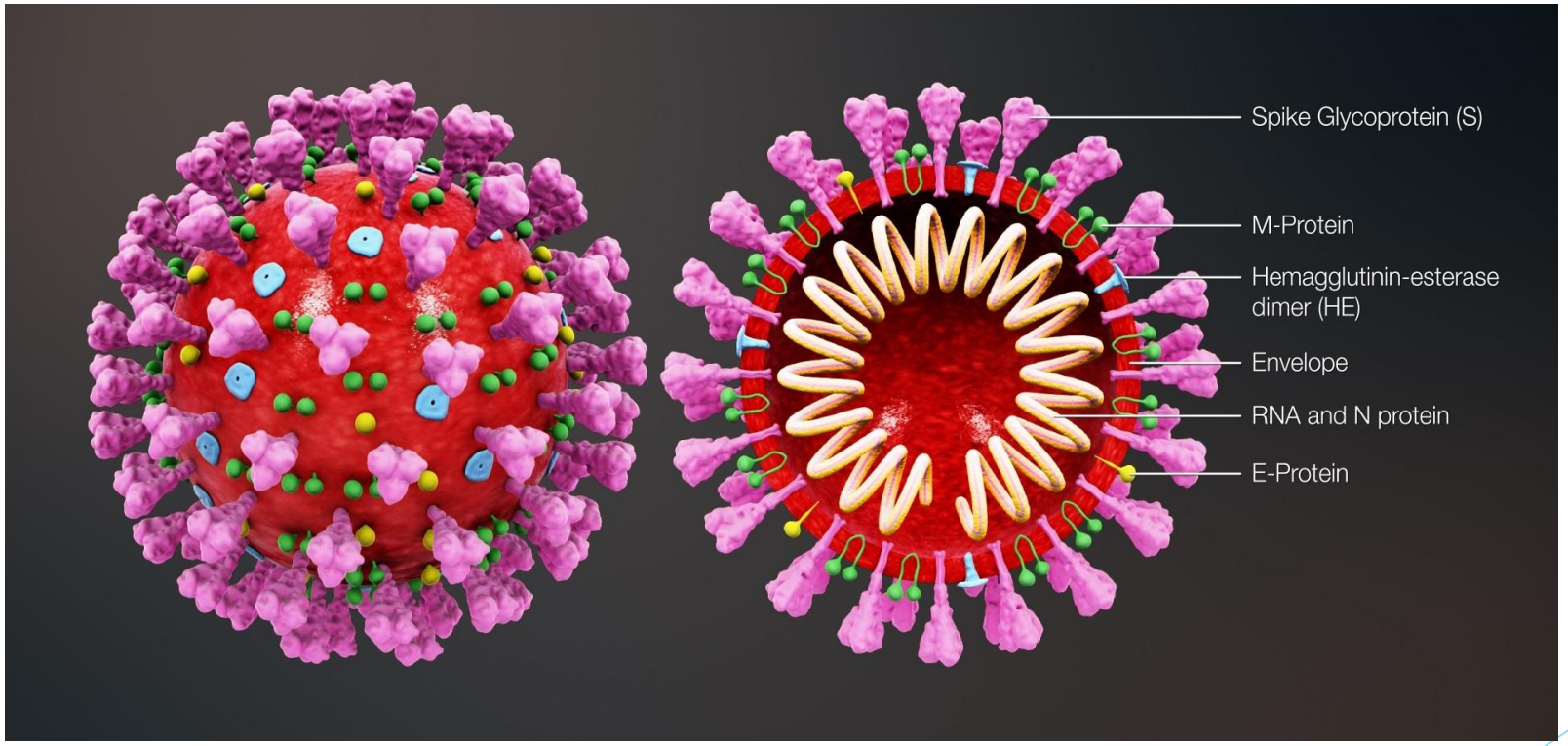
neurologic manifestation covid 19 in pediatric patients



Coronavirus disease 2019 (COVID-19), which was first recognized in December 2019, and reported in Wuhan, China, is caused by novel SARS-CoV-2.

The disease was declared “a public health emergency of international concern” by WHO on January 30, 2020

“a global pandemic” on March 12, 2020.

- SARS-CoV-2 is from the *Coronaviridae* family of enveloped, positive sense, single-stranded (RNA) viruses, with relatedness to SARS-CoV and other خفاش bat-origin betacoronaviruses.[2]
- The virus spike (S) protein is both key to human infection and the major antigen for humoral immunity and as such is the antigen used in licenced vaccines.
- The primary human cell receptor for the S protein receptor binding domain (RBD) is Angiotensin-Converting Enzyme 2 (ACE2)
- Mutations in the SARS-CoV-2 RBD are associated with enhanced ACE2 affinity and are considered to underpin key characteristics of variants such as Delta , which show increased transmissibility and immune evasion.
- The ACE2 protein is present on upper and lower respiratory tract, gastrointestinal tract and endovascular epithelia.

Pathophysiology of covid 19

- this disease affects adults and children differently
- Some of this difference may be attributed to the generally milder course of pulmonary disease:

1. mucosal immunity in children may prevent the establishment of SARS-CoV-2 infection.
2. innate immune responses in the upper respiratory tract may be more effective in children

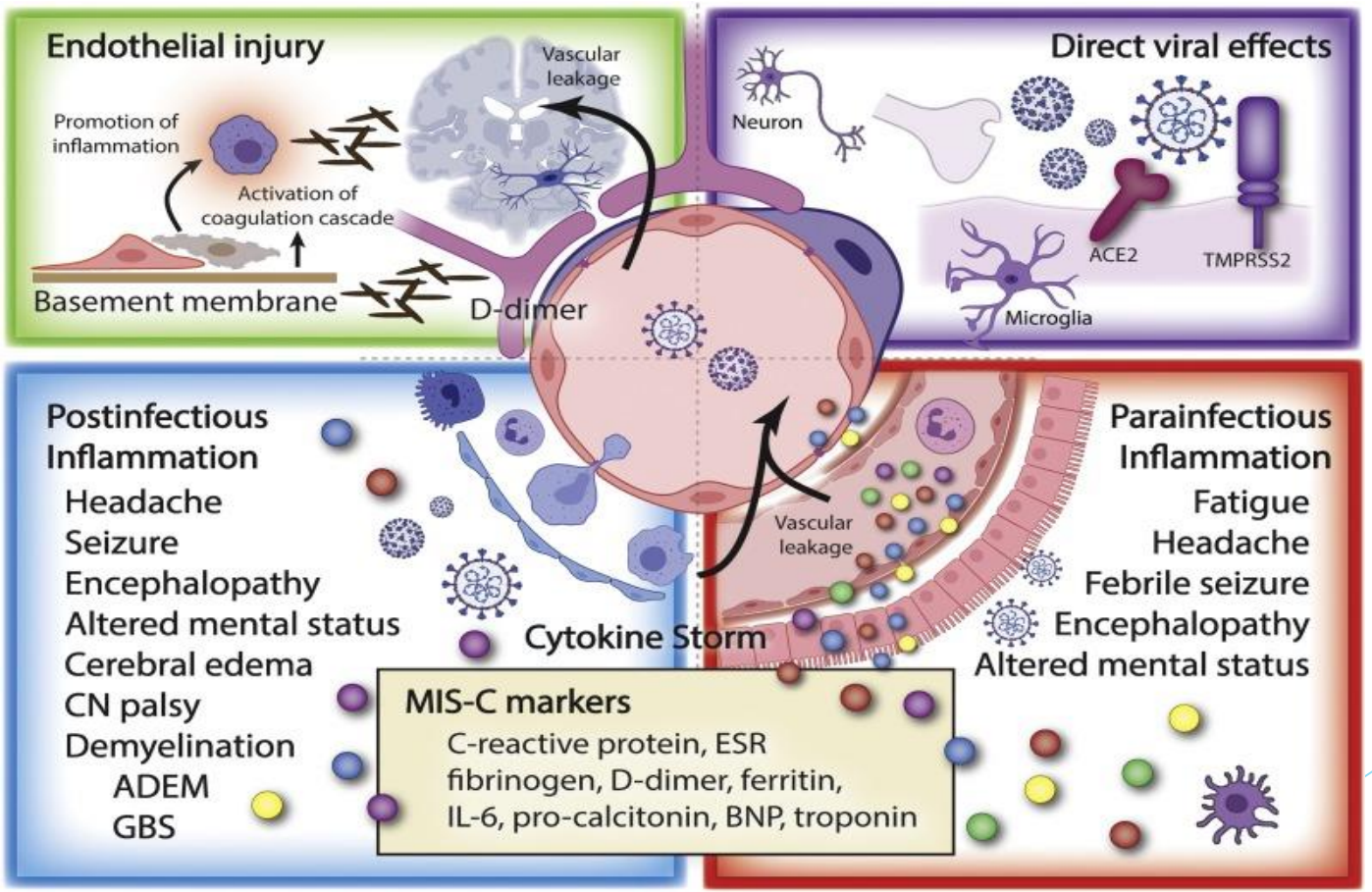
- and fewer comorbidities in children
- ongoing development of a child's nervous system, with differential expression of cell receptor targets over time, likely of susceptibility to the various infectious and post-infectious mechanisms of COVID-19-related neurological injury.
- two-thirds of patients with neurological manifestations had positive COVID-19 antibody testing, whether in isolation or in combination with PCR testing; whereas two-thirds of patients without neurological manifestations had only positive PCR testing, which is likely more indicative of active infection. Like many immune-mediated illnesses, symptoms may persist long after the acute viral trigger has cleared and may manifest in surprising ways.
- Limited evidence suggests particular HLA genotypes may confer vulnerability to (or protection from) severe disease, and differences may underly variability in disease spectrum among ethnic
- The long-term impact on neurodevelopment after COVID-19 deserves further investigation. The timeline for resolution of neurological injury and emergence of long-term dysfunction, should it present, is still largely unclear,

