Indication of neuroimaging in children with COVID

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Brain imaging techniques

	Image/Data Quality	Temporal Resolution	Spatial Resolution	Mobility Tolerance	Scale	Safety	Cost
MRI	High	Low (~30s)	Very-High (3-6 mm)	Medium	Bulky	High	High
fMRI	High	Low (~30s)	Very-High (3-6 mm)	Medium	Bulky	High	High
X-Ray	Low	Medium (1s-10s)	Very-High (1 mm)	Low	Bulky	Low*	Low
CT-Scan	Low	Medium (10s)	Very-High (1mm)	Low	Bulky	Low*	Low
Ultrasound	Low	Hi (~1ms)	Depends on the probe element width	Low	Medium	Very-High	Low
PET	High	Low (30s-40s)	High (5mm)	Very-high	Bulky	Low*	Very-high (1-2M$)
SPECT	Medium	Very-Low	Medium (1cm)	Medium	Bulky	Low	High (0.5-1M$)
MEG	Medium	Very-High (~1ms)	Low (1cm - 2cm)	Medium	Bulky	Low	High
EEG/ERP	Medium	Very-High (~1ms)	Medium (1cm)	Low	Small	High	Low
fNIRS	High	High (0.5s-1s)	Low-Medium (0.5cm-2cm)	Medium	Small	Very-High	Very-low

Brain CT

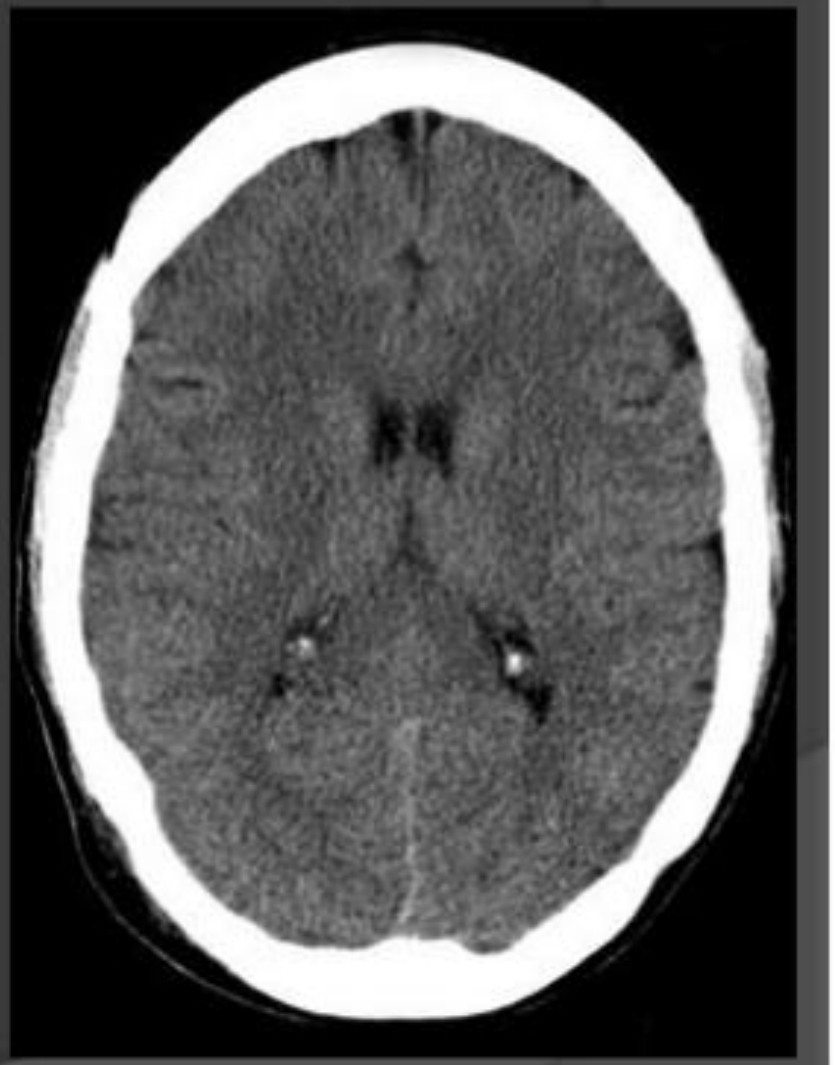
POINTS TO REMEMBER

- CT images determined only by degree to which tissues absorb X-ray
- Bone, clotted blood, calcified tissue, contrast material appear white CSF black
- The only component of brain better seen on CT scan is Calcification, which may be invisible on MRI

- Plain
- Diagnostic accuracy 82
- Contrast
- IV iodinated contrast medium
- Diagnostic accuracy 92

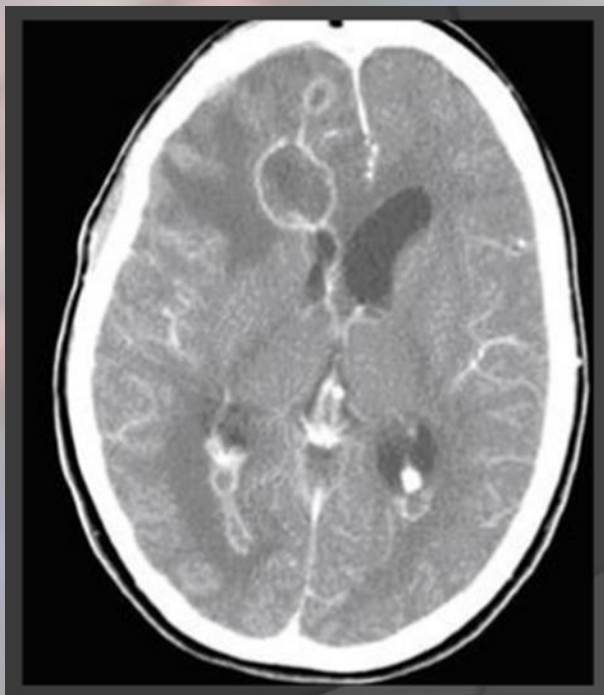
Computed Axial Tomography

- First developed in the 60's
- Digital geometry is used to create a 3 dimensional image of the internal aspects from a large series of 2 dimensional X-ray images taken around a single axis of rotation



Computed Axial Tomography

- Has advantages of quick acquisition time
- Excellent for picking up acute intracranial blood
- Uses “Houndsfield Units” to determine the density of structures identified
- Contrast can be used to better define edema or any process where there is breakdown of the BBB
- Bolus contrast administration provides vascular anatomy (CT Angiogram)
- Contrast administration is contraindicated for use with renal insufficiency or prior allergy



Contrast-enhanced CT showing brain abscess and edema

Computed Axial Tomography

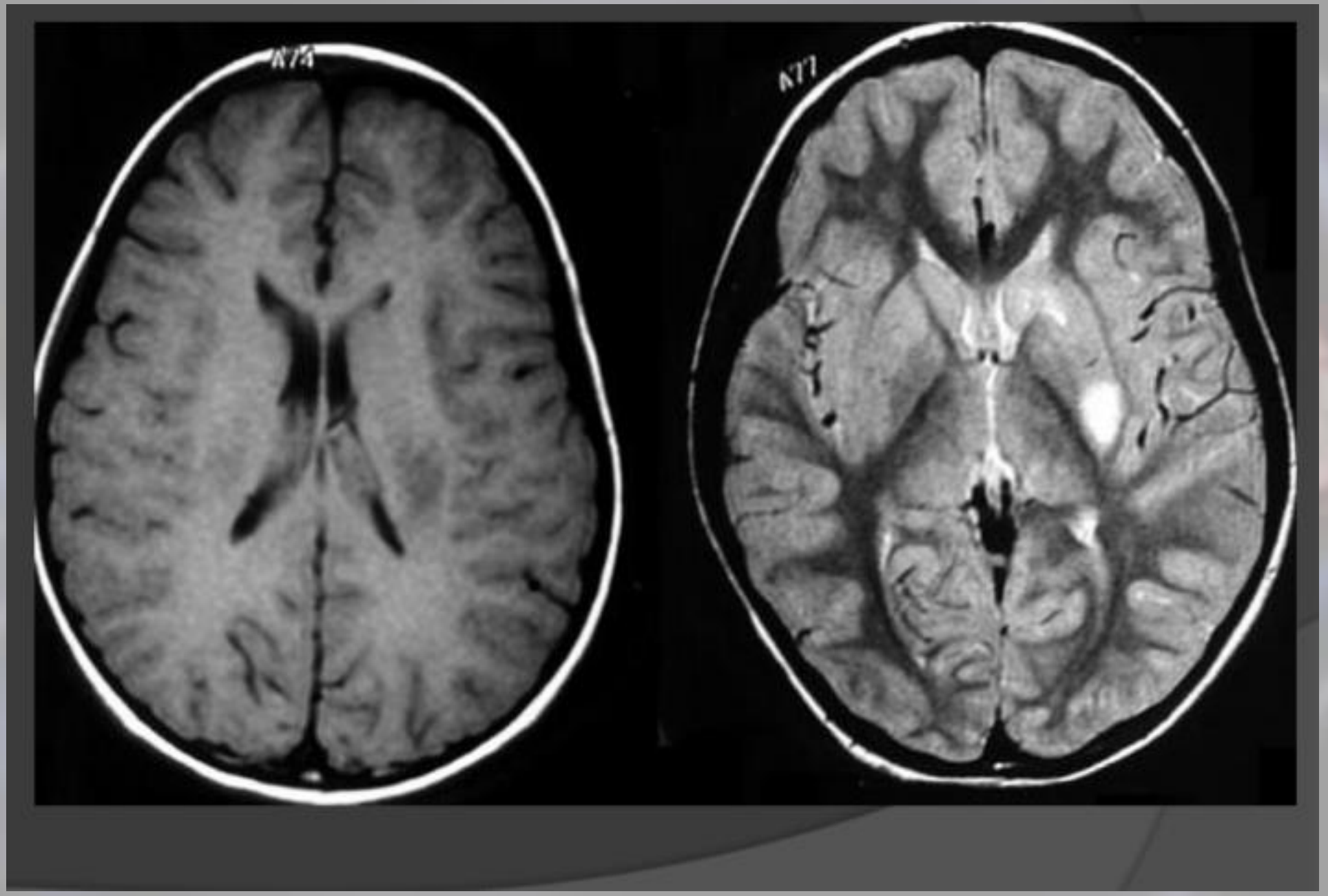
- 5 “B” things that are bright (hyperdense) on CT
  - Blood
  - Bone (or Ca^{++})
  - Brain
  - Bullet (or foreign body)
  - “Bontrast” for “Contrast”

