The Neuroimaging of Infections in Pediatrics: with a focus on COVID-19

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Dent Neurologic Institute
American Society for Neuroimaging
2021

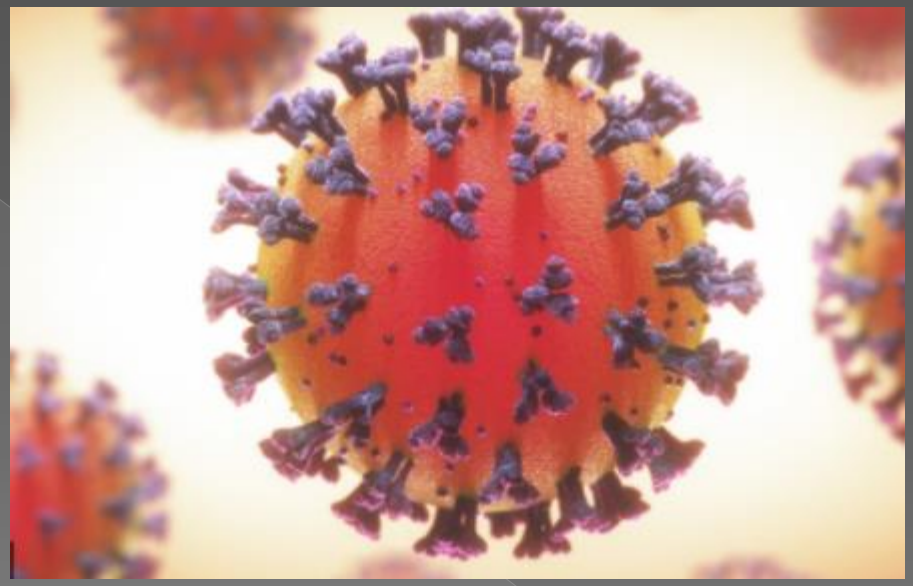
THE AMERICAN SOCIETY OF NEUROIMAGING

DENT NEUROLOGIC INSTITUTE

Conflicts of Interest

Research
Allergan/ AbbVie
Amgen/ Novartis
Avanir
Biohaven
Eli Lilly and Company
Lundbeck
Teva

Speaker
Allergan/AbbVie
Amgen
Avanir
Biohaven
Eli Lilly
Lundbeck
Teva



Pediatric Infection Exposure

- Prenatal
- Postnatal/Neonatal Pediatric
- Adolescent
- Through breast milk

- Some of these may be critical periods and imaging modalities may vary with age and infection type.

Pediatric Infection Type

- Focus on COVID-19 presentations and neuroimaging findings
- Discuss concerns for neonatal infection and any information on breast feeding
- Discuss how this infection compares to others in pediatrics

COVID-19

Stafstrom and Jantzie (Sept 2020) Covid -19: Neurologic Considerations in Neonates and Children, *Children*, 7, 133

- Neurologic involvement adults approx 36%
- 2-5 % infections involve children
- 80% were mildly affected
- Termed ***multisystem inflammatory syndrome in children (MIS-C)*** and ***pediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS)***
- Review showed 34% kids with MIS-C had increased neurologic symptoms
- Limited neuroimaging data is available

COVID-19 Children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Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study

Camilla E Lindan, MD • Kshitij Mankad, FRCR • Dipak Ram, FRCPCH • Larry K Kociolek, MD • V Michelle Silvera, MD • Prof Nathalie Boddaert, MD • et al. Show all authors • Show footnotes

Published: December 15, 2020 • DOI: https://doi.org/10.1016/S2352-4642(20)30362-X • Check for updates

- Neuroimaging cases of encephalitis in children (0-18 yrs) with SARS-CoV-2 from 8 different countries
- 5 neuroradiologists/ 4 had to agree
- 38 cases (60 submitted)
- **4 Categories**

1. **Acute COVID-19** 12 (32%)
2. **Asymptomatic acute/subacute COVID-19** 8 (21%)
3. **MIS-C** 11(29%)
4. **Indeterminate** 7 (18%)

COVID-19: ADEM

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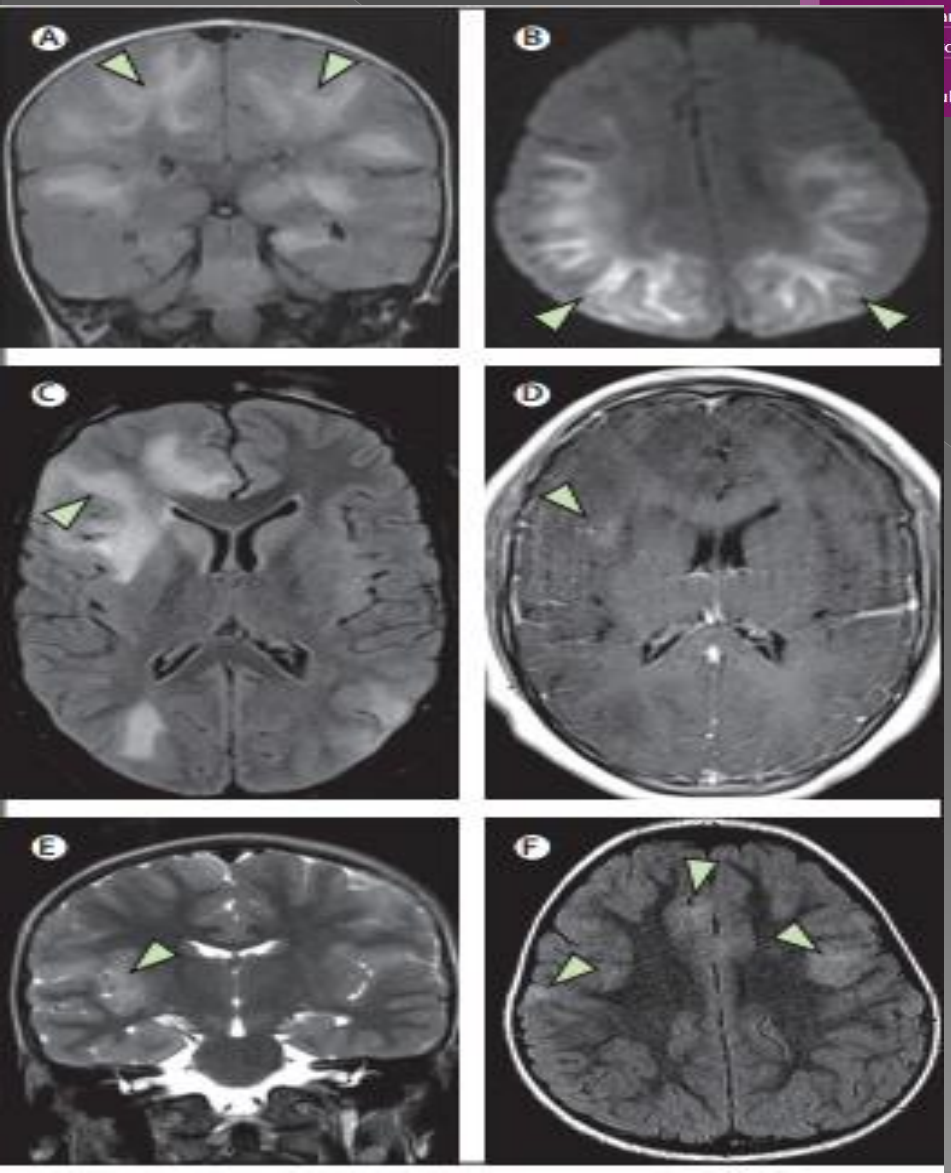

Figure 1: ADEM-like brain changes

(A, B) A 1-year-old boy (case 2) with acute COVID-19 showed confluent areas of high signal in the subcortical white matter on coronal FLAIR imaging (A; arrows), and reduced diffusion on DWI trace (B; arrows). (C, D) A 13-year-old boy (case 4) showed similar changes on FLAIR imaging with associated mass effect in the right frontal lobe (C; arrow). This area showed some subtle enhancement on postcontrast T1-weighted imaging (D; arrow). (E, F) In a 4-year-old boy (case 38) with an indeterminate timepoint of exposure to SARS-CoV-2, ADEM-like changes were seen on coronal T2-weighted images (E; arrow) and axial FLAIR images (F; arrows). This child was positive for antibodies to myelin oligodendrocyte glycoprotein. ADEM=acute disseminated encephalomyelitis. DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery.

