PANDA webinar 2021

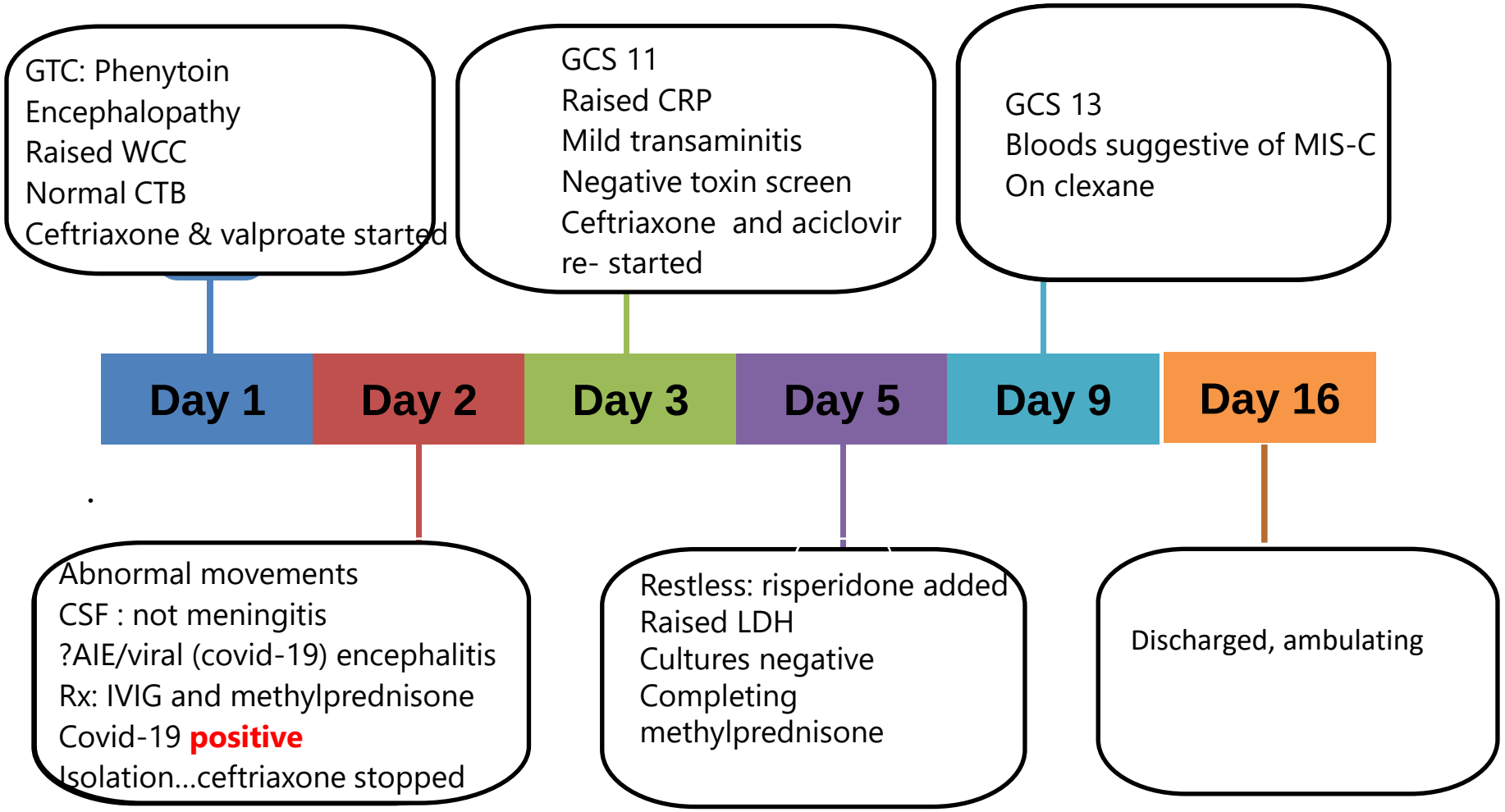
Phindile Mteshana

Vignette 1: Choreo-athethosis and dystonia

- 9-yr old
  - Status epilepticus…1st onset GTC for 15min
  - Preceding headache and fever
  - On admission electrolytes, LP, CTB were normal and covid swab was done.
  - Day 2: dystonia, choreo-athetosis, encephalopathy
  - Treated with IVIG and HD steroids as suspected AIE
  - CSF: No oligoclonal bands, insufficient sample for NMDAR

Patient's timeline

Progress since admission



Vignette 2: Acute Weakness

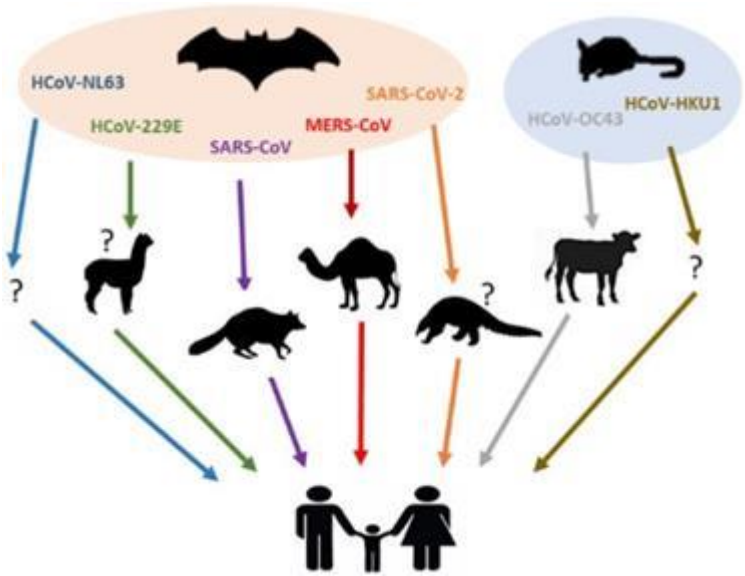
- 12 year old
  - Three day history of intermittent LL weakness
  - Associated cramps, painful knees and shoulders
  - Preceded by 2-day history of GE
  - Hypotonic, areflexic,
  - Power: weaker proximally > distally in both UL and LL
  - Differential Dx = myositis , GBS

  - Results – CSF protein 0.7
    CK 7 134
    COVID 19 positive

Diagnosis acute myositis 2ndry SARS-CoV-2


#ALIVE
As a grisly virus rampages a city, a lone man stays locked inside his apartment, digitally cut off from seeking help and desperate to find a way out.

Neurological manifestations of COVID-19



Objective

- Postulate on possible mechanisms based on current evidence and what we know from other infections
- Gain clarity on neurological manifestations of COVID
- Touch on management and prognosis

Introduction

- SARS-CoV-2 was first reported in December 2019 in Wuhan, China, and has become a global pandemic
- The first reported case in South Africa was on the 5th of March 2020
- In late April 2020, an alert about the multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 was made
- This syndrome is characterised by fever, inflammation, evidence of multi-organ involvement
- Although COVID-19 is considered to be primarily a respiratory disease, SARS-CoV-2 affects multiple organ systems including the central nervous system (CNS)
- Central nervous system manifestations are reported between 25 and 57% with less frequent symptoms of neuropathy and **musculoskeletal** signs
- Some of the earliest symptoms of COVID-19 infection include anosmia, indicating potential central nervous system involvement
- However, SARS-CoV-2 detection in the cerebrospinal fluid has been limited to a few case reports

Toklu et al. Intern Journ of Emerg Med 2020
Guan WJ, Journal of Child Neurology 2019

Neurological manifestations of COVID-19

- In adults: well studied
- Severe CNS injury in children with COVID-19 is rarely reported
- Usually associated with multisystem inflammatory syndrome in children (MIS-C), also known as paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS)
- Thought to be an inflammatory process during the latent period of the disease
- Multicenter study in the US; 5% of MIS-C cases had associated severe neurological complications this was even higher in a UK study at 14%

