Revisiting Focal Cerebral Arteriopathy

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Introduction

- Childhood AIS incidence – 1.3 – 7.9 per 100,000 children/ year.
- Mortality – 7 – 28%
- Children do not recover better than adults
  - 50% suffer long term neurological impairments
- Accurate diagnosis
  - Initial management
  - Secondary prevention and surveillance
  - Counselling families about recurrence risk

Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population based study. Lancet Neurol 2014; 13:35–43.

Arteriopathy

- Arteriopathies
  - Leading cause of childhood AIS
- Challenge
  - Distinguish between cardioembolic and arteriopathic stroke
  - Distinguish the different subtypes of arteriopathic stroke
- Arteriopathies are the strongest predictor of recurrent events and poor long-term outcome
- Types
  - Unilateral Focal Cerebral Arteriopathy – 12%
  - Arterial dissection – 11%
  - Moyamoya disease – 17%

(multinational cohort study)

Wintermark M, Hills NK, deVeber GA, et al. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study. Stroke 2014; 45:3597–3605.

Focal cerebral arteriopathy

- Nomenclature ?
  - FCA/PVA/TCA/childhood non progressive medium-large vessel angitis
- Radiological diagnosis (MRA/CTA)
- Characterised by
  - Unilateral infarction and stenosis of intracranial arteries
    - Distal (supra clinoid) ICA
    - Promixal MCA
    - ACA
  - Posterior circulation – reported 25% of cases

Subtypes

- Recent classification proposed
  - FCA-i (inflammatory)
  - FCA-d (dissection)
  - FCA with collaterals can be initial presentation of Moya Moya syndrome
    - (Differential diagnosis)

Fearn, Mackay et al 2020

FCA-i

- Vascular inflammation
  - Primary
  - Post infectious
  - Idiopathic
- *VIPS study* –
  - Infection in the week prior to stroke conferred a 6.3 fold increase risk of AIS
  - Serological evidence of often **clinically asymptomatic HSV 1 and 2 and varicella** were significantly associated with stroke.
- Monophasic course
  - Can evolve over 3 – 6 months then have stable residual arterial state
  - If progression beyond 12 months reconsider the diagnosis

Vascular infection in pediatric stroke study - 2017

FCA-i (secondary to varicella)

- Viral reactivation from the trigeminal ganglion with trans-axonal spread to the adventitia of the cerebral arteries
  - Affects ICA / MCA/ ACA (lenticulostriate basal ganglia strokes)
- Swiss – Australian study
  - History of recent varicella infection was observed in ¼ of pts with FCA
  - 28% of children undergoing LP were VZV PCR +
- History of varicella – preceding 6 – 12 months
  - Post infectious hypothesis
  - Active varicella in cerebral artery

improve outcome? Stroke 2017; 48:2375–2382.
Swiss/Australian observational study of focal cerebral arteriopathy (FCA)

FCA-d

- Intracranial dissection is an important differential diagnosis in children with FCA
- 60% of anterior circulation dissection in children affect the intracranial vessels.
- Clinical findings suggesting dissection
  - New head or neck pain 7- 10 days prior to the stroke
  - Ipsilateral horner syndrome
  - Cervical bruit
- A case series of 4 children with malignant MCA infarction
  - Diagnosis of dissection was made at post mortem *(IPSS study)*
- No difference between antiplatelet over anticoagulation