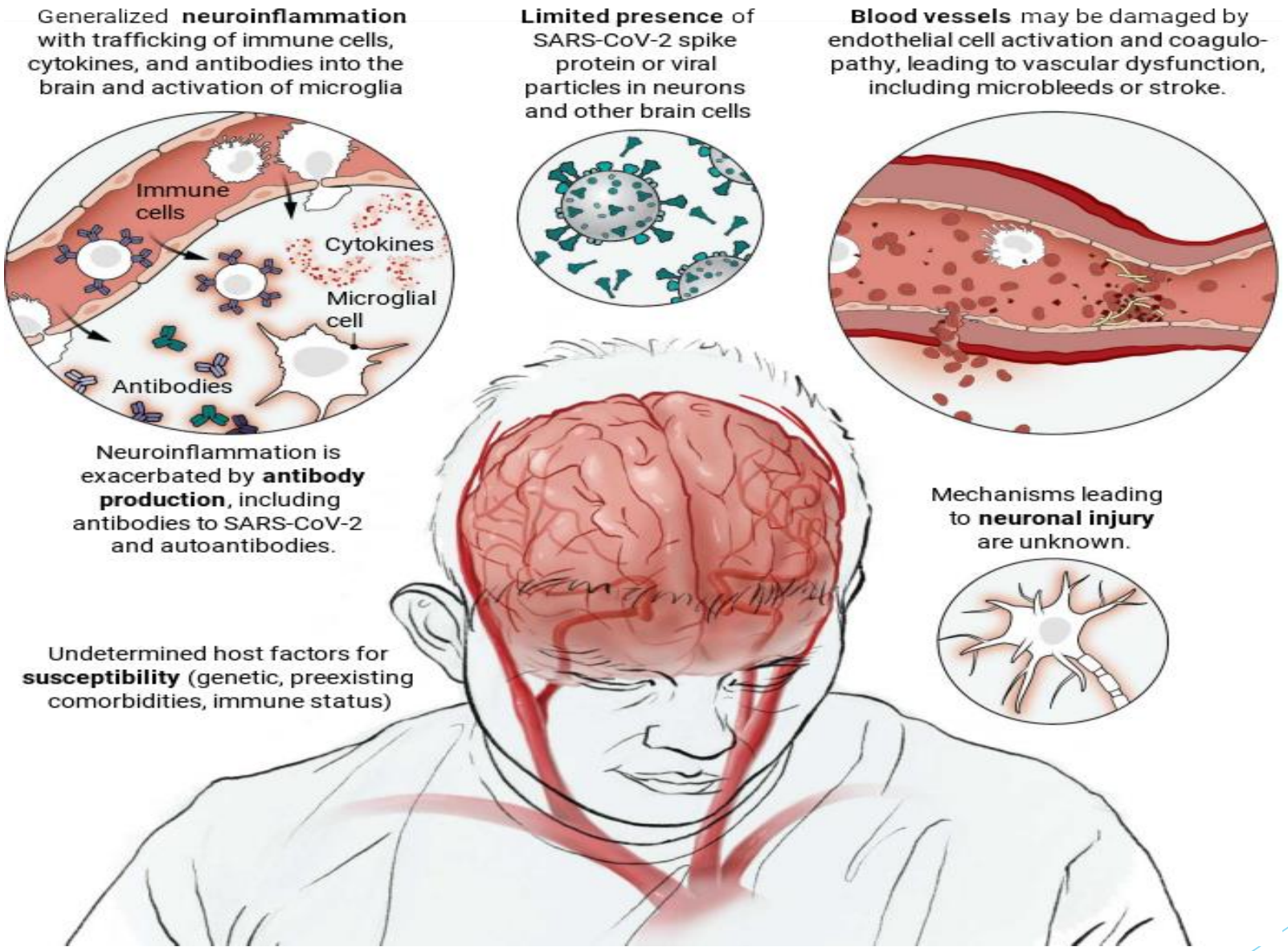
The clinical observations suggest that SARS-CoV-2 could be responsible for many neurological manifestations, which can be divided into three different scenarios, related to the presumed pathophysiologic mechanism:

- 1)Neurological involvement during COVID-19;
- 2)Neurological involvement that arises after the recovery from COVID-19;
- 3)Neurological involvement during MIS-C.
- The first condition could be caused by direct invasion of CNS by the virus through hematogenous dissemination or neuronal retrograde dissemination. the virus can pass to the bloodstream and then enters the brain by either infecting endothelial cells of the blood-brain barrier or epithelial cells of the blood-CSF barrier in the choroid plexus, though the binding between spike protein and ACE2 receptor.
- furthermore, coronavirus can infect leukocytes, that disseminate towards other tissues and cross the blood-brain barrier to access the CNS (the so-called Trojan horse mechanism) .
- In neuronal retrograde dissemination, the virus can gain access to CNS though the infection of olfactory neurons, using retrograde axonal transport . This pathophysiologic mechanism could explain how SARS-CoV-2 can induce encephalitis and vasculitis leading to cerebrovascular accidents; the detection of the virus in the CSF samples using RT-PCR is an important sign of its neurotropism.

- The second condition could be related to a post-infectious immune-mediated mechanism: SARS-CoV-2 might induce an autoimmune response after a latent period following the infection illness , correlated to the hypothesis of "molecular mimicry" between microbial and self-antigens. For example, GBS is characterized by ascending paralysis, occurring after the resolution of COVID-19 symptoms (fever and cough): it is caused by a cross-reaction against gangliosid-components of the peripheral nerves .
- The third condition, could be explained though indirect mechanism caused by the novel coronavirus: the cytokine storm, characterized by high levels **TNF-α, IL-1ß, IL-6, IL-12, and INFγ**. The integrity of the blood-brain barrier may be disrupted by cytokine-driven injury without CNS direct invasion by the virus . Moreover, the hyperinflammatory state can lead to a pro-coagulable state: initial vasculitis causes the **disruption of vascular integrity**, the exposure of **thrombogenic basement membrane** and, finally, the **activation of the clotting cascade** .
- Children with MIS-C exhibit alteration of inflammatory biomarkers (**procalcitonin, CRP, fibrinogen, ferritin, D-dimer, IL-6),** that suggest a possible **involvement of the immune system in the pathogenesis of this syndrome** .
- neurological involvement with MISC: children could complain of **headache, confusion, altered mental status, stiff neck or meningism** . In the course of MIS-C, neurological complications, such as **ADEM , pseudotumor cerebri , cerebral edema , seizure , cerebral stroke** and cytotoxic **lesions of the corpus callosum** have been described .
- During **hyperinflammatory** state, the **corpus callosum**, especially the **splenium**, is highly **vulnerable** to excess of cytokines and glutamate release from astrocytes because of its **high concentration of cytokines and glutamate receptors**: this higher density leads to a tendency of **cytotoxic edema of the corpus callosum** when cytokine storm occurs . Despite the great **variability of neurological manifestations, from mild to severe ones, the prognosis is favorable in the majority of cases.**

Direct viral effects upon the nervous system, endothelial injury, and downstream effects of para- and post-infectious inflammation, have each been proposed as potential etiologies of the neurological manifestations of COVID-19. SARS-CoV-2 may cross into CNS via a variety of mechanisms. Endothelial injury may precipitate thrombotic events, as well as release of virus and inflammatory mediators. Cytokine release due to pulmonary or systemic infection may instigate neurological sequelae. And, post-infectious inflammation induced by SARS-CoV-2 may trigger autoimmune phenomena, such as demyelinating disease and encephalopathy. The multisystem inflammatory syndrome in children associated with SARS-CoV-2 may represent a spectrum of para- and post-infectious complications, separate but similar to other inflammatory conditions in children known to sometimes present with neurological sequelae.BNP (B-type natriuretic peptide




