Red Flags, Key Diagnostic Markers and Early Intervention in Children with Stroke

PANDA Workshop
November 23rd, 2019

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Staff Neurologist, Division of Neurology,
The Hospital for Sick Children

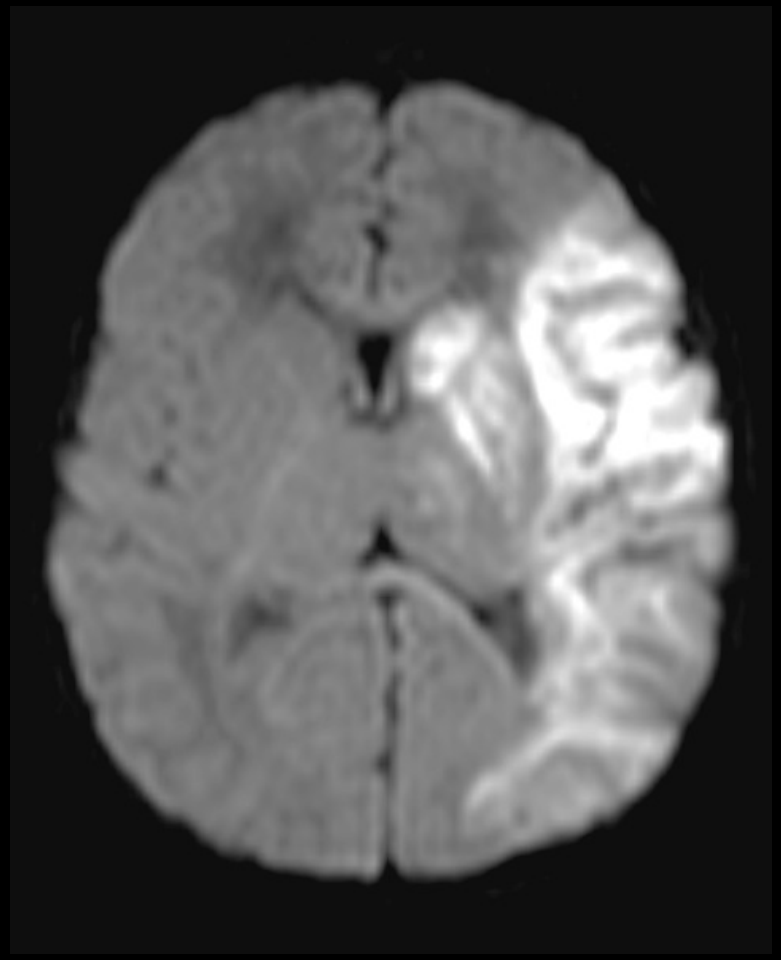
Objectives

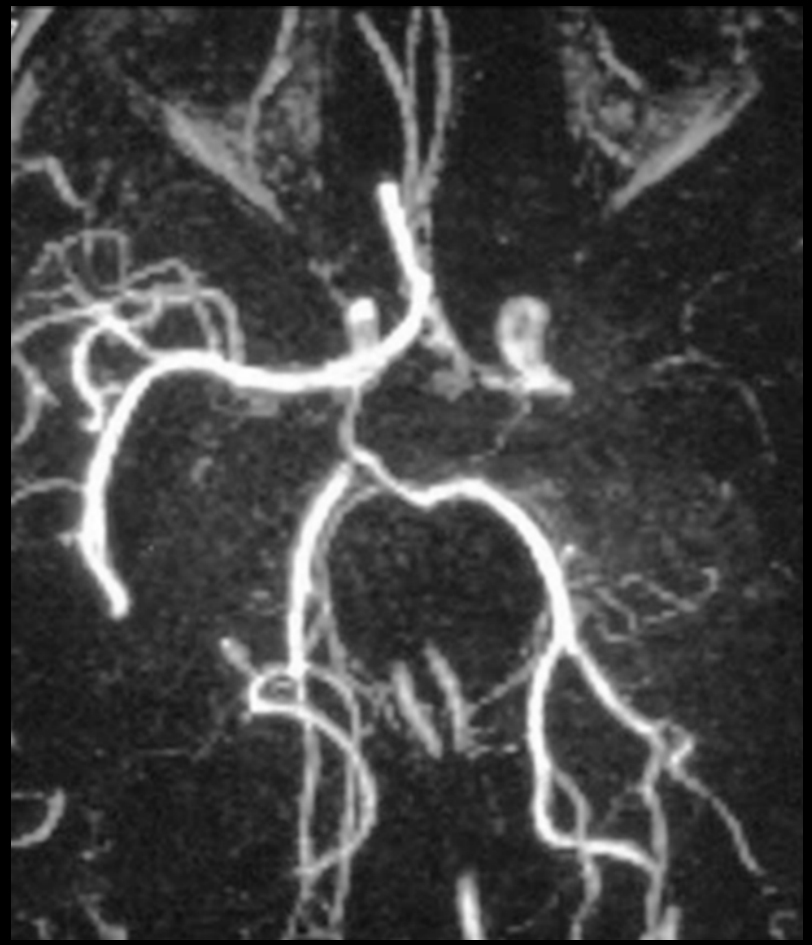
- Diagnosis
- Risk stratification
- Outcome prediction
- Early intervention

Questions ?

- Will my child have another stroke?
- How will he/she recover?
- Can I do something?

Childhood Arterial Ischemic Stroke

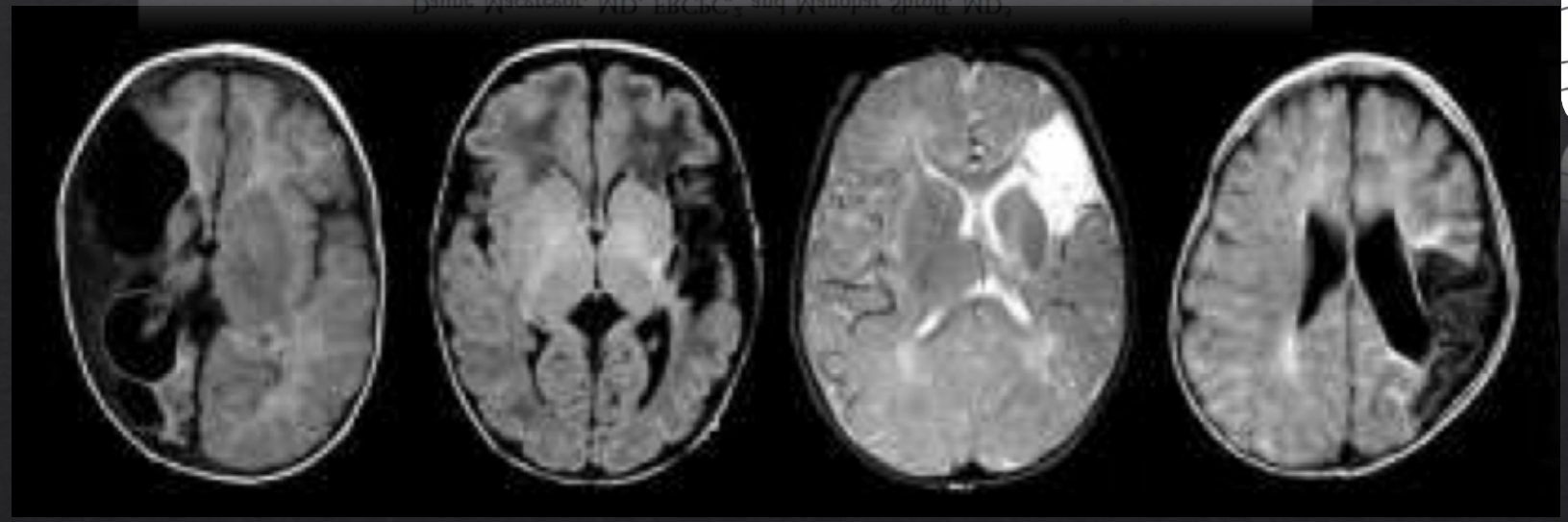


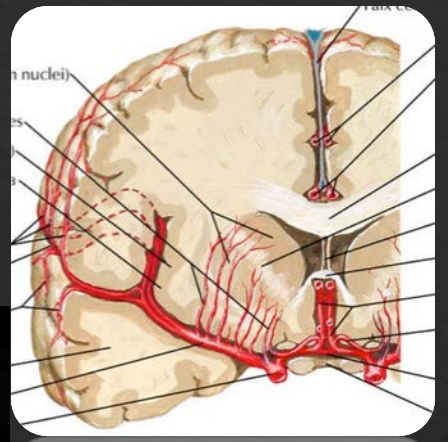


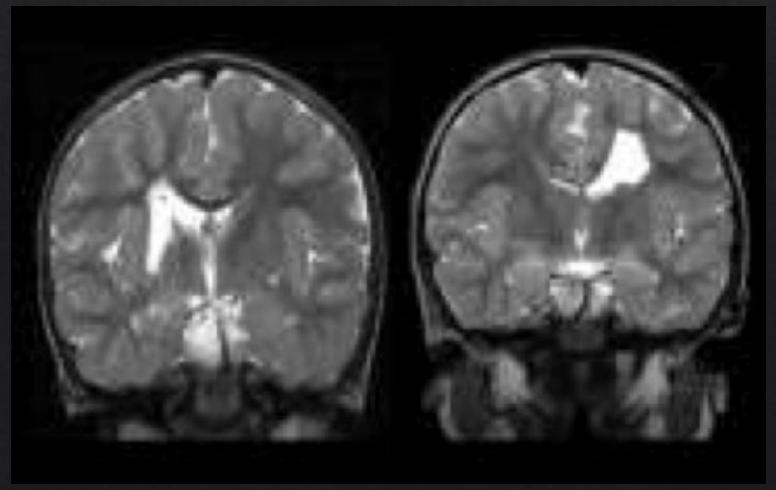
Diagnosis I

Presumed Perinatal Ischemic Stroke: Vascular Classification Predicts Outcomes

Adam Kirton, MD, MSc, FRCPC,[1] Gabrielle deVeber, MD, MHSc, FRCPC,[2] Ann-Marie Pontigon, BScH,[2] Daune Macgregor, MD, FRCPC,[2] and Manohar Shroff, MD[3]





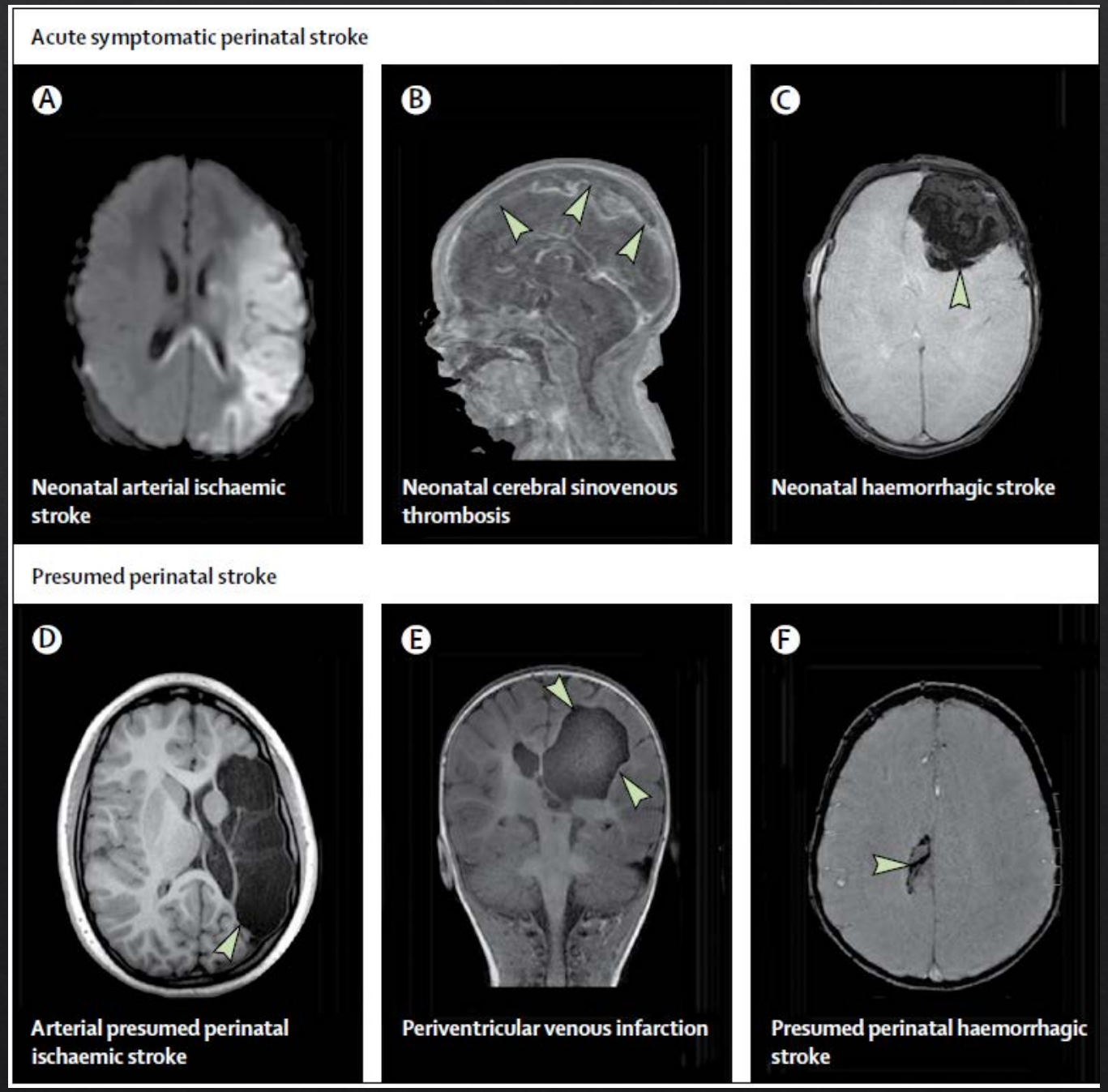


Classification

- Perinatal Stroke Classification based on three questions :
  - When did the injury occur (before or near birth)?
  - What was the mechanism (ischemic or hemorrhagic; arterial or venous)?
  - When was the child first symptomatic (acutely as a newborn or later in infancy)?