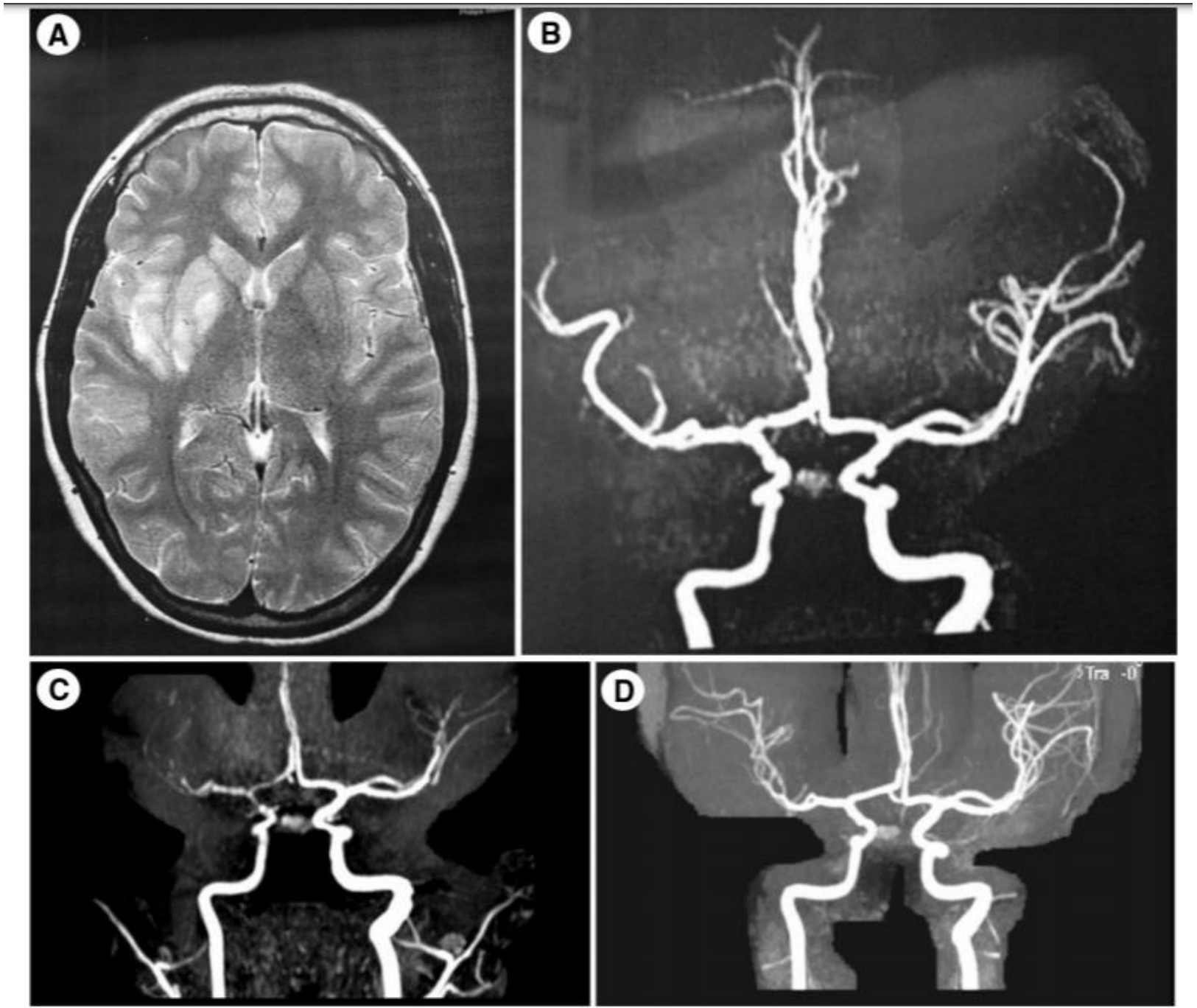
Table 1. Unilateral focal cerebral arteriopathy: clinical and imaging clues to specific diagnoses

	FCA-i	FCA-d	Unilateral Moyamoya
Clinical features	Hemiparesis and speech disturbance Stuttering onset history of preceding viral infections including history varicella exposure in previous 6 months	Hemiparesis and speech disturbance Headache, history of trauma (but often spontaneous)	Preceding history of TIAs. Headache, hemiparesis and speech disturbance, hemisensory deficits, seizures Triggered by fever, infection History of preceding TIAs
Parenchymal imaging MRI	Subcortical lenticulostriate territory Infarction	Subcortical or mixed subcortical/cortical infarction	Cortically based or border zone infarction Established white matter changes. Ivy sign on FLAIR imaging
Luminal imaging (time of flight) MRA	Stenosis, irregularity distal ICA, proximal MCA, ACA	Tapered occlusion or stenosis of ICA, proximal MCA, ACA	Stenosis or occlusion distal ICA ± MCA and ACA. Basal lenticulostriate 'puff of smoke' collateral vessels

Adopted from Focal cerebral arteriopathy and childhood stroke – Fearn and Mackay et al