COVID-19: ADEM Commonalities

- Most cases of **ADEM** occur about 7 to 14 days after an **infection**, or up to three months following a vaccination.
- The most commonly associated **infectious** agents =

Cytomegalovirus (CMV)
Epstein-Barr virus (EBV)
Herpes simplex virus (HSV)
Human herpes-virus-6
Influenza virus,
Hepatitis A
HIV
Mycoplasma pneumonia

COVID-19: Neuritis

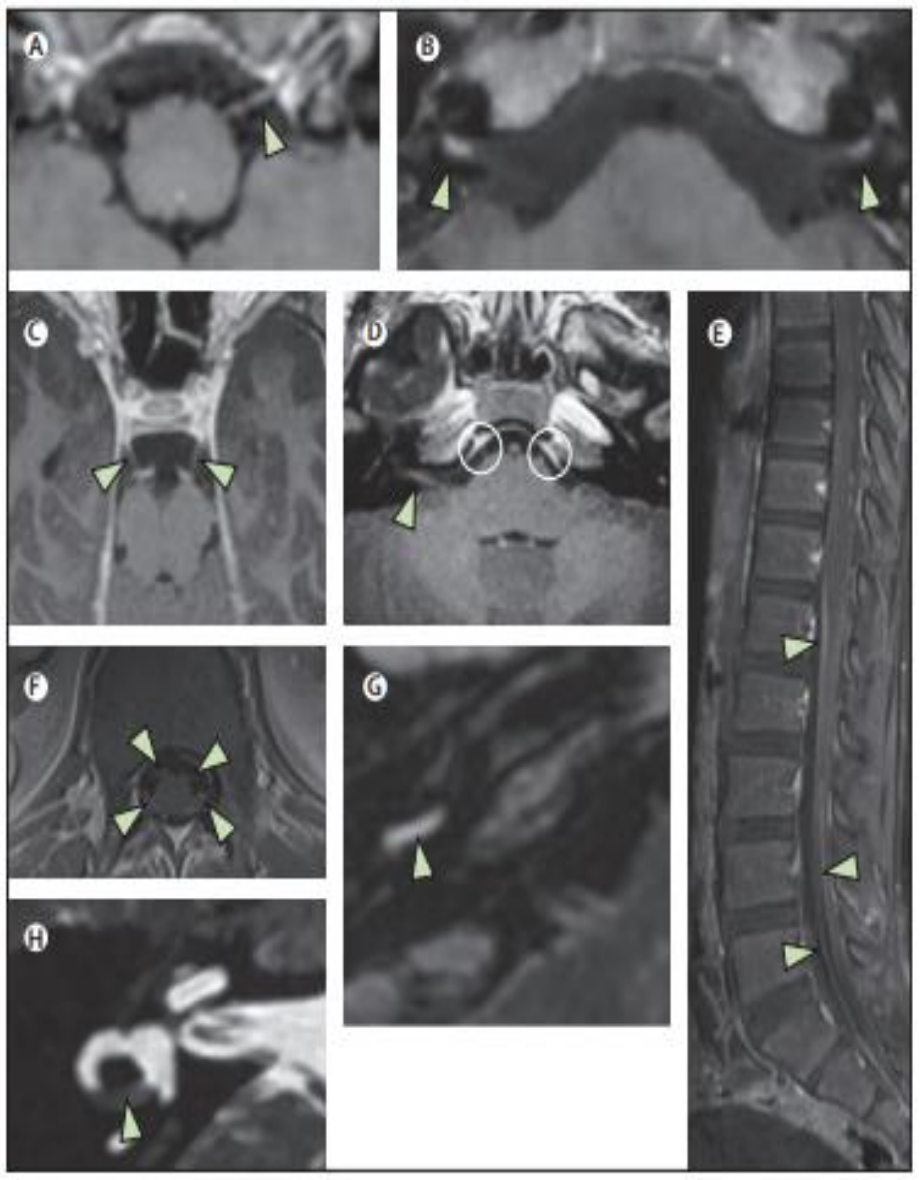

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Figure 2: Neuritis

(A, B) A 5-year-old boy (case 6) with acute COVID-19 presented with acute facial paralysis in conjunction with respiratory failure. He had marked enhancement and thickening of multiple cranial nerves, for example the 12th nerve on the left (A; arrowhead) and the seventh nerves bilaterally (B; arrowheads). (C–F) A 9-year-old boy (case 7), also with acute COVID-19, showed similar cranial nerve enhancement of his third nerves (C; arrowheads) as well as his seventh and eighth nerves (D; arrowhead [shown on patient's right side]) and his sixth nerves bilaterally (D; circles). This child also had enhancement of the cauda equina (E; arrowheads) as well as his cervical spine nerve roots (F; arrowheads). (G, H) A 13-year-old boy (case 33) with labyrinthitis with enhancement of the basal turn of the cochlea (G; arrowhead) and partial obliteration of his horizontal semicircular canal (H; arrowhead). All panels show T1 postcontrast images except for panel H (fast-spin echo T2 image).

Other causes can includes sarcoidosis, syphillis, tuberculosis, varicella zoster, Epstein-Barr Virus

COVID-19: Myelitis

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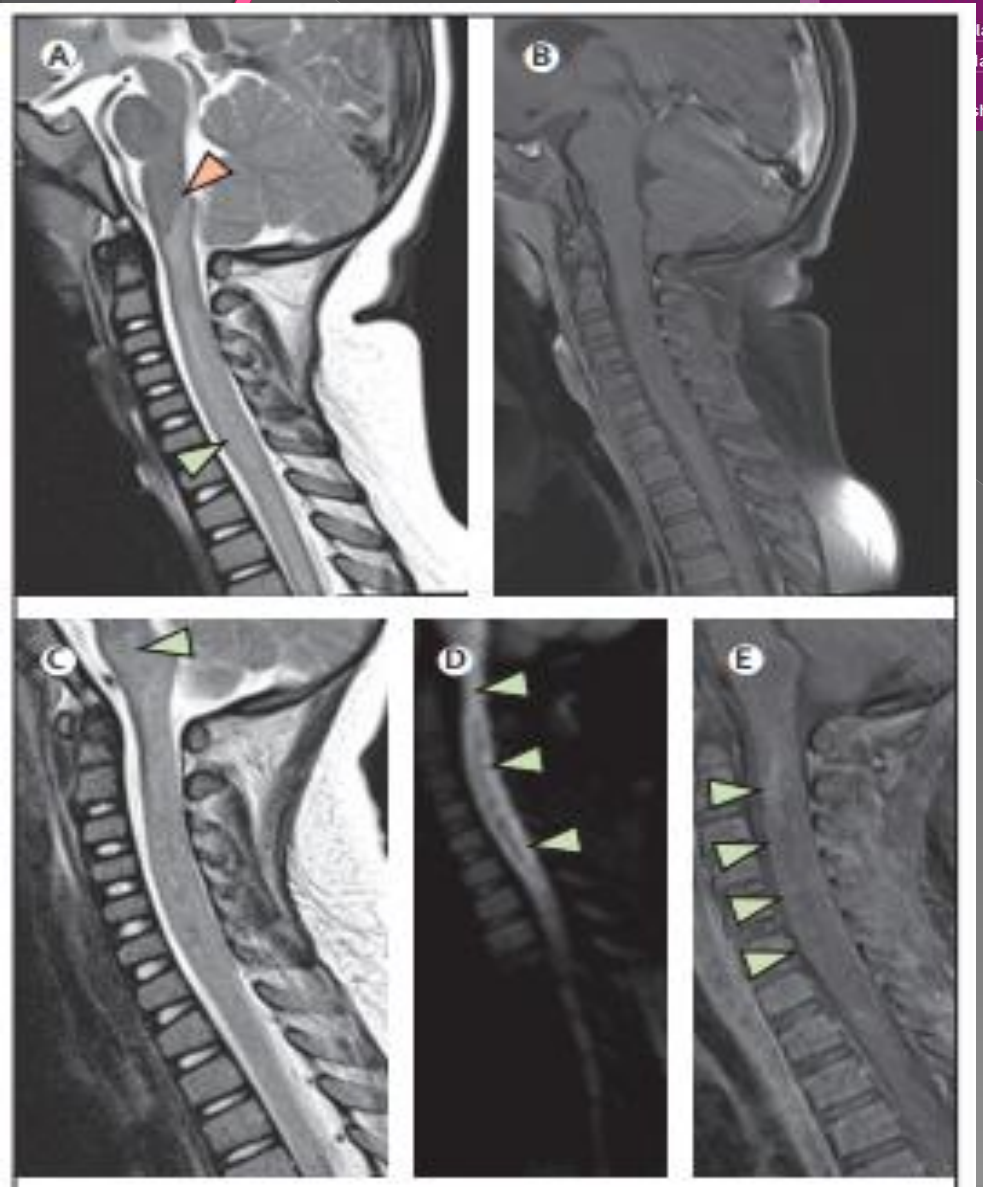

