with greater enhancement of the anterior nerve roots.

Diffuse cranial nerve enhancement with or without associated abnormal enhancement of the spinal nerve roots has been described in the setting of CVOID-19. In 38 children evaluated by Lindan et al, they observed abnormal nerve enhancement in 12 patients (32%) and labeled the term "neuritis".[23] As opposed to GBS, it was interesting to note that they did not find imaging findings correlating with cranial nerve deficits. Similar imaging findings have also been reported in adults with acute COVID-19.

Conclusion

In this review, we share our experience in imaging of nonvascular neuroimaging manifestations of pediatric neuro-COVID-19. Neurological involvement of COVID-19 is rare in the pediatric population. The most common nonvascular neurological manifestation of acute COVID-19 infection is that of ADEM-like picture on neuroimaging. Entities such as acute cerebellitis, isolated acute myelitis, diffuse cranial nerve enhancement, reversible cerebral vasoconstriction syndrome describe elsewhere in the literature were not discussed in detail due to the lack of proven cases at our institutes.[44] This limitation notwithstanding, we hope the reader will find this review helpful in understanding the varied imaging findings of pediatric neuro-COVID-19.

Conflict of Interest
None declared.

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