T2 axial

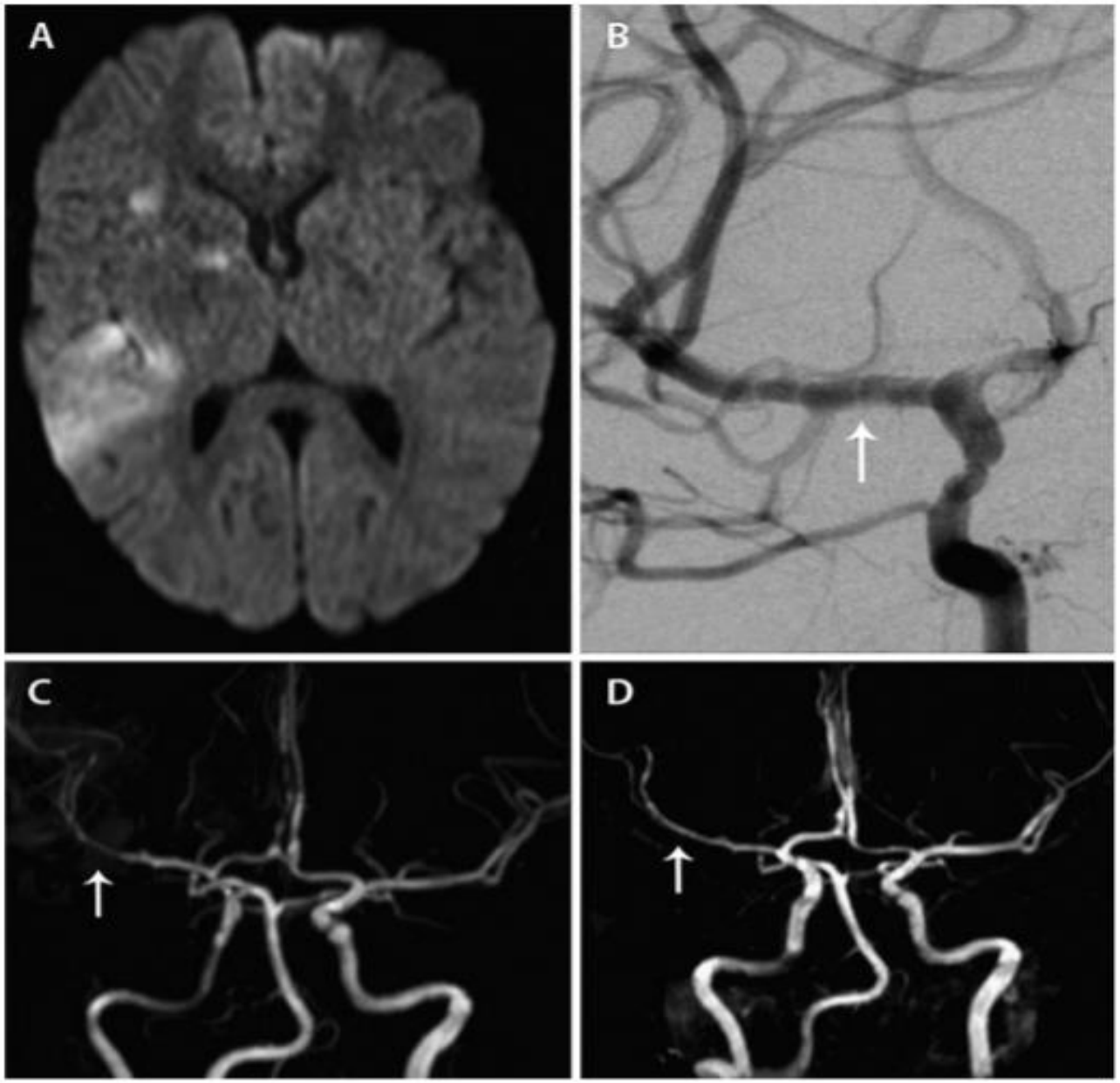
MRA - admission



MRA – 3 months

MRA – 12 month

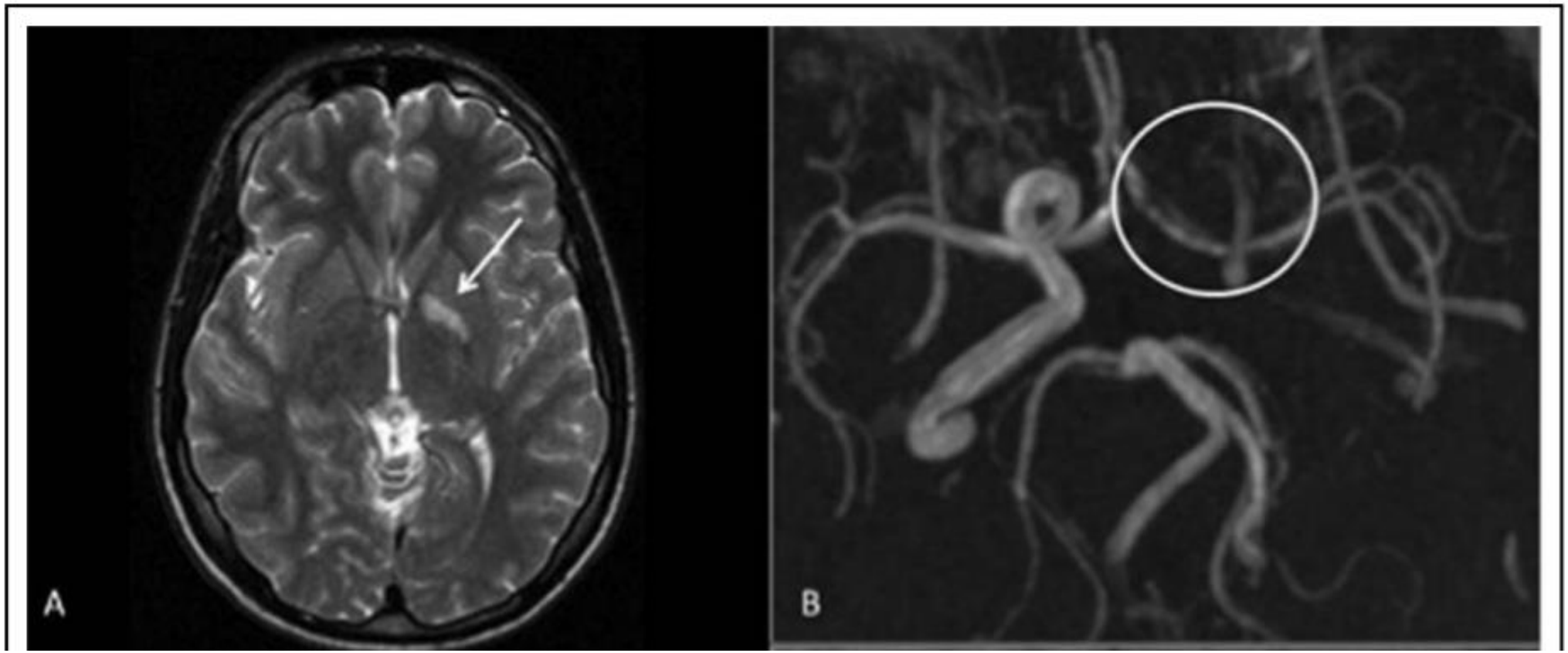
DWI



Striae – cerebral angiogram

C&D

MRA



A. Magnetic resonance imaging (MRI; arrow) showing left basal ganglia diffusion restriction. B. MR angiography non-visualization of distal internal carotid artery and (circle) signal irregularity in left anterior cerebral artery and middle cerebral artery

Conventional angiography (arrow) left middle cerebral artery **contrast filling defect suggestive of recanalizing thrombus or double lumen**. D, MR vessel wall signal hyperintensity (circle) suggestive of intramural thrombus.