Figure 3: Acute necrotising myelitis

(A–H) A 3-year-old girl (case 5), who was living in a household with multiple family members who had COVID-19, presented with acute SARS-CoV-2 infection with positive PCR result. Symptoms included acute respiratory failure, confusion, limb weakness, and vomiting. Initial T2-weighted imaging (A) showed central cervical cord signal abnormality (green arrowhead) extending up to the obex (pink arrowhead) but sparing the medulla. No enhancement was seen in the cervical and thoracic cord on the initial T1-weighted postcontrast imaging (B). 4 days later, more extensive myelitis was seen with new involvement of the medulla on T2 imaging (C; arrowhead), new reduced diffusion seen on diffusion trace images (D; arrowheads), and progressive enhancement seen on T1 postcontrast imaging (E; arrowheads). 3–5 weeks later, marked cord atrophy and necrosis were seen on sagittal T2 imaging

COVID-19: Myelitis

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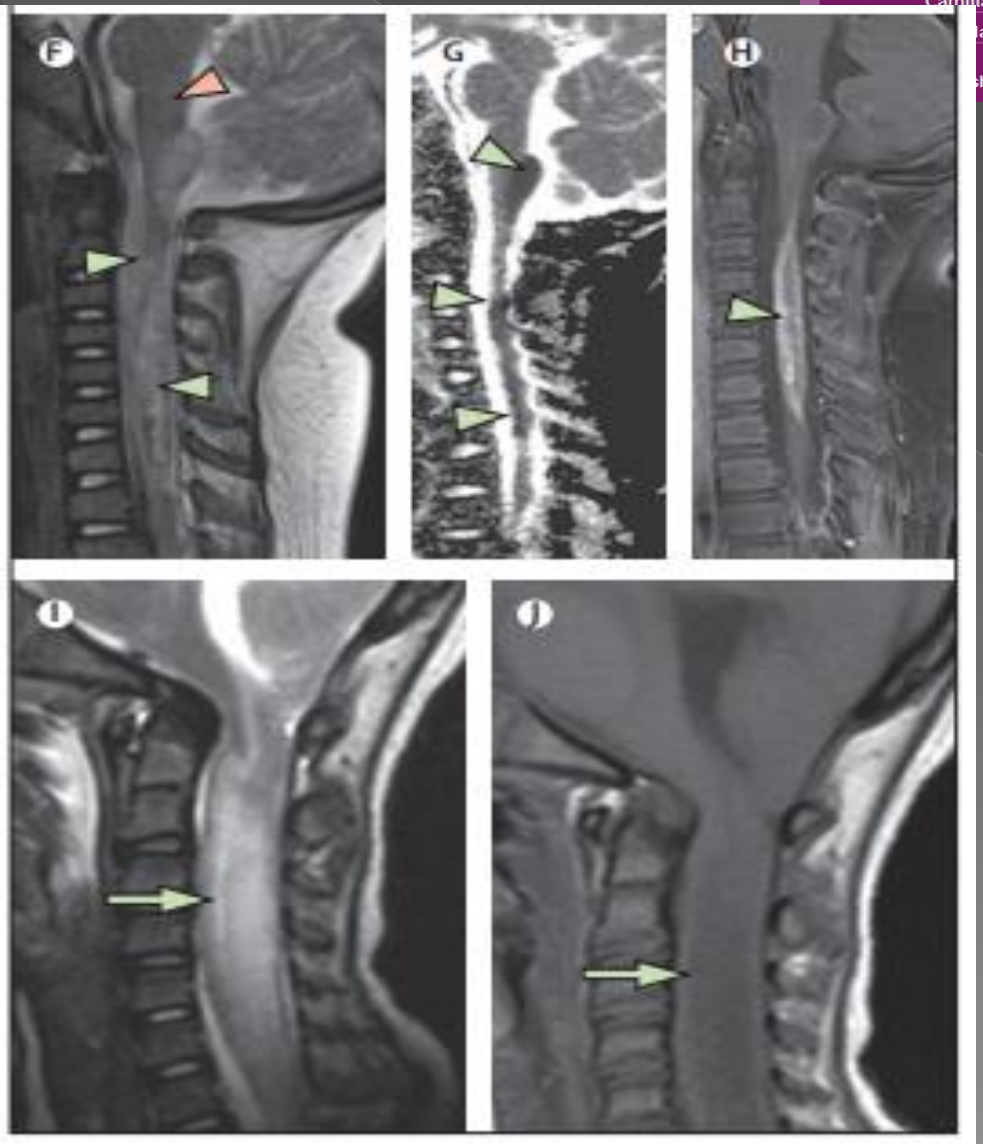
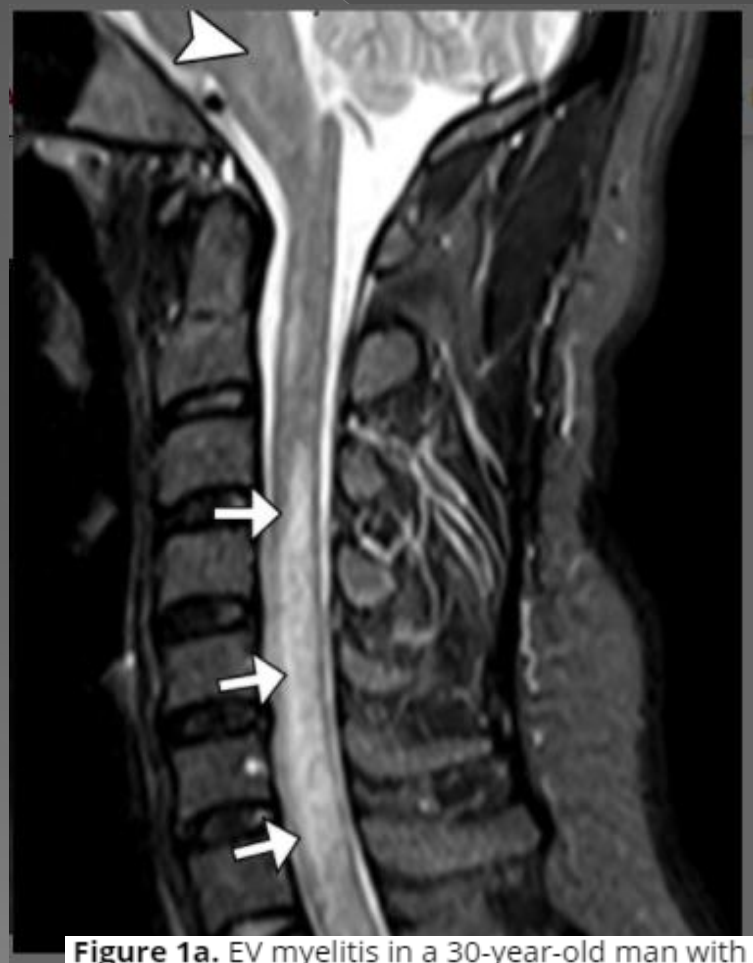


(F; green arrowheads) with resolution of the medullary signal change (pink arrowhead). Persistent and varied areas of reduced diffusion were seen on sagittal apparent diffusion coefficient maps (G; arrowheads) in addition to enhancement on T1 postcontrast sagittal imaging (H; arrowhead), suggesting ongoing active disease. (I, J) For comparison, a second case of severe myelitis in a 5-year-old girl (case 8) with acute COVID-19 is shown. Sagittal T2-weighted (I) and sagittal T1-weighted (J) images show profound cord swelling (arrowheads). This child (case 8) died with biopsy-proven tuberculous granulomata and electron microscopic evidence of SARS-CoV-2 viral inclusions in the brain. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

COVID-19: Myelitis similar in enterovirus

Lourenco do Carmo, R et al
Neuroimaging of Emergent and Reemergent Infactions Radiographics vol 39 No 6



A recent common case of acute flaccid myelitis in children, also meningitis, encephalopathy, and other

Figure 1a. EV myelitis in a 30-year-old man with acute onset of paraparesis. **(a)** Sagittal short inversion time inversion-recovery (STIR) MR image shows an extensive hyperintense longitudinal cervical spinal cord lesion (arrows). Additional discrete hyperintensities are seen in the medulla oblongata (arrowhead). **(b)** Axial T2-weighted MR image reveals expansion of the spinal cord and hyperintensities in its central gray matter and surrounding white matter (arrow).