Generalized **neuroinflammation** with trafficking of immune cells, cytokines, and antibodies into the brain and activation of microglia
Immune cells
Cytokines
Microglial cell
Antibodies
Neuroinflammation is exacerbated by **antibody production**, including antibodies to SARS-CoV-2 and autoantibodies.
Limited presence of SARS-CoV-2 spike protein or viral particles in neurons and other brain cells
Blood vessels may be damaged by endothelial cell activation and coagulopathy, leading to vascular dysfunction, including microbleeds or stroke.
Mechanisms leading to **neuronal injury** are unknown.
Undetermined host factors for **susceptibility** (genetic, preexisting comorbidities, immune status)

Clinical Presentation of COVID-19 Disease in Children

- acute COVID-19 - both complicated and uncomplicated
- post-infectious multi-system inflammatory syndromes
- post-acute sequelae of COVID-19 (PASC) also known as ‘Long COVID’. ‘Long COVID’ in children is poorly characterised, but likely less frequent than in adults.
- As the number of cases increased globally, it was recognized that SARS-CoV-2 not only induces respiratory symptoms but also can affect multiple organ systems, including the kidneys, gastrointestinal tract, heart, and brain

- neurological complications in approximately, 36% of the total COVID-19 patients
- all human coronaviruses induce neurologic complications. However, neurological complications caused by COVID-19 are at a higher extent than that of SARS and MERS.
- Growing evidence indicates that COVID-19 impacts both the central nervous system (CNS) and peripheral nervous system (PNS) to cause respective complications due to either direct infectiousness or immune-mediated disease in response to COVID-19 infection.
- In addition, histopathological changes such as CNS infarction due to cerebral thromboembolism and viral RNA in CNS further indicate the impact of SARS-COV-2 on CNS alterations .

patients with COVID-19 are diagnosed with taste and smell dysfunction, nausea, and headache, ataxia, seizure, papilledema, ophthalmoplegia, hyporeflexia, cranial nerves impairment and different clinical spectra, such as, meningoencephalitis, and idiopathic intracranial hypertension ,encephalopathies, transvers Myelitis, Rhabdomyolysis, Guillain-Barré syndrome; Miller Fisher syndromes, acute necrotizing hemorrhagic , hemophagocytic lymphohistiocytosis, cognitive syndrome, affective disorder, and cerebrovascular complications such as strokes, intracerebral haemorrhages, and CNS vasculitis.rhabdomyolysis may occur as a part of MIS-C. increased incidence of juvenile dermatomyositis (JDM), which may be attributable to true dermatomyositis, prolonged post-viral myositis. New onset myasthenia gravis (MG) that patient developed acetylcholine receptor antibody positive ocular MG 72 h after resolution MIS-C secondary to COVID-19

- these neurological complications are presented differently based on undetermined host factors for **susceptibility:genetic,preexisting underlying comorbidities,immune statuse and age .**

- Of hospitalized children who tested or were presumed positive for SARS-CoV-2, 44% developed neurological symptoms, and these kids were more likely to require intensive care than their peers who didn't experience such symptoms
- The most common neurologic symptoms were **headache and altered mental** status, known as acute encephalopathy.
- The most common neurologic manifestations linked with acute COVID-19 were headache, acute encephalopathy and seizures, while youths with MIS-C most often had headache, acute encephalopathy and dizziness. Rarer symptoms of both conditions included loss of smell, vision impairment, stroke and psychosis.

- **neurological manifestations** were more common in kids with MIS-C compared to those with acute SARS-CoV-2, and children with MIS-C were more likely than those with acute illness to have two or more neurologic manifestations.

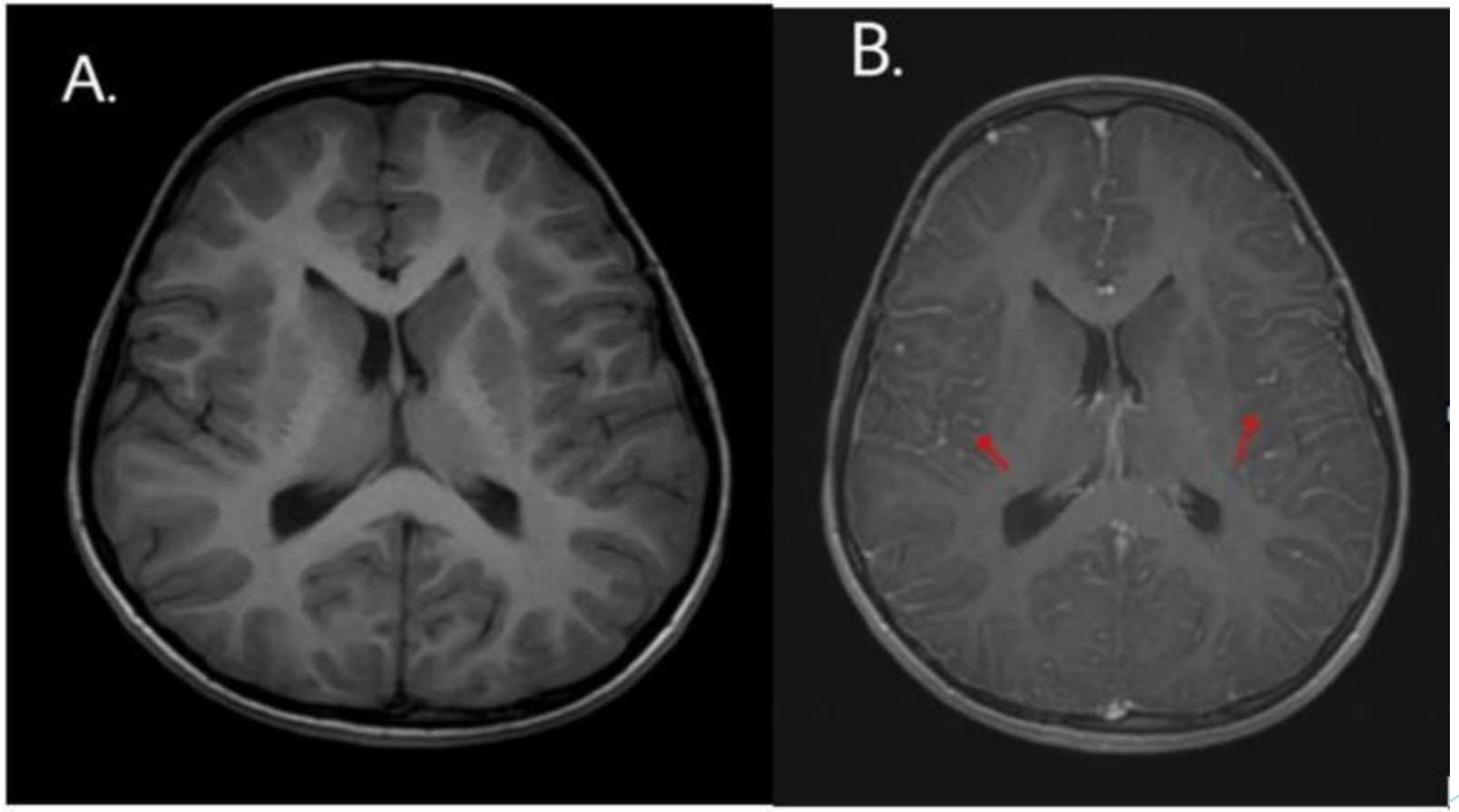
- predominant neurologic and psychiatric symptoms, such as difficulty with memory, concentration, and ability to accomplish everyday tasks, frequent headaches, alterations in skin sensation, autonomic dysfunction, intractable fatigue, and in severe cases, delusions and paranoia , that may persist for months after infection now called Long Covid neuropsychiatric syndromes (brain fog),
- May be seen in patients that are less than 50 years old and were healthy and active prior to infection, were never hospitalized during their acute COVID-19 illness, reflecting mild initial disease.
- Many of the symptoms are similar to those of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is also a postinfectious syndrome caused by a variety of infectious agents may be common host susceptibility factors that underlie these illnesses.
- The heterogeneity of symptoms affecting individuals with Long Covid and the difficulties in ascertaining which symptoms may be a consequence of SARS-CoV-2 infection versus aggravation of preexisting or coincidental conditions pose enormous challenges for mechanistic understanding and approaches to treatment.
- Serial imaging routinely revealed focal areas of brain atrophy in individuals after documented COVID-19 compared with a parallel group without COVID-19, PET imaging also show decreased metabolic activity in the brain in people with Long Covid . the pathophysiology may be residual immune activation or persistent autoimmune disturbance or dysfunction(including nonspecific neuroinflammation and antineural autoimmune dysregulation), ongoing endothelial activation or vascular dysfunction, or residua of injury during acute disease.
- These patients often also experience stigma, employment difficulties, and mental health challenges.
- It is uncertain whether unforeseenبیش بینی نشدهneurological consequences may develop years after initial infection. With millions of individuals affected, nervous system complications pose public health challenges for rehabilitation and recovery and for disruptions in the workforce due to loss of functional capacity. There is an urgent need to understand the pathophysiology of these disorders and develop disease-modifying therapies

Focal Seizures in a Child Following COVID-19 Infection

- A six-year-old previously healthy male child presented to with a history of fever (five days), cough (three days), and new onset of multiple abnormal involuntary movements.
- The parents described twitching movements on the right side of his face, with deviation of the mouth and drooling of saliva from the left angle of the mouth. These episodes were accompanied by slurred speech and lasted for two to three minutes on each occurrence.
- The parents reported no history of loss of consciousness, eye-rolling, abnormal movements of limbs, or bowel/bladder incontinence.
- On examination, the child was noted to be tachycardic (118 bpm) and tachypneic (34/min), with low oxygen saturations (80%) in room air. He was afebrile (98.6°F) and had normal blood pressure (100/60 mmHg). Respiratory examination on auscultation revealed left-sided crackles.
- Neurological examination revealed drowsiness, impaired immediate memory recall, and slurred speech, but he was oriented to place and person and had no other focal neurological deficits.