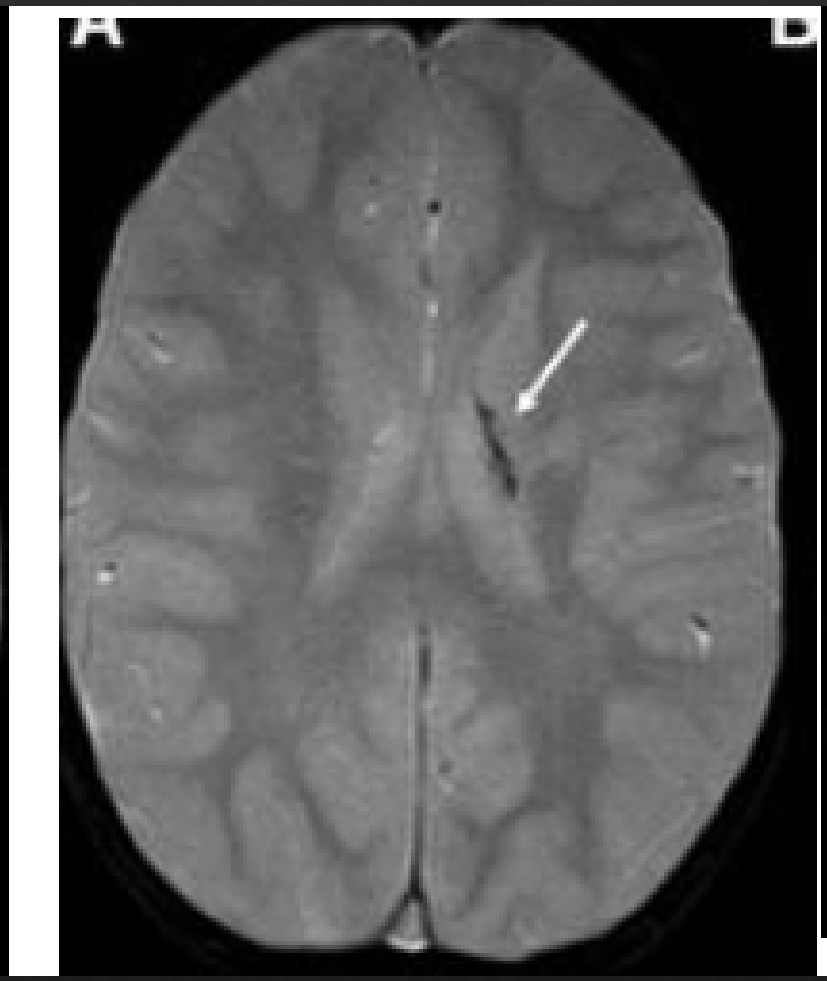
50 %

50 %

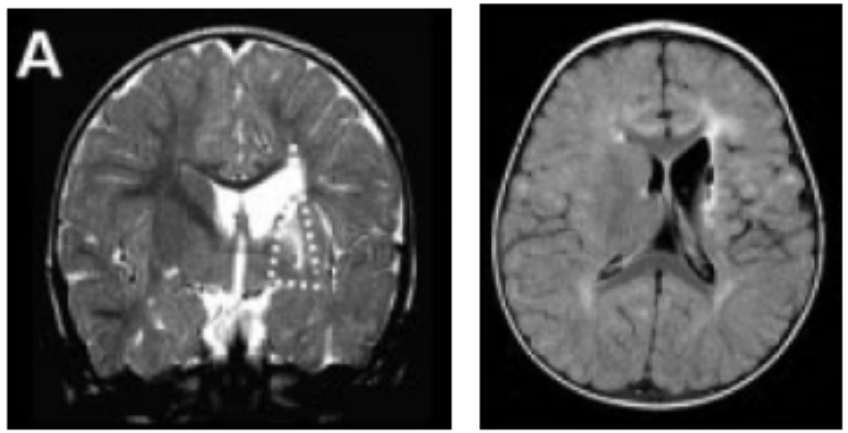
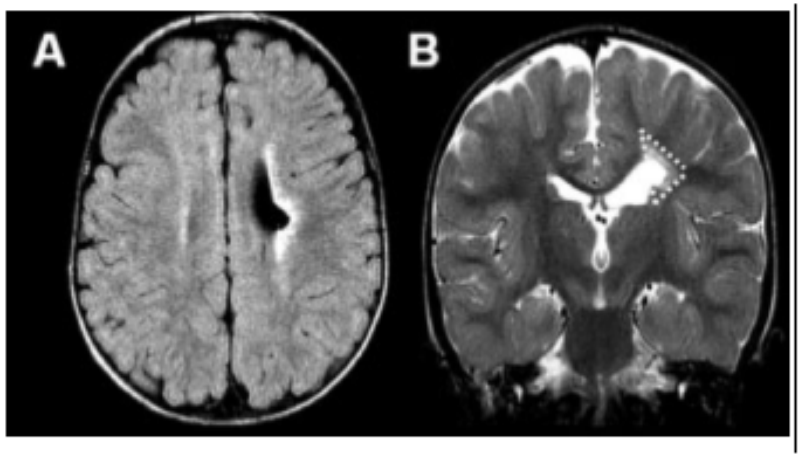


Dunbar & Kirton, The Lancet Child & Ado Health, 2018

MRI Appearances Venous Injury

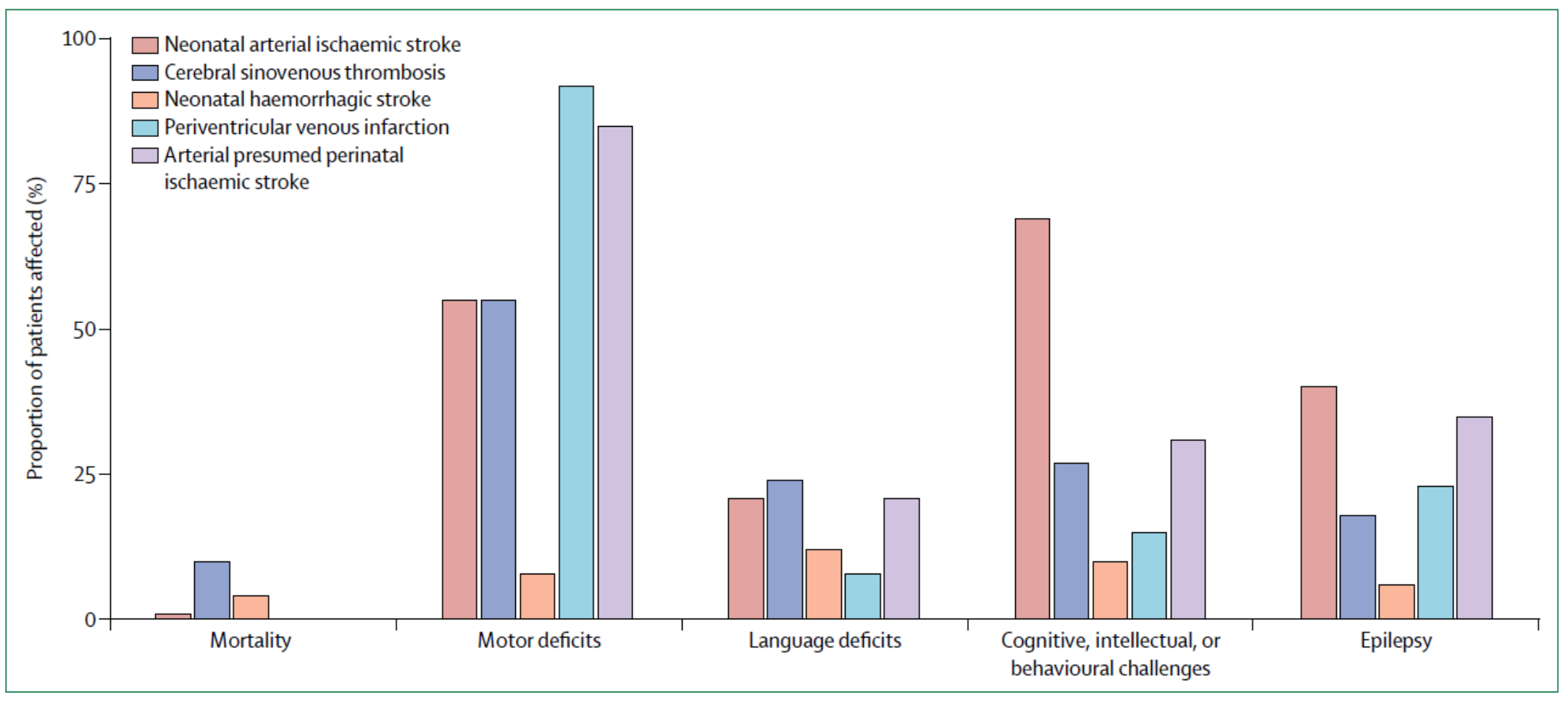


PPVI : Differential diagnosis

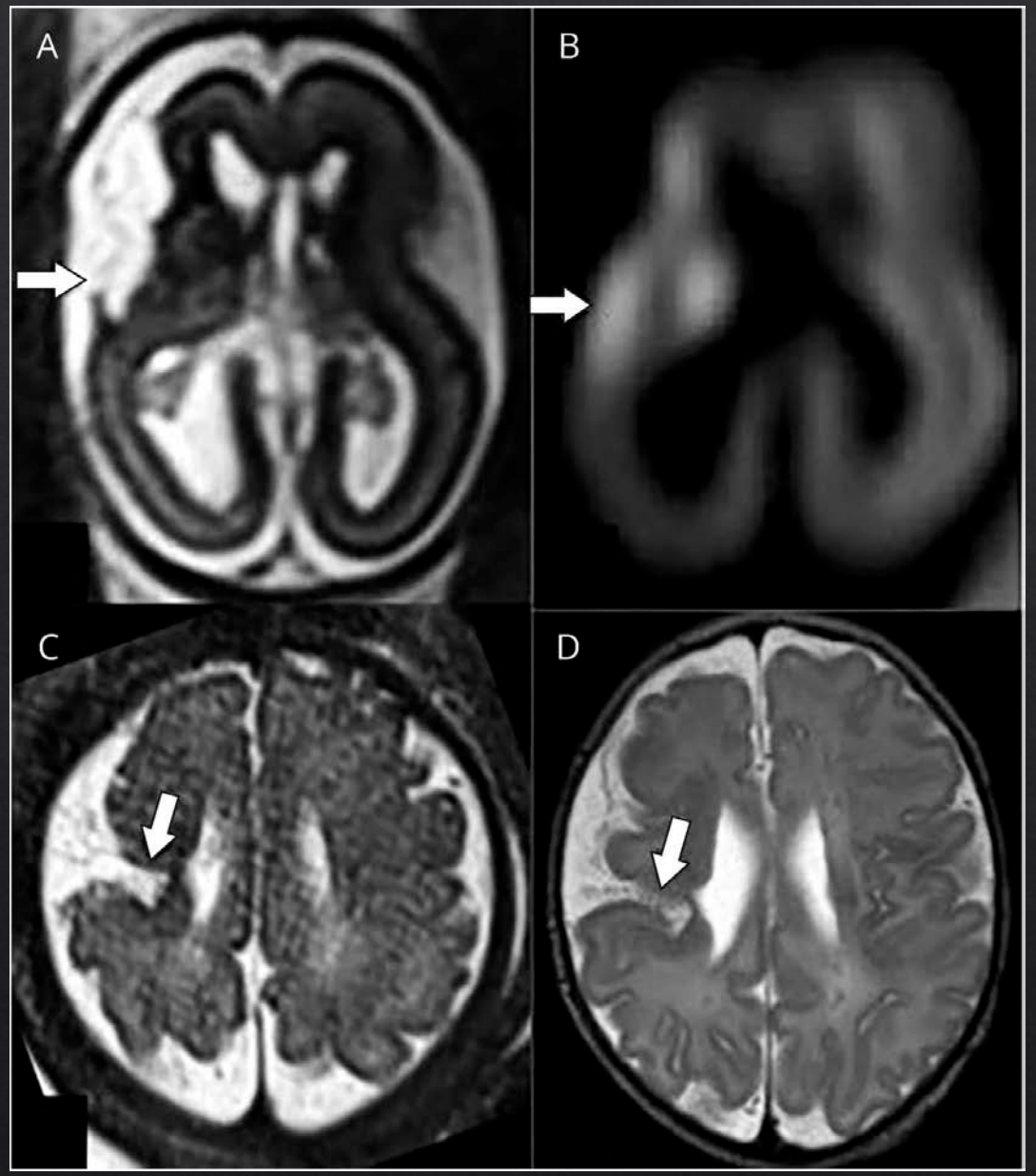
Lateral lenticulostriate presumed perinatal stroke	***Periventricular venous infarction***
BG involvement > Periventricular WM	*Periventricular WM > BG involvement (caudate body and posterior putamen)*
	Maximal at Centrum semiovale > corona radiata + PLIC
Cranial triangle 	*Caudal triangle* 
No hemosiderin gradient	*Presence of hemosiderin gradient (within infarct or germinal matrix)*

Courtesy of M. Moharir

Outcomes



Kirton & Dunbar, The Lancet Child & Ado Health, 2018

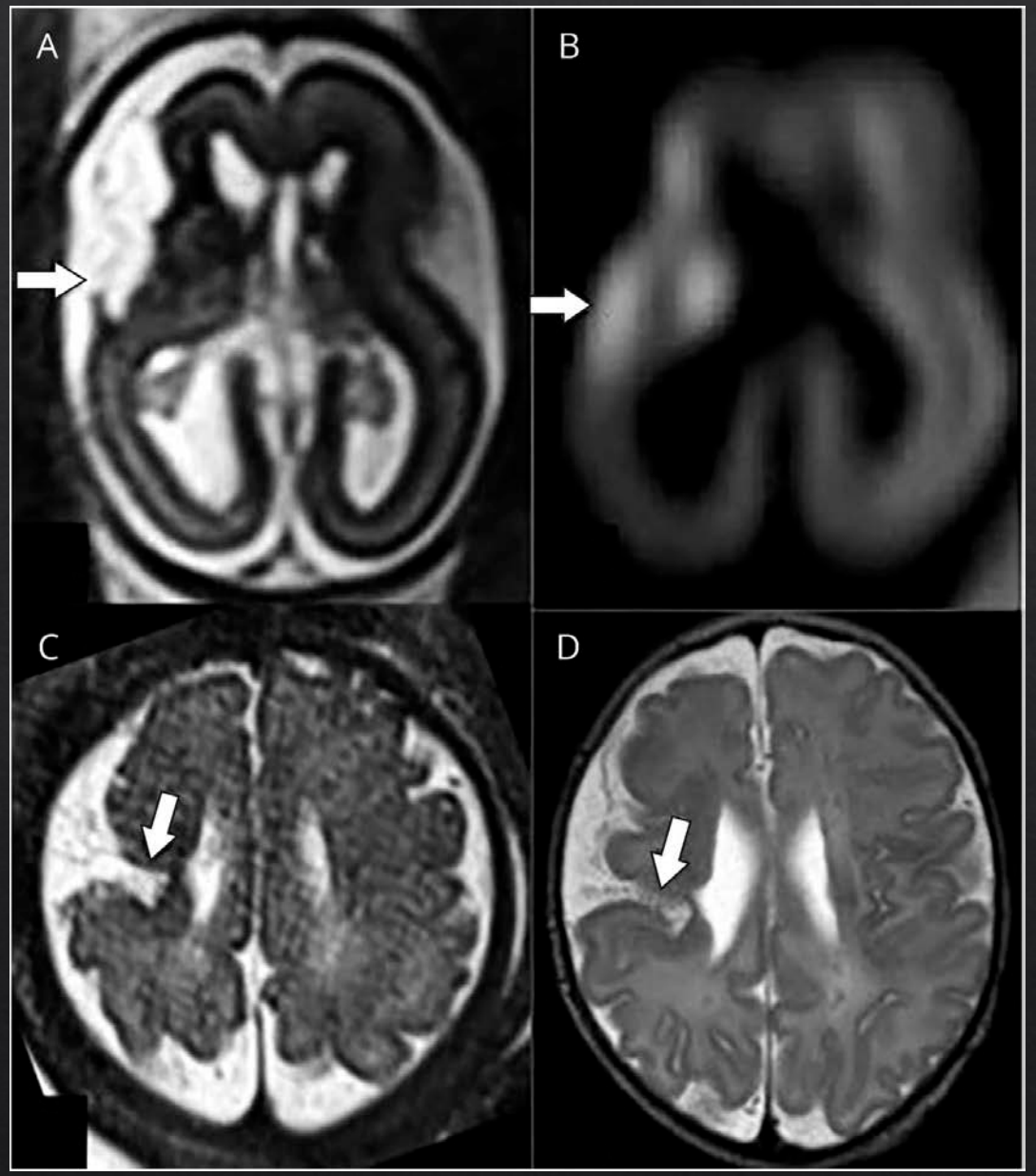


A US 21/40 gestation increased signal intensity within the entire thickness of cortical mantle, and obscuration of cortical layers in affected zone

B Acute DWI R MCA territory at 21/40

C Focal volume loss w parenchymal cleft

D Schizencephalic cleft lined by gray matter extending from the pial surface to the ventricular margin with focal tenting of the ventricular margin on postnatal testing



CLINICAL/SCIENTIFIC NOTES

COL4A1 and fetal vascular origins of schizencephaly

Roha Khalid, MD, Pradeep Krishnan, MD, Kathleen Andres, NP, Susan Blaser, MD, Steven Miller, MD, Mahendranath Moharir, MBBS, and Nomazulu Dlamini, MBBS, PhD

Neurology® 2018;90:232-234. doi:10.1212/WNL.0000000000004890

A US 21/40 gestation increased signal intensity within the entire thickness of cortical mantle, and obscuration of cortical layers in affected zone

B Acute DWI R MCA territory at 21/40

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COL4A1-related disorders

- small-vessel brain disease of varying severity
- eye defects (retinal arterial tortuosity, Axenfeld-Rieger anomaly, cataract)
- systemic findings (kidney involvement, muscle cramps, elevated CK, cerebral aneurysms, Raynaud phenomenon, cardiac arrhythmia, and hemolytic anemia).