Camilla E Lindan, Lancet Child Adolesc Health 2020

Neurological disease associated with COVID-19

Para-infectious manifestations

- Anosmia
- Myalgia/myositis
- Encephalopathy
- Stroke
- Meningitis
- Encephalitis
- Seizures
- Central hypoventilation
- Sensory neuropathy

Post-viral syndromes

- ADEM
- Acute necrotizing haemorrhagic encephalopathy
- Transverse myelitis
- Gullian Barre syndrome
- Acute polyradiculoneuritis
- MIS-C
- Chronic fatigue syndrome

Nath, neurology 2020

Neurological manifestations of COVID-19 and their mechanisms

ANNALS *of Neurology*

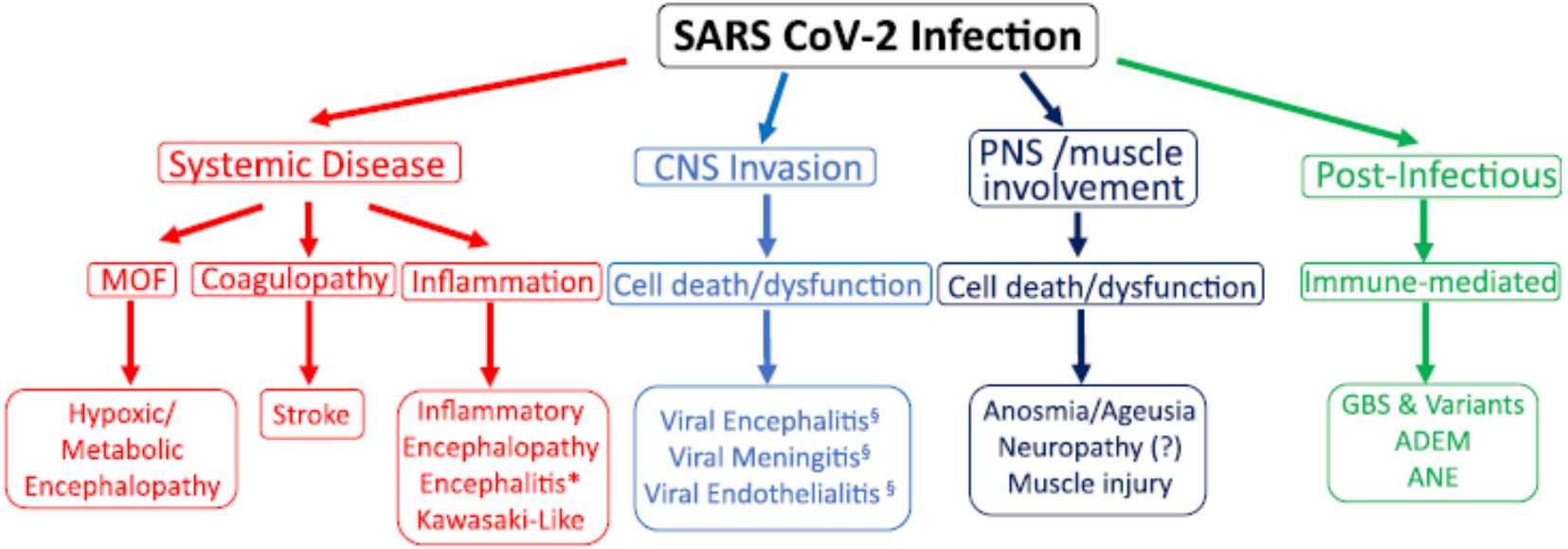


FIGURE: Mechanisms of severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) neuropathogenesis. SARS-CoV-2 pathogenic effects on the nervous system are likely multifactorial, including manifestations of systemic disease, direct neuro-invasion of the central nervous system (CNS), involvement of the peripheral nervous system (PNS) and muscle, as well as through a postinfectious, immune-mediated mechanism. MOF = multi-organ failure; GBS = Guillain-Barre syndrome. *CNS inflammation (CSF pleocytosis and proteinorrachia) with no evidence of direct viral infection of CNS; §direct evidence of viral invasion (reverse transcriptase-polymerase chain reaction positive [RT-PCR+], biopsy); ADEM = acute disseminated encephalomyelitis; ANE = acute necrotizing encephalopathy. [Color figure can be viewed at www.annalsofneurology.org]

Igor.J. Koralnik et.al, Ann Neurol 2020
Otávio Melo Espíndola et.al, International Journal of Infectious Diseases 2021

Mechanisms…

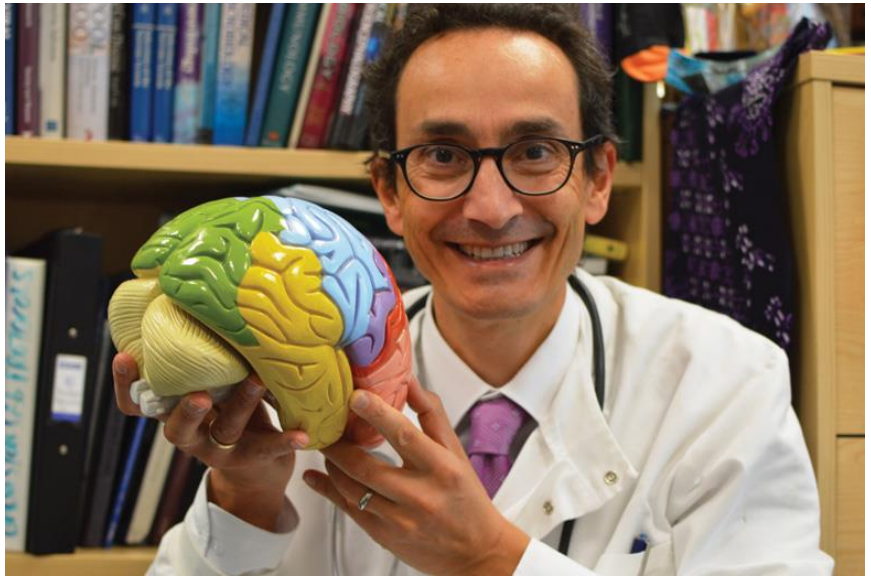
- Two cell membrane proteins are major targets for SARS-CoV-2 invasion
  - Angiotensin-converting enzyme 2 (ACE- 2)
  - Transmembrane protease, serine 2 (TMPRSS2)
- Animal models have shown expression on both glial and neuronal cells with transcriptomics in humans confirming low but consistent expression in different parts of the brain

- 3 major mechanisms
  - Systemic Inflammatory response
  - Prothrombotic state
  - Direct viral infection

Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Sylviane Defres, Jim Sejvar, Tom Solomon

1. Systemic Inflammatory response
2. Prothrombotic state
3. Direct viral infection



Neurocrit Care
https://doi.org/10.1007/s12028-020-01049-4

NEUROCRITICAL CARE SOCIETY

REVIEW ARTICLE

Neurological Involvement in COVID-19 and Potential Mechanisms: A Review

Ghazal Aghagoli[1*], Benjamin Gallo Marin[1], Nicole J. Katchur[7], Franz Chaves-Sell[10,11], Wael F. Asaad[1,2,3,4,5,6] and Sarah A. Murphy[8,9]