COVID-19: Co-infections

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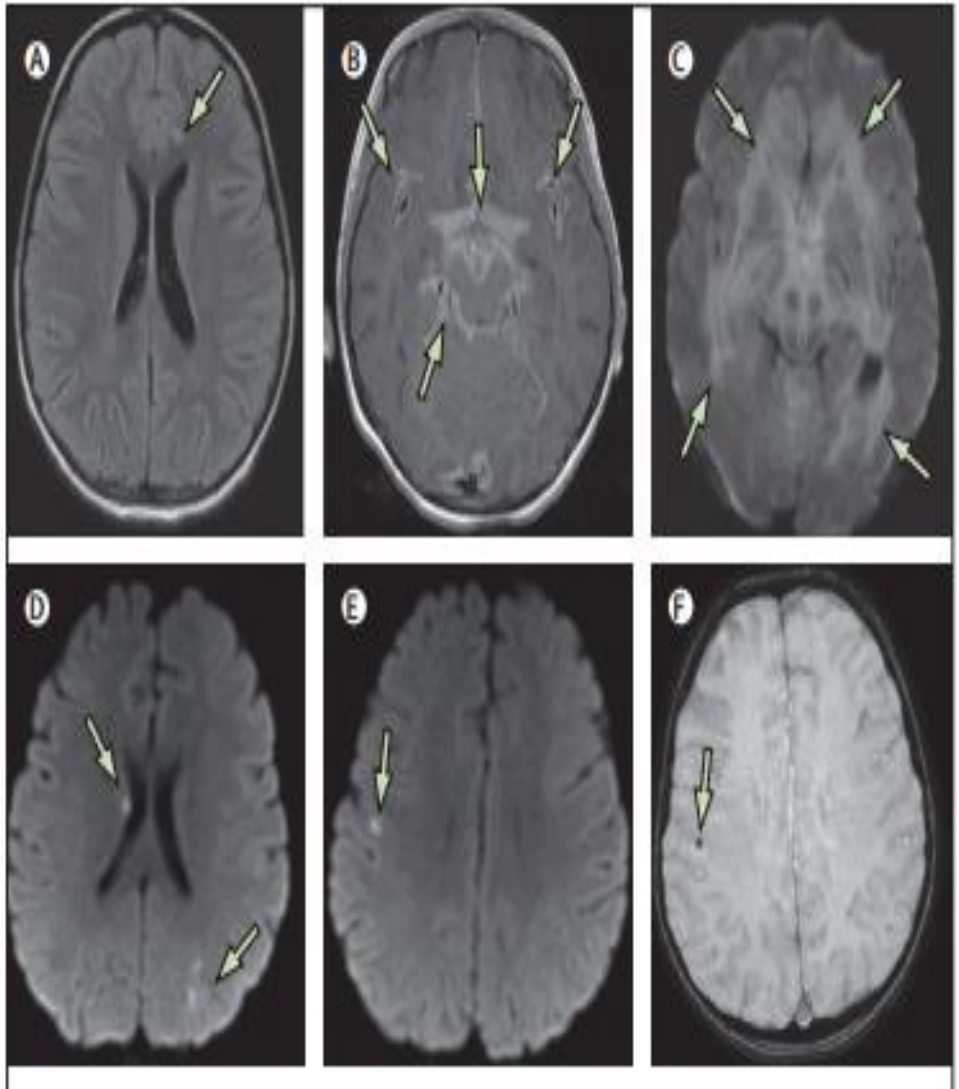

Figure 4: Fatal co-infections

(A–C) 5-year-old girl (case 8) presented with fever, headache, and seizures. Initial MRI showed an acute small left frontal infarct on axial FLAIR imaging (A; arrow). 5 days later she had extensive leptomeningeal enhancement in the basilar cisterns and perisylvian regions on postcontrast T1-weighted imaging (B; arrows). Findings progressed and, 3 weeks after presentation, markedly reduced diffusion on diffusion trace imaging (C; arrows) and oedema of the brain parenchyma were observed. The patient's brain biopsy was positive for SARS-CoV-2 viral inclusions on electron microscopy and positive for tuberculosis granulomata despite no tuberculosis contact. (D–F) A 5-year-old girl (case 9) presented with encephalopathy and acute respiratory distress and became septic with meticillin-resistant *Staphylococcus aureus* and varicella zoster virus infections, both of which were culture positive in the blood and CSF. She had multiple small foci of reduced diffusion on axial diffusion trace imaging, in keeping with microinfarcts (D, E; arrows), some of which had associated microhaemorrhage (F; arrow). This patient died 15 days after symptom onset.

Case 1: Tuberculosis
Case 2: MERSA and varicella zoster

COVID-19: Vasculitis

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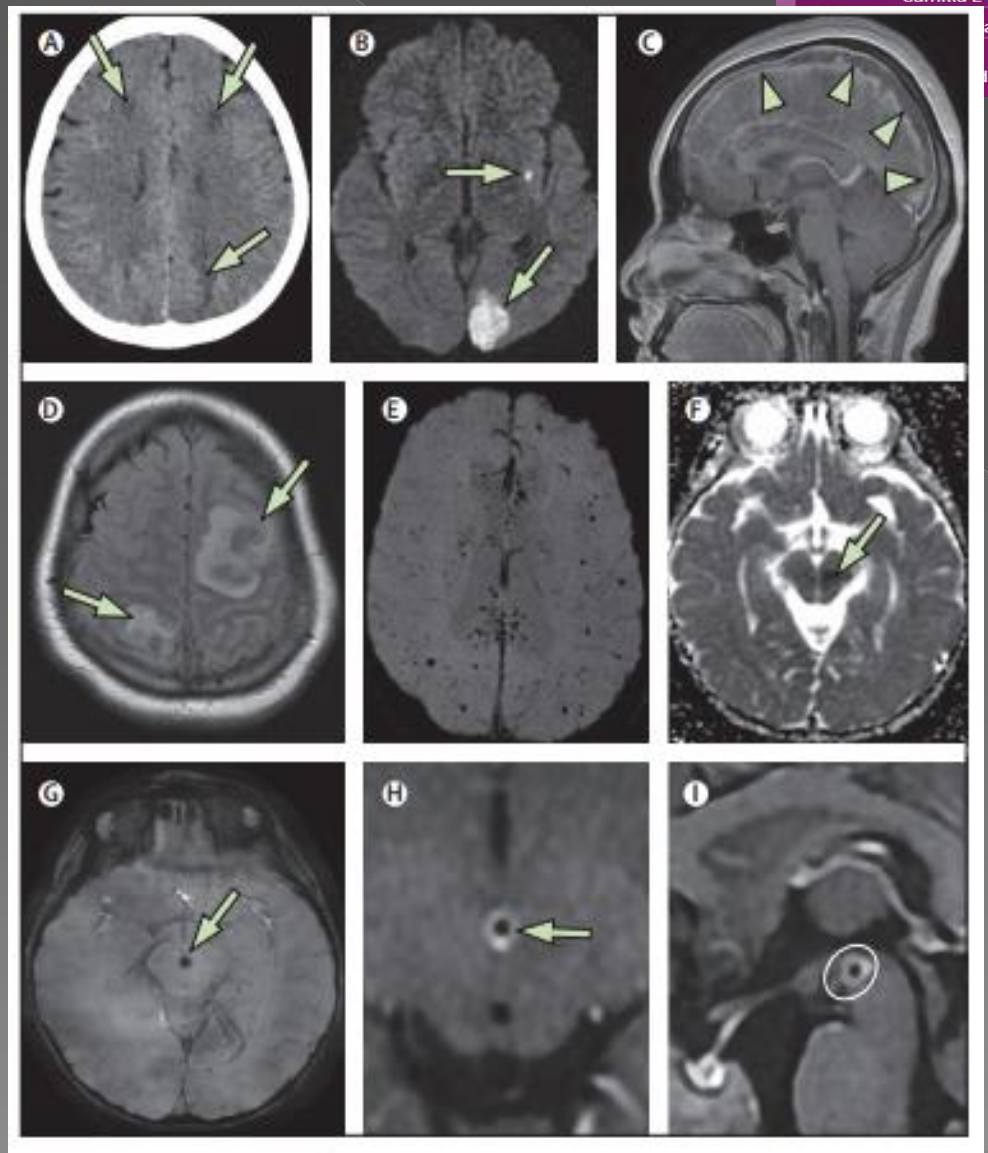