Mental Health

- Coppens AM, Roberts SD, Westmacott R, Crosbie J, **Dlamini N**, Williams TS. Secondary attention-deficit/hyperactivity disorder following perinatal and childhood stroke: Impact on cognitive and academic outcomes. Child Neuropsychology 2017: 30: pp 1-21.

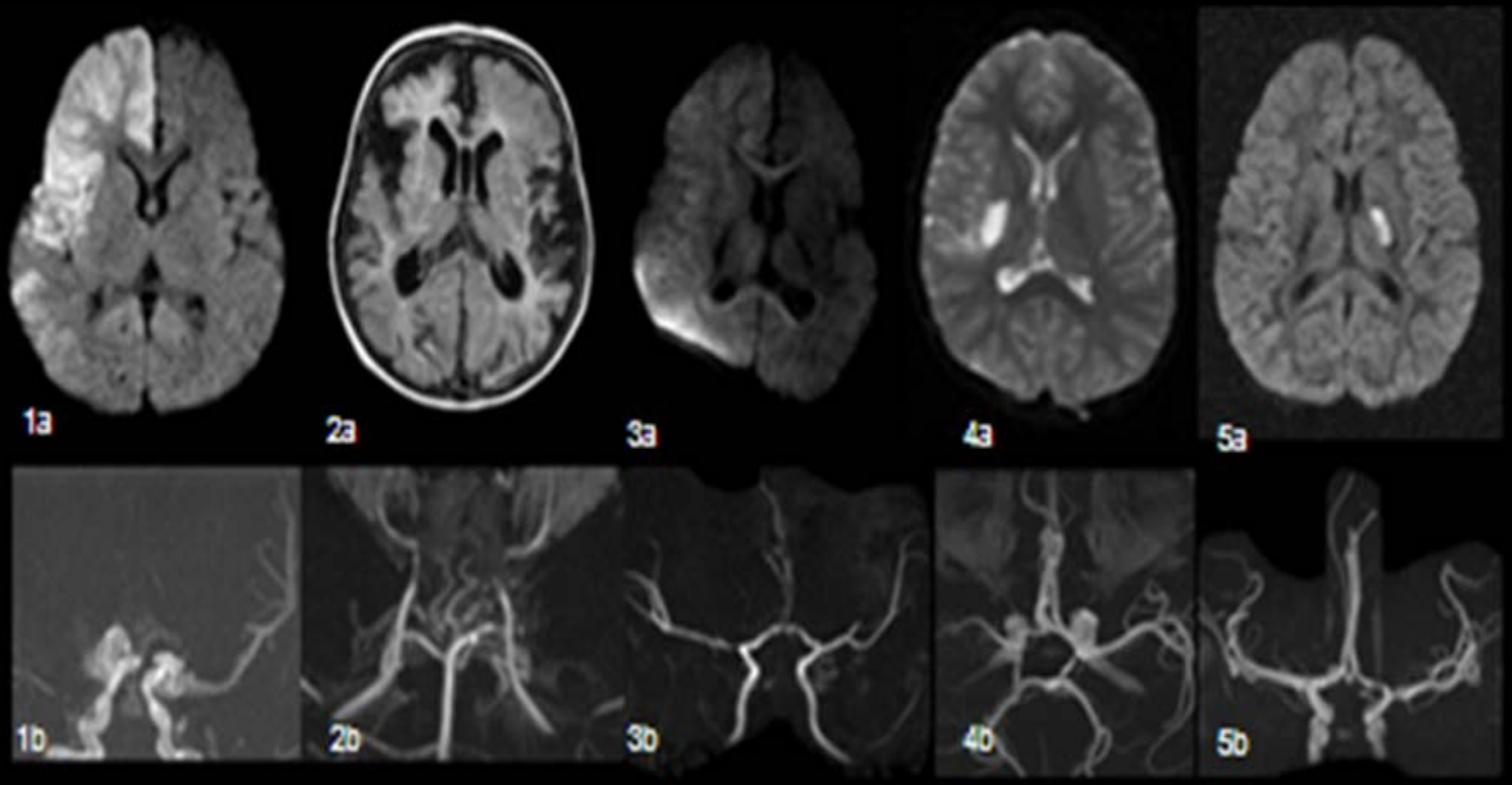
  - *13% received a post-stroke diagnosis of ADHD.*
  - *No clear association between brain lesions, size or laterality amongst this group,*
  - *children with presumed perinatal diagnoses and persistent seizures more likely to receive ADHD diagnosis*

- Westmacott R, McDonald K, deVeber G, MacGregor D**,** Moharir M, **Dlamini N**, Askalan R, Williams T. Neurocognitive Outcomes in Children with Unilateral Basal Ganglia Arterial Ischemic Stroke and Secondary Hemi-Dystonia. Child Neuropsychology 2017: 12: pp 1-15

  - children w BG stroke and dystonia had higher incidence executive function and attention problems, and less inhibitory control - ?maladaptive plasticity

Diagnosis II

Arteriopathies of Childhood



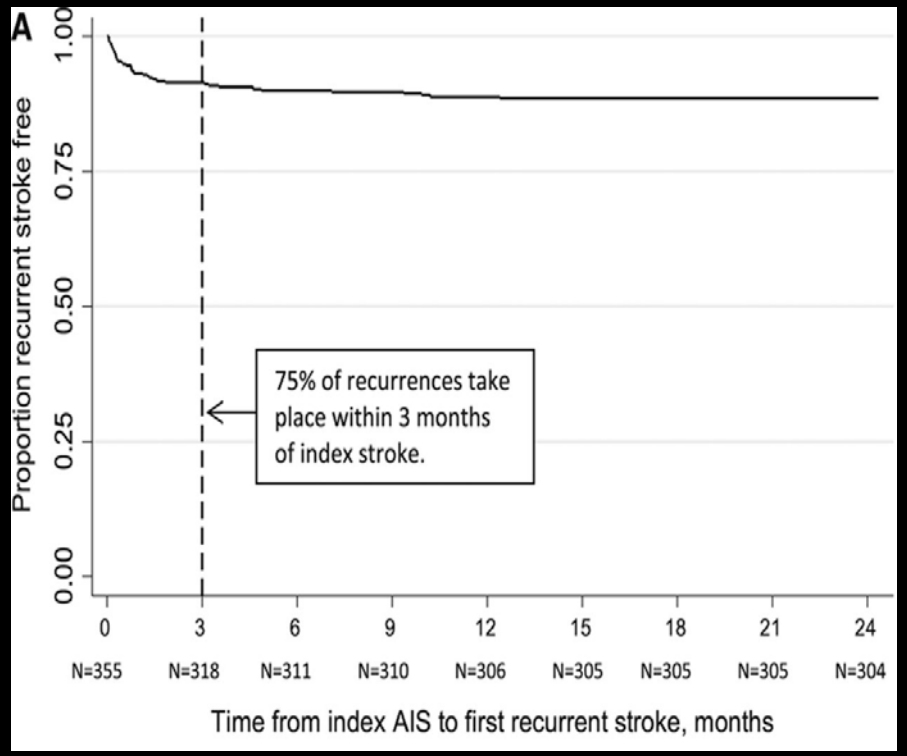
Bilateral MM

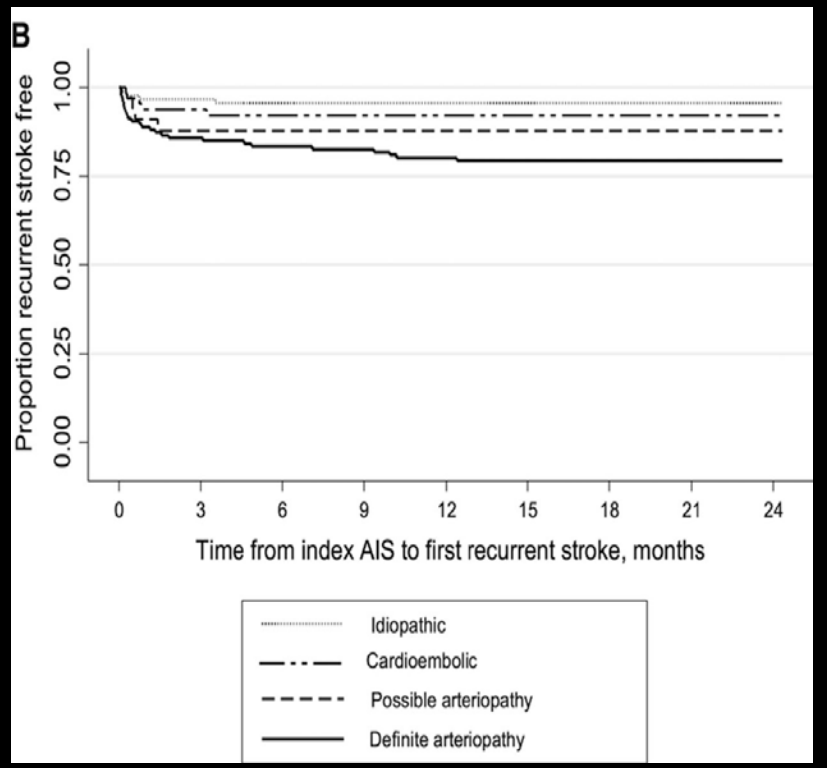
Takayasu arteritis

Transient Cerebral Arteriopathy

Risk of Recurrent Arterial Ischemic Stroke in Childhood: A Prospective International Study

Kaplan–Meier curves demonstrating recurrent stroke-free survival in (A) all 355 children with arterial ischemic stroke (AIS) and (B) the same children stratified by stroke subtype.





Idiopathic

Arteriopathy

32% Moyamoya; 25% Transient Cerebral Arteriopathy; 19% Dissection

Heather J. Fullerton et al. Stroke. 2016;47:53-59

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Commentary

Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children Workshop

Nomazulu Dlamini MD, PhD [a,*], Max Wintermark MD [b], Heather Fullerton MD [c,d], Stephen Strother PhD [e], Wayne Lee MSc [a], Bruce Bjornson MD [f,g], Kristin P. Guilliams MD [h,i], Steven Miller MD [a], Adam Kirton MD [j,k], Christopher G. Filippi MD [l,m], Alexandra Linds MSc [a], Rand Askalan MD, PhD [a], Gabrielle deVeber MD [a]

Pediatric Neurology xxx (2017) 1–13

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Review Article

The Potential for Advanced Magnetic Resonance Neuroimaging Techniques in Pediatric Stroke Research

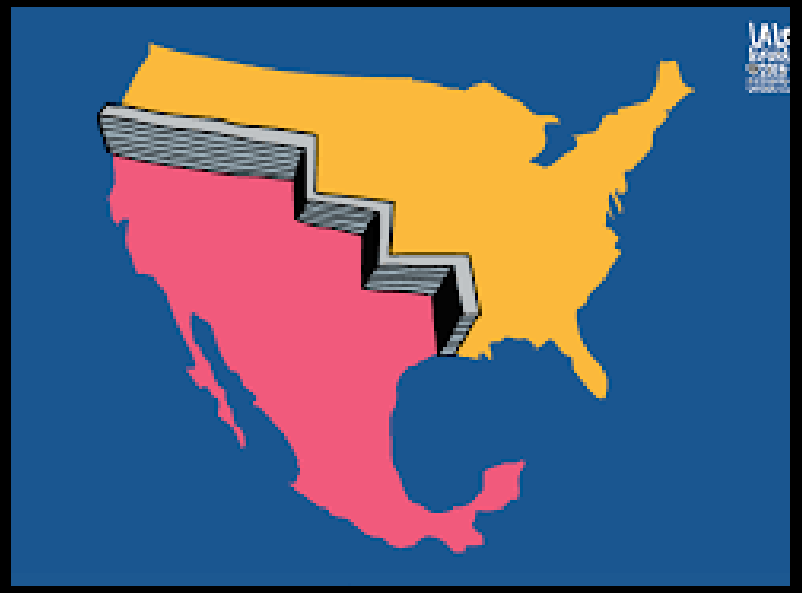
Trish Domi PhD [a,b], Arastoo Vossough MD, PhD [c], Nicholas V. Stence MD [d], Ryan J. Felling MD, PhD [e,f], Jackie Leung MASc [a,b], Pradeep Krishnan MD [g], Christopher G. Watson PhD [h,i], P. Ellen Grant MD [j,k], Andrea Kassner PhD [a,b,l,*]

Imaging Stroke Mechanisms

Cerebral Artery Wall Pathology	Wall Imaging MRI
Cerebral artery lumen (e.g., occlusion)	MRA
Perfusion drop	Perfusion imaging, CVR, SWI
Brain tissue cell death	DWI, DKI
Recanalization	MRA
Reperfusion	Perfusion imaging, CVR
Blood-brain barrier breakdown	Gadolinium enhancement
Hemorrhagic conversion of bland infarct	SWI
Neuronal salvage	??
Reperfusion injury	DCE
Plasticity and repair	fMRI, MEG
Rewiring	DTI