Magnetic Resonance Imaging

- Developed in the 80's
- Powerful magnetic fields cause water molecules to align along their dipoles
- Radiofrequency waves produce an electromagnetic field which transiently knocks the molecules out of alignment
- When water molecules re-align within the magnetic field they release energy (photons) which are detected by scanners and following a lot of computer mumbo-jumbo an image is produced

Magnetic Resonance Imaging

- T-1 Imaging
  - Water is dark. Fat (Myelin) is bright
  - Gadolinium contrast used to show breakdown of BBB
- T-2 Imaging
  - Water is bright. Fat is dark.
  - FLAIR (same as T2 except water is “blacked out”)
- Diffusion Imaging
  - Shows restricted Diffusion of water suggesting cell death
  - ADC Mapping takes into account brightness of background T2 signal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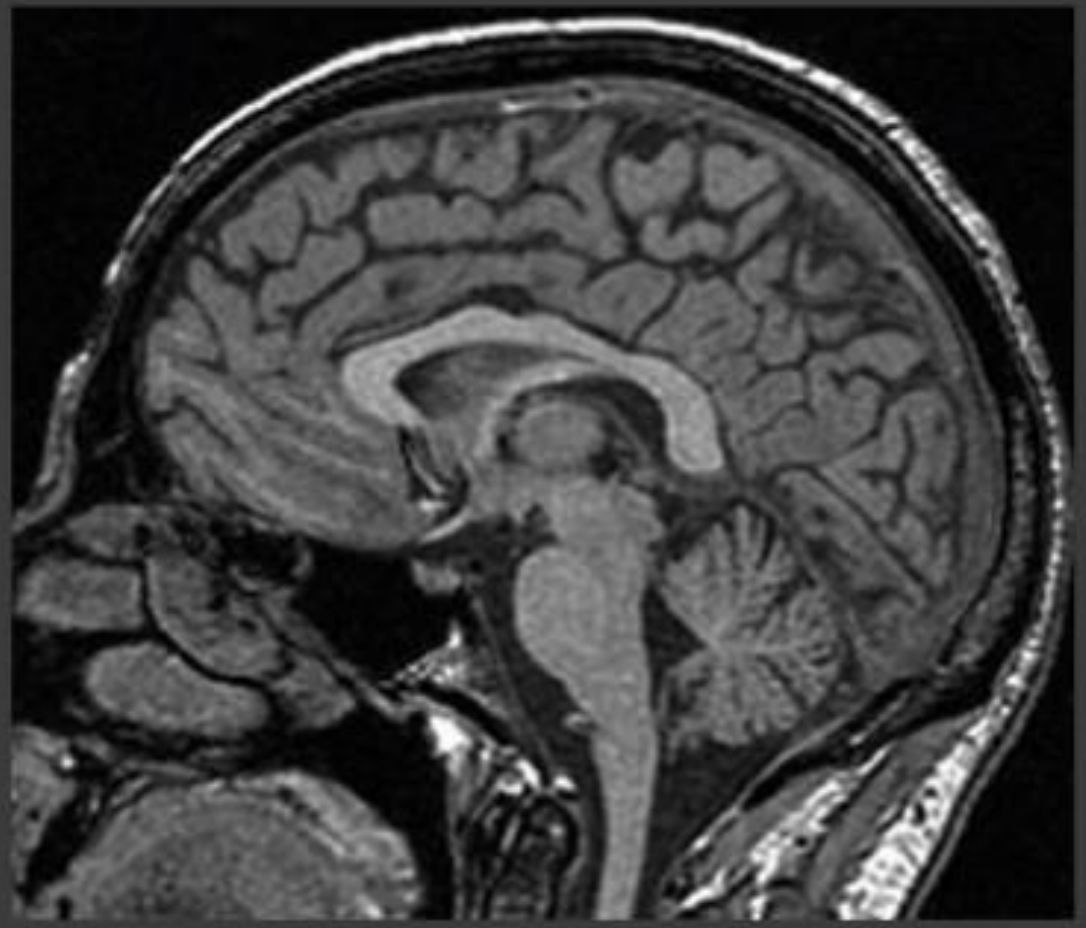
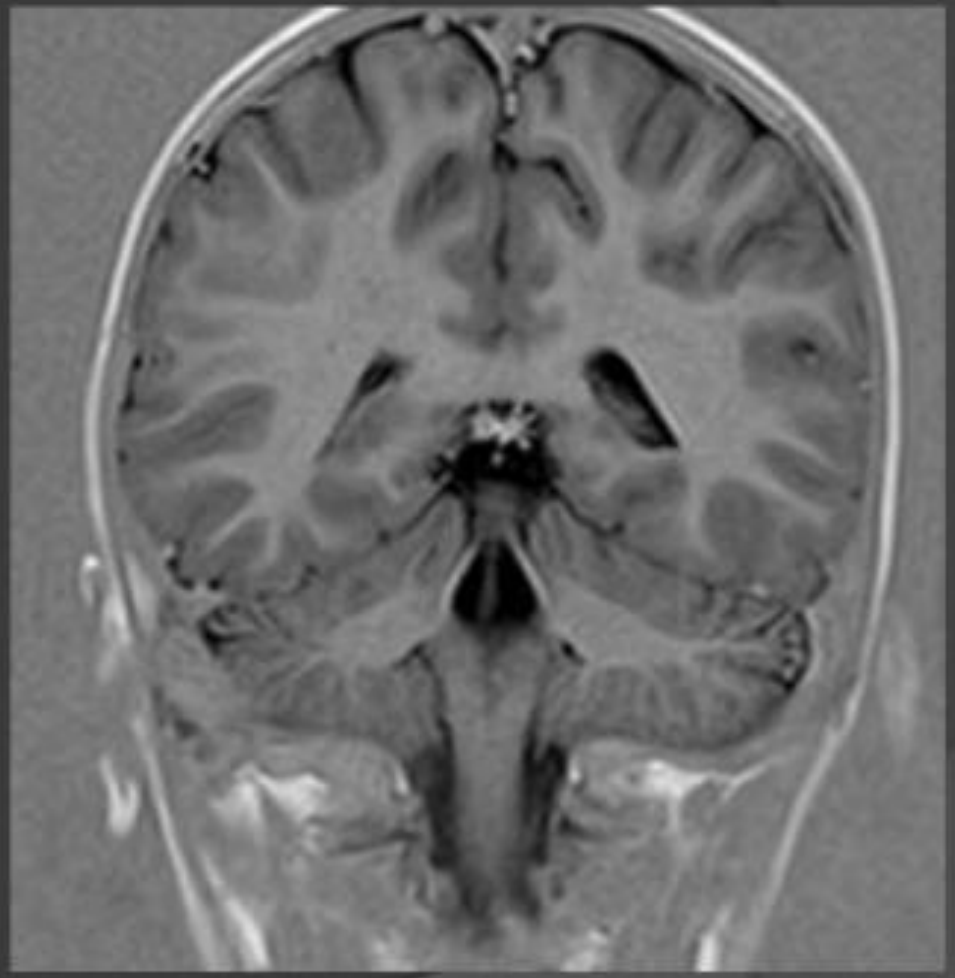
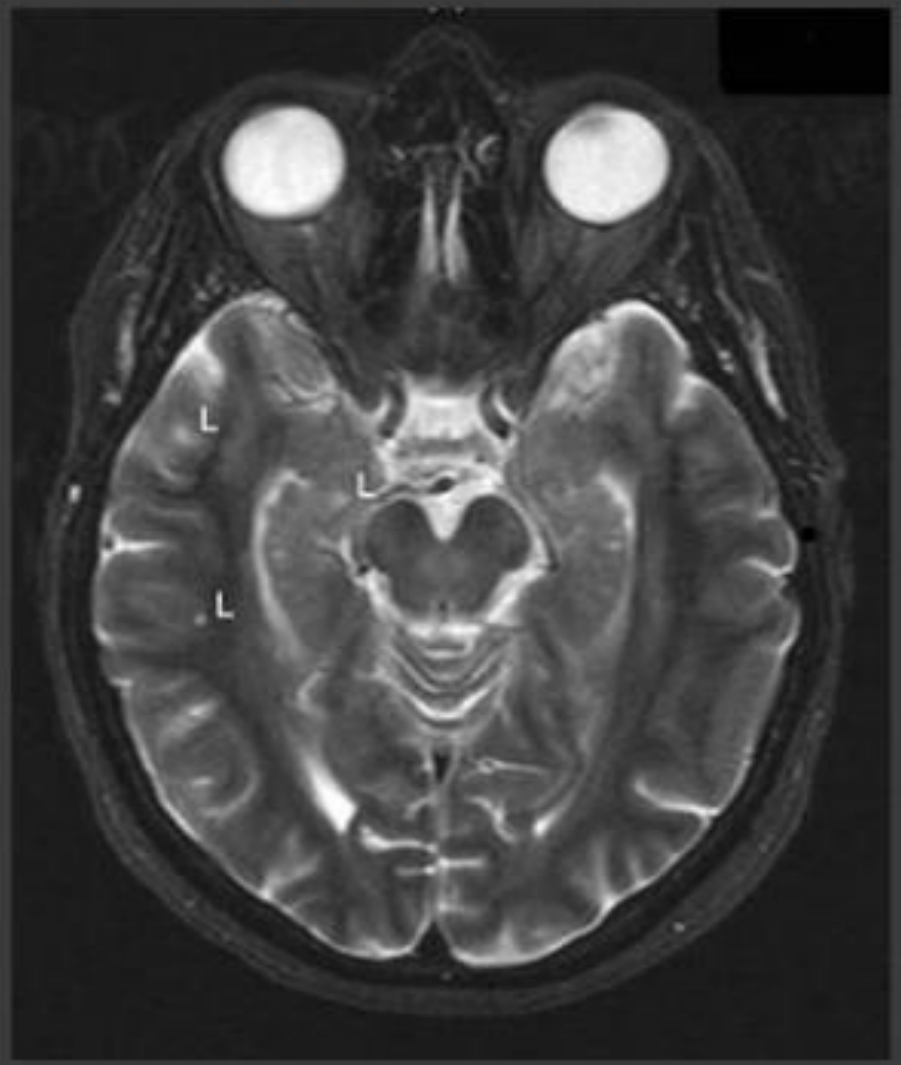