Intracranial Dissection Mimicking Transient Cerebral Arteriopathy in Childhood Arterial Ischemic Stroke. Nomazulu Dlamini

New modalities – Vessel Wall Imaging (VWI)

- Provides adjunctive information to luminal imaging
- Pre and post contrast, high resolution fat saturated T1 weighted sequence (axial and coronal planes)
  - Black blood imaging sequence
    - Suppresses the blood flow signal
    - Focused assessment of the vessel wall
    - Differentiate between vascular lesions (atherosclerosis, inflammatory and dissection)
    - Monitor disease progression in Varicella Zoster
  - Precontrast – intramural blood (dissection)
  - Enhancement of postcontrast – FCAi (thickening of vessel wall).
- Concentric vs eccentric enhancement

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	FCA-i	FCA-d	Unilateral Moyamoya
VWI	Wall thickening and concentric enhancement postcontrast study	Hematoma on precontrast study Intramural eccentric enhancement	Concentric vessel wall narrowing and thickening
DSA	Focal or segmental stenosis ± web-like banding	Double lumen or intimal flap	As for MRA. Six vessel study to demonstrate extent of basal and external to internal native collaterals

Adopted from Focal cerebral arteriopathy and childhood stroke – Fearn and Mackay et al

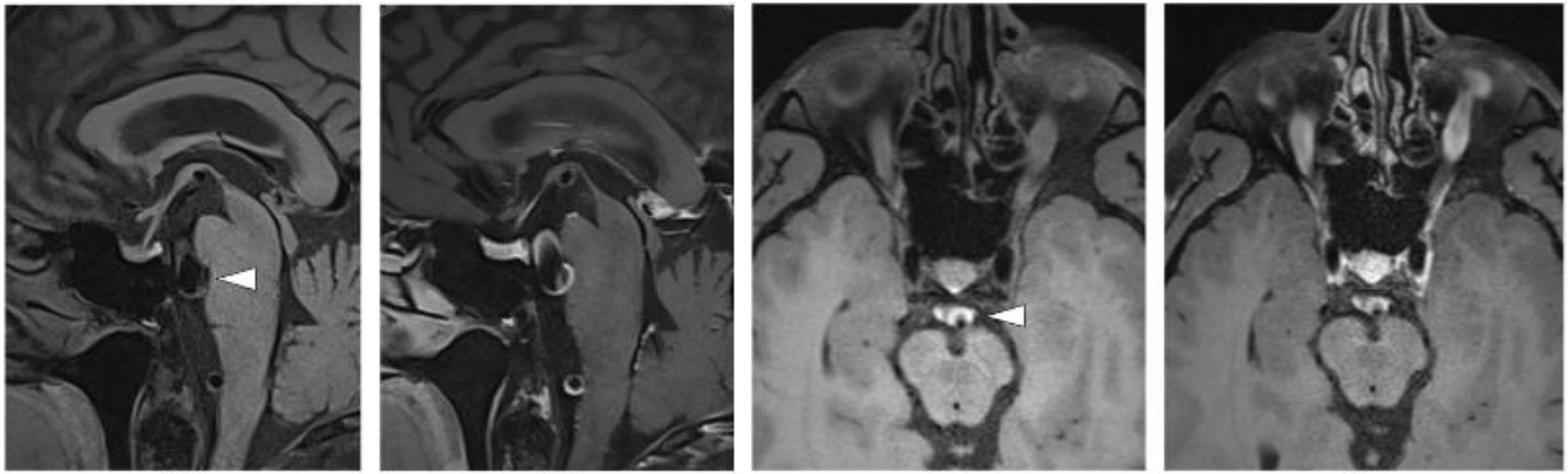
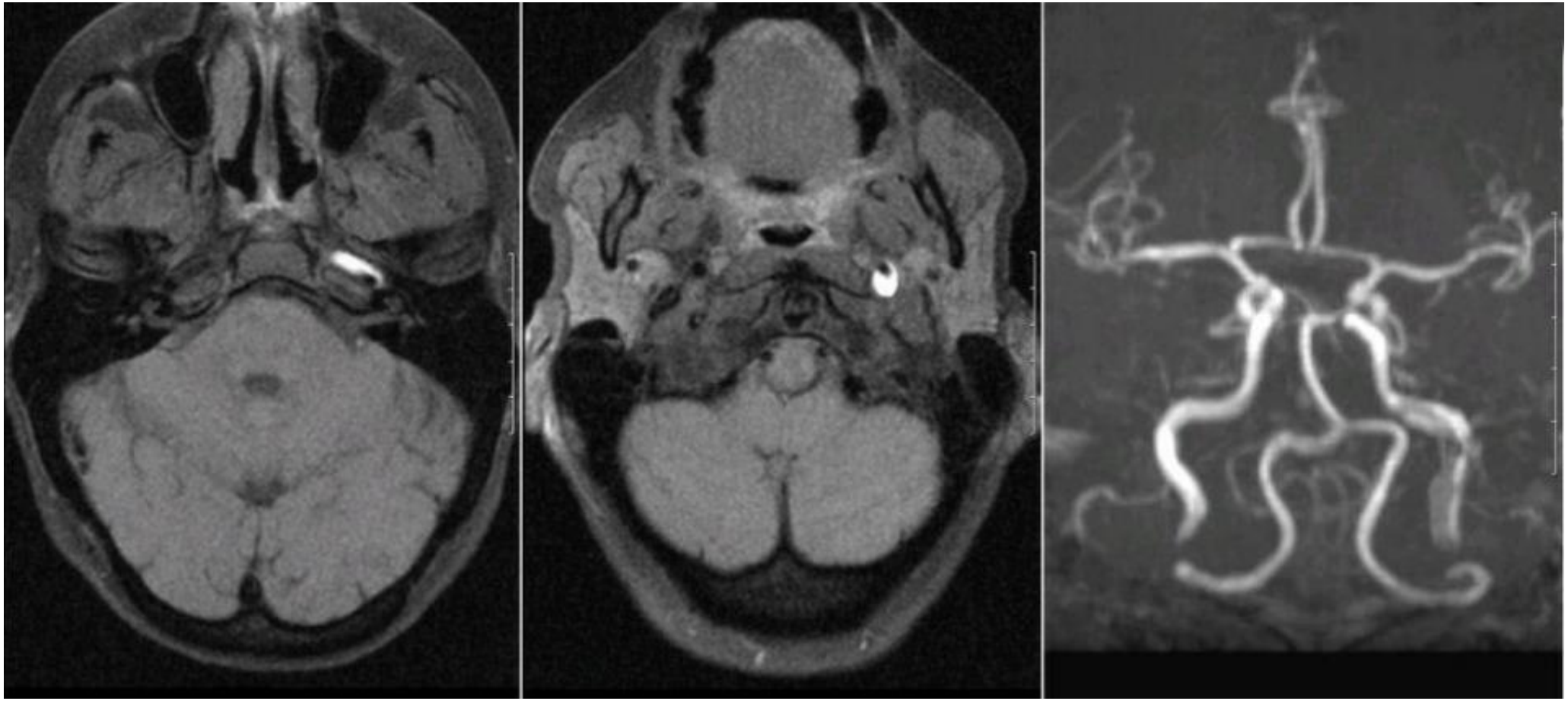