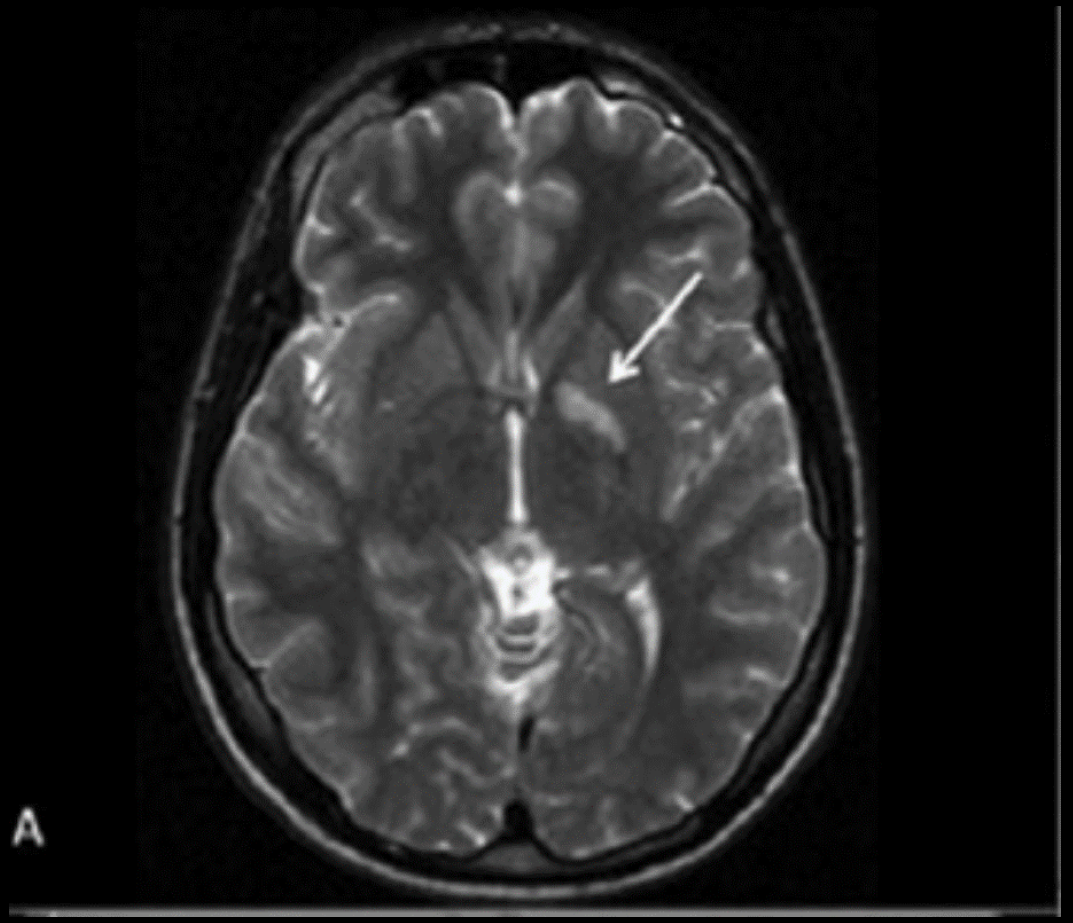
Dlamini et al Ped Neurology 2017

Wall Imaging

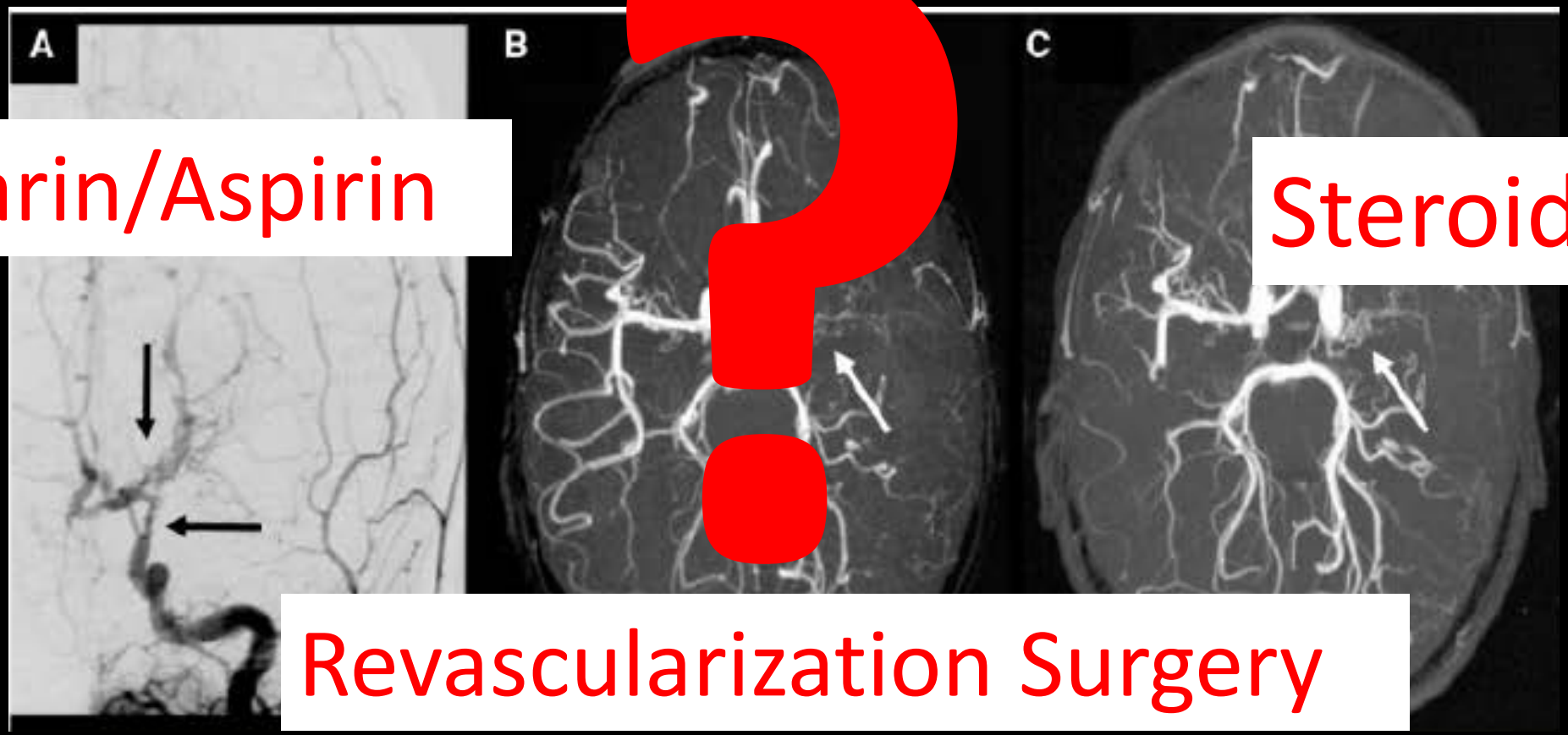


Amy

3 year old with sudden right hemiparesis



Treatment



Heparin/Aspirin

Steroids

Revascularization Surgery

Transient cerebral arteriopathy
vs
Intracranial Dissection

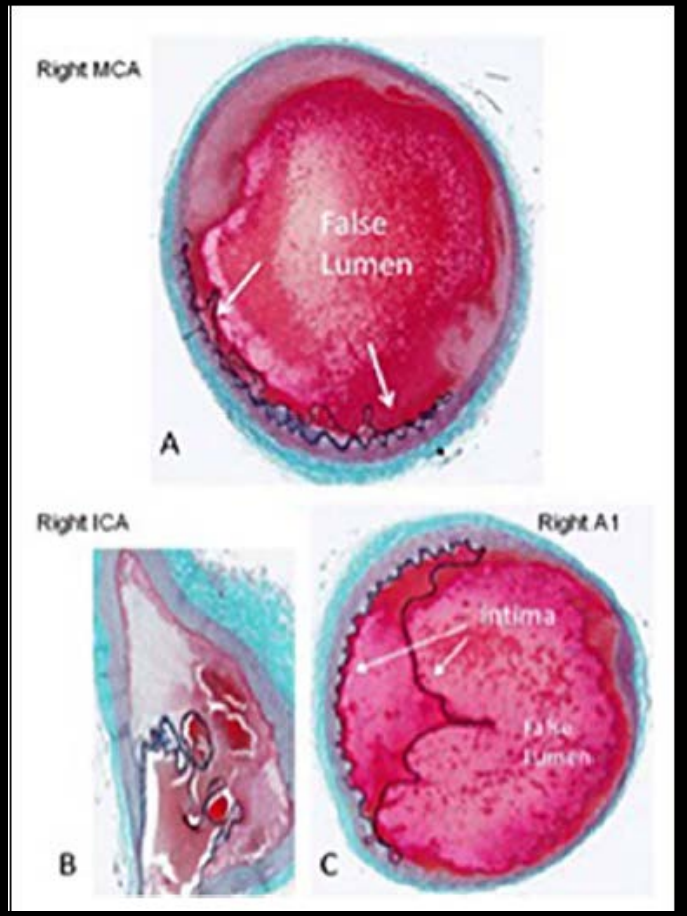


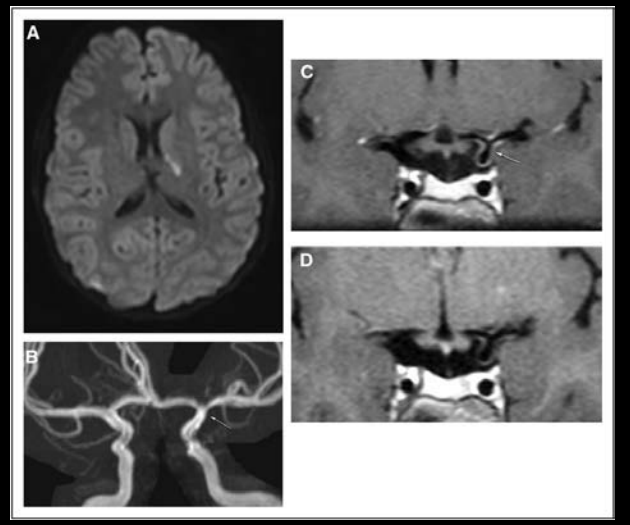
Table 1. Initial Radiological and Pathological Findings

Case	Age, y, (sex)	Trauma	Infarct Territory[a]	Vascular Imaging[a]	Initial Diagnosis	Final Diagnosis
1	10 y (F)	No	R MCA[a] (C; BG)	R dICA/ M1[a] hMCA	TCA	Postmortem ICAD
2	6 y (F)	No	R MCA[b] (C; BG)	R M1[b]	TCA	Postmortem ICAD
3	6 y (F)	Minor head bump	L MCA/ACA[a] (C; BG)	L dICA/M1/A1[a] hMCA	TCA	Postmortem ICAD
4	17 y (M)	No	L MCA[a] (BG)	L dICA/M1/A1[b]	TCA	ICAD

Dlamini et al, J Child Neuro 2011

Arterial Wall Imaging

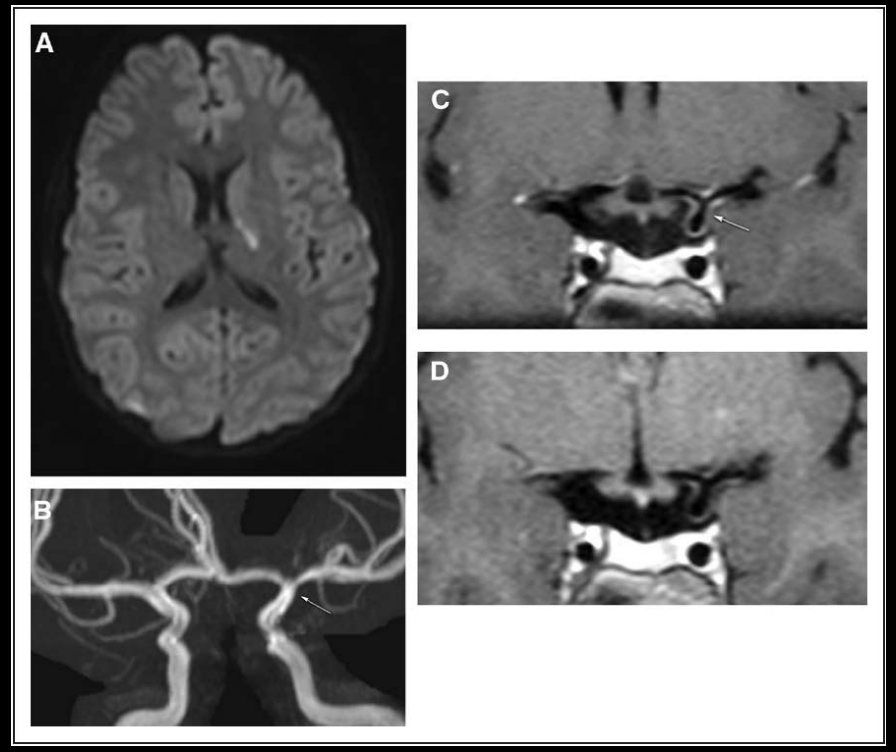
- Feasible
- Patterns of enhancement suggestive of aetiology
- Temporal relationship to enhancement, and disease activity



Dlamini et al, Stroke 2018;
Stence et al, Stroke 2017;

Arterial Wall Imaging

- Contrast
- Mechanism of enhancement
- Time
- Mimics
- Lack of aetiologic specificity
- Feasible



Dlamini et al, Stroke 2018;
Stence et al, Stroke 2017;

Predicting Outcome

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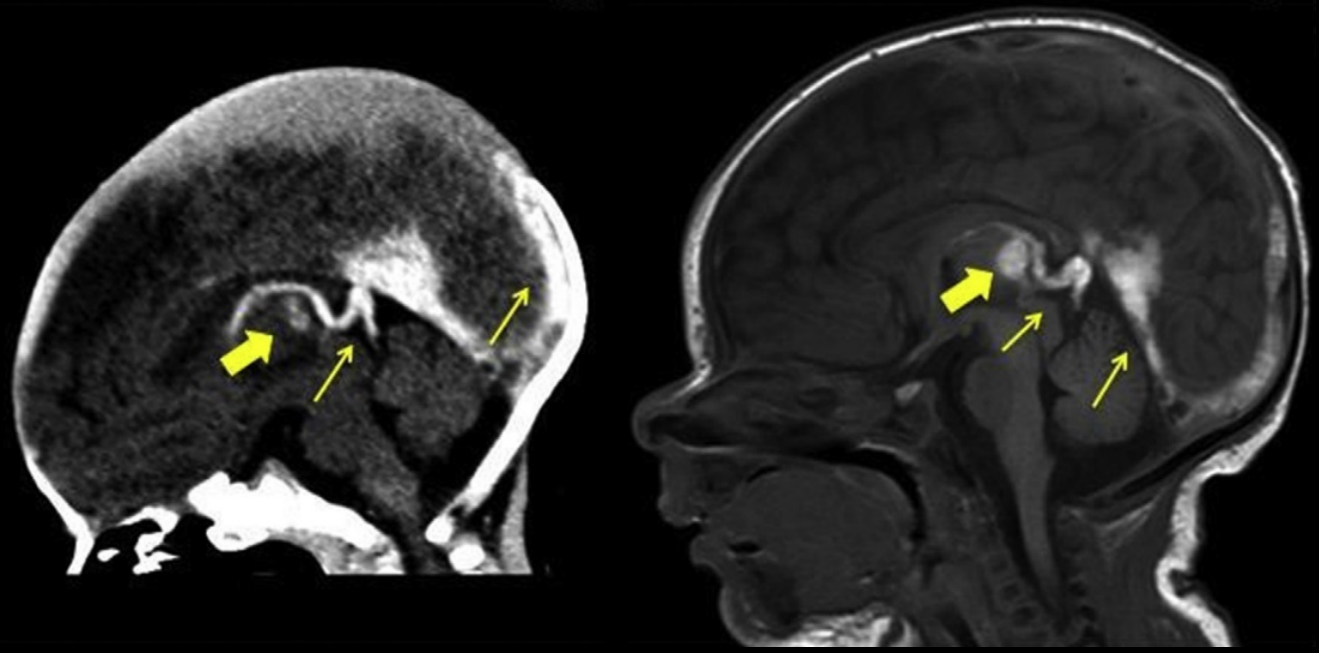
Clinical Observations

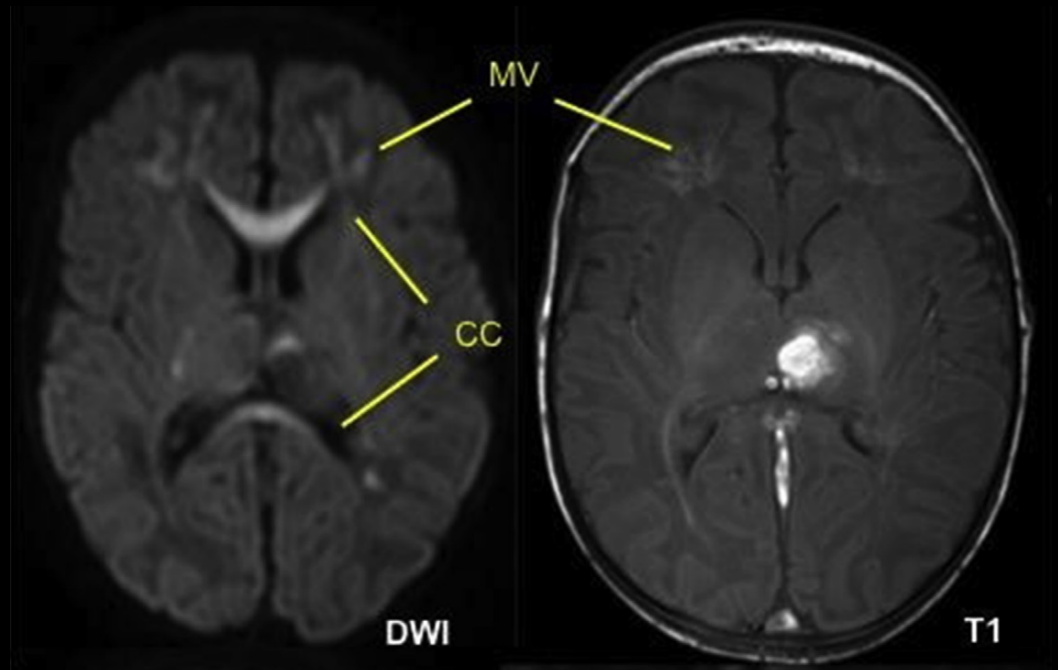
Prognostication Value of Descending Corticospinal Tract DWI Signal in Neonatal Cerebral Sinovenous Thrombosis