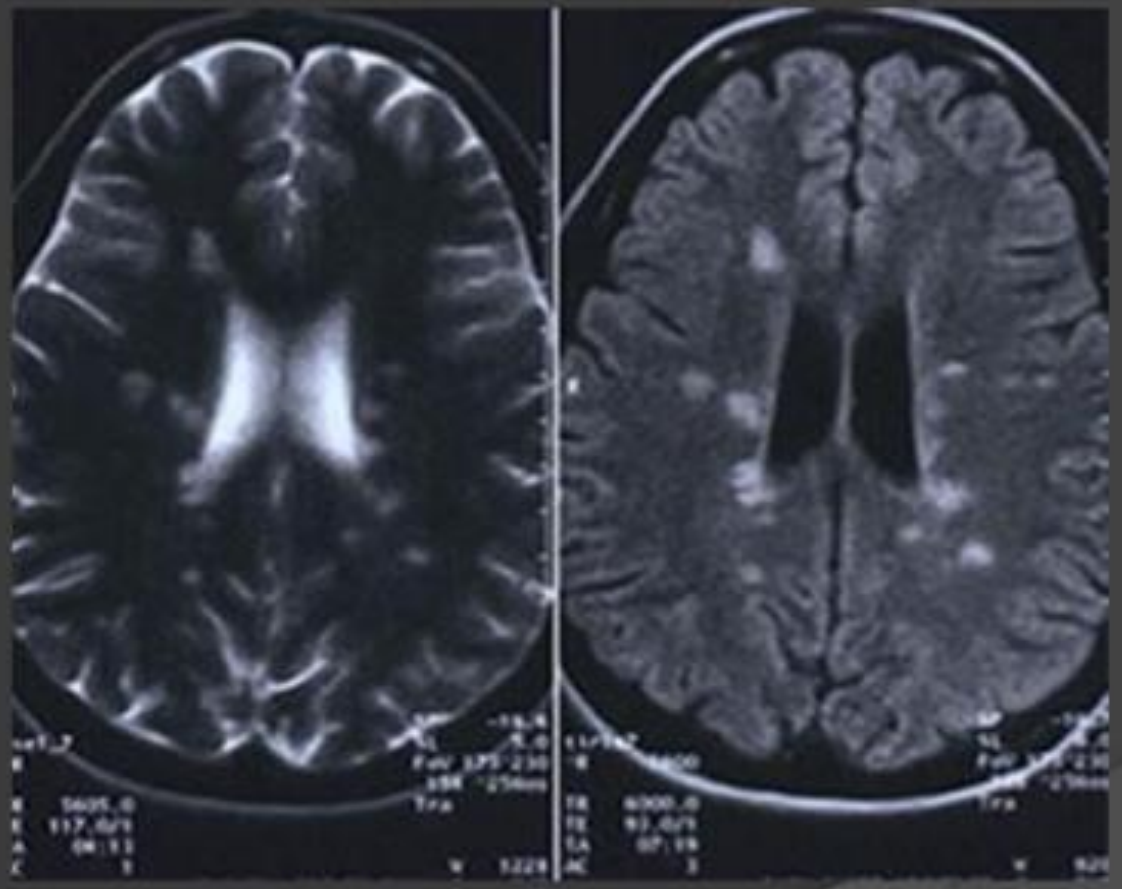
T1 Saggital Plane



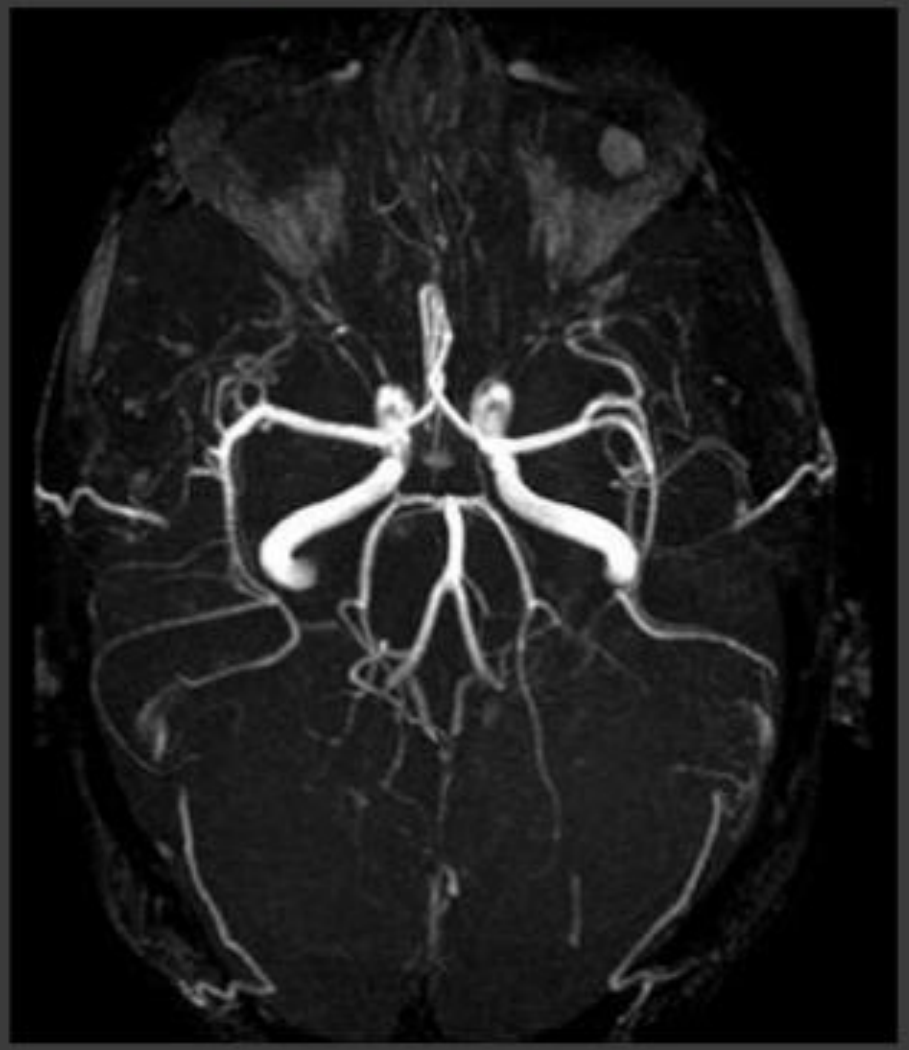
T1 Coronal Plane



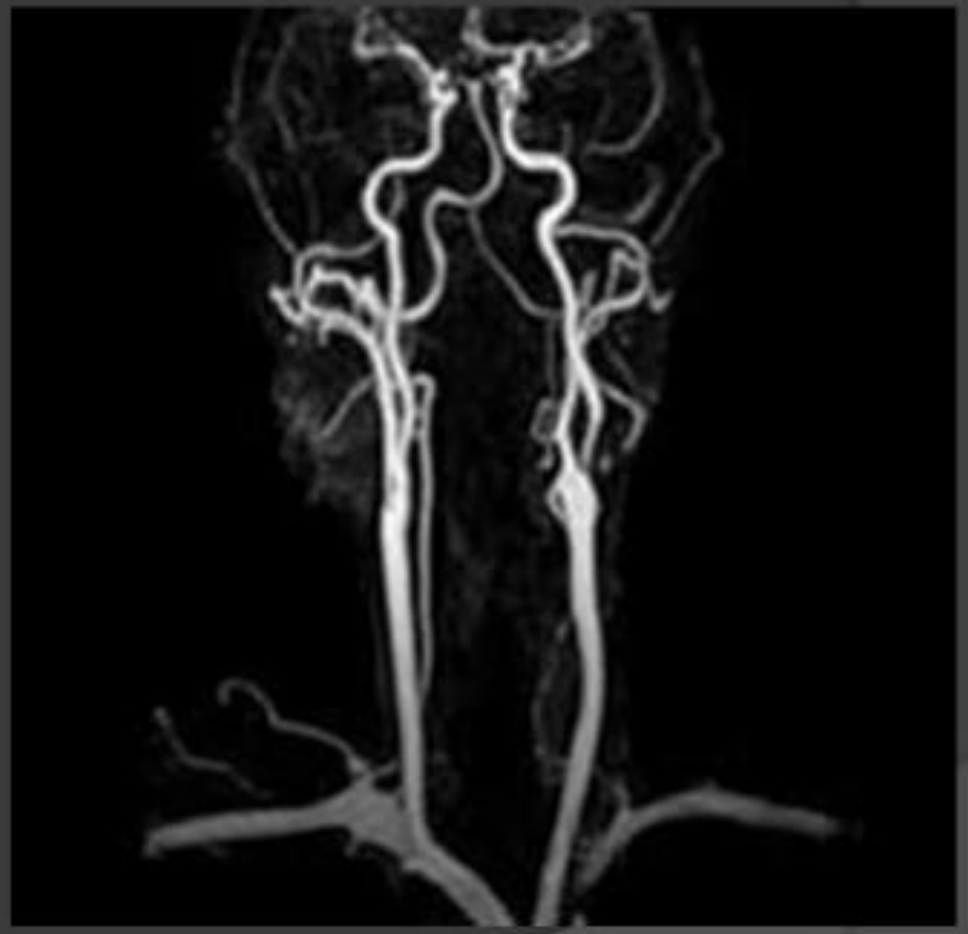
T2 Axial image



T2 and FLAIR of Multiple Sclerosis

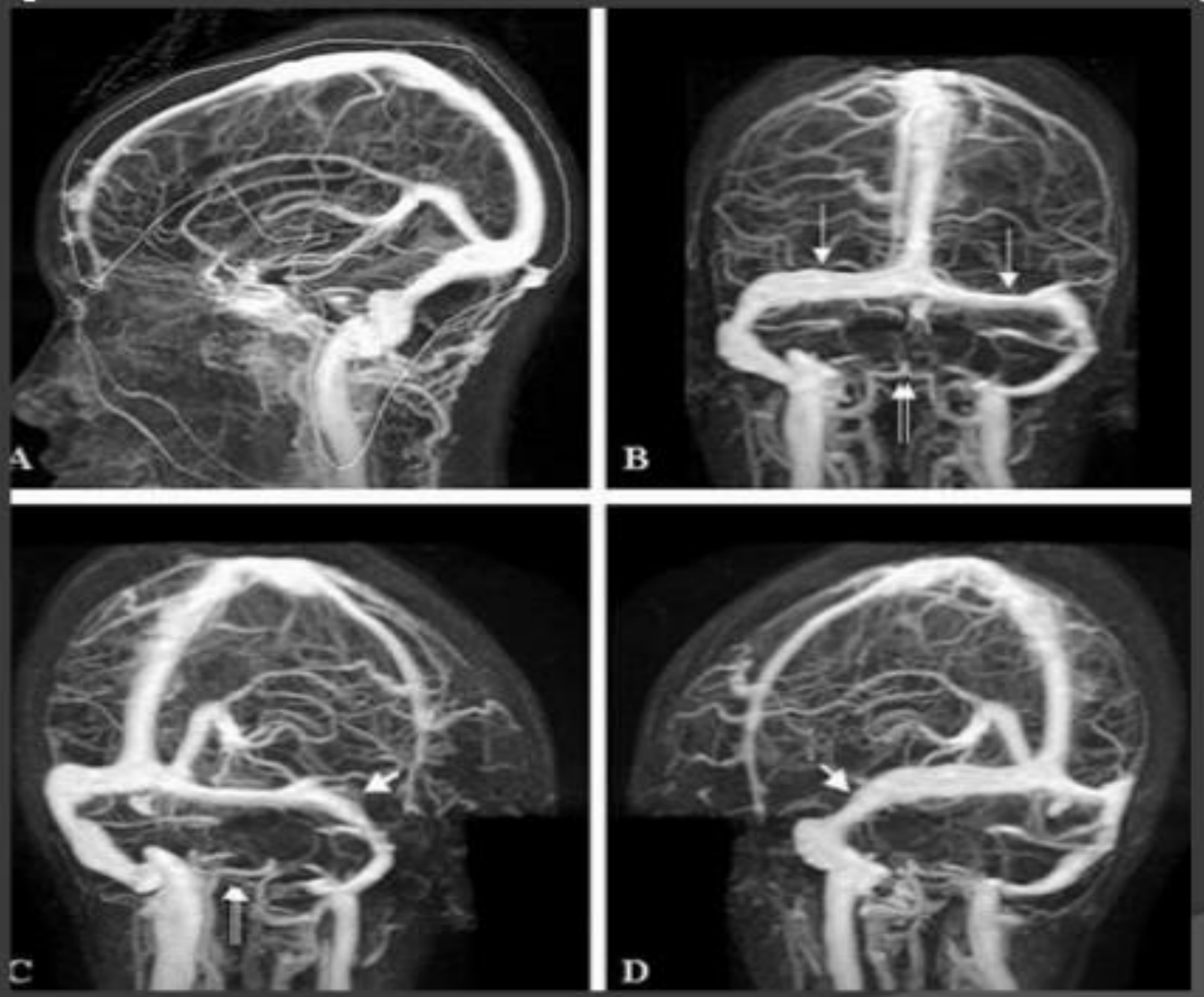


T.O.F. MR Angiogram of
The Cerebral Vessels

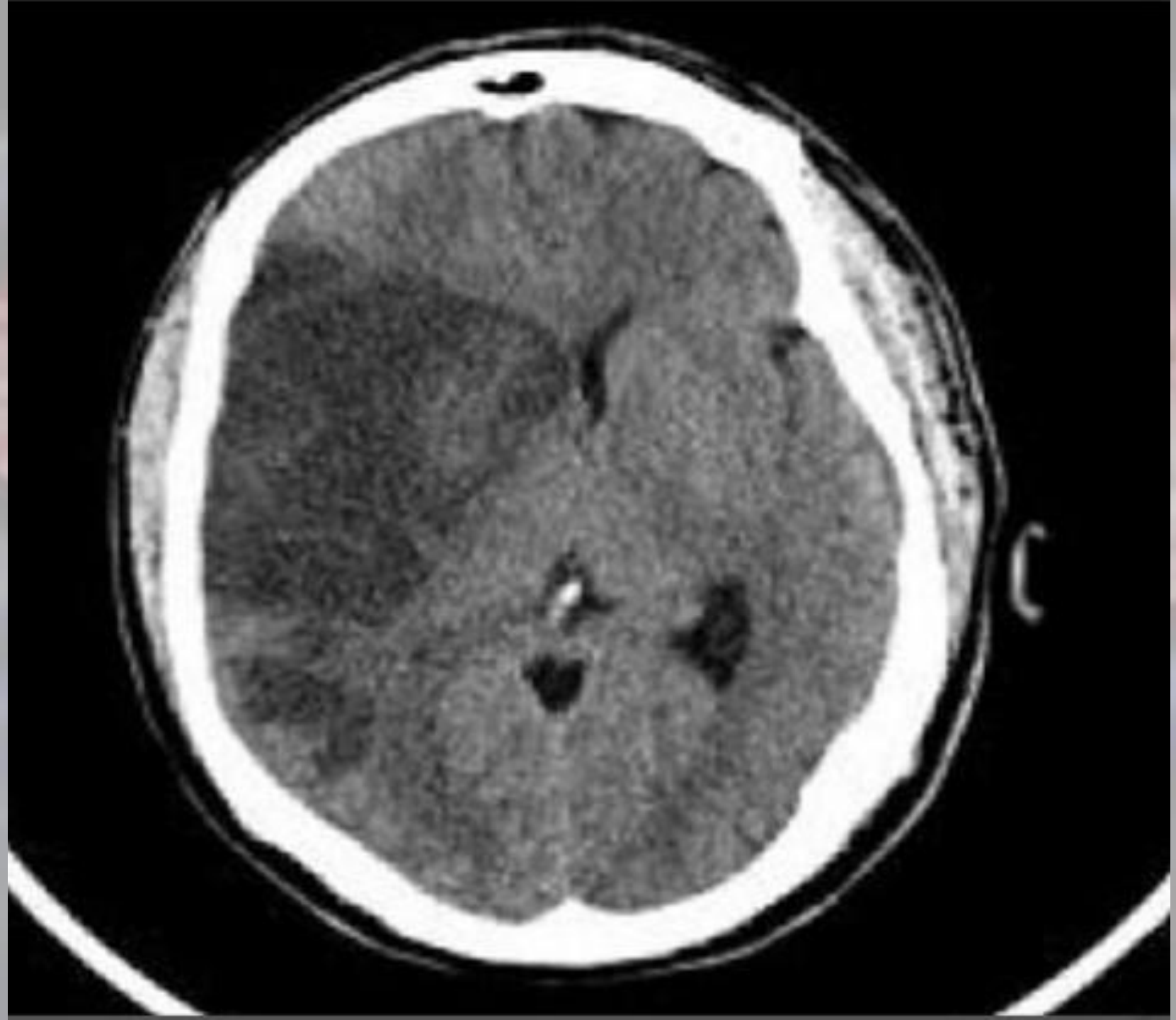


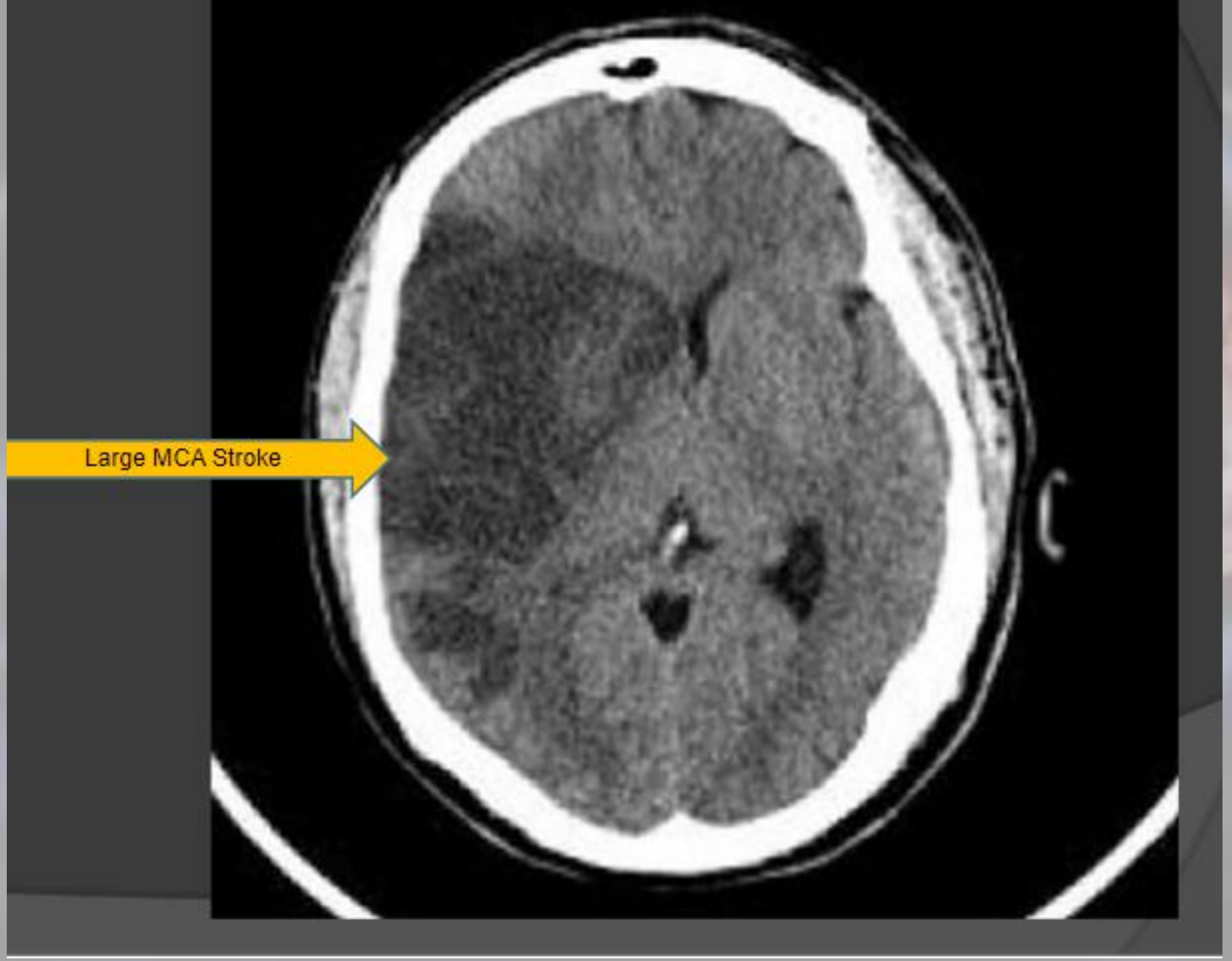
Gadolinium Contrast Injected