Figure 2 Intracranial arterial dissection. (a) Unenhanced and (b) contrast-enhanced sagittal T1W vessel wall images depict luminal flap in the basilar artery (arrowhead in a), associated with eccentric wall enhancement (arrow in b). (c) Unenhanced and (d) contrast-enhanced axial T1W vessel wall images from a different patient depict intramural haematoma along the basilar artery (arrowhead in c), without appreciable wall enhancement (arrow in d).

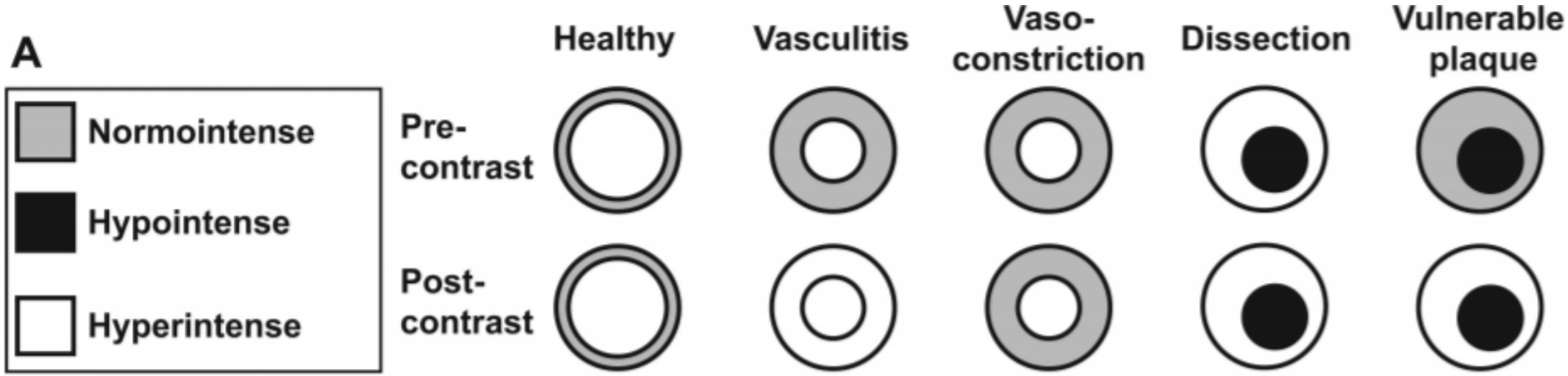


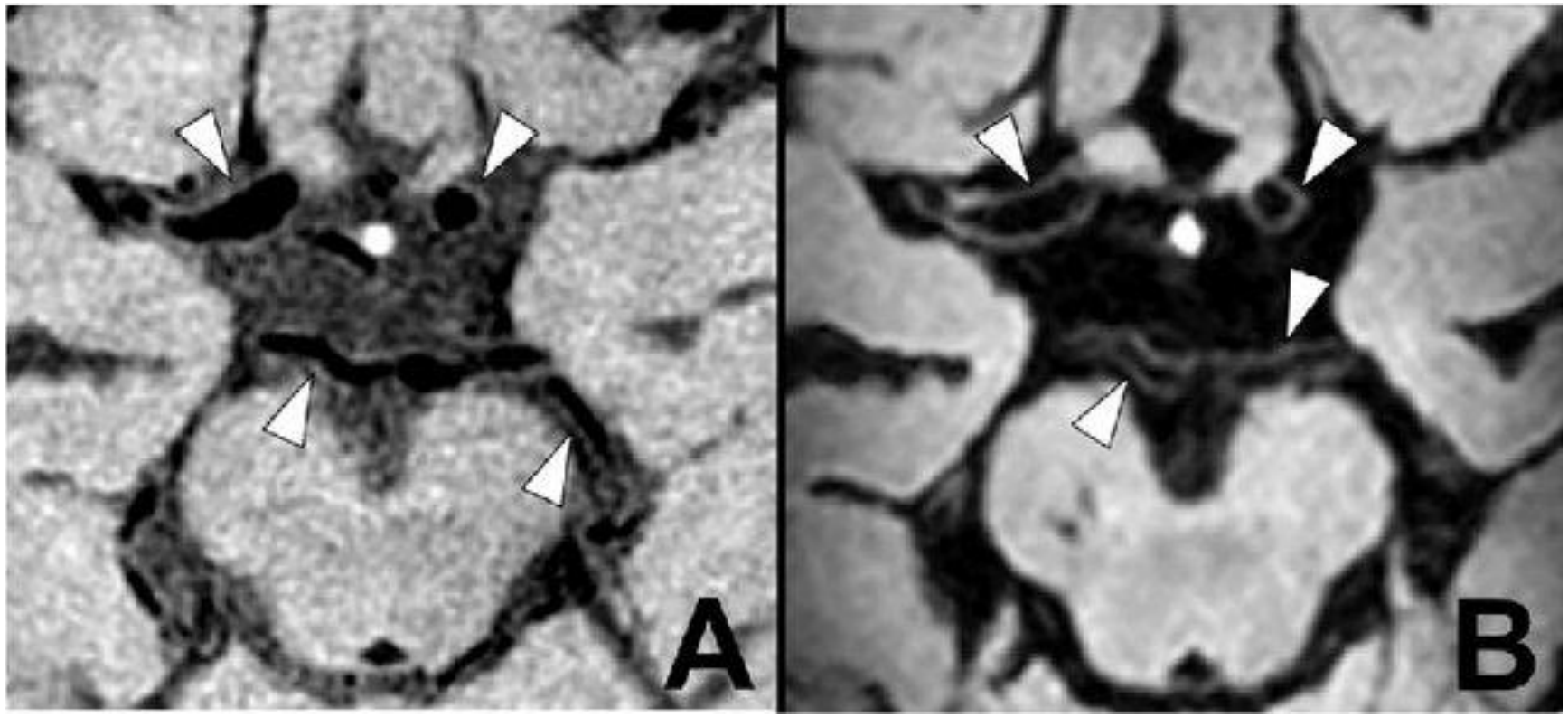
Axial fat suppression MRI

MRA

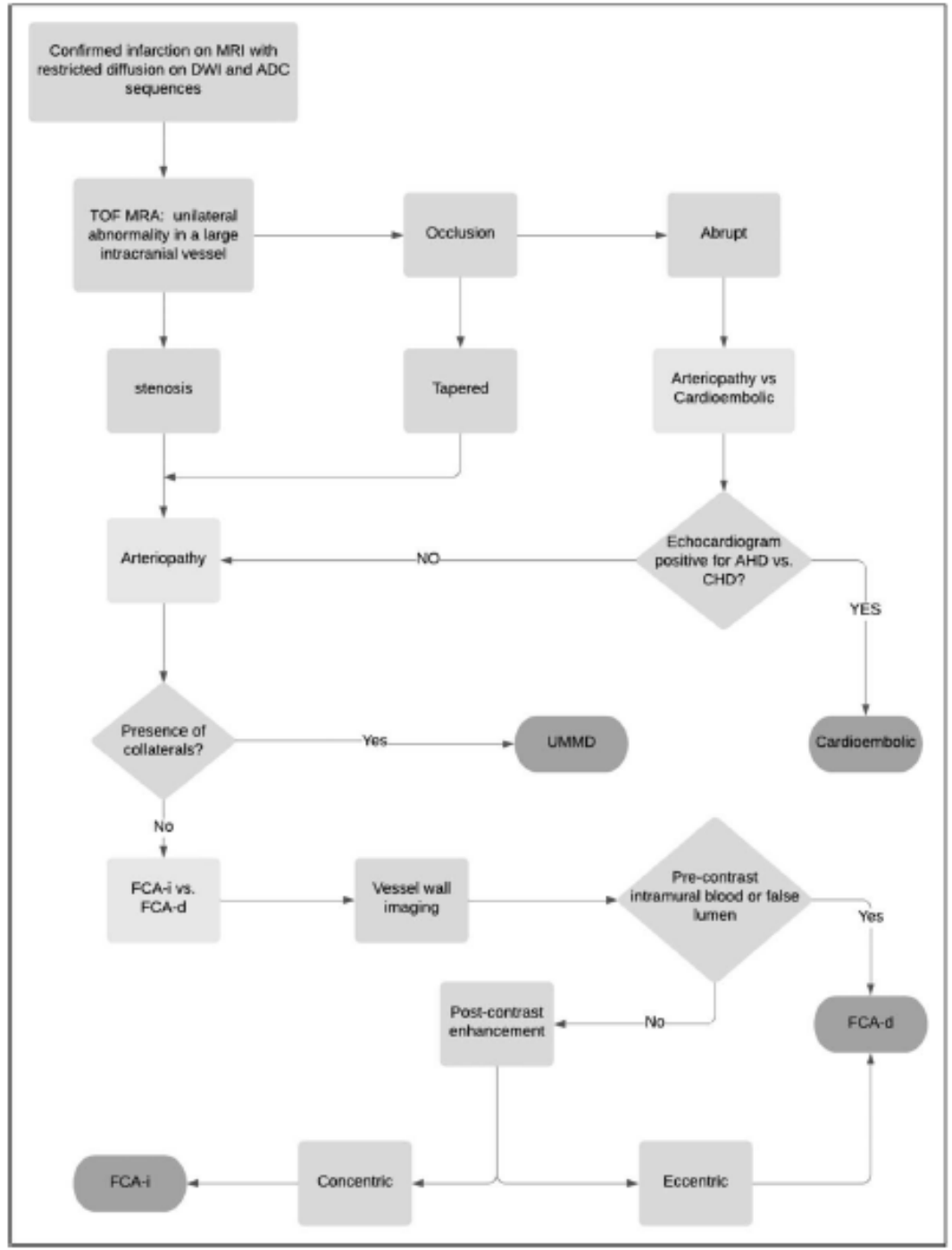
Vessel wall enhancement of MCA – secondary to varicella

Different patterns - VWI





VWI


Confirmed infarction on MRI with restricted diffusion on DWI and ADC sequences
TOF MRA: unilateral abnormality in a large intracranial vessel
Occlusion
Abrupt
stenosis
Tapered
Arteriopathy vs Cardioembolic
Arteriopathy
NO
Echocardiogram positive for AHD vs. CHD?
YES
Presence of collaterals?
Yes
UMMD
Cardioembolic
No
FCA-i vs. FCA-d
Vessel wall imaging
Pre-contrast intramural blood or false lumen
Yes
Post-contrast enhancement
No
FCA-d
FCA-i
Concentric
Eccentric

Serum and CSF Markers

- VIPS Study
  - Arteriopathy severity in children with FCA correlated with **acute serum levels of CRP** but not other inflammatory markers
  - CSF
    - IL 6, IL8, CXCL1 – RAISED
    - Viral PCR
- Other markers for inflammatory disease
  - ANA, C3, C4

Treatment – thrombolysis and thrombectomy

- Strong evidence in adults – benefit of reperfusion therapies in stroke
- Pediatric data
  - Limited evidence (retrospective case reports / small uncontrolled series)