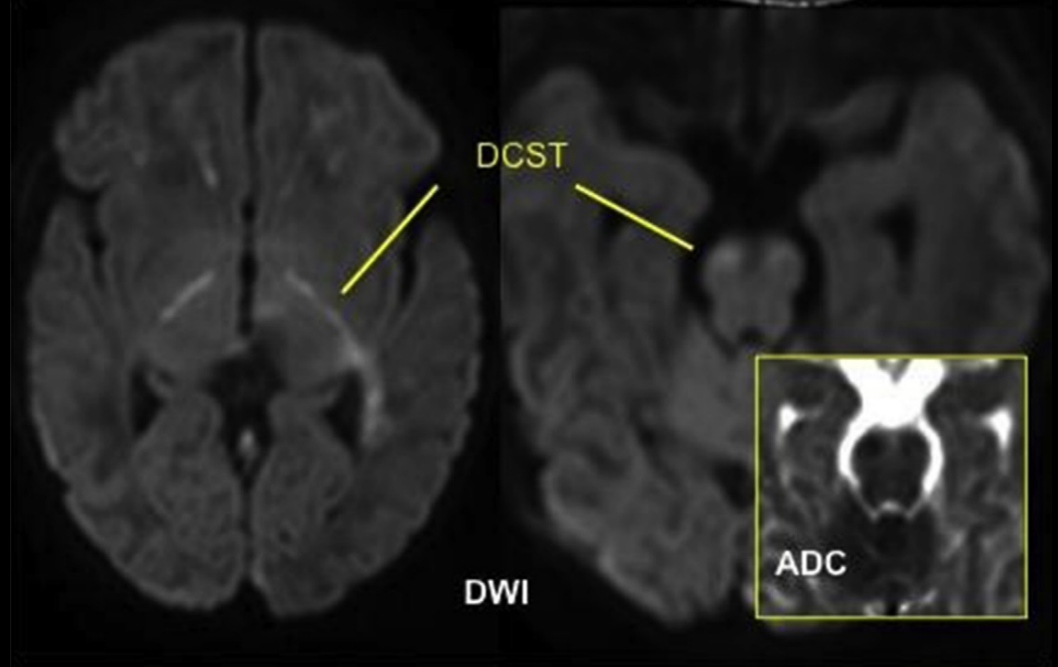
Matsanga Leyila Kaseka MD [a], Mahendranath Moharir MD [b], Gabrielle deVeber MD [b], Daune MacGregor MD [b], Rand Askalan MD, PhD [b], Nomazulu Dlamini MD [b,*]

CT- Day 8 of Life

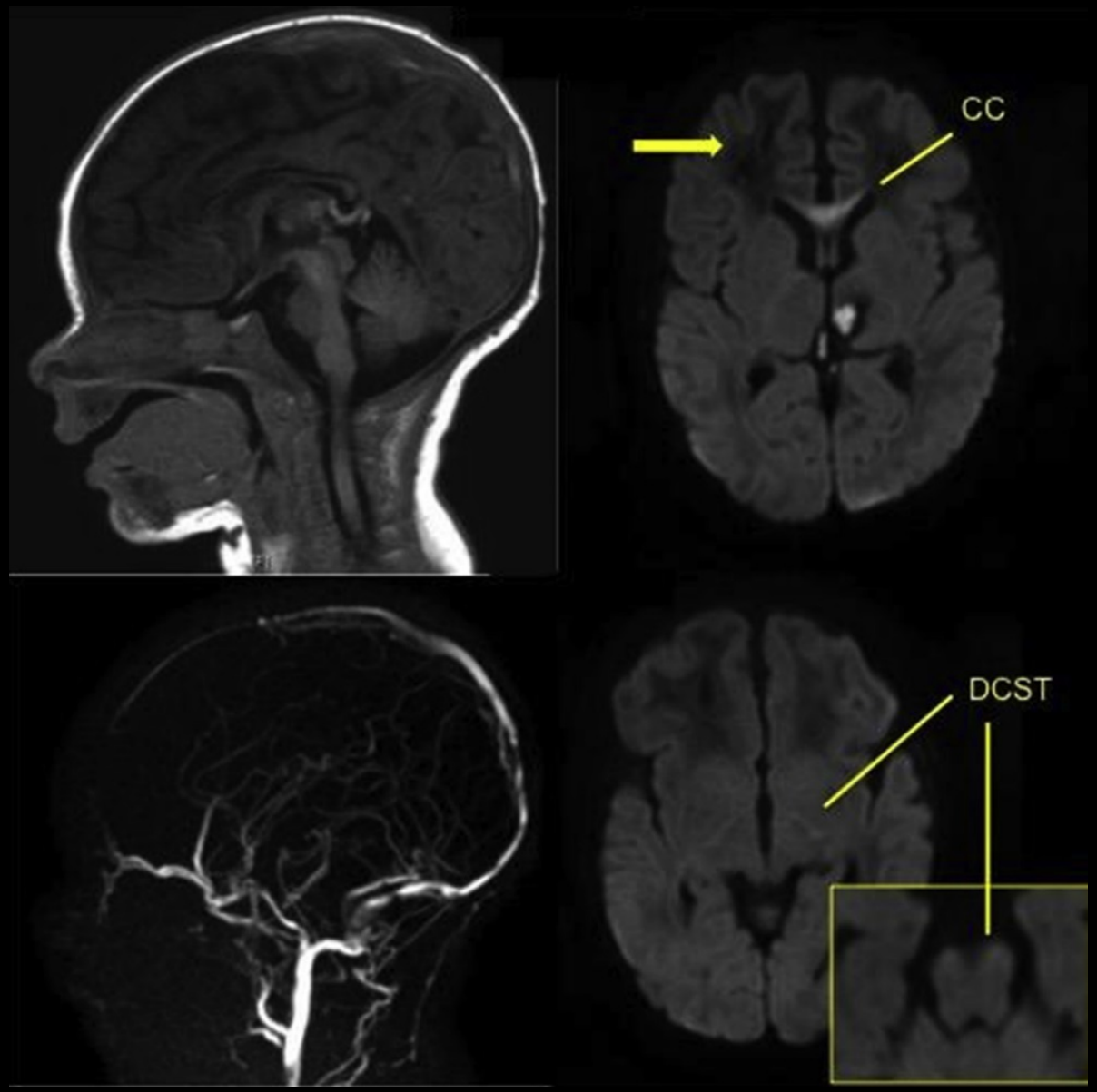


MRI Day 12





Kaseka et al, Ped Neurology, 2016



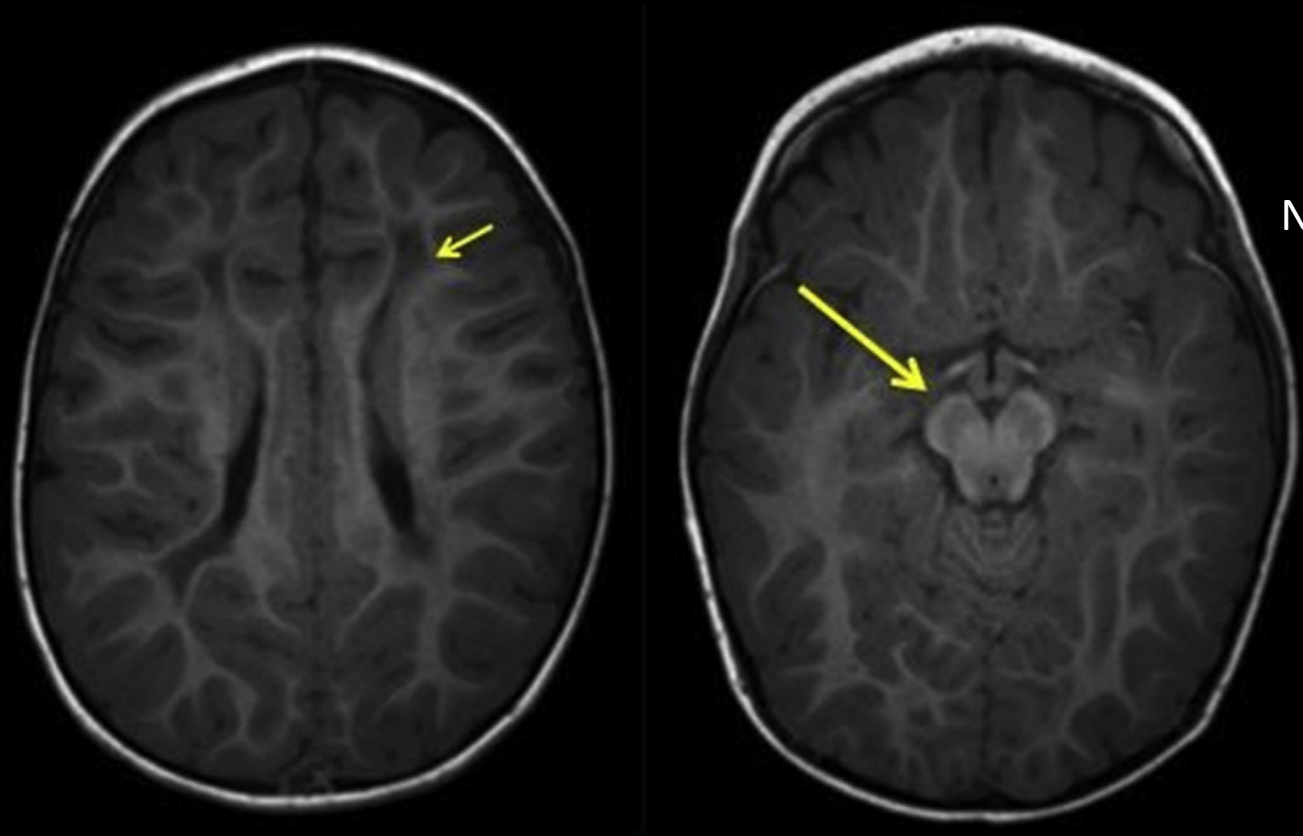
24 days of life

Recanalization of the venous system, and persistent diffusion restriction

Multiple cavities in the depth of the frontoparietal WM bilaterally (large arrow)

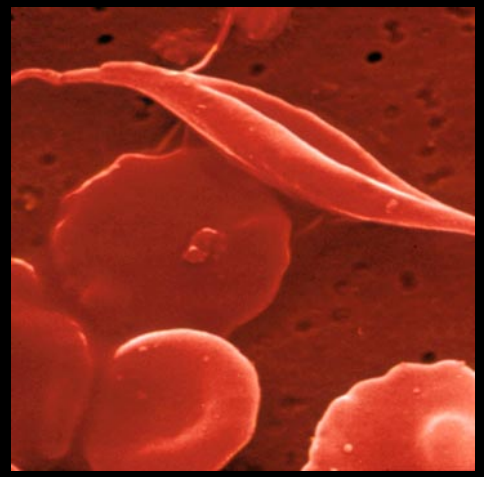
Resolved DCST

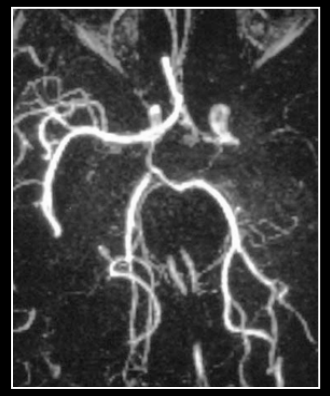
Axial FLAIR at 15 months

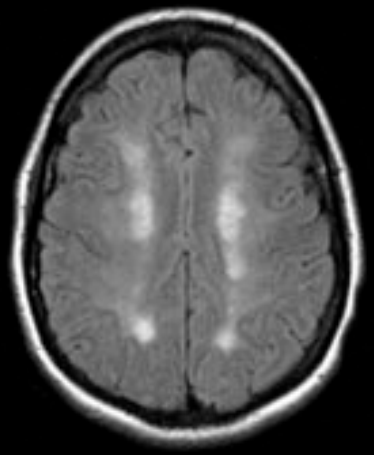


No Wallerian degeneration of DCST

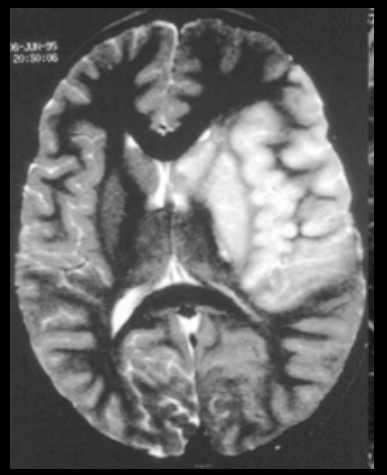
Periventricular encephalomalacia (small arrow) with persistent ↑ T2 FLAIR and loss of subcortical white matter. Previous cystic changes mostly resolved.

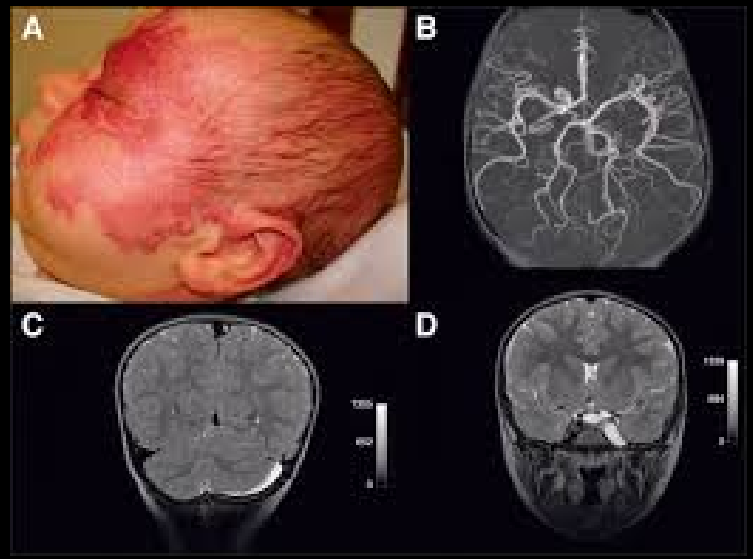




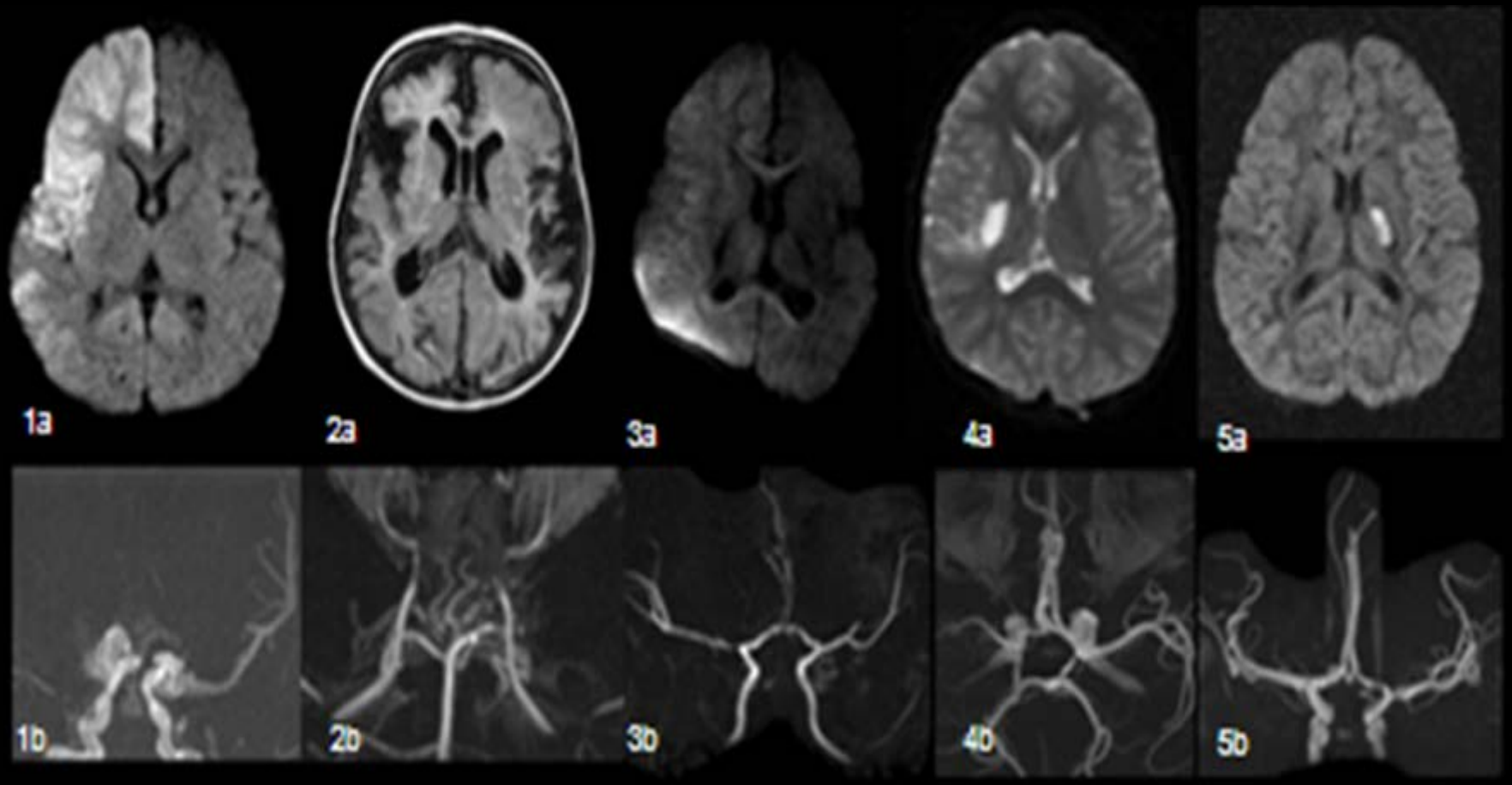


Risk of Occurrence
Risk of Recurrence
?