- The child was admitted to the neuro-intensive care unit, and treatment was initiated. He was kept on nil per oral (NPO) and an orogastric (OG) tube was placed. After OG tube placement, oxygen was given via face mask at 5 L/min to maintain saturations above 95%. The patient was started on IV fluids (0.45% dextrose) at 2/3 normal requirement (in view of meningitis). Injection ceftriaxone IV 2g 12 hourly (200 mg/kg/day) and injection acyclovir IV 300 mg eight hourly (15 mg/kg/dose) were started because of high suspicion of herpes simplex encephalitis. Lorazepam, 1 mg IV, was ordered for acute seizure episodes. Additional supportive treatment included injection paracetamol 300 mg IV eight hourly (15 mg/kg/dose), injection pantoprazole 20 mg IV 24 hourly (1 mg/kg/day), and injection ondansetron 3 mg IV 12 hourly (0.15mg/kg/dose), as needed. Although lorazepam was effective for acute episodes, seizures continued to occur. Injection levetiracetam IV was added, beginning with a 400 mg loading dose (20 mg/kg/dose), followed by 200 mg IV given 12 hourly (10mg/kg/dose).
- A complete blood count with differential (CBCD) showed an elevated total leukocyte count of 19,510 cells/mm^3 with 78.5% neutrophils and 13.9% lymphocytes. CRP was elevated at 53.6 mg/dL. A chest x-ray performed on admission revealed bilateral lung parenchymal involvement with right upper lobe infiltrates and left lower lobe consolidation. A CT lung screen showed a left basal lung collapse attributed to aspiration rather than infection. The MRI brain plain with contrast showed diffuse meningeal enhancement on both sides and altered signal intensity in the bilateral capsule-ganglionic and temporal regions - features suggestive of probable meningoencephalitis (Figures *1A*-*3B*).

Axial T1-weighted MRI of a six-year-old boy with COVID-19 encephalopathy (A) without contrast - normal and (B) with contrast - diffuse leptomeningeal involvement in bilateral cerebral hemispheres



- CSF was normal limits showing no significant increase in WBC, and the viral meningitis panel (including herpes simplex virus {HSV PCR}) was negative. Because the brain MRI showed symmetrical involvement,
- CSF autoimmune encephalitis panel, including tests for serum neuromyelitis optica (NMO) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies all negative results.
- The negative CSF analysis suggested the encephalitis was an inflammatory reaction and not an acute viral leptomeningeal encephalitis.
- Oropharyngeal and nasopharyngeal {RT-PCR}) for COVID-19 and indicated the patient was infected with the disease.
- D-dimer , serum ferritin , and LDH were all within normal range, with interleukin-6 (IL-6) (8.17 pg/mL) being mildly elevated. CRP showed a decreasing trend.

- A brief EEG was performed on day two of admission, after starting antiepileptic drugs (AEDs) and while the patient was stable and not having any seizure activity. No epileptiform activity was observed; however, based on the classic clinical presentation and the experience of the pediatric neurologist the abnormal movements were considered to have a high correlation with seizure activity. Later on day two, the seizures returned; therefore, lacosamide was added, with injection lacosamide IV 200 mg administered at a loading dose (10 mg/kg) followed by 100 mg 12 hourly (5 mg/kg/dose).
- The child continued to have frequent, afebrile seizures, each lasting at least three to five minutes. Lorazepam continued to be effective for acute episodes (evidence that the involuntary movements represented seizure activity). However, because of the persistent seizures, up to five days, one lasting more than five minutes, on day three of admission, he was started on maintenance therapy with sodium valproate IV 200 mg 12 hourly (10 mg/kg/dose) and injection phenytoin IV 20 mg 12 hourly (2 mg/kg/day). Because blood culture, CSF culture, and HSV PCR were negative, acyclovir and ceftriaxone were discontinued. Despite the AEDs, the child continued to have focal seizures and a deteriorating sensorium. Changes in behavior, including increased sleepiness, decreased interaction with parents, and decreased eye contact, were also noted. Early on the fourth day of admission, he was started on injection methylprednisolone IV 600 mg 24 hourly (30 mg/kg/day), given for five days, and intravenous immunoglobulins IV 20 g (1g/kg/day), given for two days.

- Following the administration of steroids, the frequency of seizure episodes decreased dramatically. The child's symptoms improved, and, as a result, he was taken off oxygen support. His sensorium and behavioral changes improved, and he remained seizure-free during the whole course (five days) of methyl-prednisolone therapy. Three days after the completion of the five-day course of methylprednisolone, the child started having similar involuntary movements involving the right side of the face along with lips and tongue, though they were less frequent, only one to two episodes per day, and of shorter duration. As a result, the patient was additionally started on oral clobazam (5 mg in the morning and 2.5 mg at night). The seizure frequency and duration eventually decreased to an average of one every four to five days, each lasting less than five minutes. The patient was discharged at the end of the second week of admission.
- The child was followed up for six months, with regular visits every two months. In the first three months of follow-up, the child had two episodes of seizures that were shorter in duration. The patient was advised to continue on oral AEDs, sodium valproate 200 mg twice daily, levetiracetam 400 mg twice daily, phenytoin 50 mg twice daily, and lacosamide 37.5 mg twice daily, for the next six months. Phenytoin was gradually tapered and stopped after one month, valproate and lacosamide were stopped after three months, and levetiracetam was to be continued for a year. Over the following months, there were no episodes of involuntary movements. Follow-up EEGs at three and six months did not show any seizure activity. The patient was advised to continue attending follow-up appointments for one year.

- new-onset focal seizures and epilepsy should be considered a delayed central nervous system manifestation of COVID-19 infection
- among children, multisystem inflammatory syndrome following COVID-19 infection may also play a causal role in developing post-viral seizures