MR Angiogram of the Cervical Vessels

MR Angiogram of Cerebral Vessels



MR Venogram of the
Cerebral Sinuses and Draining Veins




Large MCA Stroke

DWI

- focal regions of cytotoxic edema and restricted diffusion hyperintense on DWI
- while sub-acute and chronic phases which set in after the first 4 days following an ischemic event appear normal to hypointense.
- ADC maps differentiates the falsely hyperintense chronic lesions from acute ischemia which also have an accentuated hyperintensity on DWI by maintaining the hyperintensity of the chronic lesion on the ADC map.
- The use of ADC thresholds may also help improve reproducibility of outcomes

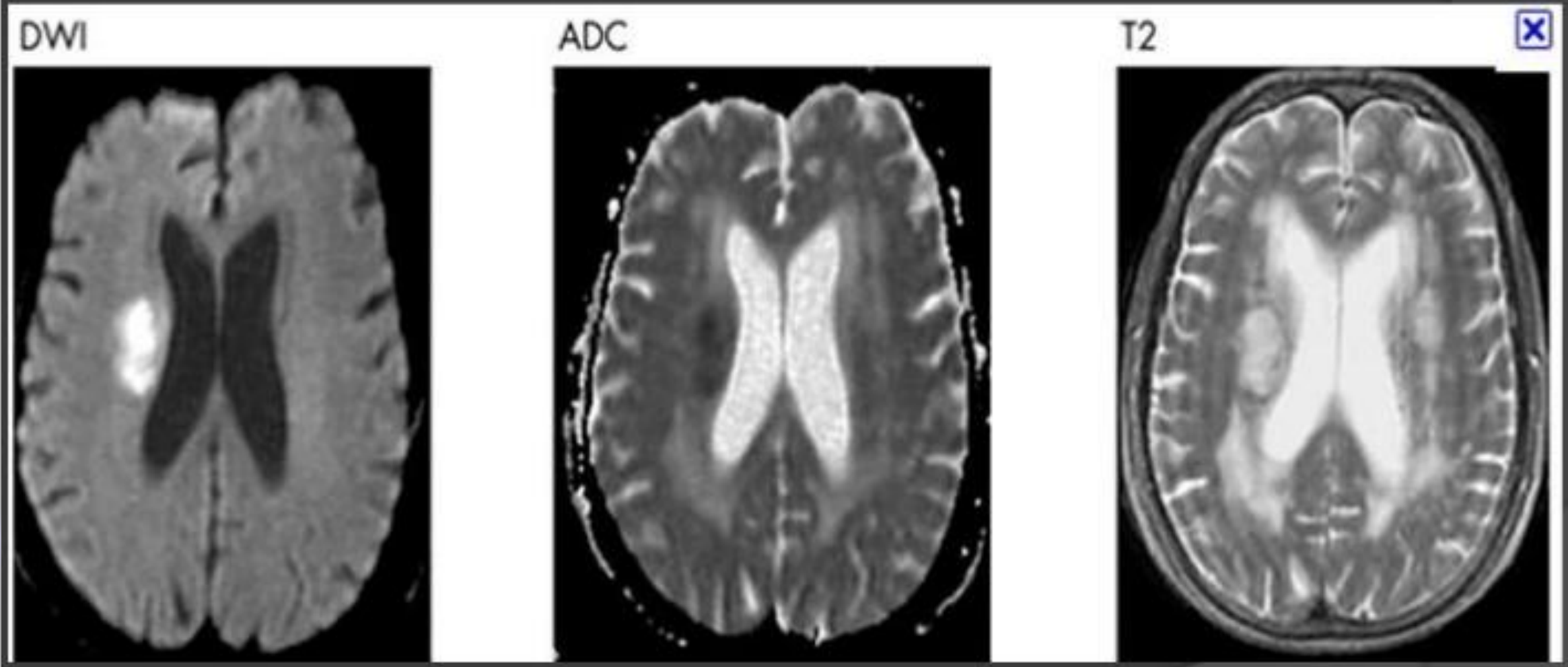
- initial DWI lesion volume correlates well with the final infarct volume and neurological and functional outcomes and could, therefore, serve as an early prognostic tool.