Risk of Occurrence or Recurrence?



Bilateral MM

Takayasu arteritis

Transient Cerebral Arteriopathy

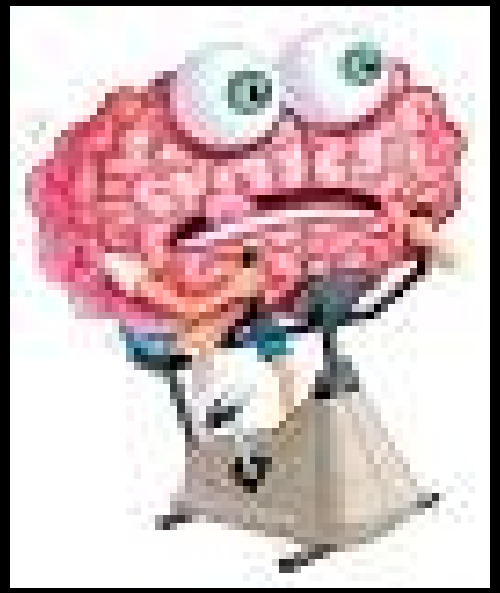
BOLD CVR

Cerebrovascular Reactivity

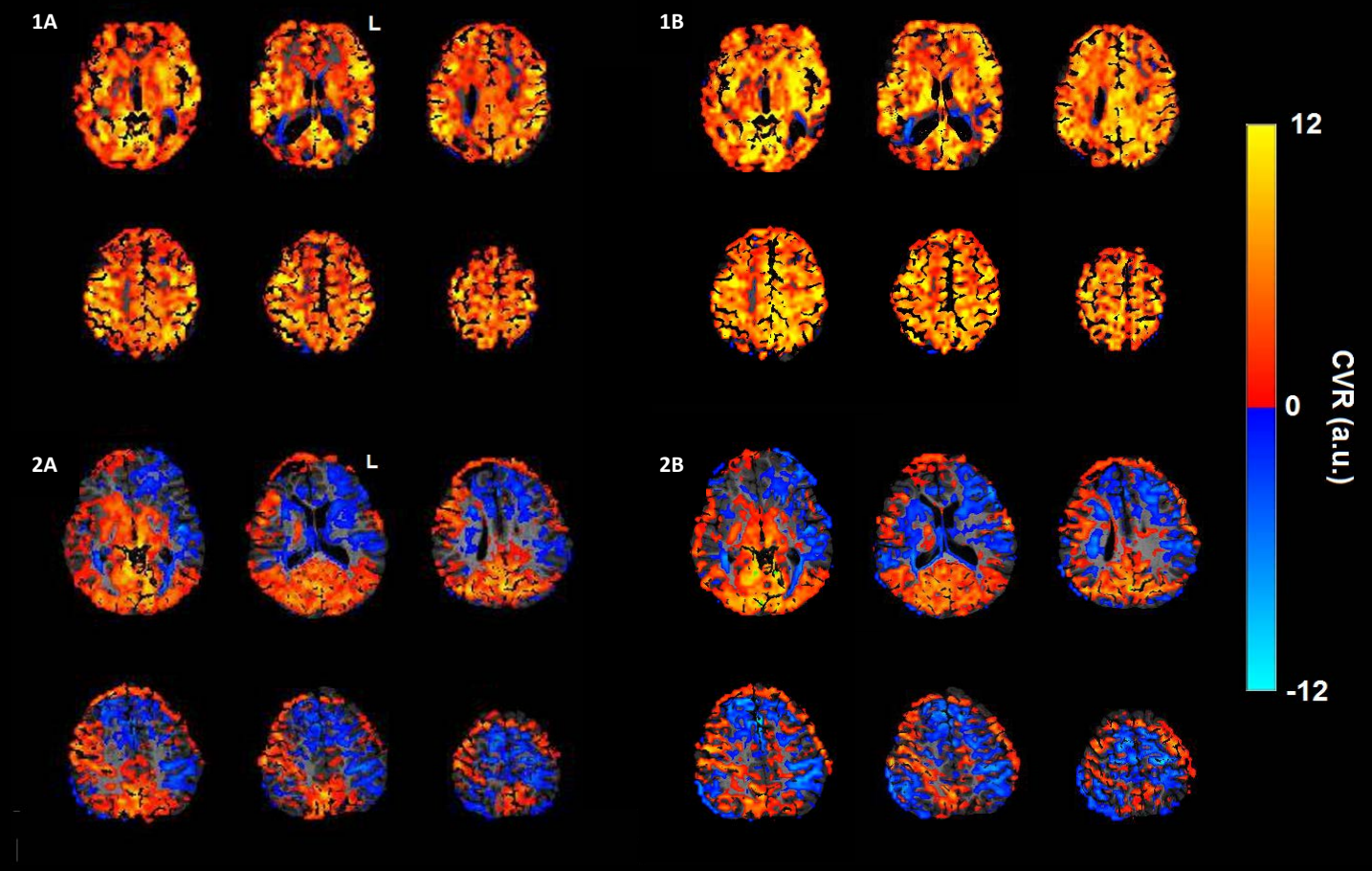
$$CVR = \frac{\Delta \text{ cerebral blood flow (CBF)}}{\Delta \text{ amount of stimulus}}$$

- marker of cerebrovascular reserve (CVres)
- predictor of ischaemic risk

  Gupta et al, 2012; Silvestrini et al, JAMA 2000
- cognitive decline Marshall et al, Neurology 2012



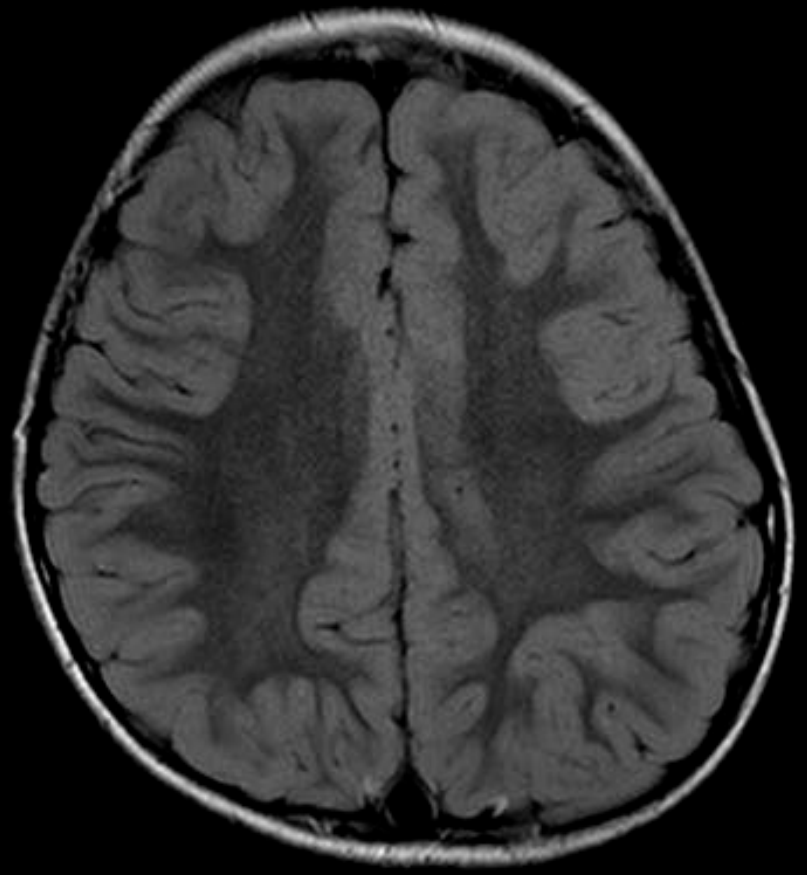
CVR maps



1A-1B Kappa 0.711 Interobserver Hemispheric Kappa 0.83 and 1

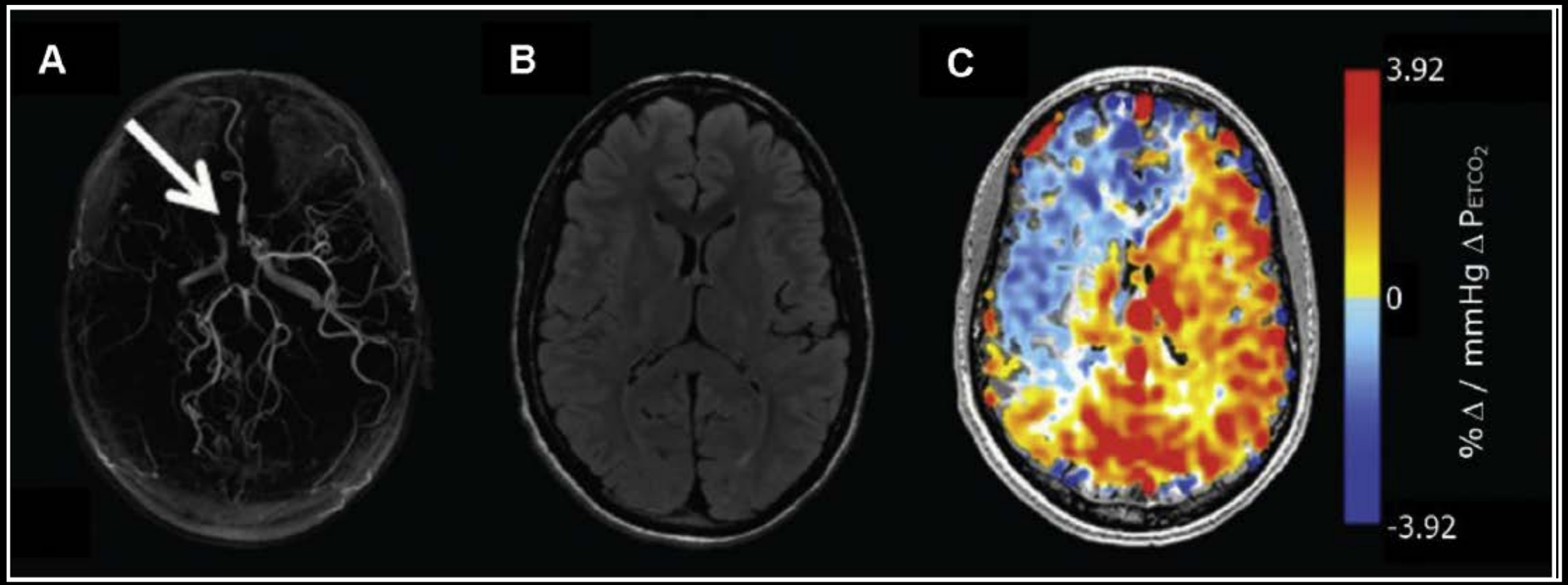
Dlamini et al, AJNR, 2018

Moyamoya and CVR

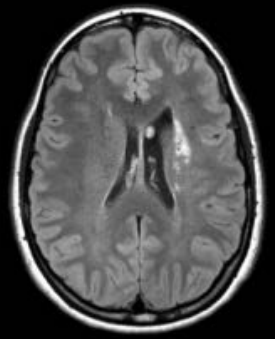


5 year old Chinese girl with headache and paroxysmal episodes of limb parasthesia

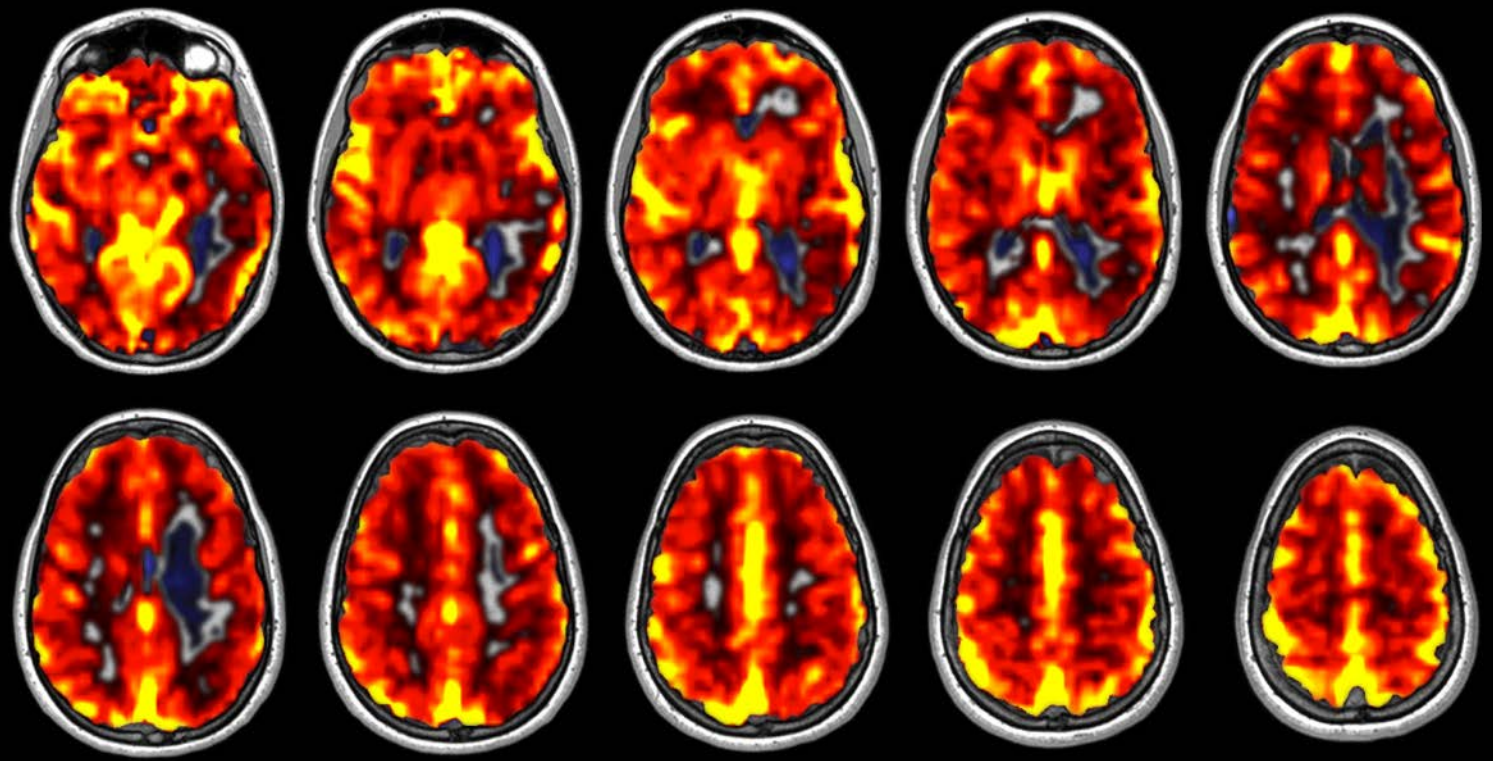
17-year-old patient with moyamoya and paroxysmal episodes of limb parasthesia