Figure 5: Vasculitic and thrombotic findings

(A, B) A 15-year-old girl (case 12) presented 27 weeks pregnant with fever, seizures, and hypertension, and COVID-19 pneumonia. Her CT at presentation (A) showed low-density areas in multiple locations (arrows). MRI 7 days later (B) showed small focal infarcts and a larger left occipital infarct (arrows) on diffusion trace imaging, findings compatible with unusually severe posterior reversible encephalopathy syndrome. (C, D) A 15-year-old girl (case 20) with subacute COVID-19 and no classical respiratory symptoms presented with fever, confusion, and headache. Complete occlusive thrombosis of the superior sagittal sinus was shown by the large filling defect in the postcontrast sagittal T1-weighted image (C; arrowheads), with resultant bilateral haemorrhagic venous infarcts on axial FLAIR images (D; arrows). (E) A 15-year-old girl (case 27) with multisystem inflammatory syndrome in children who also developed multiple microthrombi, as shown on SWI. The microthrombi were relatively clinically silent and showed partial resolution at 3 weeks with full clinical resolution of symptoms at 3 months after presentation. (F–I) A 2-year-old girl (case 32, indeterminate category) presented with fever and pharyngeal pain with an acute left midbrain infarction (arrow) shown on the apparent diffusion coefficient map (F; arrow). She had a thrombus in the feeding anterior perforator vessel on SWI (G; arrow) and marked associated vessel wall enhancement on postcontrast T1 arterial wall imaging (H, arrow; I, circle). FLAIR=fluid-attenuated inversion recovery. SWI=susceptibility-weighted imaging.

Infections, drugs, environmental triggers, and autoimmune diseases

COVID-19: Splenial lesions, Myositis

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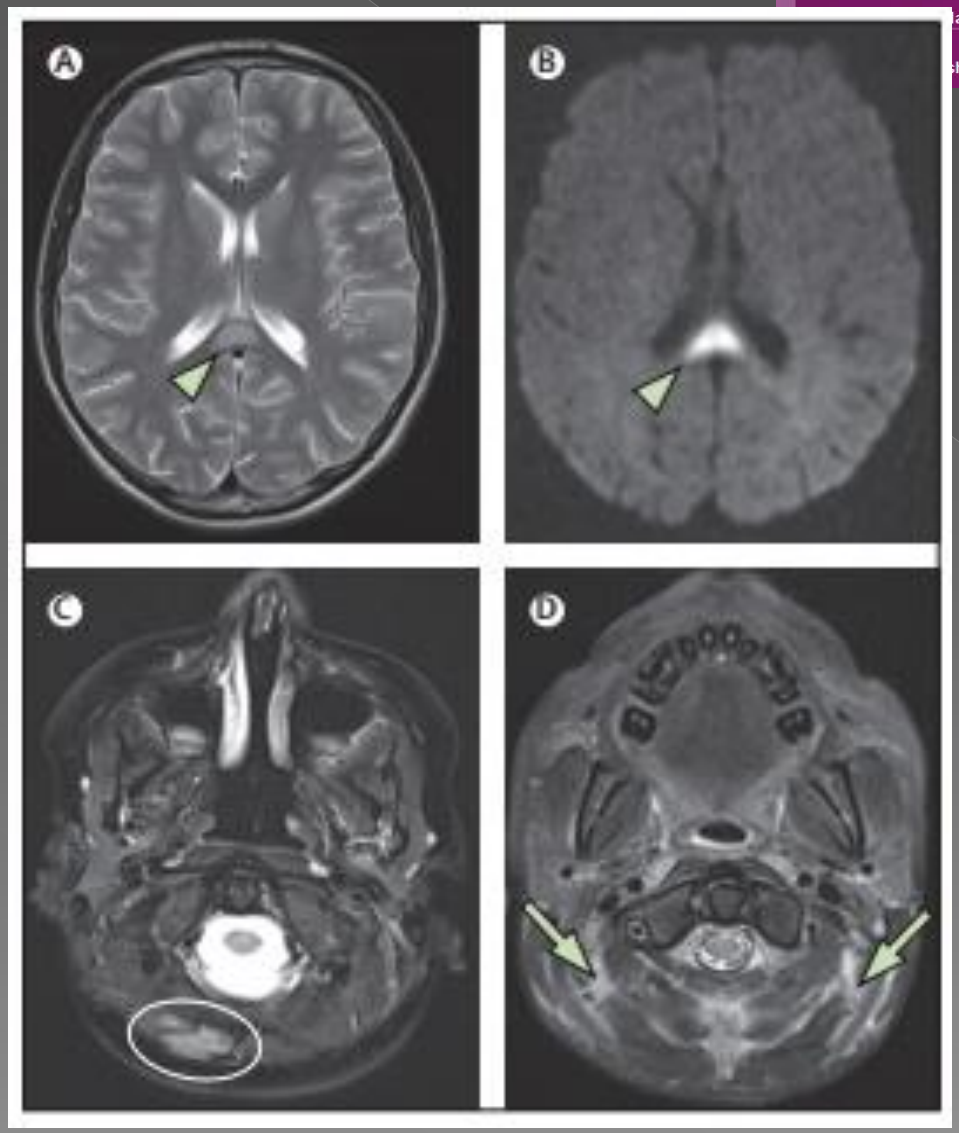


Figure 6: Myositis and splenial lesions

(A) Axial T2-weighted image in a 14-year-old boy (case 26) with the classic appearance of a splenial lesion (arrowhead) in post-COVID-19 MIS-C. This lesion showed reduced diffusion at presentation (arrowhead), as shown by the diffusion trace image in the same patient (B). Four patients with MIS-C were also noted to have myositis, which could be focal (C; oval), as seen in an 8-year-old boy (case 28), or diffuse (D; arrows), as seen in a 9-year-old boy (case 23) on axial T2-weighted fat-saturated images. MIS-C=multisystem inflammatory syndrome in children.