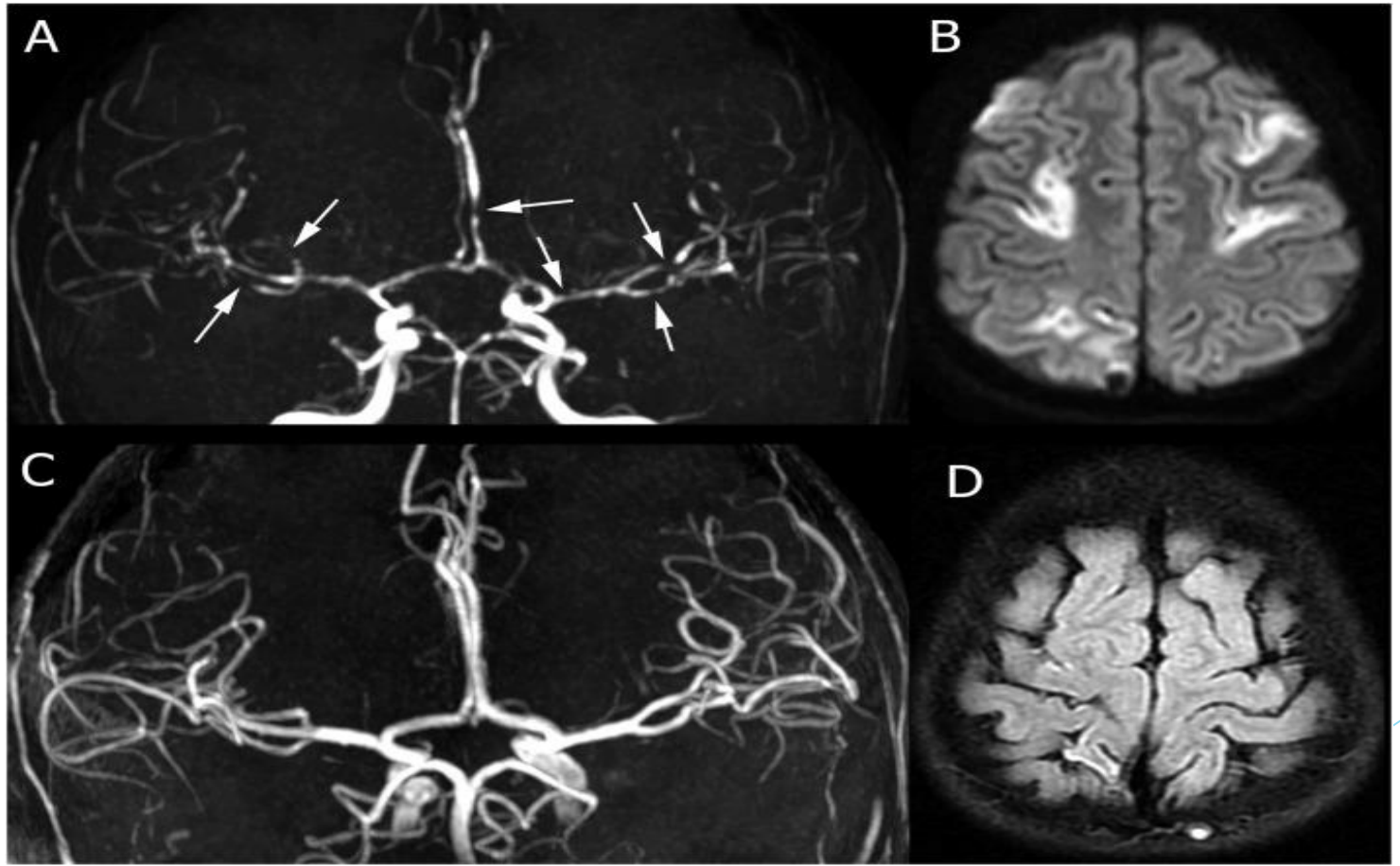
IIH(benign intracranial hypertension or pseudotumor cerebri

- A 10-year-old, previously healthy girl presented to the ophthalmology clinic as she was complaining of eye dryness and a recurring headache lasting 2 months. She also complained of difficulties closing her eyes fully while sleeping. Examination showed bilateral papilledema, with tortious blood vessels and disc hyperemia, and elevated optics disc. A B-scan ocular ultrasound was done and showed no evidence of drusen body.
- She was immediately referred to ER to be seen by a pediatric neurologist. A brain CT was performed, which showed no acute intracranial abnormality.
- She reported a history of headache for the past 2 months, which she described as mild, frontal, intermittent, and throbbing in nature, and which improved without medication.
- Upon examination she looked well with normal general and neurological exam except for bilateral papilledema and left eye ptosis(reported to be since birth).
- The patient was admitted as a case of headache with papilledema for further investigations. Upon active screening of COVID-19, she was found to be positive. A further history of exposure was taken, and her mother mentioned that her father had been admitted to hospital with COVID-19.
- A lumbar puncture showed an opening pressure of 22 cmH_2O. CSF analysis revealed WBC 1, RBC 31, protein 0.25, glucose 3.20, and serum glucose 4.8.
- Brain magnetic resonance imaging (MRI), orbital MRI, and brain MR venogram, were not done due to social reasons. The patient was discharged on acetazolamide 5 mg/kg/day with an increment planned up to 15 mg/kg/day. An appointment with a neurologist was scheduled for 2 weeks, for follow-up, with brain MRI and MR-venogram to be performed as soon as possible.

Reversible Cerebral Vasoconstriction Syndrome and Multisystem Inflammatory Syndrome in Children With COVID-19

- Two pediatric patients with clinical findings compatible with severe MIS-C and hemodynamic compromise presented to the hospital. During their hospitalization course, they developed thunderclap headaches and neurological deficits. Both were receiving vasoactive agents, intravenous immunoglobulin, and immunosuppressants. Imaging studies showed marked multifocal cerebral vasoconstriction in both cases and infarcts in one. After controlling inflammation and elimination of triggers, both patients were ultimately symptom free upon discharge. Cerebral vasoconstriction had completely resolved on follow-up imaging. Although a variety of symptoms including headaches may be seen in pediatric COVID-19 patients with MIS-C, RCVS should be considered as a differential diagnosis in cases of thunderclapصاعقه headache accompanied by neurological signs in these patients. Imaging findings and follow-up are also key in establishing the diagnosis.

FIGURE 1 Initial and follow-up imaging for patient 1. (A) Magnetic resonance angiography (MRA) demonstrates multifocal areas of vasoconstriction in multiple vascular territories (arrows). (B) Diffusion-weighted images a week after presentation show multifocal acute infarcts in different vascular territories. (C) Follow-up imaging after five months demonstrates complete resolution of the foci of vasoconstriction on MRA. (D) Fluid-attenuated inversion recovery images demonstrate small residual areas of chronic infarct in the cortical regions.



Posterior Reversible Encephalopathy Syndrome (PRES). in a Child with Sickle Cell Disease and SARS-CoV-2 Infection

- 7-year-old male child patient with sickle cell disease (SCD), who presented with acute encephalopathy and nonconvulsive (electrographic only) seizures immediately prior to the onset of severe symptomatic SARS-CoV-2 infection, manifesting as **respiratory failure**, **systemic inflammatory response**, and **hypertension**. Brain imaging confirmed hyperintense lesions consistent with PRES. Following aggressive symptomatic management including antiseizure medication, immunomodulatory treatment of SARS-CoV-2 infection, and intensive blood pressure control, he made a full neurological recovery. PRES has been observed in adults with SARS-CoV-2 infection, but there are few published reports of this neurological manifestation in children. **PRES** should be a consideration in children with **SARS-CoV-2 infection presenting with acute neurological decompensation**, especially in the setting of **preexisting risk factors for cerebrovascular dysregulation such as SCD.**