- Current guidelines
  - Allow for TPA - >2 years (same timeline as adults)
  - FCA-i not a contraindication to TPA
  - Contraindications
    - Moya Moya
    - Intracranial dissection
    - PACNS
  - Thrombectomy – few cases reports on clot retrieval in children
    - More studies needed
- Local – time to make a diagnosis is way beyond 4 – 6 hours !!!

Treatment

- *As recurrences occur for the great majority in the first 6 months after the index event, aspirin 5 mg/kg/day is recommended for at least 18 months to 2 years.*

Antiviral treatment

- Role of acyclovir in VZV positive patients
  - Acyclovir given until PCR negative
  - Acyclovir recommended for 2 weeks
    - Strong association between herpes group of infection and stroke
    - Varicella zoster and focal cerebral arteriopathy

Immunotherapy - Steroids

- Australian Swiss study
  - 21 children (Steroid + aspirin) vs 53 (aspirin)
  - Significant lower levels of neurological impairment in combined therapy group
  - Methylprednisone – 10 – 20mg per kg for 3 – 5 days
    - Oral taper over several weeks
- PASTA TRIAL
  - Multicentre, randomized control trial
  - Outcome – neurological improvement at 6 months
- FOCAS TRIAL
  - PHASE 2
  - North American study
  - Assess the safety and dosing of steroids
  - Use FCASS score

Serial vascular imaging

- Repeat imaging at 3 months and 12 months
- Aim of repeat imaging
  - Increases diagnostic certainty
    - Differentiate between the subtypes
    - monitor for vascular progression
  - Radiological progression unexpected in FCAd
    - Surveillance imaging still important as can develop false aneurysms