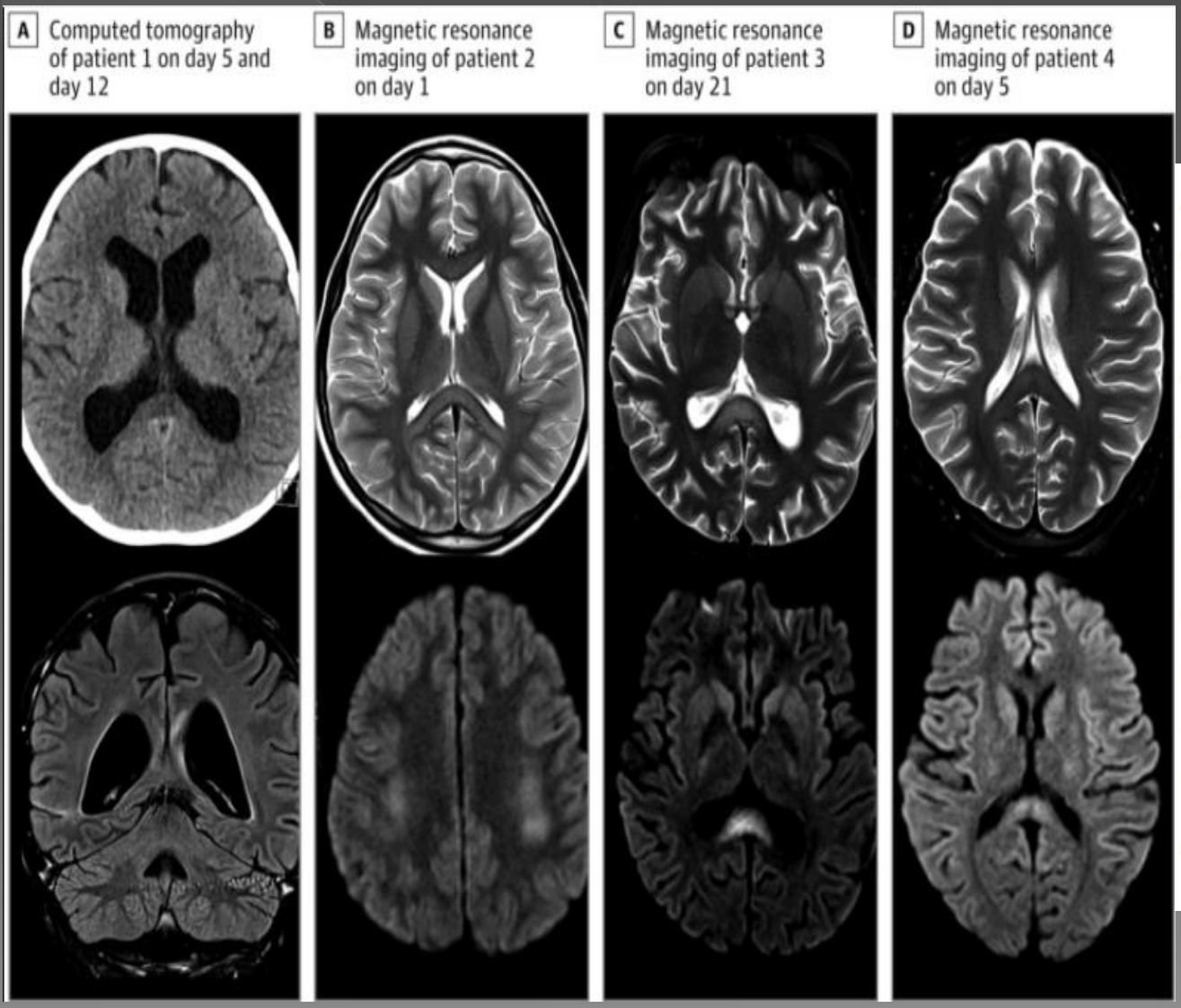
COVID-19 Children

Abdel-Mannan, et al (July 2020) Neurologic and Radiologic Findings Associated with COVID-19 Infection in Children, *JAMA Neurol.* 2020;77(11):1440-1445.

- 27 children with MIS
- 4 with neurologic symptoms in ICU (8,9,15 yrs)
- Encephalopathy, headaches, brainstem and cerebellar signs, weakness, ↓ DTRs
- **CSF**- 2 patients: no COVID or oligoclonal bands
- **EEG**- 3 patients: mild excess slowing
- **EMG**- 3 patients: mild myo/neuropathic changes
- NMDA, MOG, aquaporin-4 - negative

COVID-19: Splenial lesions

Abdel-Mannan, et al (July 2020) Neurologic and Radiologic Findings Associated with COVID-19 Infection in Children, *JAMA Neurol.* 2020;77(11):1440-1445.



A, Computed tomography image of patient 1 on day 5 (top), during intensive care admission, showing hypodensity of the splenium of the corpus collosum (SCC). Coronal fluid-attenuated inversion recovery performed on day 12 (bottom) shows resolution of the changes previously seen on computed tomography, with persistent signal changes in the genu and SCC without restricted diffusion (not shown). B, Axial T2 magnetic resonance image of patient 2 on day 1, showing signal changes of the genu and SCC (top) and bilateral centrum semiovale with restricted diffusion (bottom). Repeated imaging on day 6 (not shown) demonstrated resolution of the restricted diffusion, with minimal signal changes remaining on T2-weighted imaging. C, Axial T2 magnetic resonance imaging of patient 3 on day 21, showing hyperintensities (top) with restricted diffusion (bottom) in the SCC and bilateral centrum semiovale (not shown). D, Axial T2 magnetic resonance imaging of patient 4 on day 5 (top), showing signal change in the SCC with mild restricted diffusion (bottom).

COVID-19

Lin, J et al (Nov2020) Cytotoxic Lesion Of the CC in and Adolescent with MIS and SARS-CoV-2 Infection, AJNR AM J Neuroradiol 41:2017-19

- Case study 13 yo female
- Fever, diarrhea, cough, N/V, dizzy, unstable gait
- Hypotension, nml WBC, ↑neutrophils, ↓lymphocytes, thrombocytopenia, hyponatremia, ↑LFTs, ↑CRP,↑ ESR,↑BNP,↑troponin
- Infectious disease WU was negative blood/CSF
- Covid PCR - day1, + day 2 CSF and day 3 PCR
- **Dxed MIS-C and SARS-CoV-2**
- **Txed with IVIG, CTX, vancomycin and improved**
- **They initially thought this was Kawasaki disease**

COVID-19

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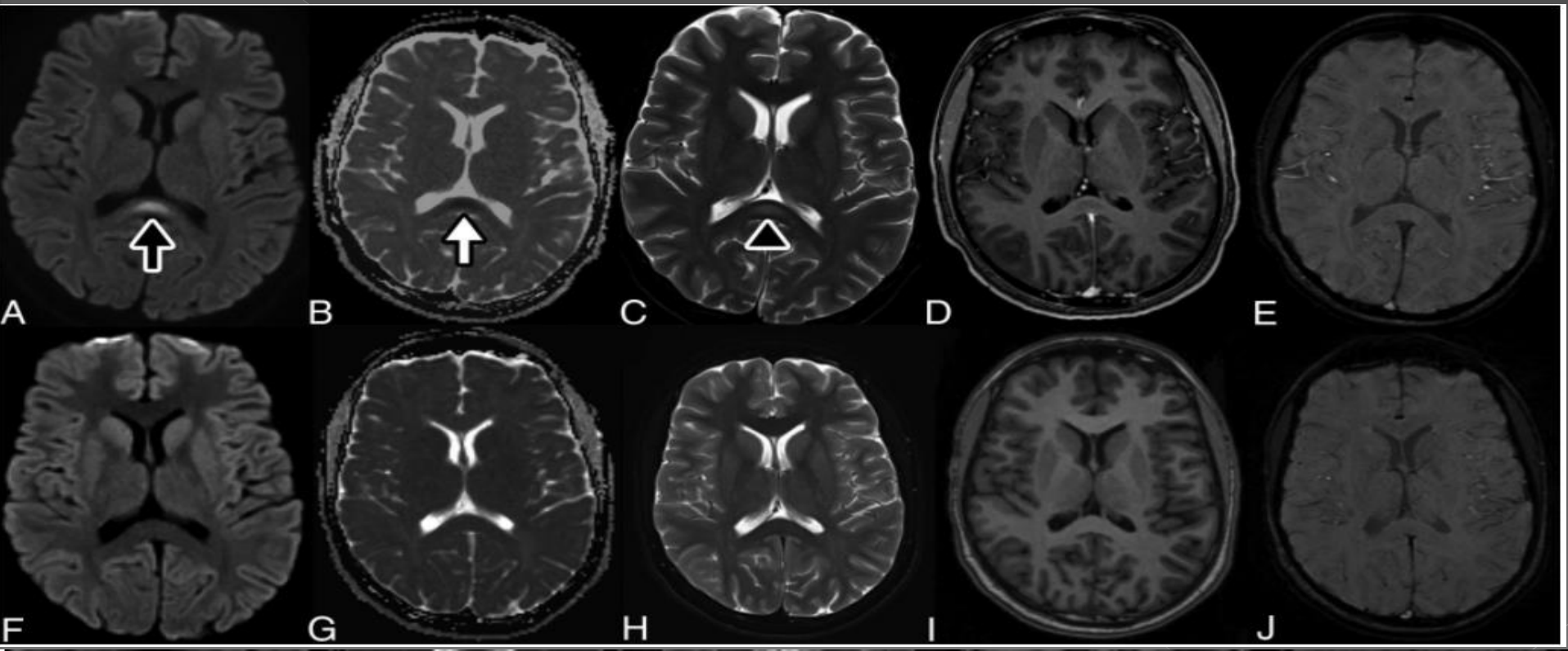

CLOCC in an adolescent with MIS-C and SARS-CoV-2.. MR image of the brain demonstrates a nonspecific focus of increased signal in the splenium of the corpus callosum on DWI sequences at *b*=1000 s/mm^2 (*black arrow, A*) with associated loss of signal on apparent diffusion coefficient maps (*white arrow, B*) corresponding to restricted diffusion. The apparent diffusion coefficient for the lesion is 0.44×10^{-3} mm^2/s. This lesion corresponds to a faint focus of abnormal increased signal on T2WI spin-echo sequences (*black arrowhead, C*). The lesion also demonstrates a lack of contrast enhancement on T1WI postcontrast thin-section image (*D*) and absent susceptibility, suggesting absent hemorrhage on SWI (*E*). The imaging findings suggest a cytotoxic lesion of the corpus callosum. Follow-up DWI (*F*) and ADC maps (*G*) with T2WI (*H*), T1WI (*I*), and SWI sequences (*J*) after 2.5 months demonstrate resolution of the lesion after therapy.