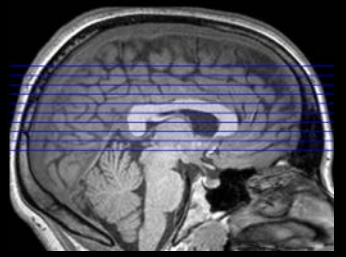


Han et al, 2011



Transient Cerebral Arteriopathy and CVR





% ΔMR / mmHg

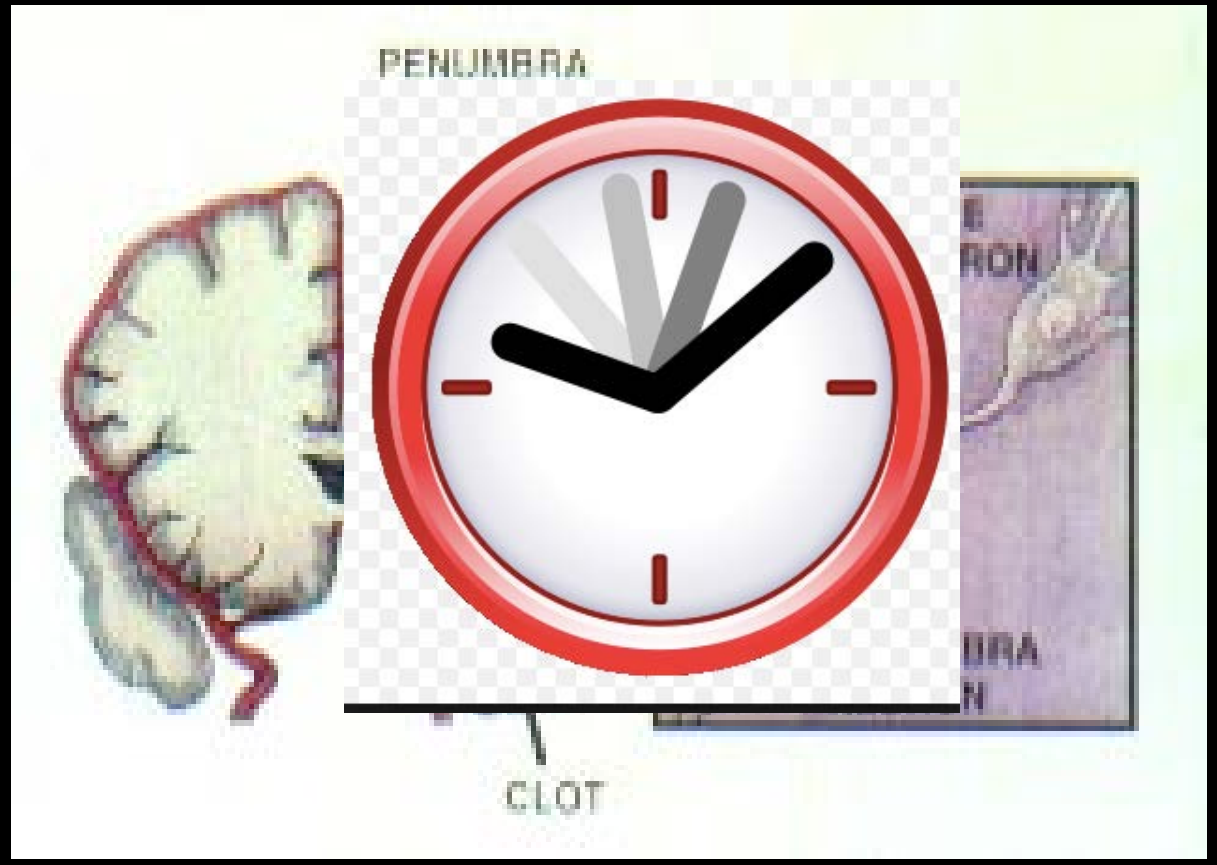
Dlamini et al Ped Neuro Jan 2017

Treatment

Early Management of Ischaemic Stroke in Children

1. Prevent further strokes
2. Prevent secondary brain injury
3. Find the cause

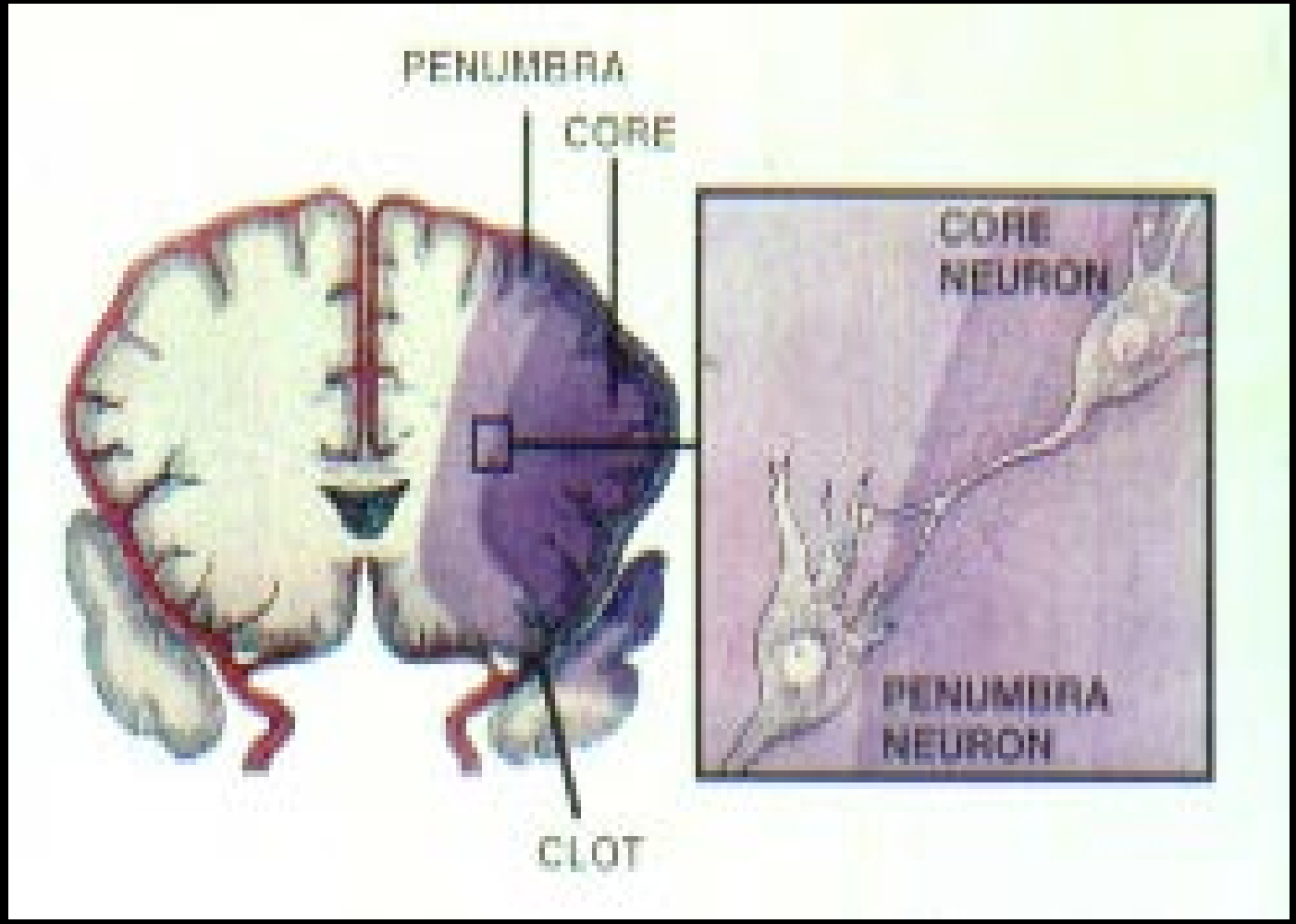
Time is Brain



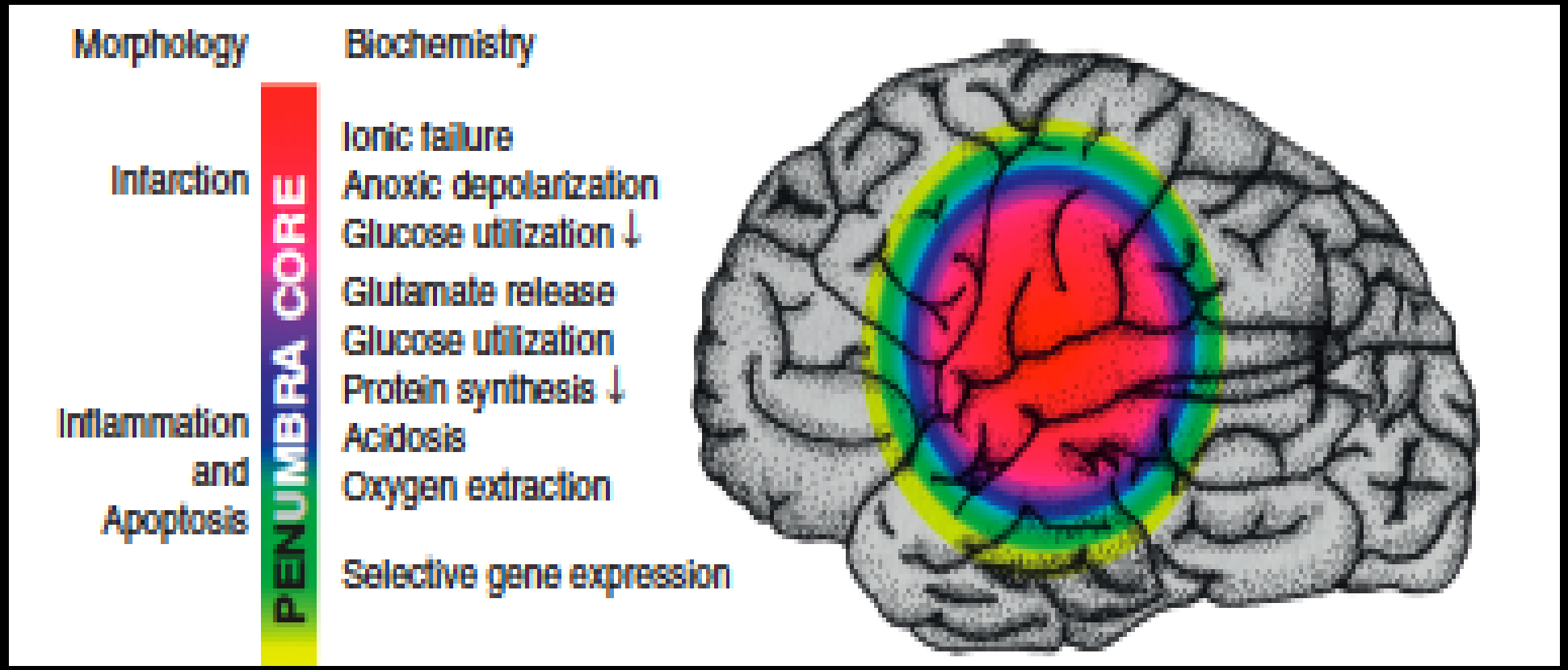
Each *minute* after a stroke 1.9 million neurons are lost

Saver JL. Time is brain—quantified. Stroke

Focal ischaemic injury to the brain: penumbra

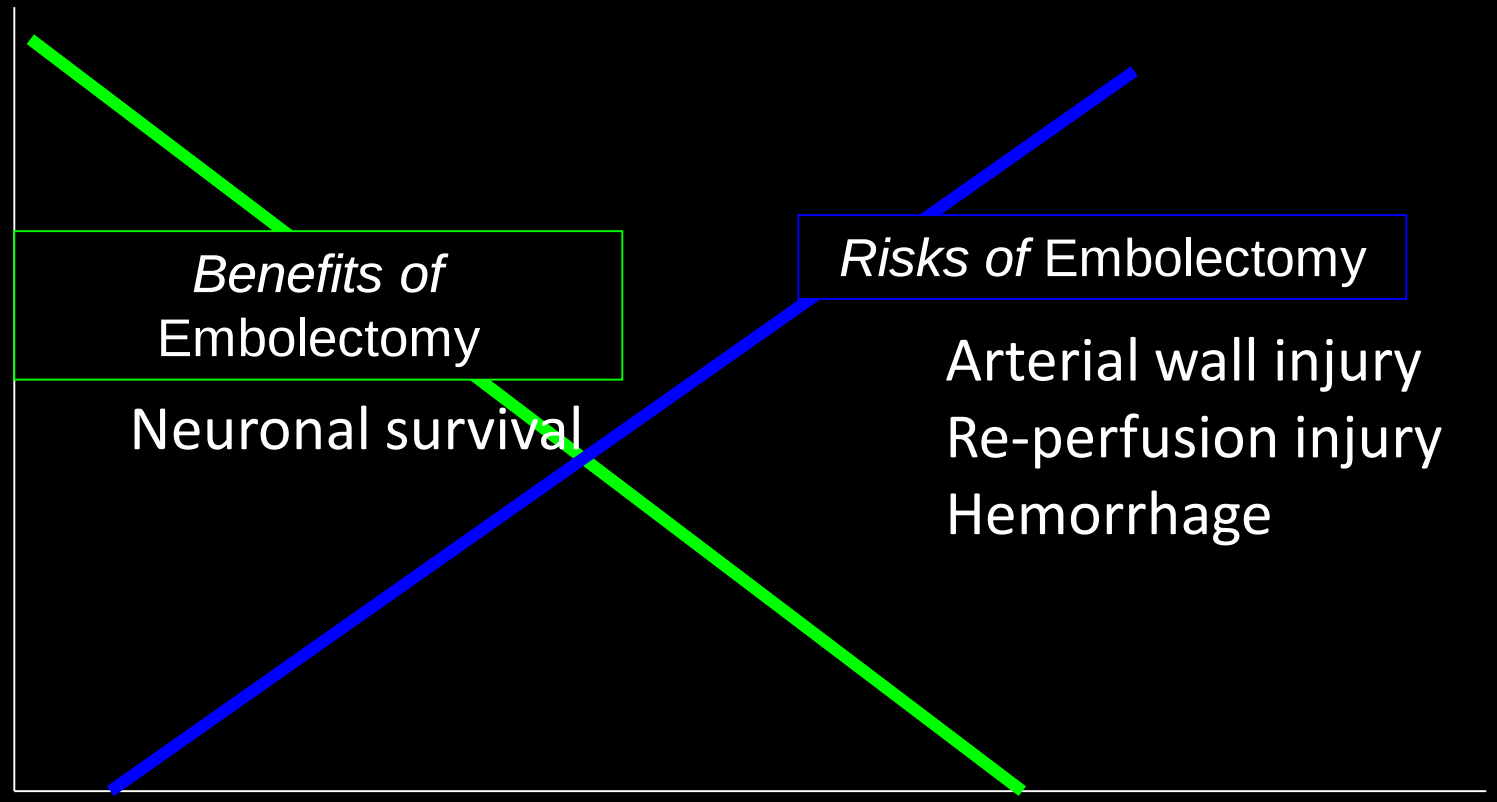


Neuronal Injury: Energy Failure



Dirnagl U. Trends Neurosci 1999

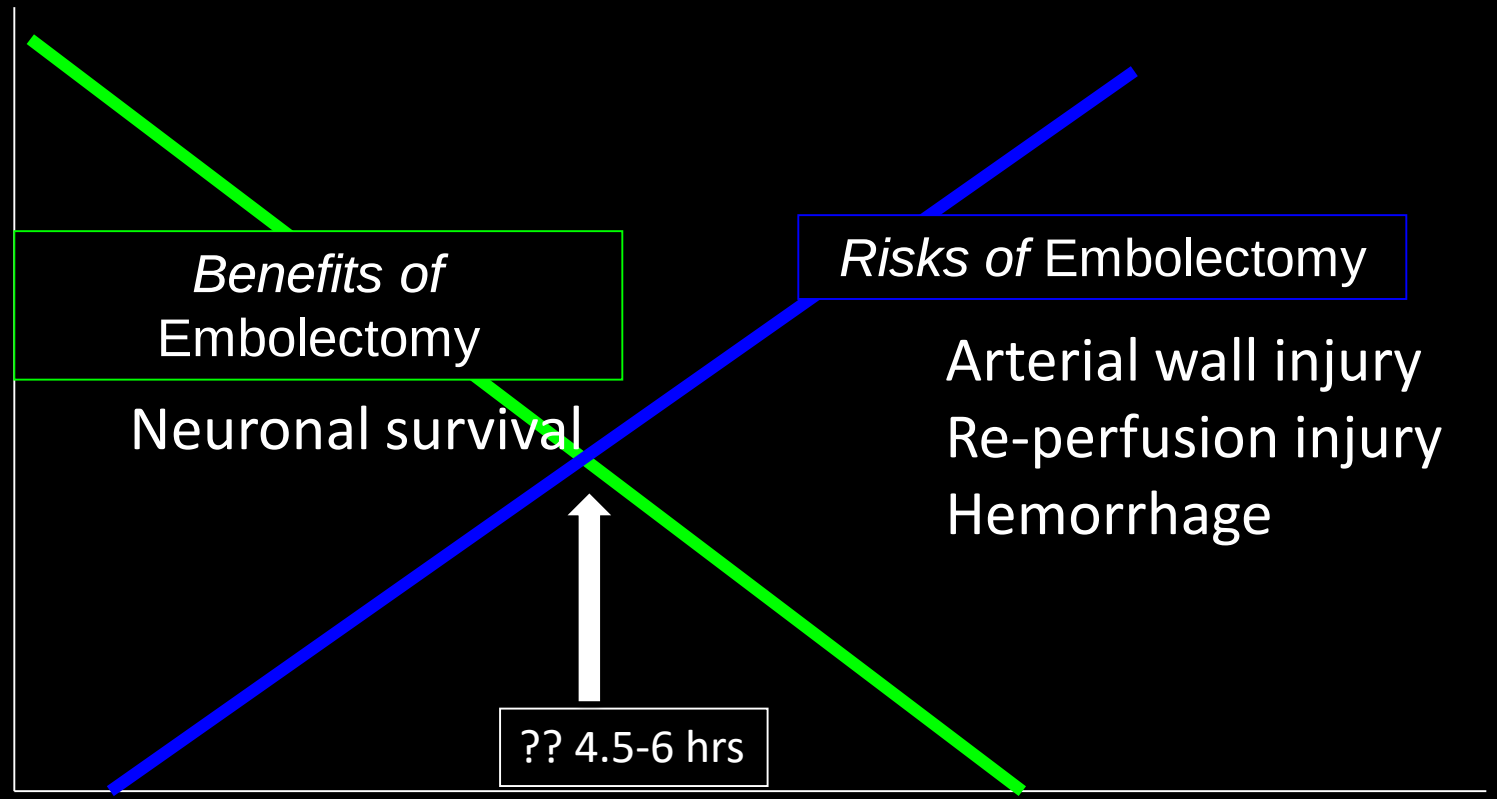
Thrombolysis / Embolectomy??