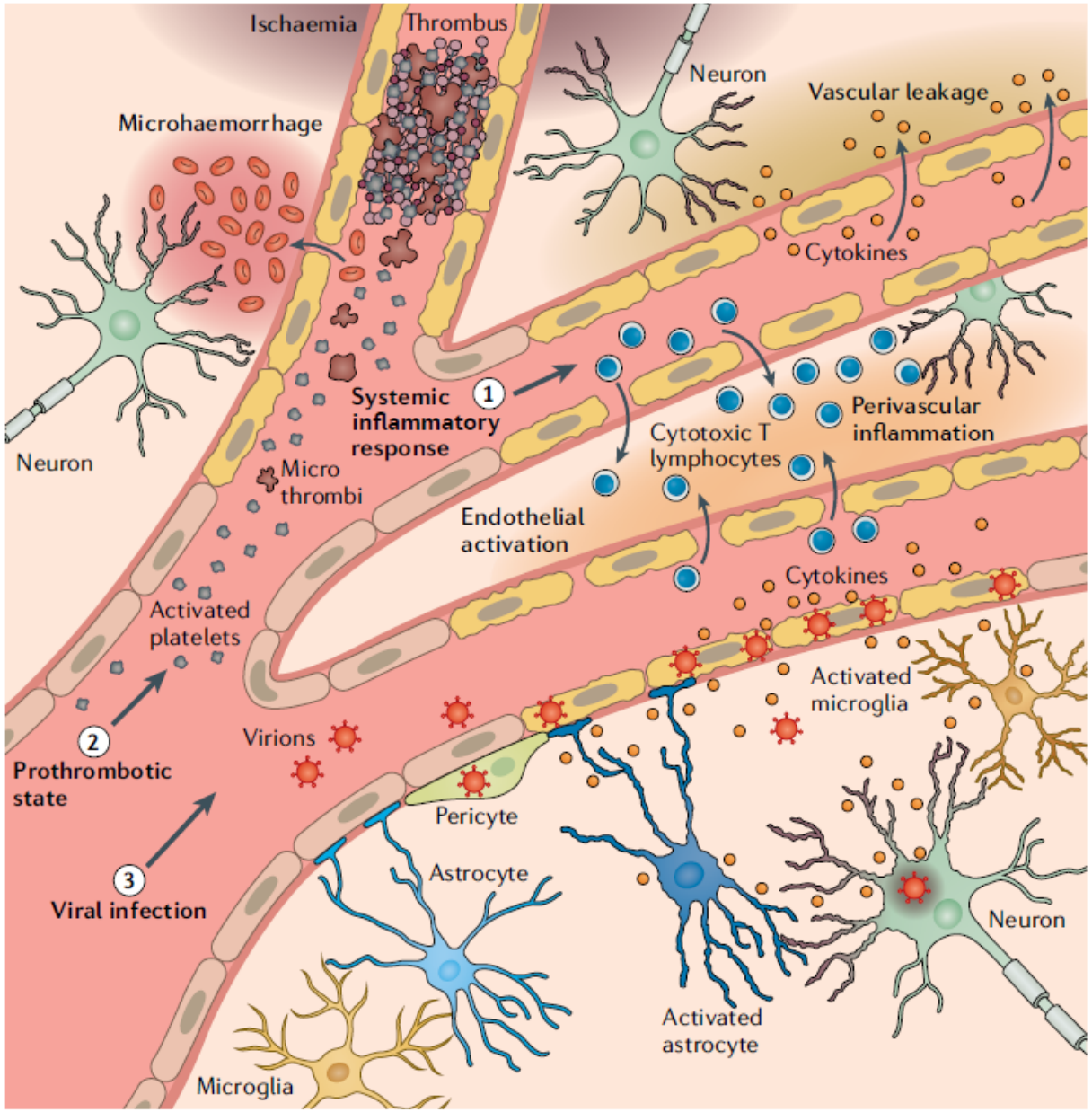
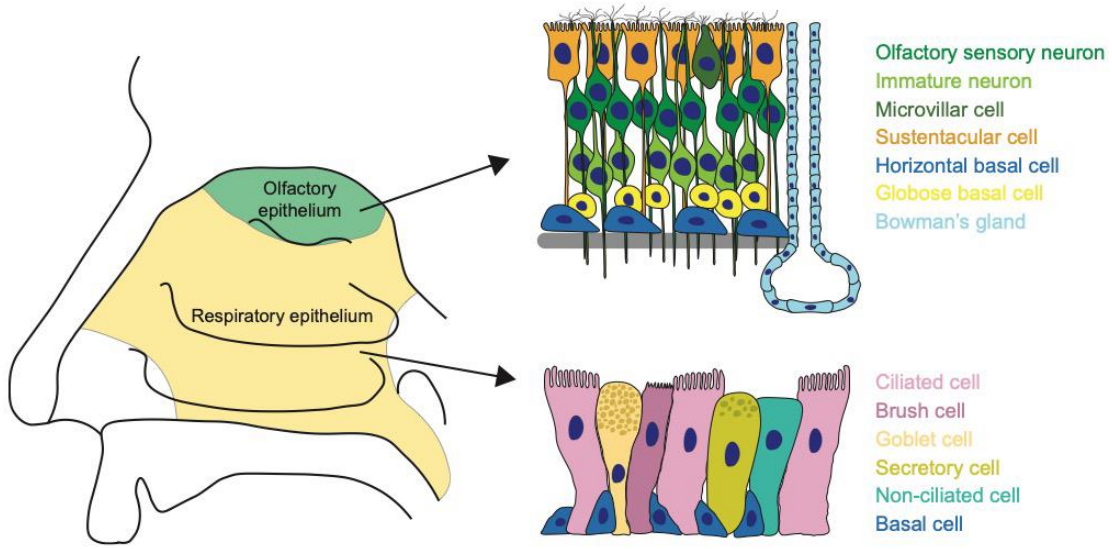


Fig. 1 | **Current understanding of predominant COVID-19 neurological disease mechanisms.** Mechanisms include a systemic inflammatory response (1), a prothrombotic state (2) and direct viral invasion (3).

Tom Solomon, Nature reviews neurology 2020

COVID-19 without MIS-C: Anosmia

- The earliest and most commonly reported
- **Olfactory sensory neurons (OSNs)** are responsible both for detecting odours in the nasal airspace, and for transmitting information about odours to the brain
- In both mouse and human **OSNs** do not express two key genes required for CoV-2 entry, ACE2 and TMPRSS2
- In contrast, olfactory epithelial support (non- neuronal) cells and stem cells express both of these genes, as do cells in the nasal respiratory epithelium
    - Horizontal basal cells
    - Substentacular cells
    - Bowman's glands cells
- Indirect effect
    - Affecting the function of the supporting cells
    - Inflammatory cytokines
    - Water and ion balance



Brann et.al, Sci Adv 2020
Igor.J. Koralnik et.al, Ann Neurol 2020

COVID-19 with MIS-C: Strokes

- COVID-19 patients are at a much higher risk to suffer stroke (7-fold), and 2-6% progress to cerebrovascular disease (Fifi and Mocco, Lancet neurology 2020)
- Viral infections activate coagulation, haemostasis and inflammation
    - Risk of stroke increases by **2.9** following hospitalization with flu like symptoms