COVID-19

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Cytotoxic Lesions of the Corpus Callosum (CLOCC) -

- Can be seen with infection, toxins, nutritional deficiencies, and Kawasaki disease.
- In Kawasaki = hyper-inflammation→ macrophages →cytokines →T cells recruited →breakdown BBB → CC vulnerable due to high cytokine and glutamate receptors.
- Causes cognitive changes, weakness, seizures and hallucinations

COVID-19 Children

Hameed, S et al (Jun2020 accepted) Spectrum of Imaging findings at …in MIS in Children with COVID-19 Infection, radiology 2021;298:E1-E10

Study of 35 Children with MIS, evaluating ALL imaging findings-

- CXR, US, CT and MRI of multiple systems, evaluated.
- Neurologic imaging of 6 children (16%) underwent brain imaging. CT head (4) and MRI (3), both (1).
- Only one was abnormal CT= large ACA and MCA infarct in a child that had been on ECMO for 24 hrs.

COVID-19: Neonatal

Jain, P et al (June2020) Manifestations in Neonates Born to COVID-19 Positive Mothers Indian J Pediatr, 5:1

Case series: 2 babies born to COVID + mothers

Case 1:

- Pre-op **COVID found +** after delivery for mom
- Mother asymptomatic
- Female baby 18 hrs old **– COVID** with no symptoms

Case 2:

- C-section for fetal distress/meconium, mom COVID +
- Resuscitation, ventilation, Abn CXR opacities, metabolic acidosis, severe thrombocytopenia, sterile blood cx
- Baby developed shock and seizures
- Neuro exam dec tone and DTRs
- **MRI: restricted diffusion in periventricular deep WM in frontal and parietal lobes, with subdural hemorrhage**
- PCR COVID day 3, 5, 8 negative, discharged day 12

COVID-19: Pre and postnatal

Analysis of SARS-CoV-2 vertical transmission during pregnancy

Claudio Fenizia, Mara Biasin, Irene Cetin, Patrizia Vergani, Davide Mileto, Arsenio Spinillo, Maria Rita Gismondo, Francesca Perotti, Clelia Callegari, Alessandro Mancon, Selene Cammarata, Ilaria Beretta, Manuela Nebuloni, Daria Trabattoni, Mario Clerici & Valeria Savasi

Nature Communications **11**, Article number: 5128 (2020) | Cite this article

- Report 30 COVID positive mothers at delivery

Table 4 Summary of maternal and foetal SARS-CoV-2 genome (a) and anti-SARS-CoV-2 antibody (b) detection.

From: Analysis of SARS-CoV-2 vertical transmission during pregnancy

(a)	Maternal plasma (*n* = 30)	Vaginal swab (*n* = 31)	Placenta (*n* = 31)	Umbilical cord plasma (*n* = 30)	Umbilical cord (*n* = 12)	Amniotic fluid (*n* = 6)	Milk (*n* = 11)
Pos, % (*n*)	6.7 (2)	3.2 (1)	6.4 (2)	3.3 (1)	0 (0)	0 (0)	9.1 (1)

(b)	Maternal plasma (*n* = 30)	Umbilical cord plasma (*n* = 30)	Milk (*n* = 10)
IgM, % (*n*)	32.1 (9)	3.3 (1)	10 (1)
IgG, % (*n*)	63.3 (19)	40.0 (12)	0 (0)
IgM/IgG, % (*n*)	32.1 (9)	3.3 (1)	0 (0)

COVID-19: Pre and postnatal

Analysis of SARS-CoV-2 vertical transmission during pregnancy

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in maternal and umbilical cord plasma. We detect SARS-CoV-2 genome in one umbilical cord blood and in two at-term placentas, in one vaginal mucosa and in one milk specimen. Furthermore, we report the presence of specific anti-SARS-CoV-2 IgM and IgG antibodies in one umbilical cord blood and in one milk specimen. Finally, in the three documented cases of vertical transmission, SARS-CoV-2 infection was accompanied by a strong inflammatory response. Together, these data support the hypothesis that in utero SARS-CoV-2 vertical transmission, while low, is possible. These results might help defining proper obstetric management of COVID-19 pregnant women, or putative indications for mode and timing of delivery.

Therefore close monitoring of these children and possibly considering neuroimaging studies on these children if necessary is a consideration.

COVID-19: Neonatal

Stafstrom and Jantzie (Sept 2020) Covid -19: Neurologic Considerations in Neonates and Children, *Children*, 7, 133 (accepted July 2020)
Zimmer, et al (Jan 2021) Prenatal exposure to viral infection and neuropsychiatric ….for the COVID pandemic Brain, Behavior and Immunity vol 91, Jan 2021, p 756-70

Possible neurotropism of SARs-CoV-2

- Studies show 36 to 84% with neurologic symptoms
- 2 case reports of persistent hypometabolism in olfactory gyrus and other brain regions on 18F-FDG PET
- Several hypotheses for neuroinvasion (cytokines permeable BBB, hypoxic edema, ACE-2 through lungs, BBB, bleed, or binding to olfactory epithelium (neuropilin-1 receptor)

COVID-19: Neonatal

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SARs-CoV-2 in pregnancy

- 25,351 pregnant women positive (Oct 8, 2020)
- 55 pregnant, infected pts 9% IUGR
- Maternal SARS-CoV-2 infections seems to be less severe than SARS-CoV-1 or MERS
- There are mixed studies on possible increased preterm births
- Concerns about C-section with infected mothers, 1.6 -5% with + RT PCR babies.
- There is no literature about the sensitivity or specificity for nasal swabs in neonates.

COVID-19: Compare to adult

Klironomos, S et al Nervous System Involvement in Coronavirus 2019… Radiology 2020; 297:E324-34

- 185 adults with Covid-19 =(mean 62 yrs, 138 male)
- Ct brain =222, MRI brain= 47, MRI spinal =7
- Central and Peripheral involvement
- Intra-axial susceptibility 74%
- MRI – ovoid shape with c/w microvascular with predilection for CC 59%
- Juxtacortical lesions 36%
- Leukoencephalopathy 44%
- Cytotoxic lesion CC 1 person
- Olfactory bulb abnormal 19%
- Optic nerve subarachnoid spaces enlarged 56%
- Enhanced – parenchyma 15%
  leptomeninges 15%
  CN 10%
  spinal nerves 50%

COVID-19: Compare to Zika Virus

Pool, K et al Association between neuroimaging and clinical outcomes… Jama July 31, 2019; 2(7)

- 110 infants (gest age 38.4 weeks)
- 71 (65%) abnormal neuroimaging
- 96% severe Zika infection at birth/10% not
- Intra-axial susceptibility 74%

classified as having severe ZIKV infection at birth. The most common neuroimaging abnormalities were structural abnormalities including brain calcifications, especially at the cortico-subcortical white matter junction, cortex malformations, ventriculomegaly, and reduced brain volumes, followed by brainstem hypoplasia, cerebellar hypoplasia, and corpus callosum abnormalities. Frequency of abnormal imaging was higher in infants with specific clinical findings as opposed to those without them; these findings included fetal brain disruption sequence (100% vs 35%), microcephaly (100% vs 30%), congenital contractures (100% vs 58%), ophthalmologic abnormalities (95% vs 44%), hearing abnormalities (100% vs 58%), and neurologic symptoms (94% vs 10%). Four of 39 infants (10%) without initial evidence of severe ZIKV infection and normal findings on neurologic evaluation at birth had abnormal neuroimaging findings. Neuroimaging abnormalities differed by trimester of maternal ZIKV infection, with 63% of infants born to mothers infected in the first trimester, 13% of infants born to mothers infected in the second trimester, and 1% of infants born to mothers infected in the third trimester exhibiting neuroimaging abnormalities. The odds of abnormal neuroimaging were 7.9 times greater for infants with first trimester ZIKV exposure compared with other trimesters combined (odds ratio, 7.9; 95% CI, 3.0-20.4; $P < .001$).