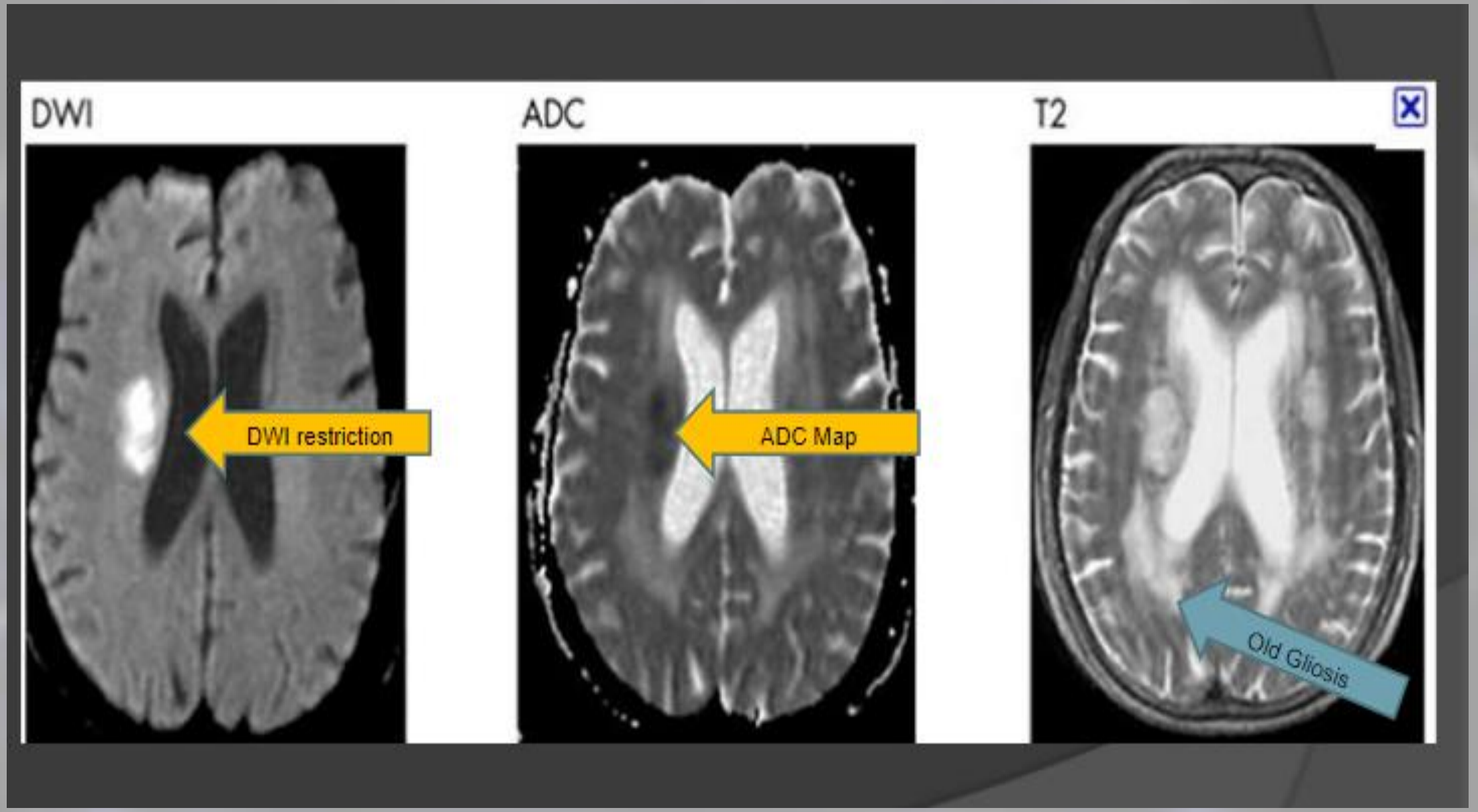
- Diffusion-weighted imaging lesion pattern can help define specific stroke subtypes

- for instance cardio embolism is associated with single cortico-subcortical lesions, multiple lesions in the anterior and posterior circulation and in multiple cerebral territories

- while large-artery atherosclerosis is associated with a watershed distribution of small lesions in one vascular territory and multiple lesions in the anterior and posterior circulation.

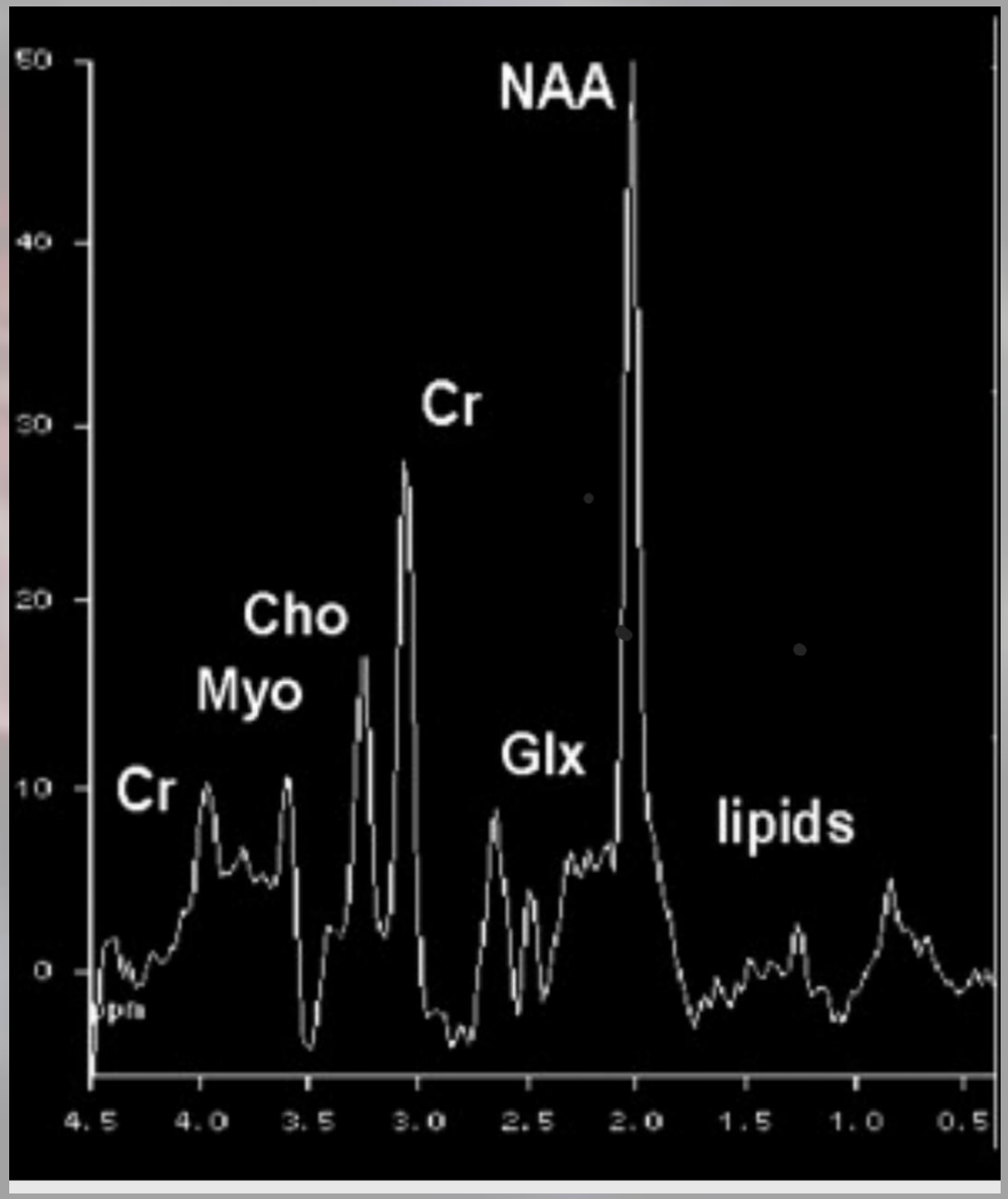
- Identifying stroke subtypes using lesion pattern on DWI may help in selecting the most appropriate method of prevention


DWI
ADC
T2


DWI
ADC
T2
DWI restriction
ADC Map
Old Gliosis

Brain MRS

Magnetic Resonance (MR) spectroscopy is a noninvasive diagnostic test for measuring biochemical changes in the brain, especially the presence of tumors. While magnetic resonance imaging (MRI) identifies the anatomical location of a tumor, MR spectroscopy compares the chemical composition of normal brain tissue with abnormal tumor tissue. This test can also be used to detect tissue changes in stroke and epilepsy.



Coronavirus disease 2019 (COVID-19)

- Evidence further suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects various brain regions linking the brain stem, eyes, mouth, and nose.
- Magnetic resonance imaging (MRI), computed tomography (CT), and MR spectroscopy (MRS) of the brain are used for the evaluation of metabolic and structural abnormalities involving enlarged volumes of various brain regions, such as olfactory cortices, hippocampus, and cingulate gyrus
- Concerning neurological and neuropsychiatric abnormalities in the COVID-19 survivors, the viral footprint in the brain is well established.

The suggested pathways of SARS-CoV-2 entry in the brain

- (i) *cytokine storm*, the unexpected massive influx of proinflammatory cytokines that likely disrupt the blood–brain barrier (BBB) leading to the structural and functional abnormality of the brain;
- (ii) *endothelial dysfunction*, endothelial cell damage and endotheliitis that potentially cause BBB injury and cerebral vascular thrombosis, resulting in cerebral microhemorrhages or brain edema; and
- (iii) *hypoxia*, elderly group with comorbidities, such as chronic hypertension and diabetes mellitus, that demonstrate neurological complications.
- Severe hypoxic brain damage further impairs small vessels, leading to periventricular neuronal demyelination or white matter microhemorrhages and widespread small vessel thrombosis.

Brain Imagining-Based Features

- For the prognosis and diagnosis of COVID-19-induced neurological manifestations, the application of noninvasive neuroimaging techniques is paramount as described below.
- CT provides images of internal organs, bones, and blood vessels.
- CT scans of patients with COVID-19 have revealed intracerebral hemorrhage (ICH) and stroke
- The literature also mentions the high proportion of hemorrhagic events, white matter abnormalities, and ischemic infarction in patients with severe COVID-19.