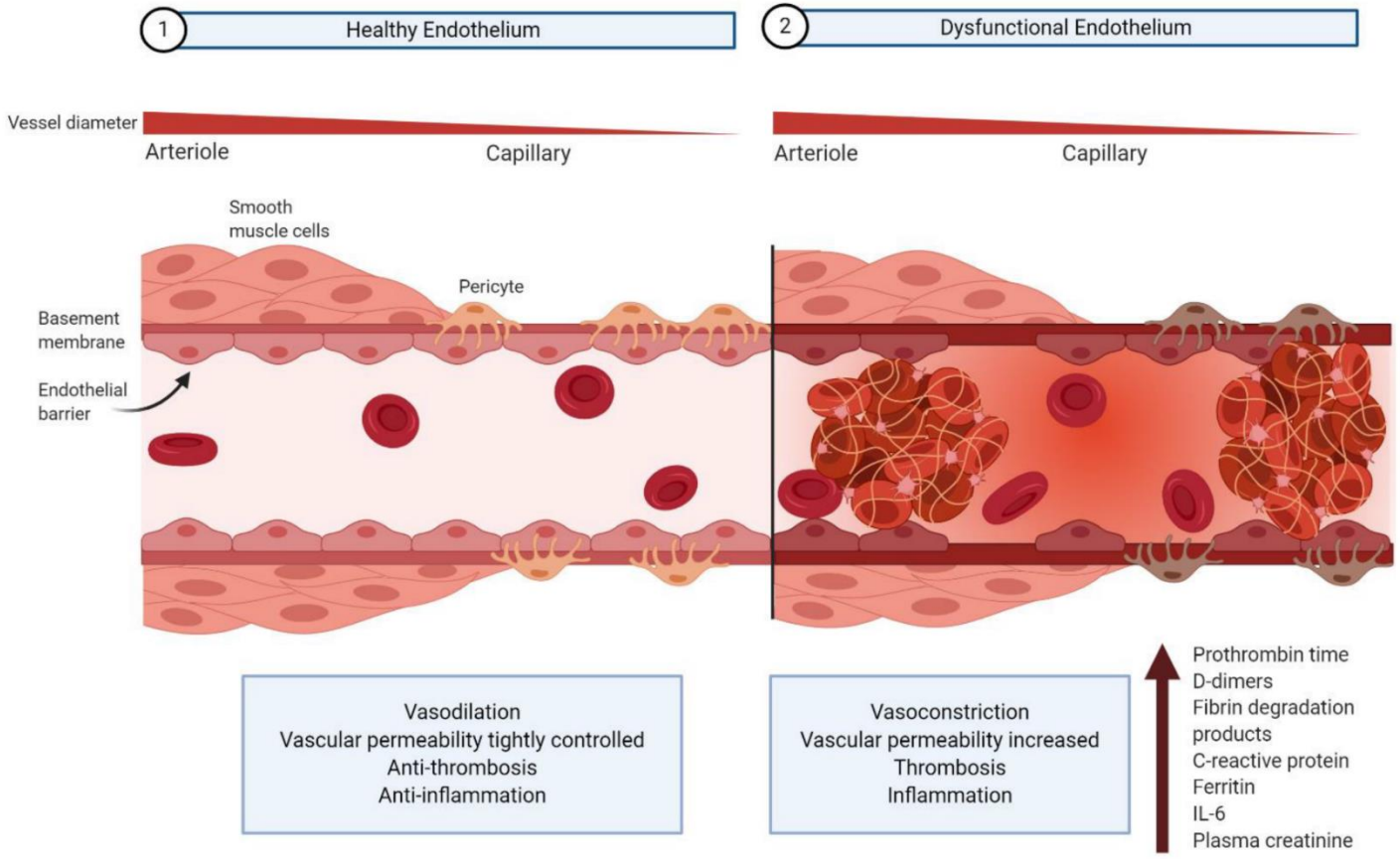
	Influenza Vaccination (N=19,063)		Tetanus Vaccination (N=6155)		Pneumococcal Vaccination (N=4416)		Systemic Respiratory Tract Infection (N=22,400)		Urinary Tract Infection (N=14,603)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Stroke										
1– 3 days	76	0.77 (0.61–0.96)	11	1.33 (0.74–2.41)	9	1.29 (0.67–2.49)	244	3.19 (2.81–3.62)	152	2.72 (2.32–3.20)
4–7 days	95	0.72 (0.59–0.88)	15	1.36 (0.82–2.26)	10	1.08 (0.58–2.01)	237	2.34 (2.05–2.66)	158	2.12 (1.81–2.48)
8–14 days	194	0.84 (0.73–0.96)	15	0.77 (0.46–1.28)	19	1.18 (0.75–1.85)	368	2.09 (1.89–2.32)	245	1.89 (1.65–2.13)
15–28 days	409	0.88 (0.80–0.97)	40	1.02 (0.74–1.39)	29	0.90 (0.63–1.30)	561	1.68 (1.54–1.82)	445	1.71 (1.55–1.88)
29–91 days	2,051	1.01 (0.96–1.06)	209	1.15 (1.00–1.32)	160	1.15 (0.98–1.35)	1,650	1.33 (1.26–1.40)	1,250	1.22 (1.15–1.30)
Baseline period	16,188	1.00	5853	1.00	4184	1.00	18,056	1.00	12,164	1.00

- Cerebrovascular complications in children are less common than in adults
- Most children have favourable outcomes

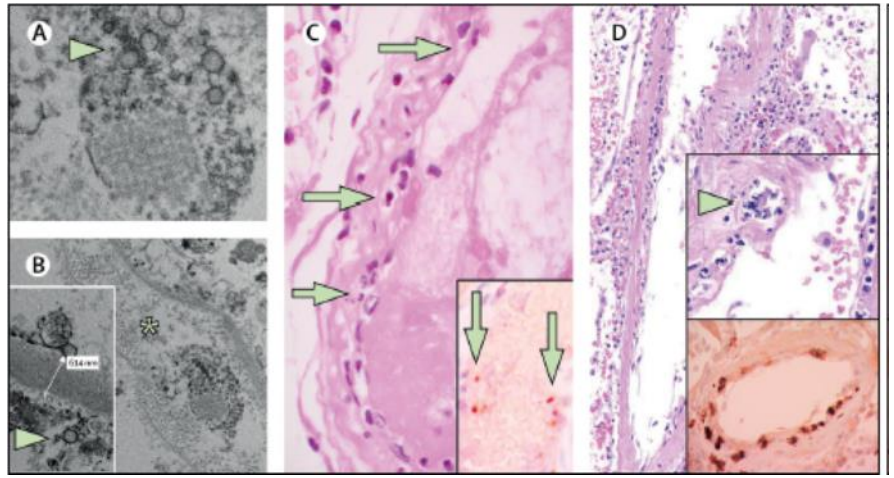
Smeeth et.al. NEJM 2004
Camilla E Lindan. Lancet Child Adolesc Health 2020

COVID-19 and Stroke

- **Endothelial cell dysfunction**: arterial and venous micro and macro-vascular complications
- **Vasculitis**: inflammation and leakage
- **Microthrombosis**→ capillary thrombosis



Bernard et.al. Viruses 2021



INFECTION OF THE ENDOTHELIUM

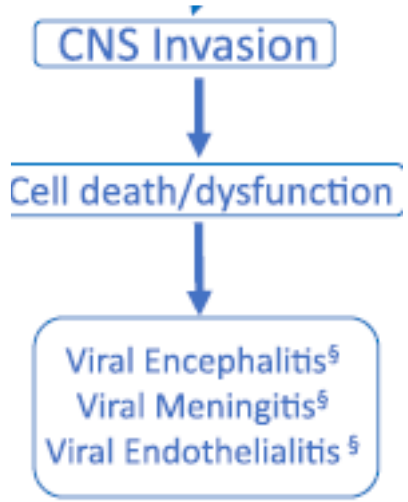
Varga et.al. Lancet 2020

Stroke and COVID-19

- Younger
- Asymptomatic of respiratory symptoms
- Large vessel stroke
- Later complication of COVID-19
- Burden of stroke in ICU is not uncommon
- Management: recognize COVID-19, anticoagulate

COVID-19 and Encephalopathy syndromes

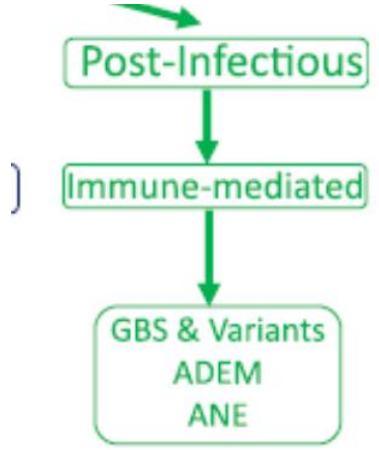
- More likely if
  - Severe COVID-19 disease: MIS-C
  - Comorbidities
- Micro- haemorrhage
- Hypoperfusion
- Systemic inflammatory response
  - Cytokine storm
- Increased permeability of BBB