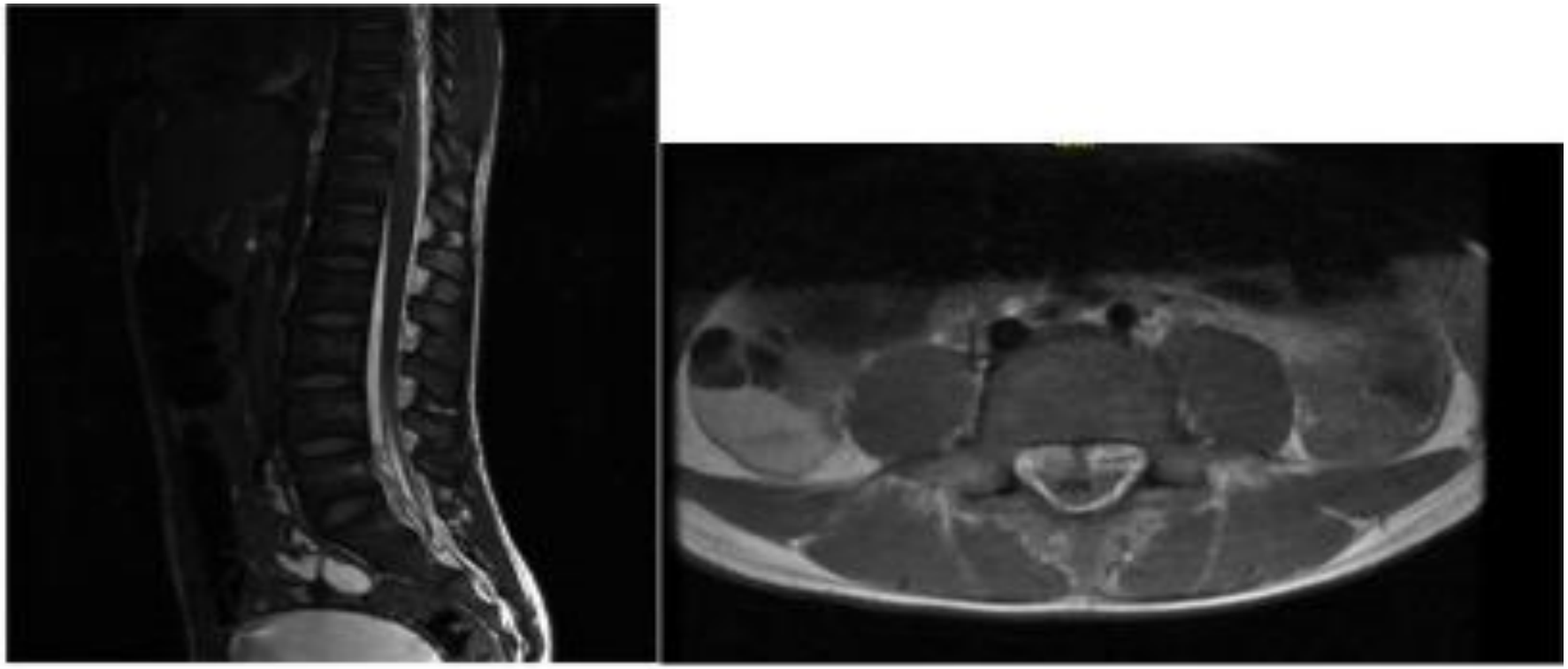
ADEM

- a case of ADEM in a pediatric patient with MIS-C related to SARS-CoV-2 infection. The diagnosis : a polyfocal, clinical central nervous system (CNS) event with a presumed inflammatory demyelinating cause; an encephalopathy that cannot be explained by fever.
- no new clinical and MRI findings emerging 3 months or more after the onset; abnormal brain MRI during the acute phase .
- The close temporal relationship between encephalopathy and SARS-CoV-2 infection in patient allowed to consider the novel coronavirus as the trigger of the immune-mediated response against CNS
- she presented fever, mucocutaneous involvement, lymphadenopathy, diarrhea and neurological symptoms associated with elevated inflammatory markers and the presence of antibodies against SARS-CoV-2 fulfilled the criteria for the diagnosis of MIS-C, the search for the novel coronavirus in the CSF was not
- patient was treated with glucocorticoids and immunoglobulin with a complete recovery; the outcome was favorable.

Miller Fisher syndrome

- A 9-year-old, previously healthy boy presented with dysarthria and gait instability noted since wake up this am. Two days prior to that he complained of mild headache that responded to simple analgesia.
- On exam, he was able to follow commands with intact comprehension, and demonstrated fluent hypophonic speech. Cranial nerve examination was normal, except for a mild lateral gaze limitation bilaterally. There was normal tone and power in all extremities, with normal reflexes throughout and a flexor plantar reflex bilaterally. His sensory examination was normal. Cerebellar examination showed mild appendicular dysmetria with overshooting. His gait was wide-based, with an abnormal tandem gait. Brain computed tomography (CT) with angiogram was non-revealing. Baseline laboratory examinations in the ER were all normal, including complete blood count, electrolytes, creatine phosphokinase, renal and liver function tests.
- On the second day after admission, he developed dysphagia with difficulty on swallowing liquid; on that day, the result of his nasopharyngeal swab test for COVID-19 was positive. Lumbar puncture was attempted but was not successful.
- Four days after presentation, he complained of diplopia, and upon re-examination, he was noted to have bilateral ptosis with worsening of his extraocular movements. He exhibited external ophthalmoplegia with severe limitation of extraocular movements in all directions, with a normal pupillary response to light, and without a relative afferent pupillary defect.
- He then had diminished reflexes in the upper and lower limbs.
- At that point a provisional diagnosis of Guillain Barré syndrome variant was suspected and was treated with intravenously administered immunoglobulin (IVIG) 2 g/kg over a period of 5 days.
- MRI of his brain and spine with contrast showed thickening and enhancement of the nerve roots of the cauda equina and conus medullaris, with no acute intracranial pathology (Fig. 1). Nerve conduction studies were not done due to the current COVID-19 pandemic situation.
- Diagnosis of Miller Fisher syndrome was later confirmed by positive ganglioside antibodies in the serum, specifically GQ1b (IgM and IgG) antibodies.
- On the third day of starting IVIG, he showed improvement of dysphagia and diplopia. His extraocular movements, ptosis, and ataxia improved significantly over the subsequent days and he began to mobilize without assistance.
- He was discharged approximately 2 weeks after admission.
- Two weeks after discharge, the patient had mild ataxic gait with normal extraocular movements

Fig. 1. Sagittal and axial spine magnetic resonance imaging showing thickening and enhancement of the nerve roots of the conus medullaris, cauda equina, exiting nerve roots exiting from L5 to S2.