Brain MRI

- MRI is a unique noninvasive technique used to monitor structural details of the brain.
- MRI-based findings in COVID-19 patients include atrophy and gliosis involving the left temporo-parietal lobe, i.e., hemorrhagic rim enhancing lesions within the medial temporal lobes of the patients
- Data from patients with/without ICH lesions suggest that hemorrhagic complications are frequently associated with those under intensive care.
- Axial diffusion and gradient-echo sequences in these patients reveal acute infarcts and microhemorrhages

Fluid-Attenuated Inversion Recovery (FLAIR)

- According to the literature, FLAIR images from patients with COVID-19 demonstrate hyperintense signal changes in the right mesial temporal lobe and slight hippocampal atrophy; extensive patchy areas of abnormal signal involving bilateral frontoparietal white matter; cortical FLAIR signal abnormality in frontal, parietal, occipital, and temporal lobes; and multiple areas of restricted diffusion associated with edema.
- Susceptibility-weighted imaging has revealed extensive superimposed hemorrhages in the parietooccipital region.
- nonconfluent multifocal white matter hyperintense lesions along with variable intensification.
- Such hemorrhages indicate clinical implications as they are often associated with severe respiratory conditions.

Diffusion-Weighted Imaging (DWI)

- DWI indicates hyperintensity and acute ischemic stroke with the foci of hyperintensity scattered within the territory associated with neurological symptoms, such as headache and transient generalized seizure.

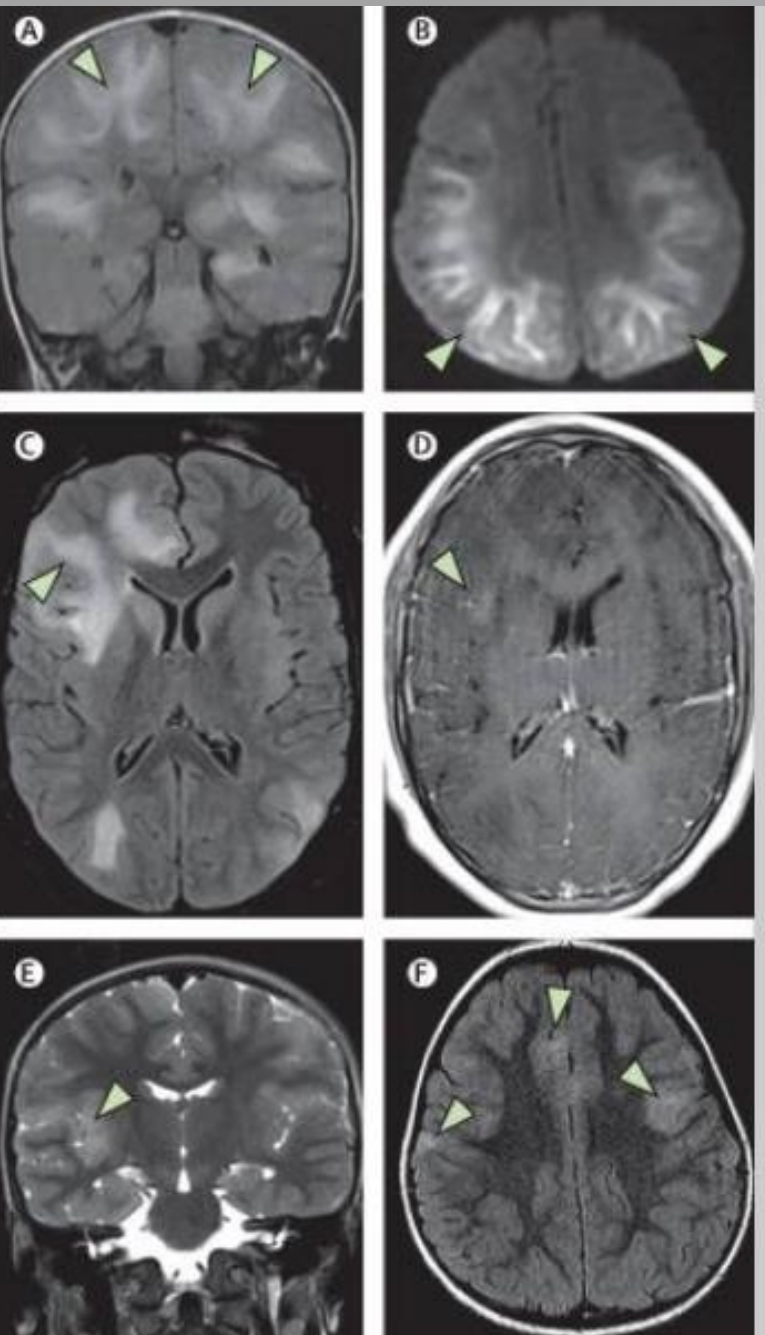
Diffusion Tensor Imaging (DTI)

- DTI maps have shown that patients recovered from COVID-19 are more likely to have enlarged hippocampi, olfactory cortices, Heschl's gyrus, cingulate gyrus, insulas, and Rolandic operculum.
- These patients presented statistically significant higher bilateral gray matter volumes indicating disruption in microstructures.
- MRS studies reflect metabolite abnormalities.

- The patient with white matter abnormality presented the abnormality of choline and *N*-acetyl-aspartate concentrations.
- The patient with white matter disorder showed more pronounced alterations reflecting neuroinflammation.

- Patients with severe COVID-19 potentially demonstrate cytokine storm syndrome that triggers ischemic strokes.
- Other anomalies include ICH, hypoxic–ischemic encephalopathy, and ischemic stroke.
- White matter in the subcortical region of the brain protects nerve fibers from injury.
- White matter abnormalities are reportedly the most persistent neuroimaging pattern observed in these patients.
- The abnormalities are presented as converging hyperintensities on T2/FLAIR of MRI along with unnatural restricted diffusion and hypointensities on CT and T1W imaging in deep white matter, subcortical and middle cerebellar peduncles, corpus callosum, and corticospinal tracts,
- causing nonspecific neurological signs.
- COVID-19-associated coagulopathy often presents cerebral venous thrombosis and large vessel occlusion

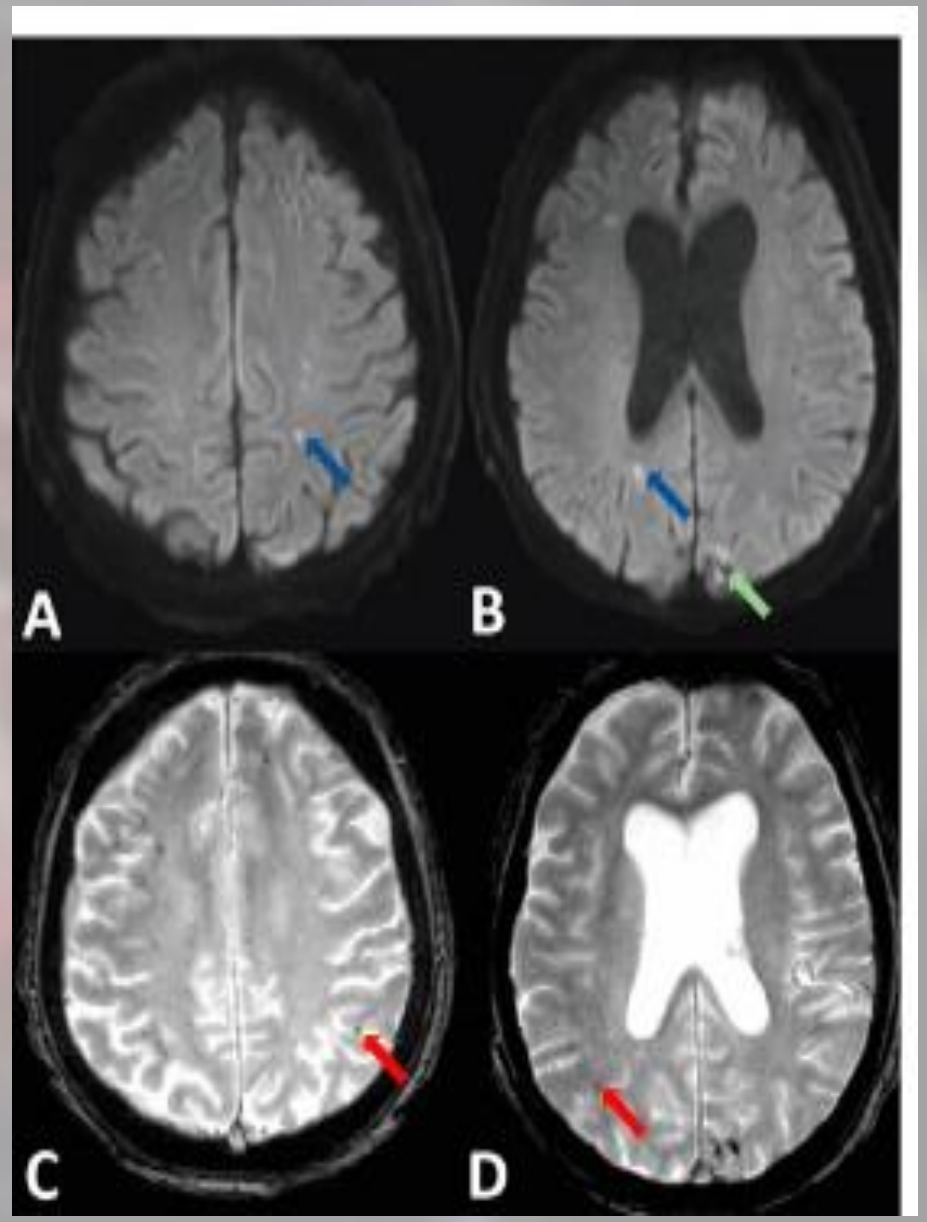
- The most frequent imaging findings in category 1 were compatible with autoimmune manifestations, observed in six (50%) of 12 patients, as follows.
- Patchy T2 hyperintensity involving grey and white matter with or without abnormal enhancement and diffusion restriction was seen in four (33%) patients
- This imaging pattern is referred to herein as acute disseminated encephalomyelitis (ADEM)-like; this descriptive terminology is used to refer to an imaging phenotype analogous to an ADEM-like pattern, but does not imply that the patients met the clinical definition for ADEM per se.
- Two children (cases 2 and 3) with the ADEM-like imaging pattern had T2 signal changes in the splenium of the corpus callosum which, given that these patients had seizures at presentation, was thought to be compatible with this clinical presentation.
- One patient (case 4) also developed long-segment myelitis with predominant central cord T2 hyperintensity
- In the two other patients (cases 6 and 7) with autoimmune manifestations, we observed enhancement of the cranial nerves or cauda equina, or both, referred to under the general term neuritis