Igor.J. Koralnik et.al, Ann Neurol 2020

N-Methyl-D-Aspartate Receptor Encephalitis Associated With COVID-19 Infection in a Toddler

Tyler Burr, DO [a], Christopher Barton, MD [a, b], Elizabeth Doll, MD [a, b], Arpita Lakhotia, MBBS [a, b], Michael Sweeney, MD [a, b, *]



- Anti-NMDAR encephalitis after viral infections have been reported
- Case report
  - Fever, seizures. A week later pt had abnormal movements and encephalopathy
  - CSF viral screen negative. MRI normal
  - OBs: negative
  - Autoantibody testing demonstrated NMDAR-IgG positivity in the serum (1:640) and CSF (1:40)
  - HD steroids and IVIG. Back to baseline two weeks after discharge

Detection of Coronavirus in the Central Nervous System of a Child With Acute Disseminated Encephalomyelitis

E. Ann Yeh, MD, MA*; Arlene Collins, PhD‡; Michael E. Cohen, MD*; Patricia K. Duffner, MD*; and Howard Faden, MD§

- Acute disseminated encephalomyelitis: immune cell mediated
- Acute haemorrhagic encephalomyelopathy: cytokine mediated

Neurological Sciences
https://doi.org/10.1007/s10072-020-04693-y

REVIEW ARTICLE

Guillain-Barre syndrome during COVID-19 pandemic: an overview of the reports

Kaveh Rahimi[1]

- GBS: Antibody mediated
- Review of **37** published cases of GBS associated with COVID-19
- Clinical presentation and severity of these cases was similar to those with non-COVID-19 GBS
- NCS: demyelinating in **half** of the cases
- CSF: albuminocytologic dissociation in **76%** of the patients and was negative for SARS-Cov-2
- Improvement after 8wks , single dose of IVIG

Rhabdomyolysis

Coronavirus Disease 2019-Induced Rhabdomyolysis

Sreenath Meegada [1], Vijayadershan Muppidi [2], Donald C. Wilkinson III [3], Suman Siddamreddy [4], Shravan K. Katta [5, 6]

- Viral myositis was a **major** cause of rhabdomyolysis
- The mechanism of rhabdomyolysis in COVID-19 is not clear, and various mechanisms have been postulated
  - **Immunological** mechanisms play an important role in muscle damage by cross-reactivity between the virus and myocytes
  - **Direct** invasion of the myocytes like other viral illness
  - Exaggerated immunological reaction resulting in **cytokine storm** can lead to muscle damage
- Muscle weakness and elevated serum CK levels were previously reported in coronavirus case series reported in the 2003 outbreak of SARS and the 2012 outbreak of Middle East respiratory syndrome (MERS)

N Lee et al. N Engl J Med 2003; R Zutt et al.Neuromuscul Disord 2014; R Mannix et.al, Pediatrics 2006; Nathalie Tram. PIDJ 2020

Investigations

- Detection of SARS-Cov-2 in the CSF is very rare
  - Handful of case reports
- Brazil: positive CSF PCR in a patient with demyelinating disease
- Japan and Ireland: virus RNA was **detected** in CSF but not in the nasopharyngeal swab taken from a patient with meningitis/encephalitis
- This is supported by lack of detection of SARS-Cov-2 in the brain at autopsy (one case reported)

- EEG: non-specific with the major finding being slowing

EH Miller et.al, OFID 2020

Tai-Heng Chen, Jour of Neur Sc 2020

Toklu et al, Intern Jour of Emerg Med 2020

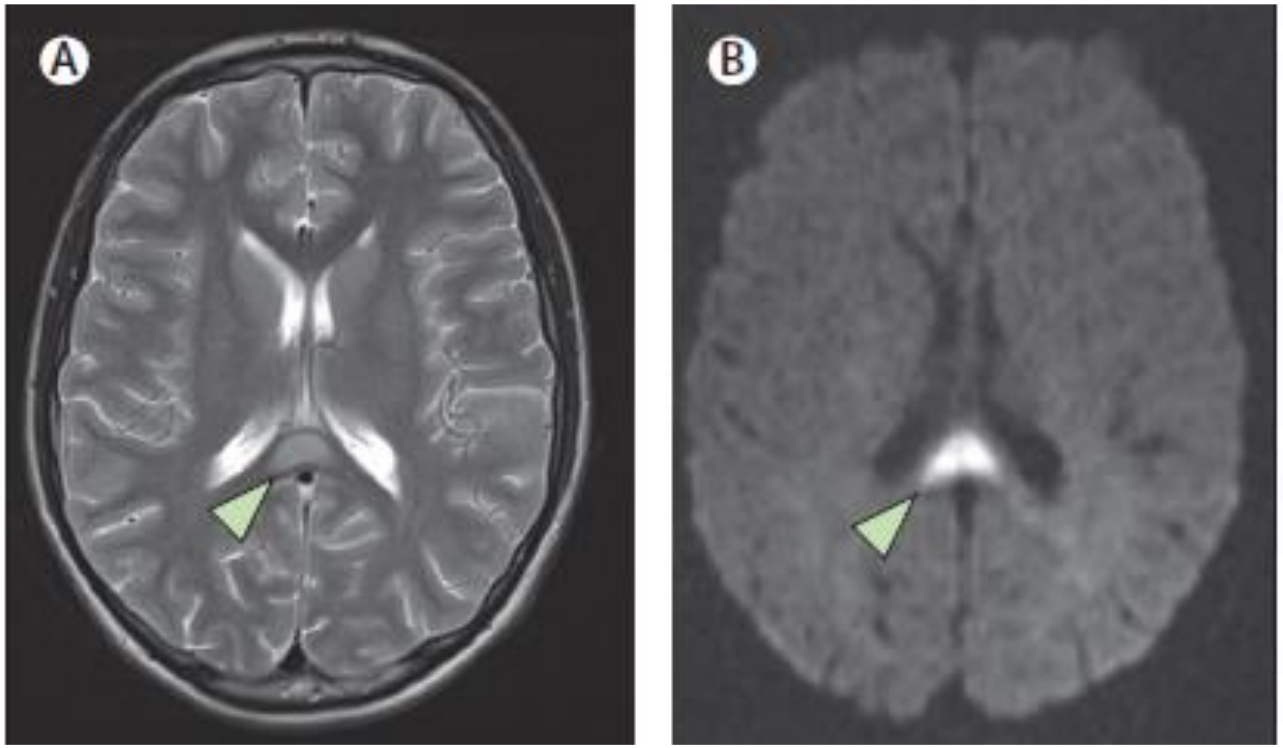
Neuroimaging manifestations in children

- The most prevalent neuroimaging manifestations observed in children resembled an immune-mediated para infectious pattern of disease involving the brain, spine, cranial nerves, and nerve roots
- Magnetic Resonance Imaging (MRI) has proved much more useful both in children and adults with encephalopathy, the most commonly reported finding is possibly reversible lesions in the splenium of the corpus callosum from inflammation induced focal intramyelin oedema
- Autoimmune manifestations
  - ADEM-like : most common
    - Anti-NMDAR, anti-MOG antibodies
  - Myelitis
    - Acute necrotising myelitis (2 cases, 1 child and 1 adult)
    - The most characteristic finding in ANE is the bilateral and symmetrical thalamus involvement with possible restricted diffusion or haemorrhage
  - Neuritis : cranial nerve involvement
- Vasculitic and thrombotic findings

Camilla E Lindan, Lancet Child Adolesc Health 2020
Tuma et al, Neurological Sciences 2021
Emily Happy Miller et.al, OFID 2020

Neuroimaging manifestations in children

- COVID-19 with MIS-C
- It has been postulated that these lesions represent intramyelinic oedema as a result of cytokine-mediated glutamate release