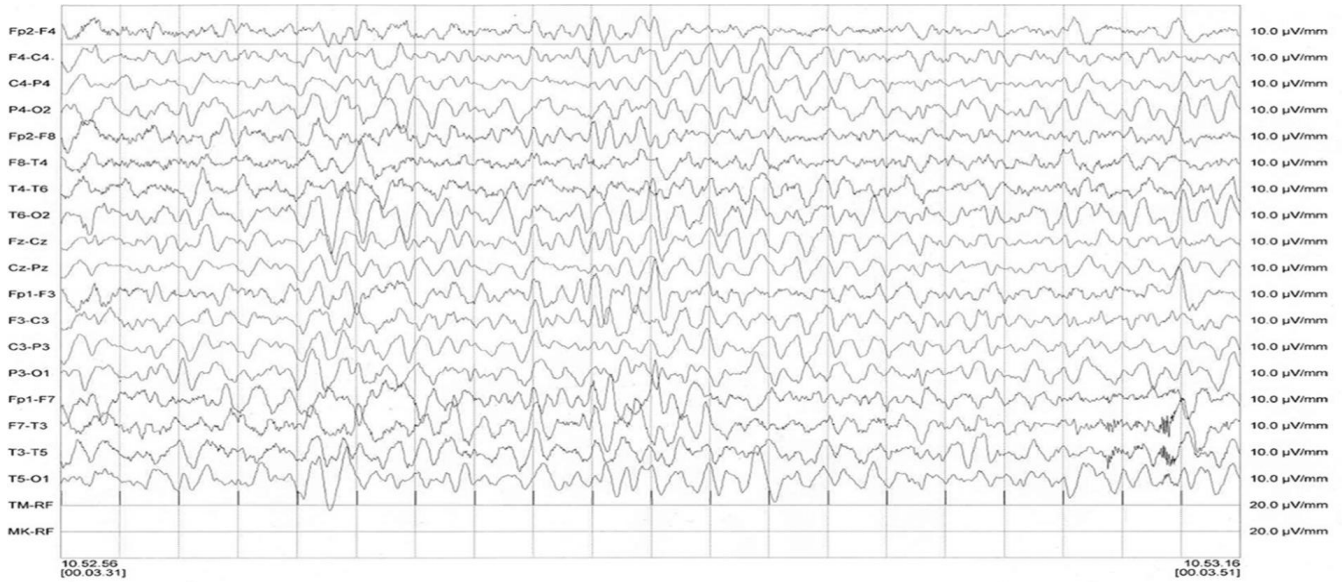
(A) Sagittal

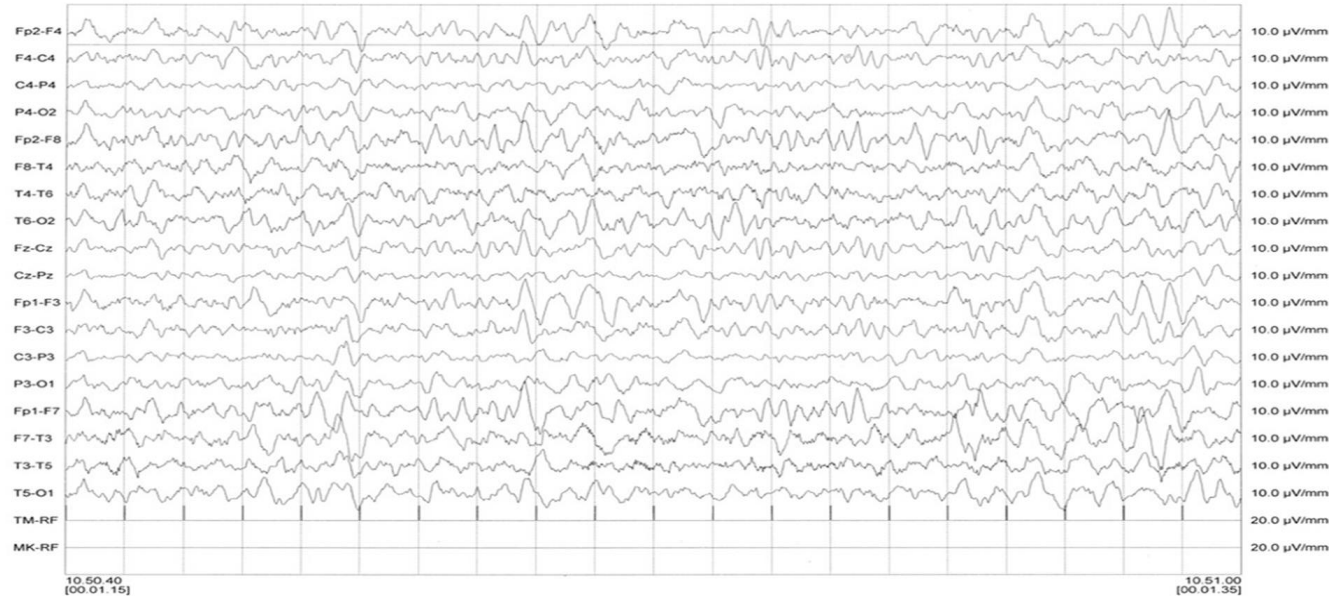
(B) Axial

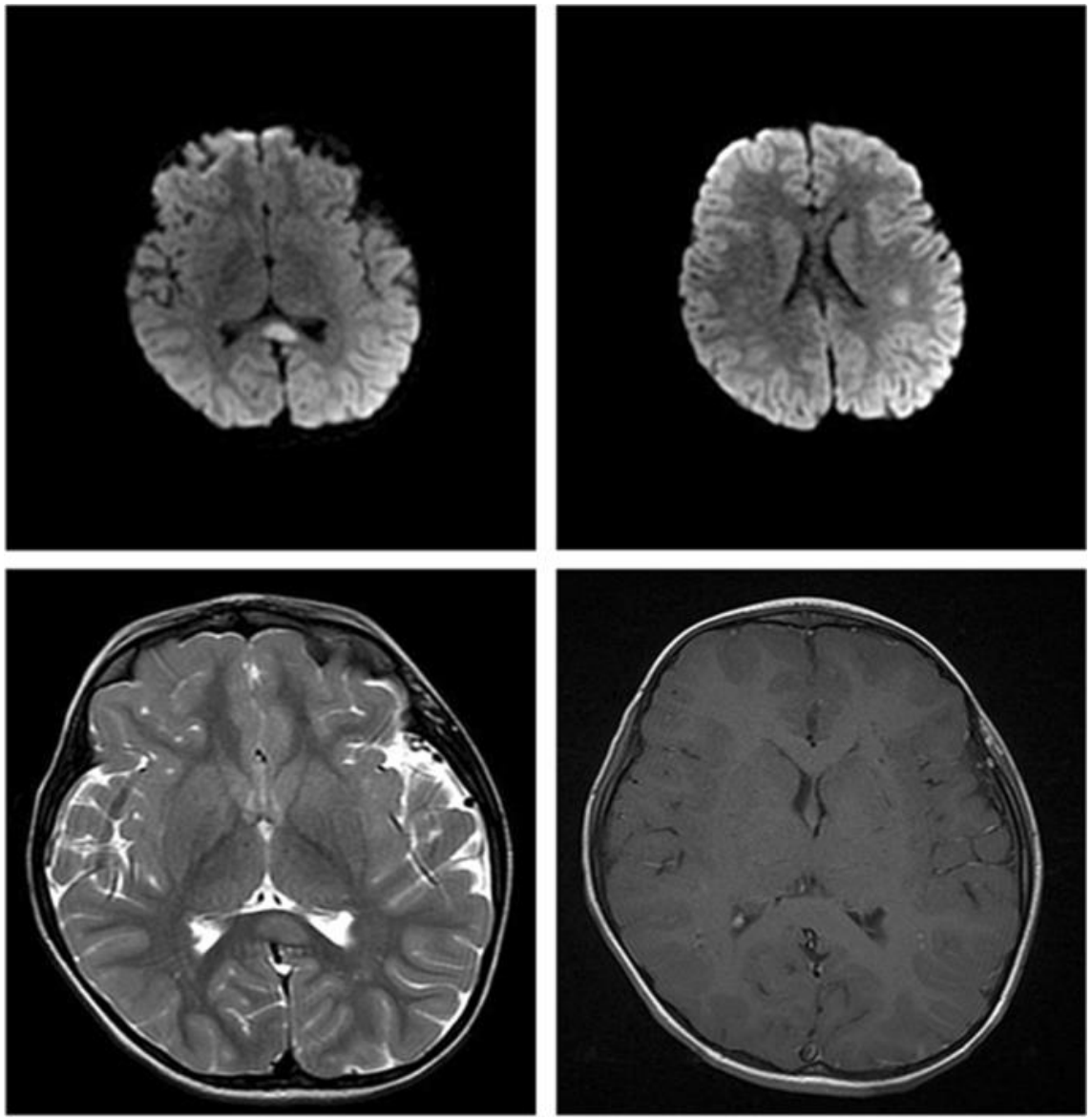
encephalitis in a COVID-19 pediatric patient

- a 5-year-old previously healthy girl started experiencing some mild, self-limiting cough symptoms associated with a fever episode. A couple of days later, she was admitted to the emergency department complaining of a painful swelling in her neck. The patient showed negativity to SARS-CoV-2 infection, as indicated by rapid swab test.
- In the following days, a sudden worsening of the clinical conditions with the appearance of neurological symptoms such as altered mental status, increased irritability, sleepiness, lack of energy, and lethargy.
- Serological investigations for HSV1, varicella-zoster, Epstein-Barr, and CMV were negative. The RT-PCR test for SARS-CoV-2 was performed using a nasopharyngeal swab which was positive. The EEG (Fig. 2) showed a slow base rhythm (theta-delta) together with synchronous bilateral potentials formed by slow waves with predominance on the right side.
- A MRI examination of the brain was immediately requested, with and without contrast medium.xial DWI demonstrated the presence of a hyperintense focal lesion in the splenium of the corpus callosum, and right parietal subcortical area. In the long TR sequences, the lesions appeared hyperintense, but did not show any contrast enhancement.These lesions were compatible with parenchymal cerebral edema due to brain inflammation in accordance with the diagnosis of encephalitis in patient with SARS-CoV-2.
- CSF was clear and colorless. CSF laboratory tests showed WBC 0.5×10^{7}/L (normal value <4), protein 0.27 g/L (normal 0.15–0.45), and normal glucose. The CSF specimen was negative for SARS-CoV-2 test. The patient did not evidence any bacterial or tuberculous infection of the CNS. Anti-HSV 1, varicella-zoster, Epstein-Barr, and CMV IgM antibodies were not detected in serum samples. After a cycle of high-dose intravenous methylprednisolone, a quick and complete remission of symptoms was observed. Two weeks later, the patient was discharged from. No consequences of the infection can be recorded at the present time.

- The early suspicion of COVID-19 encephalitis and the appropriate CSF studies were the key to establish the correct diagnosis and timely management of the pathology.
- Despite the absence of CSF pleocytosis, the suspicion of CNS encephalitis should still be considered.
- Although the conclusive diagnosis of viral encephalitis largely depends on virus isolation, this can be difficult for COVID-19, because SARS-CoV-2 dissemination is transient and its CSF titer may be extremely low .
- Consistently, anti-SARS-CoV-2 IgM and IgG were not detectable in the patient's CSF sample .
- Therefore, as mentioned before, a physical evaluation of neurological symptoms and noninvasive tests such as brain mri and EEG are important to lead a presumptive diagnosis
- After multiplication in the primary (subcutaneous, respiratory mucosa, lymph nodes) and secondary (endothelium, muscle, marrow) sites, the SARS-CoV-2 would trigger an abnormal immune and/or inflammatory response, through still not completely understood mechanisms, causing damage to the vascular endothelium of the brain, arteriolar angiopathy, and in some cases direct, onconeural damage dysimmune encephalitis .Viral epitopes resembling myelin antigens have the ability to activate myelin-reactive T-cell clones via molecular mimicry , and may thus elicit a CNS-specific autoimmune response, as in acute disseminated encephalomyelitis.
- corticosteroids therapy can be effective in the treatment of severe COVID-19-related encephalitis. it is important to highlight that the early establishment of the diagnosis and the immediate of a management plan may contribute to a better outcome.
- encephalitis in children can be a complication of COVID-19 infection, or it can be even considered initial manifestation of a not yet overt infection. neurological manifestations might be expected in COVID-19 infection, despite the absence of significant respiratory symptoms.