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Initial management	Consider tPA if presents <4.5 h Aspirin Herpes group viral serology. Consider CSF Herpes group viral PCR and IgM/IgG Consider steroids ± acyclovir	Aspirin	Correct dehydration and fever Aspirin Early neurosurgical consultation
Vascular progression	Progression in first 6 months followed by stabilization, improvement or resolution	Not typically progressive but can develop pseudoaneurysm	Progressive occlusion of distal ICAs and branches of Circle of Willis. Increasing collateral formation Recurrent strokes and TIAs
Recurrence risk	25%	19%	35%
Surveillance	3 months, 12 months MRI and MRA	3 months, 12 months MRI and MRA	DSA and assessment of cerebral perfusion reserve. Indirect or direct revascularization surgery

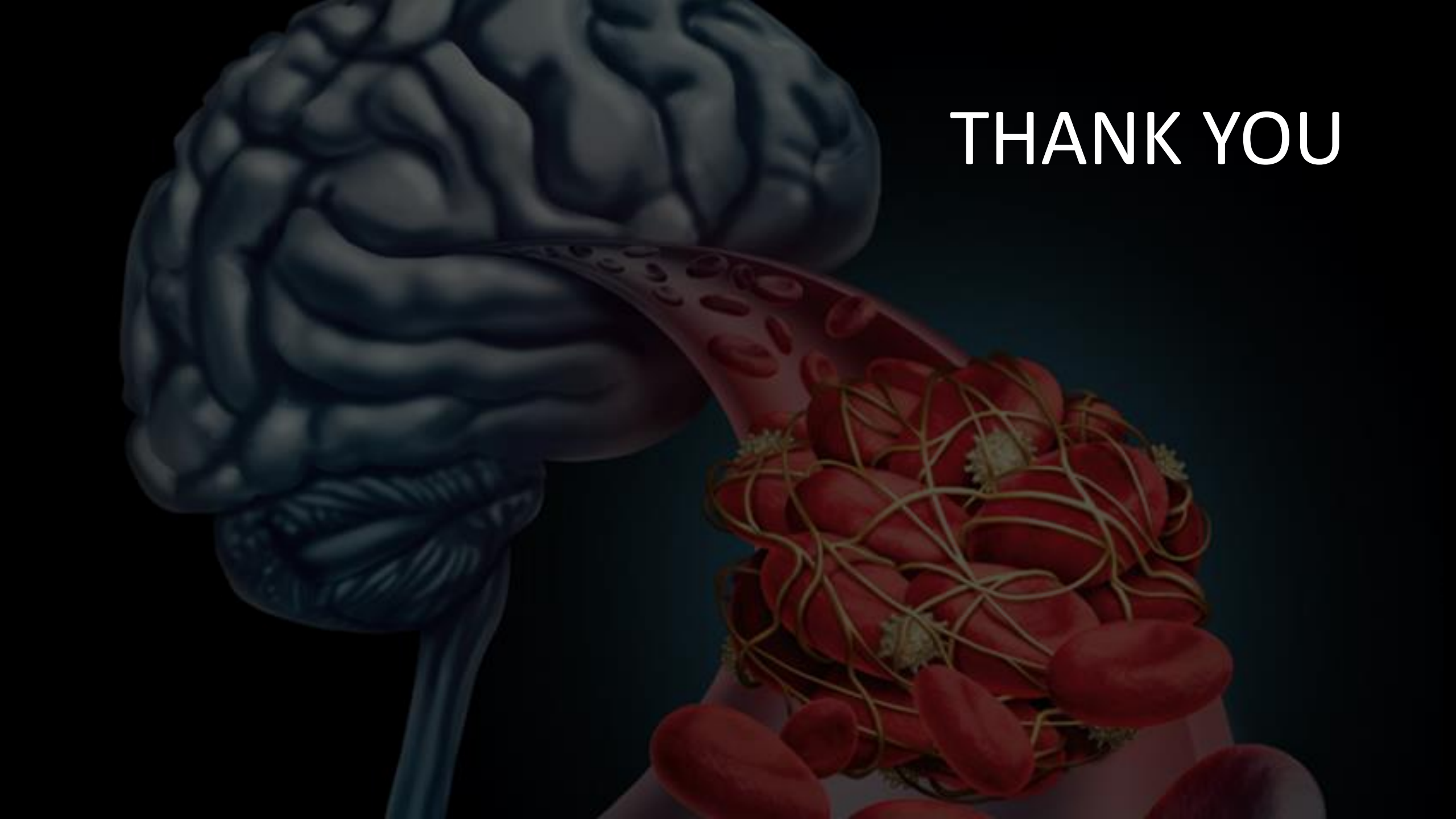
Adopted from Focal cerebral arteriopathy and childhood stroke – Fearn and Mackay et al

Outcome

- Complete or near complete recovery in more than 40% of cases
- Mainly monophasic
  - Recurrence – 3 – 25%
- FCA reported in young adults
  - Similar mode of presentation, radiological course and good long term outcome

Summary

- FCA – unilateral infarction
- Monophasic illness
- Two subtypes – recent classification
- Investigation
  - MRI /MRA/ catheter angiography. Newer imaging modalities – VWI
  - CSF
  - Serum inflammatory markers
- Rescreening MRI – 3 months and 12 months
- Treatment
  - Aspirin
  - Acyclovir
  - ?Steroids


THANK YOU