14 year old post COVID-19 MIS-C

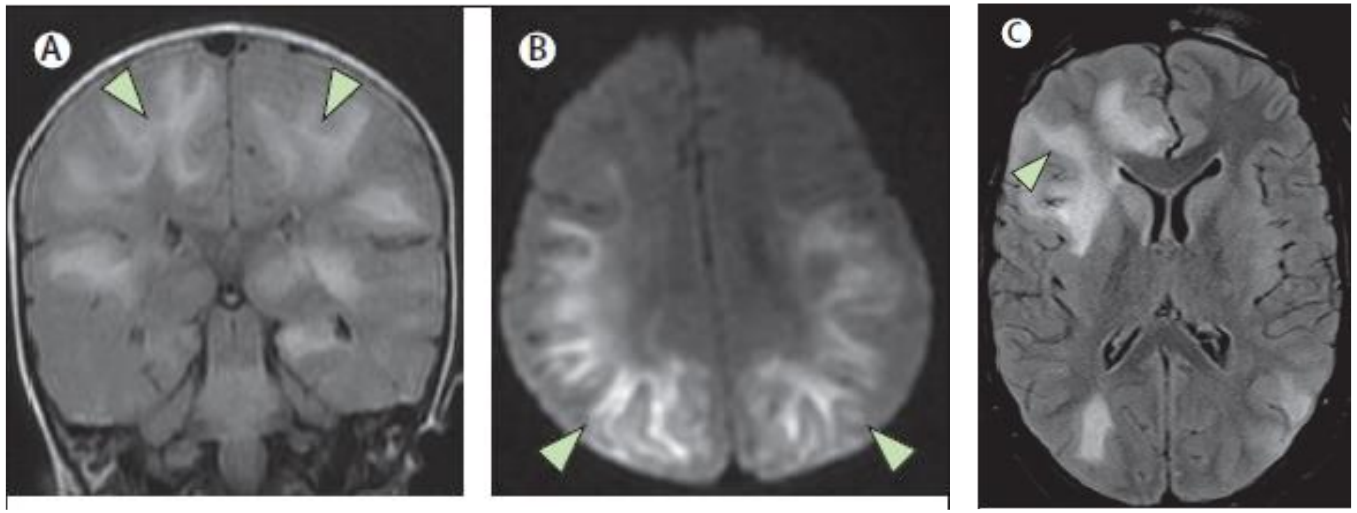
- Splenial lesions showing reduced diffusion

Camilla E Lindan Lancet Child Adolesc Health 2020

Neuroimaging manifestations in children

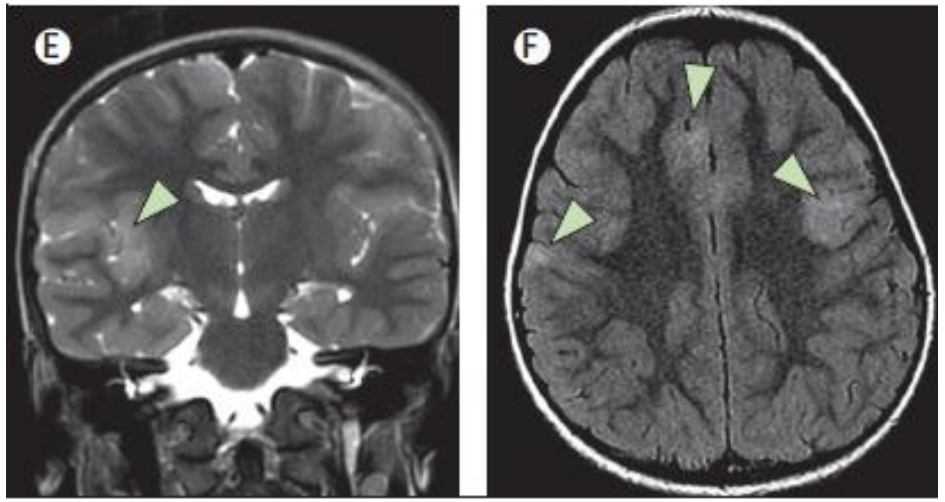
Autoimmune manifestations

ADEM-like



A 1-year-old boy with acute COVID-19

A. Confluent areas of high signal in the subcortical white matter
B. Reduced diffusion on DWI trace
C. Same as **A** with associated mass effect in the right frontal lobe



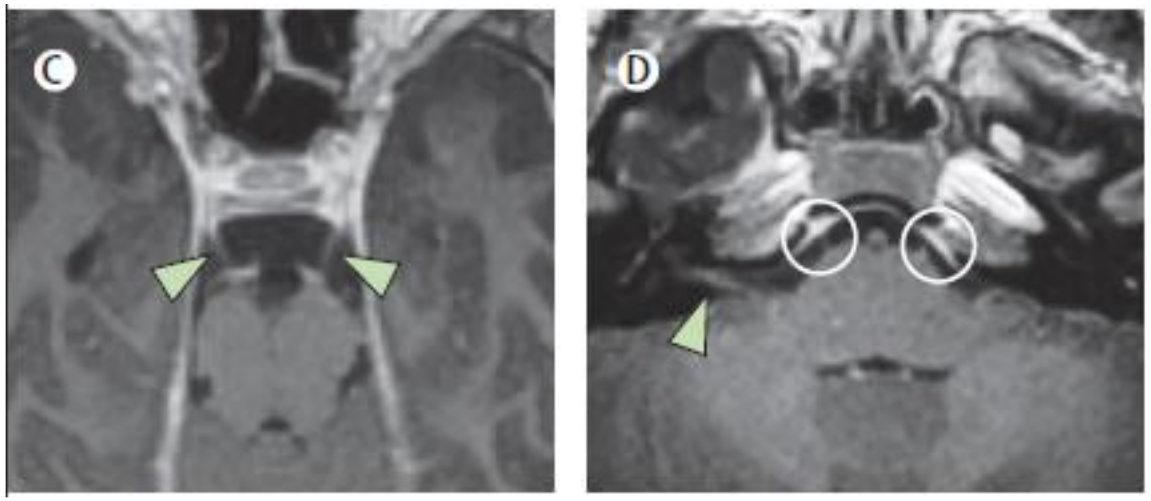
This child was positive for antibodies to **myelin oligodendrocyte glycoprotein**

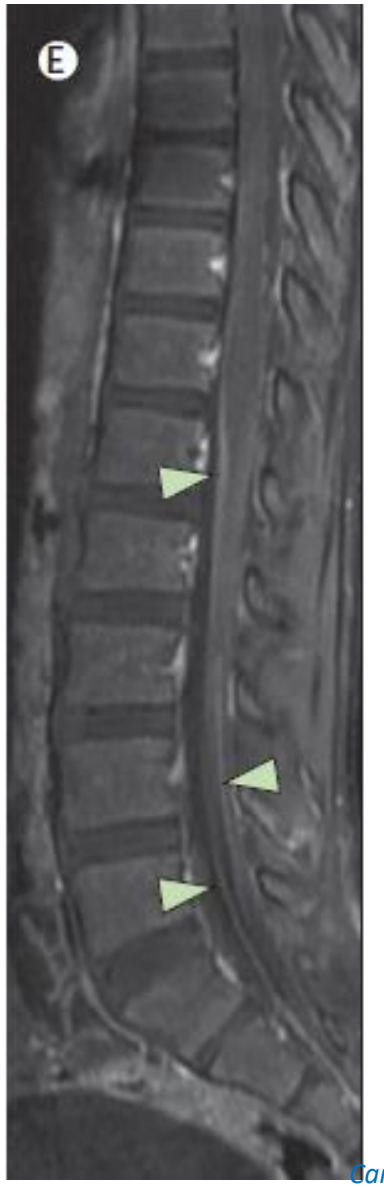
Camilla E Lindan Lancet Child Adolesc Health 2020