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
TM-RF
MK-RF
10.0 µV/mm
20.0 µV/mm
10.52.56
[00.03.31]
10.53.16
[00.03.51]


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
TM-RF
MK-RF
10.0 µV/mm
20.0 µV/mm
10.50.40
[00.01.15]
10.51.00
[00.01.35]



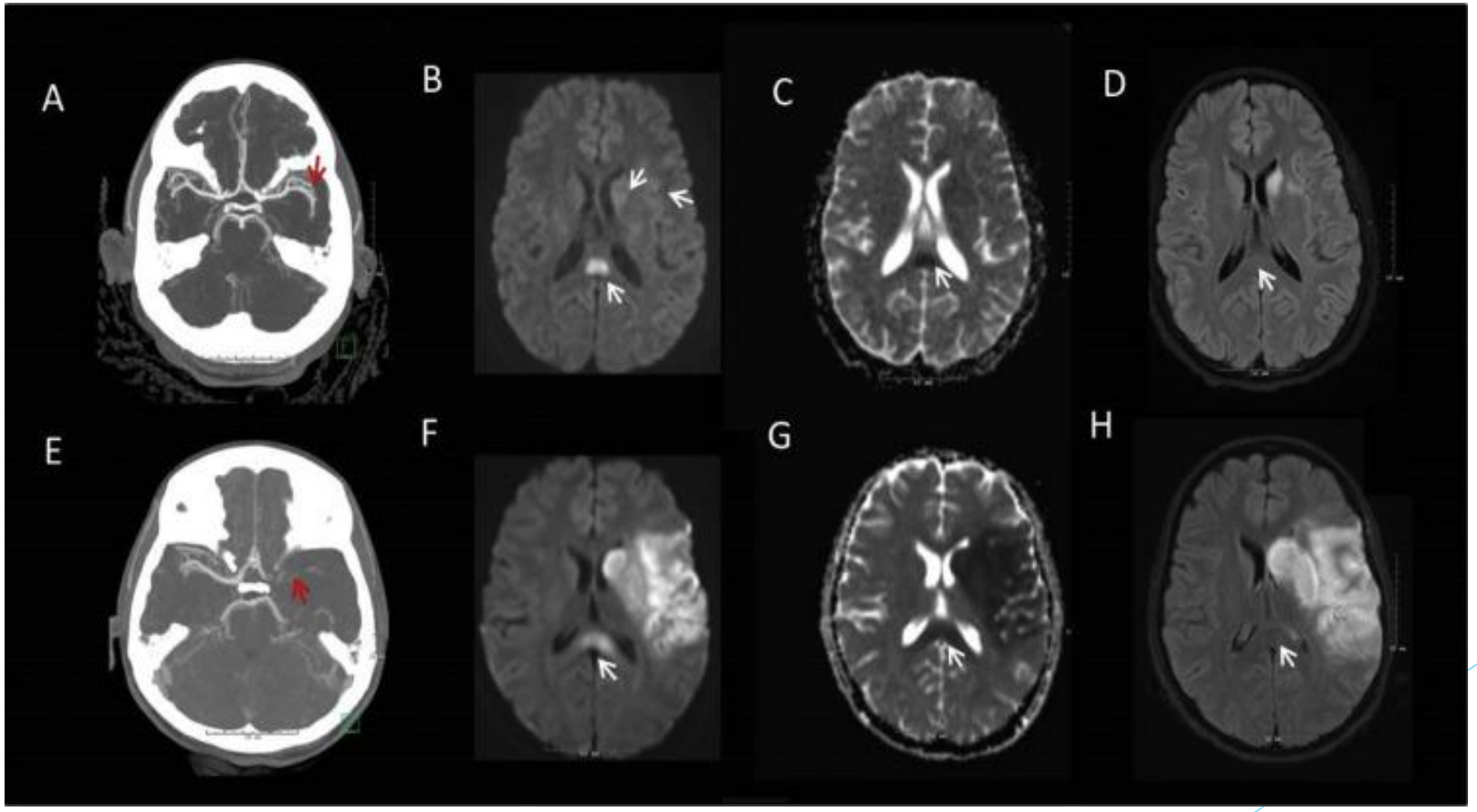
AIS due to LVO(large vessel occlusive) in children

- Patient 1
- This previously healthy right-handed 15-year-old girl awoke with acute aphasia and right hemiparesis One week prior, she had tested positive for SARS-CoV-2 after several days of fevers, headache, abdominal pain, and generalized weakness.
- Initial laboratories demonstrated leukocytosis, renal and cardiac dysfunction, and markedly elevated inflammatory markers. Transthoracic echocardiogram (TTE) with bubble study demonstrated a left ventricle ejection fraction (LVEF) of 45% with global strain and mild mitral valve regurgitation. Cardiac magnetic resonance imaging (MRI) showed small pericardial effusion. MRI brain with diffusion weighted imaging (MRI-DWI) showed scattered infarcts in the left caudate, insula, and frontal operculum and a restricted diffusion in the splenium of the corpus callosum; the latter lesion resolved on follow-up studies (Fig B-D). Lower extremity Doppler studies were negative for DVT.
- The patient met CDC criteria for MIS-C based on her known recent SARS-Cov2 infection, multisystem involvement (renal, cardiac, neurologic), and elevated inflammatory markers.[4] She was treated with intravenous immunoglobulin (IVIG) 2 g/kg and IV methylprednisolone 2 mg/kg/day for five days, followed by a three-day oral prednisone taper and therapeutic enoxaparin 1 mg/kg twice daily for three months. A repeat TTE on day six showed improved LVEF. Upon discharge, she had subtle right hemiparesis *with* a Pediatric Stroke Outcome Measure (PSOM) of 1.5, which had completely resolved (PSOM 0) at 30-day follow-up.

- Patient 2
- This previously healthy right-handed 16-year-old girl without any history of head trauma was found obtunded and nonverbal after three days of fevers, nausea, vomiting, and diarrhea. Her family had been ill with SARS-CoV-2 about a month prior.
- Upon arrival, her blood pressure was 70/40 mmHg, requiring vasopressor support. CT head showed a subtle left insular hypodensity. An initial suspicion of bacterial meningoencephalitis warranted lumbar puncture and initiation of antibiotic treatment. Five hours after initial presentation, she developed right-sided hemiparesis (National Institute of Health Stroke Scale score: 16). An urgent CT angiography head and neck showed left internal carotid artery terminus occlusion (Fig E), with unfavorable CT perfusion study. She was transferred to our institution's pediatric intensive care unit for escalation of care, where she was intubated for airway protection.
- Initial laboratories showed leukocytosis, renal and cardiac dysfunction, elevated inflammatory markers, and positive SARS-CoV-2 IgG serology. TTE demonstrated an LVEF of 35% which improved after 12 hours. An apical thrombus was confirmed on cardiac MRI, and she was started on anticoagulation with heparin drip. Several subacute infarcts were noted on MRI-DWI brain in the left insula, caudate, and frontal and temporal lobes (Fig F and G), in addition to diffusion restriction with corresponding ADC changes involving the splenium of the corpus (Fig F and G); the latter had resolved on follow-up studies five days later (Fig H).
- She was diagnosed with MIS-C based on the CDC criteria[4] and was treated with a single dose of IVIG 2 g/kg and IV methylprednisolone 1 mg/kg/day for five days followed by a three-day oral prednisone taper. Her hospitalization was complicated by a catheter-associated right lower extremity DVT. Heparin drip was transitioned to enoxaparin 1 mg/kg twice daily and aspirin 81 mg daily. Throughout her hospital stay, she made gradual improvement with speech and mobility. She was ultimately discharged to an acute rehabilitation facility with PSOM of 3. On day 41 outpatient follow-up, she was independent in all activities of daily living with mild expressive aphasia and trace right hemiparesis with PSOM of 2.

Patient 1:Axial imaging with CTA maximum intensity projection demonstrating occlusion of the distal M2 branch of the left MCA (A), MRI diffusion weighted imaging (DWI) showing restricted diffusion in the insular ribbon, caudate head and splenium of the corpus callosum (B) with corresponding ADC changes (C) and resolution of the splenial lesion on T2 FLAIR on repeat imaging (D).

Patient 2: Axial imaging with CTA maximum intensity projection demonstrating occlusion of the left ICA terminus (E), MRI DWI shows restricted diffusion in the left MCA territory and splenium of the corpus callosum (F) with corresponding ADC changes (G), and resolution of the splenial lesion on T2 FLAIR on repeat imaging (H)



- AIS due to LVO(large vessel occlusive) in children is uncommon. Even in the setting of COVID-19 and MIS-C, very few cases of AIS have been reported.
- The current literature includes nine other published cases of pediatric LVO AIS in the setting of COVID-19 , the ages range from eight to 16 years, some of which were initially asymptomatic with positive polymerase chain reaction or IgG serology. only three other reported patients met full diagnostic criteria for MIS-C. AIS and MIS-C were successfully treated with IVIG, steroids, and anticoagulation
- These two patients demonstrate an association between MIS-C and AIS due to LVO, thus expanding the literature on this rare condition. These cases illustrate the importance of early symptom recognition, timely diagnosis, and rapid intervention to improve clinical outcomes.

Pediatric Autoimmune Encephalitis Following COVID-19 Infection

- Similar to the pathogenesis of autoimmune disease, SARS-CoV-2 (COVID-19) infection has been shown to be associated with dysregulated and persistent inflammatory reactions and production of some antibodies.
- pediatric patients found to have serum SARS-CoV-2 antibodies who presented with neurologic findings suggestive of postinfectious autoimmune-mediated encephalitis.
- All cases showed lymphocytic pleocytosis on cerebrospinal fluid studies
- marked improvement in neurologic symptoms after high-dose intravenous corticosteroids.
- these cases suggest autoimmune-mediated encephalitis as yet another SARS-CoV-2 related complication.