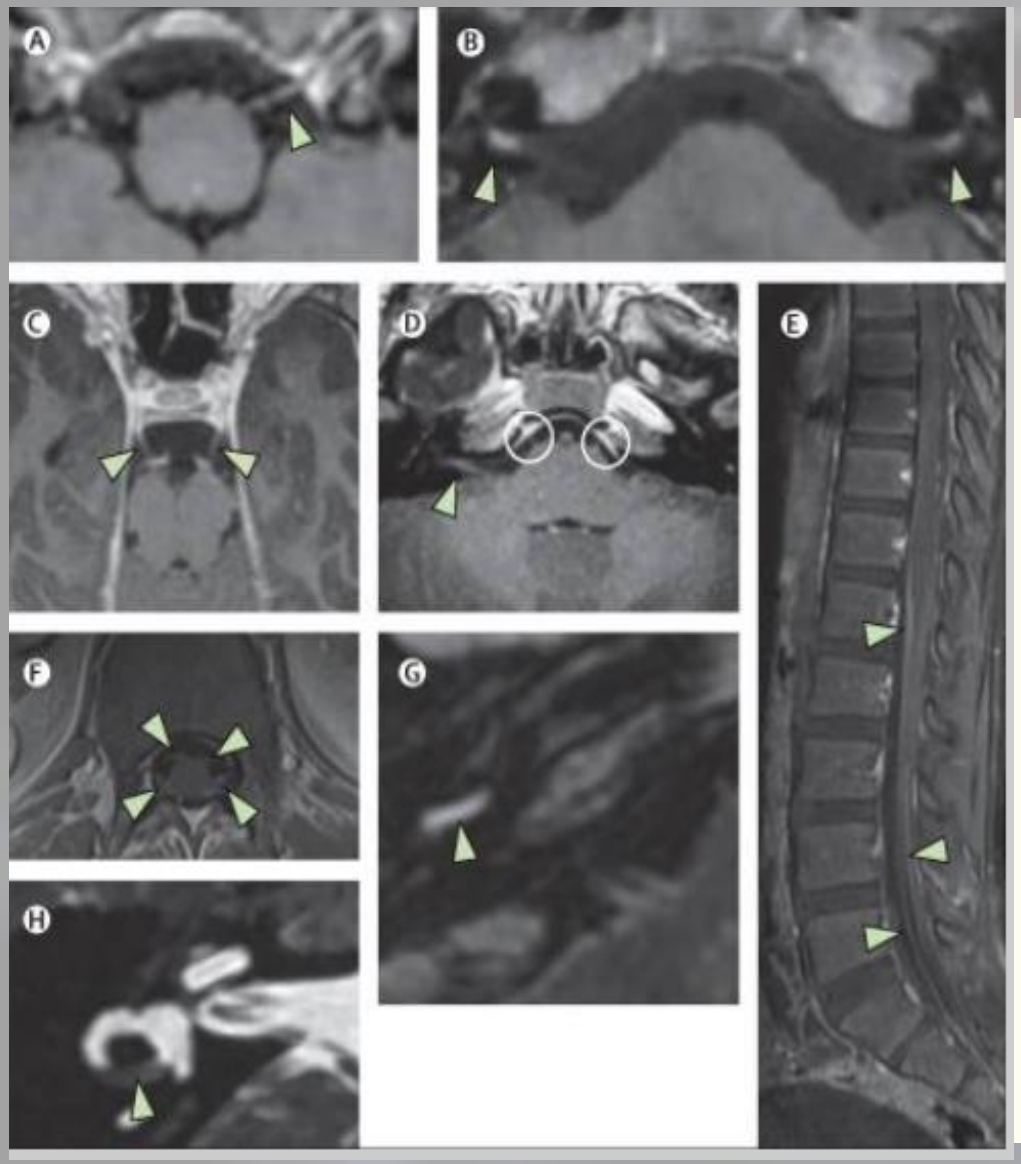


ADEM-like brain changes

(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.

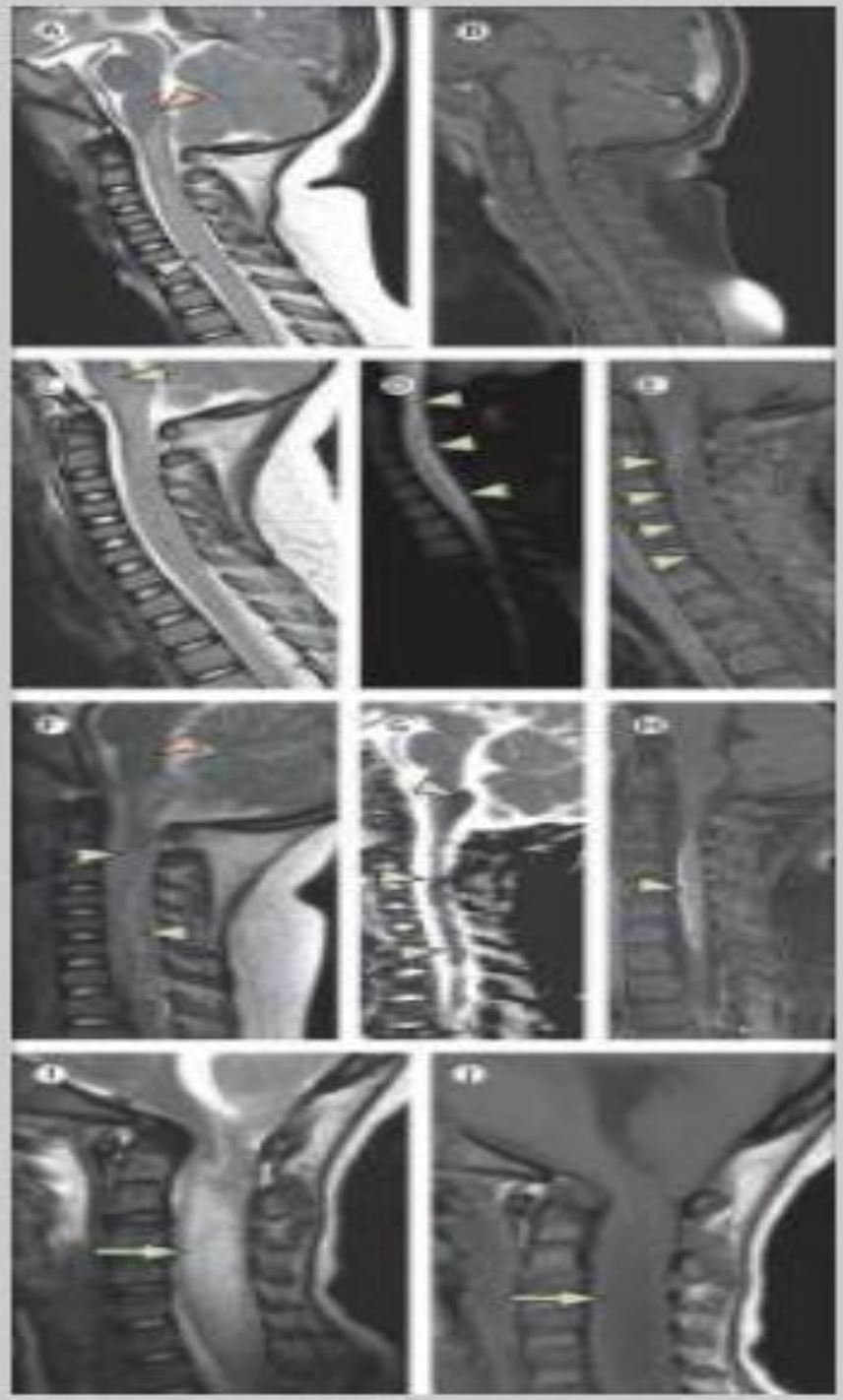
acute infarcts within the bilateral cerebral white matter (blue) and left occipital hemorrhagic infarct (green) (axial diffusion sequence); (C, D) innumerable microhemorrhages throughout the bilateral cerebral hemispheres (red) (using gradient-echo sequences).





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).



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 (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.

Thank you for listening!