Neuroimaging manifestations in children

Autoimmune manifestations

Neuritis





A 9-year-old boy with acute COVID-19

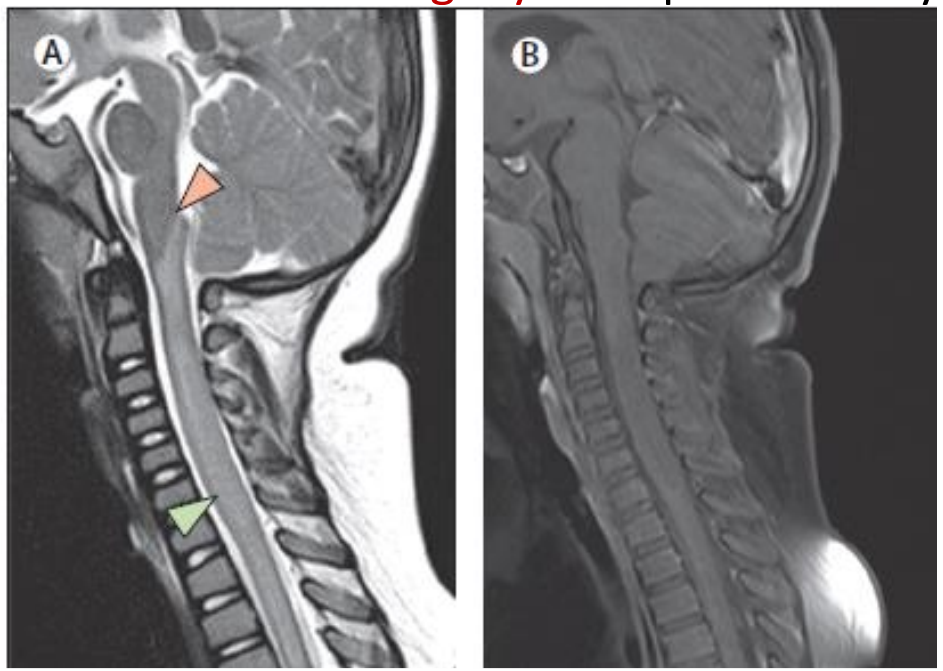
- C: Cranial nerve enhancement of his third nerves
- D: Seventh and eighth nerves (arrowhead) and his sixth nerves bilaterally (circles)
- E: He also had enhancement of the cauda equina as well as his cervical spine nerve roots

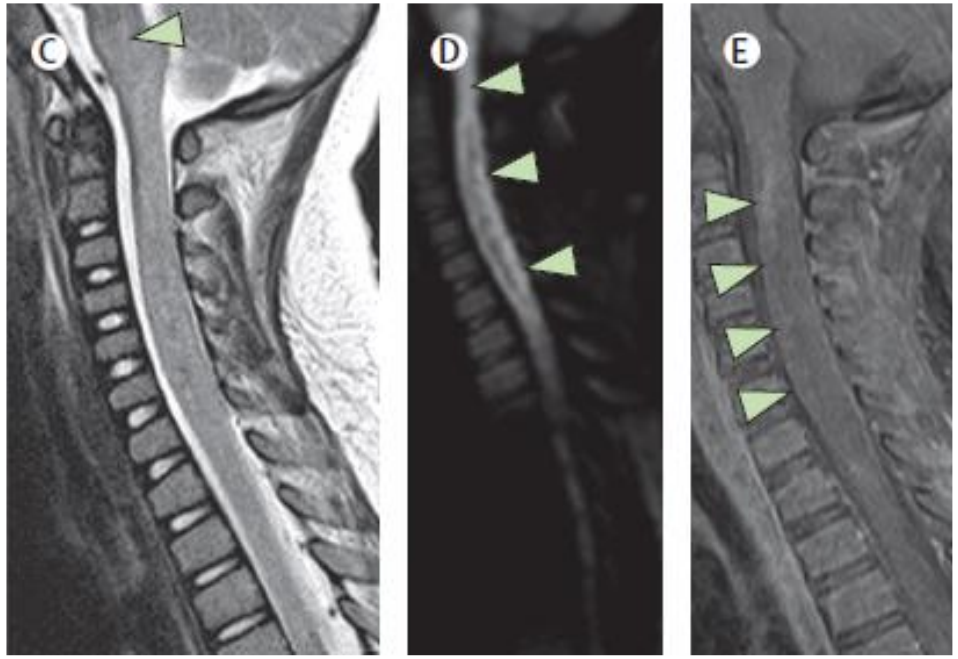
Camilla E Lindan Lancet Child Adolesc Health 2020

Neuroimaging manifestations in children

Autoimmune manifestations

Acute necrotising myelitis: permanently quadriplegic





A 3-year-old presented with acute respiratory failure, confusion, limb weakness, and vomiting

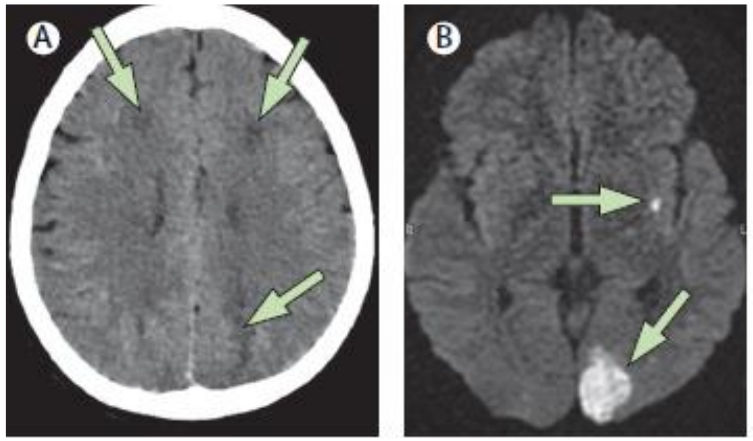
A. T2-weighted imaging: Central cervical cord signal abnormality (green) extending up to the obex (pink) but sparing the medulla
B. T1 image did not show much

C: **4 days later**, more extensive myelitis was seen with new involvement of the medulla on T2 imaging
D: New reduced diffusion seen on diffusion trace images
E: Progressive enhancement seen on T1 post contrast imaging

Camilla E Lindan Lancet Child Adolesc Health 2020

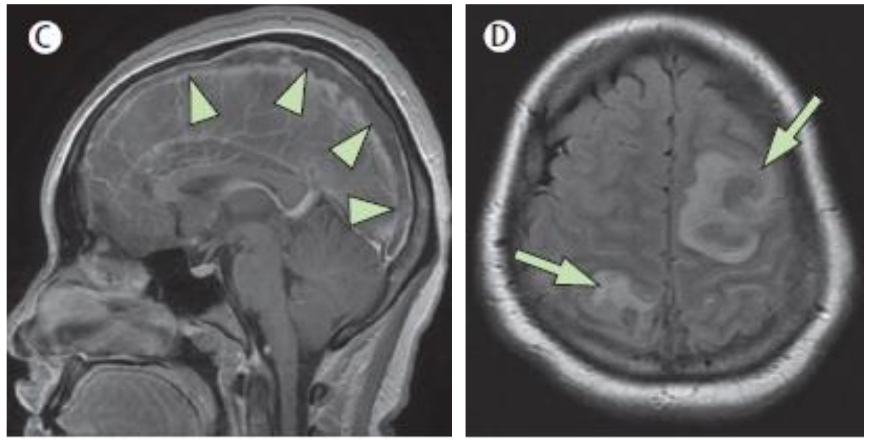
Neuroimaging manifestations in children

Vasculitic and thrombotic findings



15 year old with fever, Sz and HPT

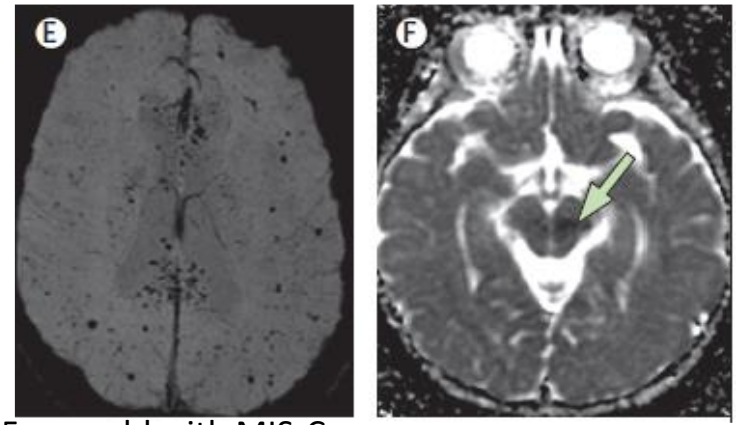
- Severe PRES



15 year old with fever, confusion and headache

- Complete occlusive thrombosis of the superior sagittal sinus with resultant haemorrhagic venous infarcts