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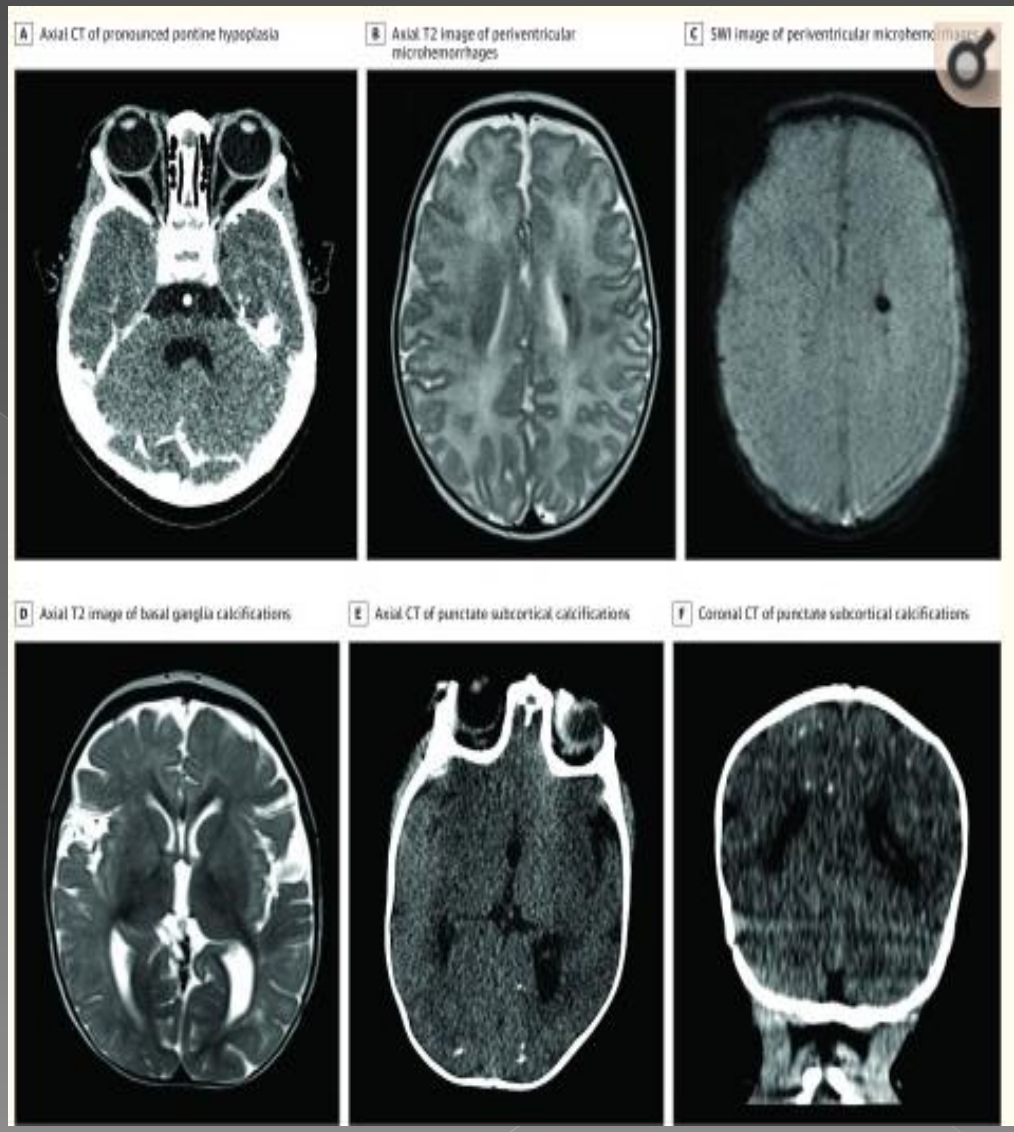
Abnormal Neuroimaging Findings in Infants Who Were Asymptomatic, Had Mild to Moderate Zika Virus Infection at Birth, or Had Normal Neurologic Evaluation Findings at Birth

A, Axial contrast-enhanced computed tomography (CT) image through the brainstem demonstrates pronounced pontine hypoplasia. B, Axial T2 image demonstrates punctate susceptibility artifact along the margin of the left lateral ventricle consistent with periventricular microhemorrhages. C, Susceptibility-weighted image (SWI) demonstrates punctate susceptibility artifact along the margin of the left lateral ventricle consistent with periventricular microhemorrhages. D, Axial T2 image demonstrates punctate susceptibility artifact in the bilateral basal ganglia consistent with basal ganglia calcifications. E, Axial CT without contrast demonstrates punctate subcortical calcifications in the occipital lobes. F, Coronal CT without contrast demonstrates multiple punctate subcortical calcifications as well as a punctate periventricular calcification along the superior margin of the right lateral ventricle.



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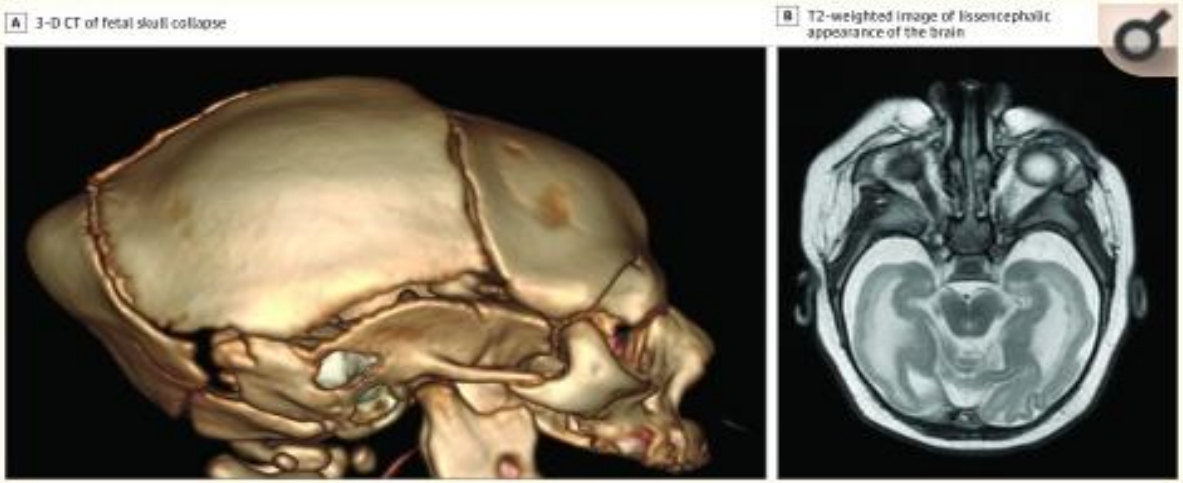

Figure 2.

Neuroimaging Findings of an Infant With Severe Zika Virus

A, Three-dimensional (3-D) computed tomography (CT) reconstruction demonstrates classic phenotypic pattern of fetal skull collapse with overlapping cranial sutures and prominent occipital protrusion. B, T2-weighted imaging demonstrates simplified gyral pattern with a lissencephalic appearance of the brain.

- **80% adult infections are asymptomatic but increase microcephaly in infants**
- **Flavavirus – single strand RNA, transmitted through body fluids**

COVID-19

- There is a paucity of comprehensive neuroimaging in pediatric patients and neonates with Covid-19.
- More coordinated large scale research studies need to be done to help us to understand who to scan, who is at risk, and how and when transmission occurs.
- Many of these studies shown were submitted in June or July – not published until October and Decmber 2020.

Questions ???
Thank you