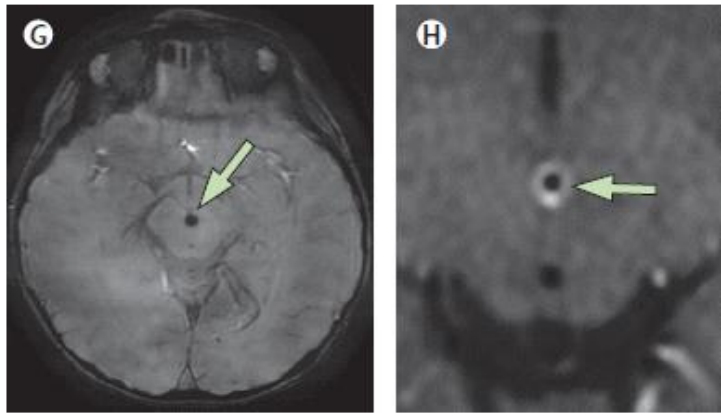
Emily Happy Miller et.al, OFID 2020



15 year old with MIS-C

- Multiple microthrombi. Clinically silent.
- Full resolution at 3months

Microhaemorrhages have also been described in adults with COVID-19-related neuroinflammatory syndromes



2 year old with fever and pharyngeal pain

- Left midbrain infarction
- Thrombus on SWI

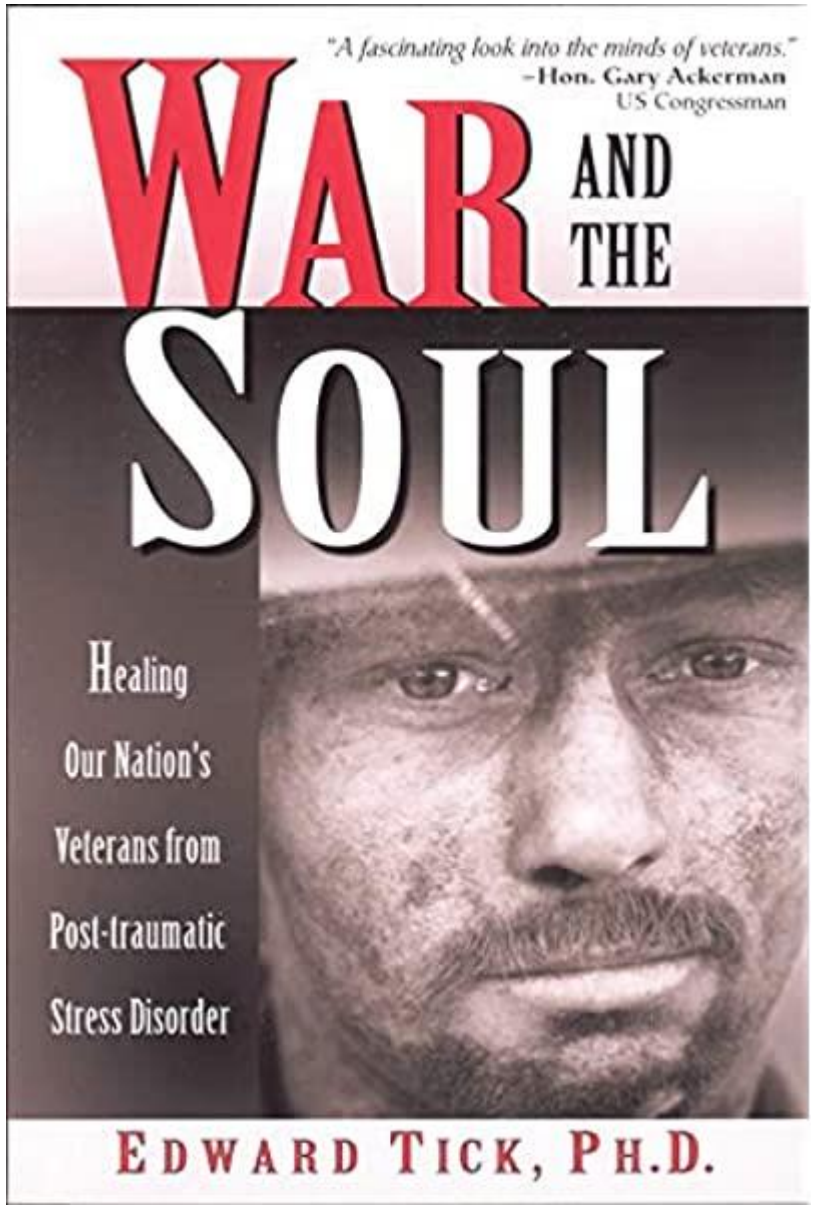
Camilla E Lindan, Lancet Child Adolesc Health 2020

Management

- Identify what the problem is
- Strokes
  - Pathway is clear
  - Follow stroke guidelines : Identify the cause, clot removal or TPA if in a dedicated stroke center
- Encephalopathy/Delirium
  - Conservative management
  - Oxygen therapy
  - Manage as per MIS-C
    - HD steroids: if there is evidence for inflammation
    - Other : IVIG or PLEX

Management

- Multi-disciplinary team
  - Physical therapy
  - Occupational therapy
  - Psychiatrist referral



CHBAH COVID experience from 1 July 2020 – 31 January 2021

		N(%)
Total COVID admissions		**128**
Neurology admissions		31 (24%) consulted on 4 (3%)
Gender	M	**17 (54.8%)**
	F	13 (41.9%)
Diagnosis	**Seizures**	**20 (64.5%)**
	Seizures known **epilepsy**	3/20 (15%)
	FS	3/20 (15%)
	First time Seizures	14/20 (70%)
	Hydrocephalus	**1 (3.2%)**
	Meningitis	**6 (19.4%)**
	Delirium	**1(3.2%)**
	Rhabdomyositis	**1(3.2%)**
	Encephalopathy	**2 (6.5%)**
Outcome	Home	27 (87.1%)
	Died	3 (9.7%)
	In the ward	1 (3.2%)

Data provided by: Z.Dangor, D. Moore

COVID Neurological Prognosis CHBAH experience

- Majority 27 (**87.1%)** of patients were discharged home with no neurological fall-out
- Three (**9.7%)** deaths all had underlying comorbidities
    1. **Seizures**: a 3m old boy with CLD, TB
    2. **Seizures and encephalopathy:** 9-year old with SLE with MOD
    3. **Seizures and encephalopathy**: 10-year old HIV positive child with CP/TBM/ epilepsy. He aspirated during a seizure

- This highlights when dealing with SARS-CoV-2 is it a direct cause or a co-incidental finding?

Data provided by: Z.Dangor, D. Moore

Take home message

- Neurological syndromes associated with COVID-19
  - Mechanisms: cause vs co-incidence
- Disease mechanisms multi-factorial
  - **Systemic Inflammatory response**
  - Prothrombotic state
  - Direct viral infection
- CSF examination for SARS-CoV-2 may not be useful
- Management of neurological conditions: as per standard guidelines
- The brain should be considered a SARS-CoV-2–susceptible organ system upon respiratory exposure

Thank you