Time: minutes - hours

Courtesy of Gabrielle deVeber

Thrombolysis / Embolectomy??



Time: minutes - hours

Courtesy of Gabrielle deVeber

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY CASE REPORT

Bacterial endocarditis in a child presenting with acute arterial ischemic stroke: should thrombolytic therapy be absolutely contraindicated?

MARILYN TAN MD[1] | DEREK ARMSTRONG MD[2] | CATHERINE BIRKEN MD[3] | ARI BITNUN MD[4] | CHRISTOPHER A CALDARONE MD[5] | PETER COX MB CHB[6] | WALTER KAHR MD PHD[7] | DAUNE MACGREGOR MD[1] | RAND ASKALAN PHD MD[1,8]

12-year-old female acute dense right hemiparesis and aphasia. MRI multiple DWI +ve lesions left hemisphere and absence of flow in the left internal carotid artery.
Rx: IA tPA within 6 hours of presentation.
Dx: Subsequently diagnosed with pneumococcal endocarditis and underwent debridement of vegetations and patch repair of the mitral valve.
Outcome: No haemorrhagic complications

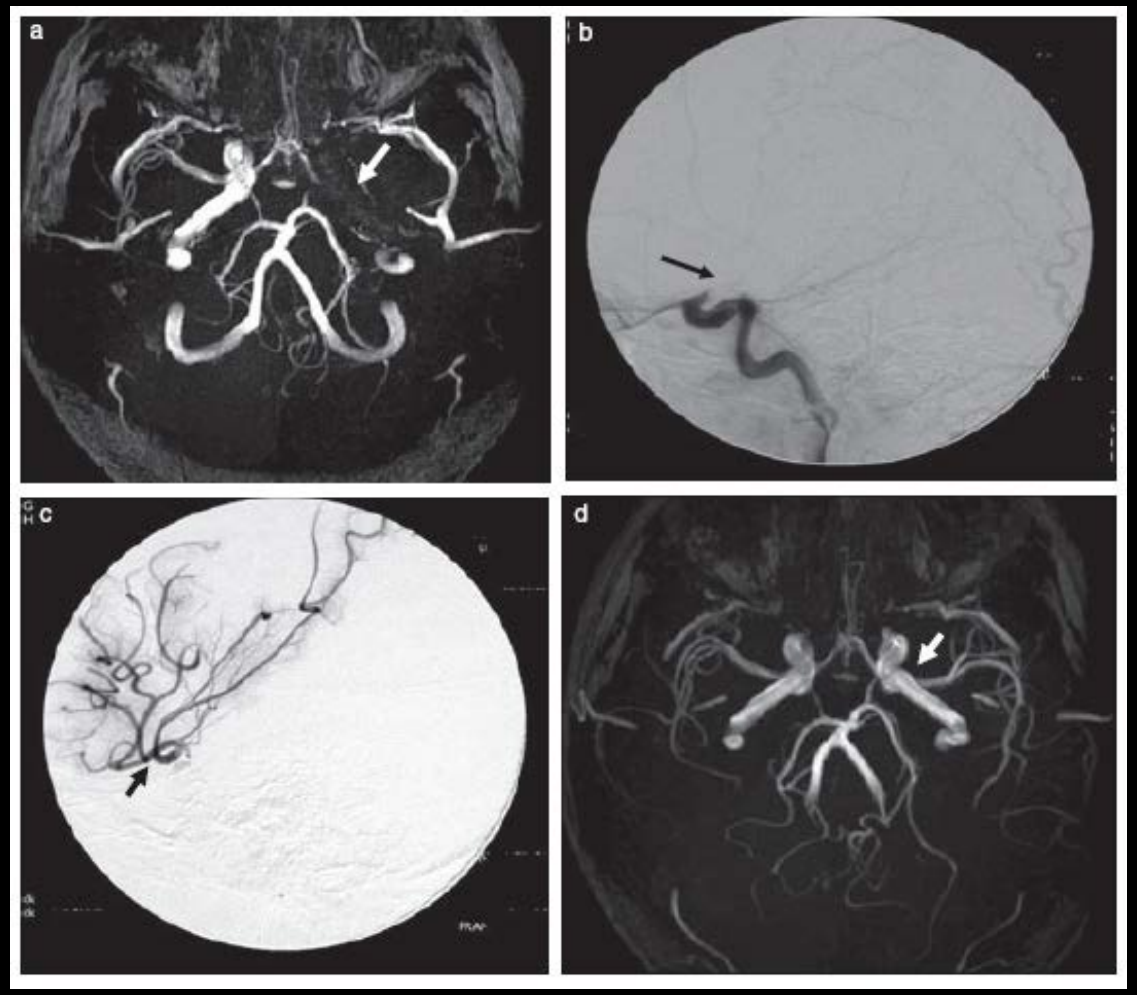
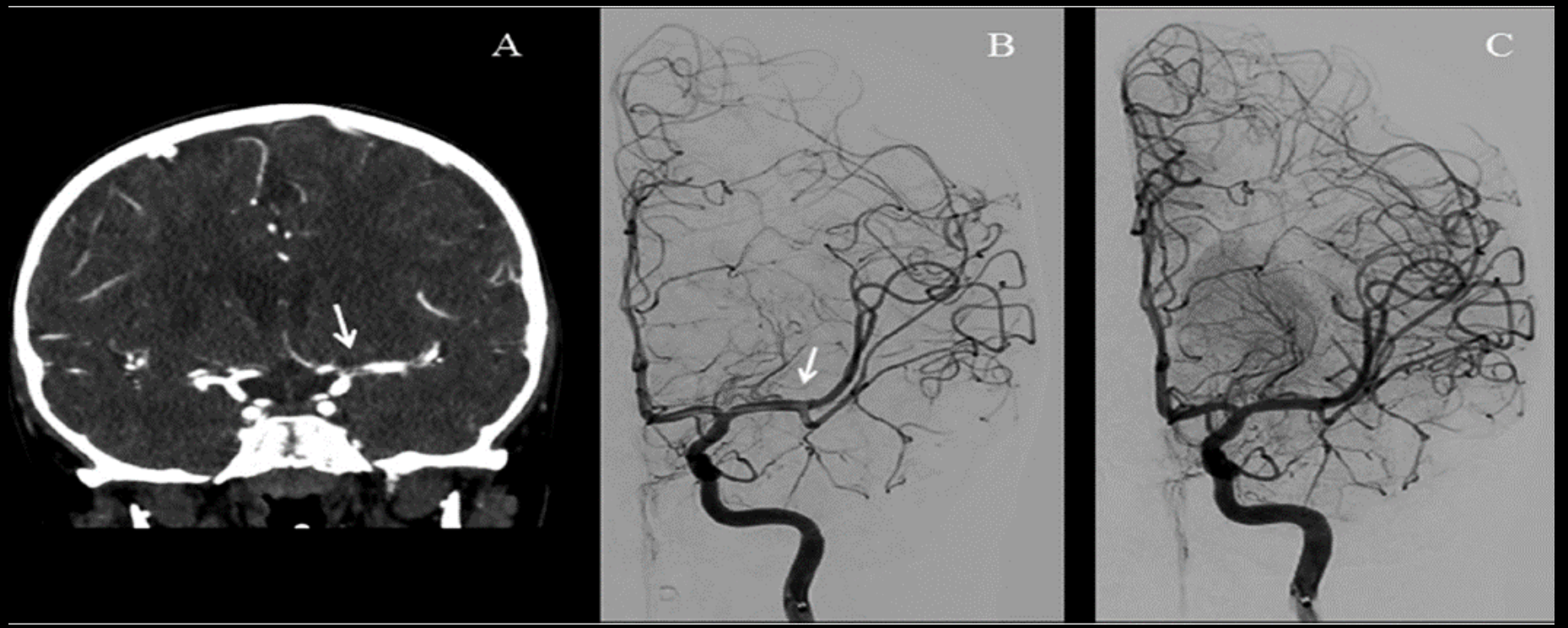


Figure 1: The patient's angiograms before and after thrombolysis. (a) Time-of-flight magnetic resonance angiogram (MRA) before thrombolysis showing a 13mm flow gap in the left internal carotid artery (LICA) bifurcation. (b) Lateral view of pre-thrombolysis contrast conventional cerebral angiogram (LICA injection) confirming the occlusion of LICA above the posterior communicating artery extending to the left middle cerebral artery (LMCA). (c) Lateral view of post-thrombolysis contrast conventional angiogram (LMCA injection) showing partial recanalization of the LMCA. (d) Time-of-flight MRA 3 days after thrombolysis showing complete recanalization of the occluded vessels.

Mechanical Thrombectomy

Topical Review

Thrombectomy for Acute Stroke in Childhood: A Case Report, Literature Review, and Recommendations

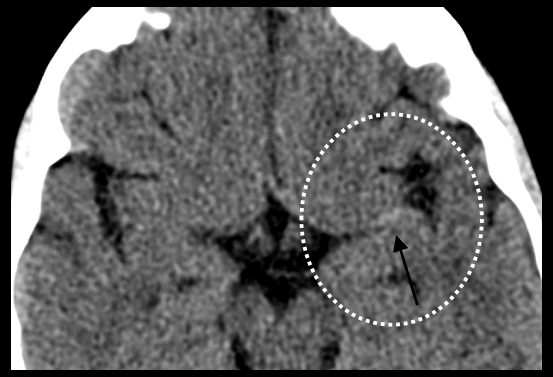


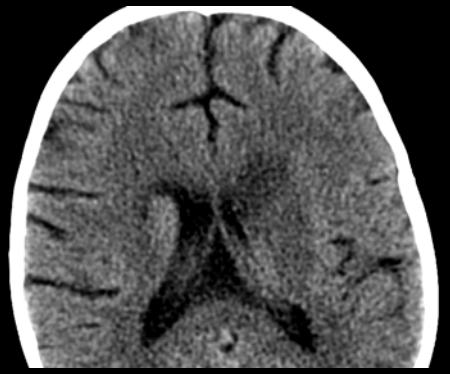
A) CT angiogram: thin linear filling defect extending from the A1 segment of the LACA to the proximal M1 segment of the LMCA
B) CA: nonocclusive thrombus in MCA bifurcation extending into the A1 and M1 segments of the ACA and MCA
C) CA: after clot removal - no residual thrombus

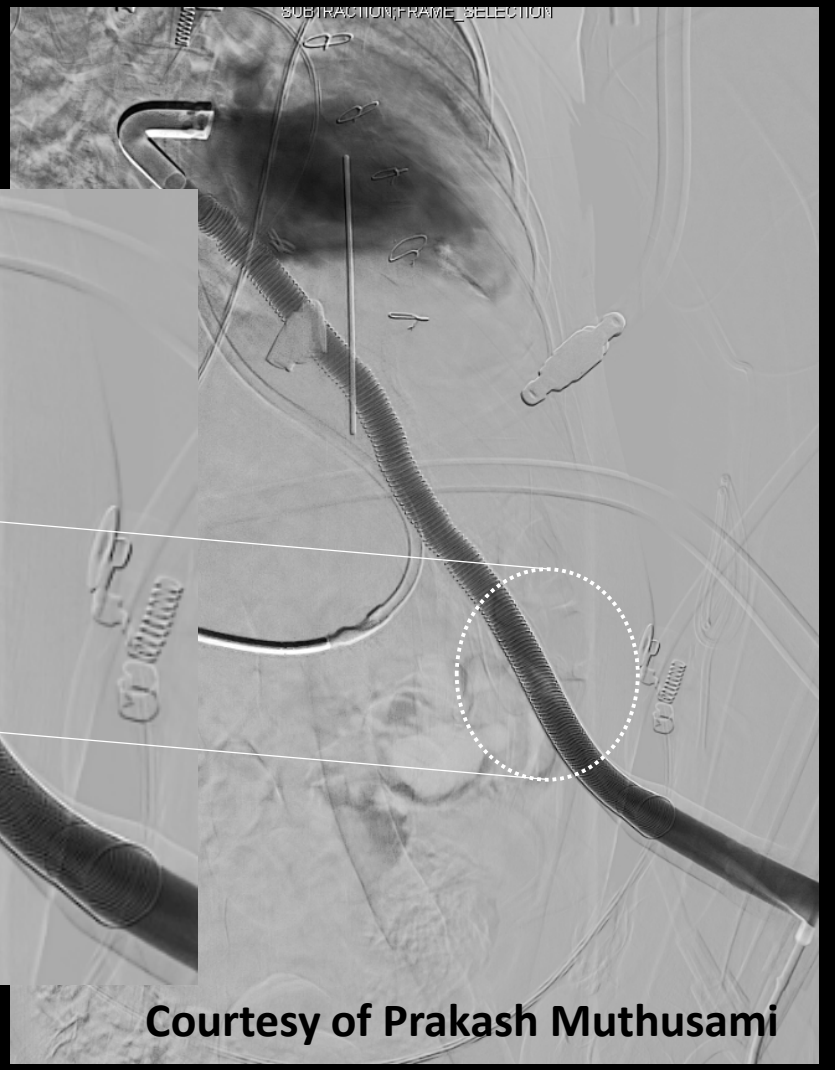
Pediatric Neurology
Buompadre, ..Dlamini 2016

4 days later, acute right hemiparesis

PedNIHSS score 12







Lung transplant that same weekend

Hyperacute stroke

Dr. Gabrielle deVeber

Dr. Mahendra Moharir Director, Stroke Program

Dr. Noma Dlamini

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Dr. Timo Krings

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Dr. Birgit Ertl-Wagner

Dr. Susan Blaser

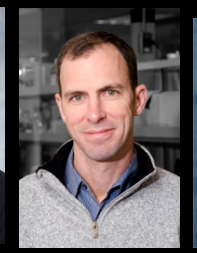
Dr. Helen Branson

Dr. Leonardo Brandeo

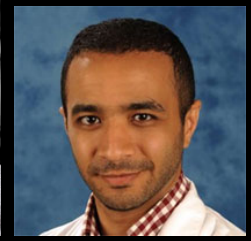
Dr. Prakash Muthusami

Dr. Manohar Shroff

Dr. James Drake



Dr. Peter Dirks



Dr. George Ibrahim

Dr. Jamie Hutchison

Courtesy of Dr Muthasami

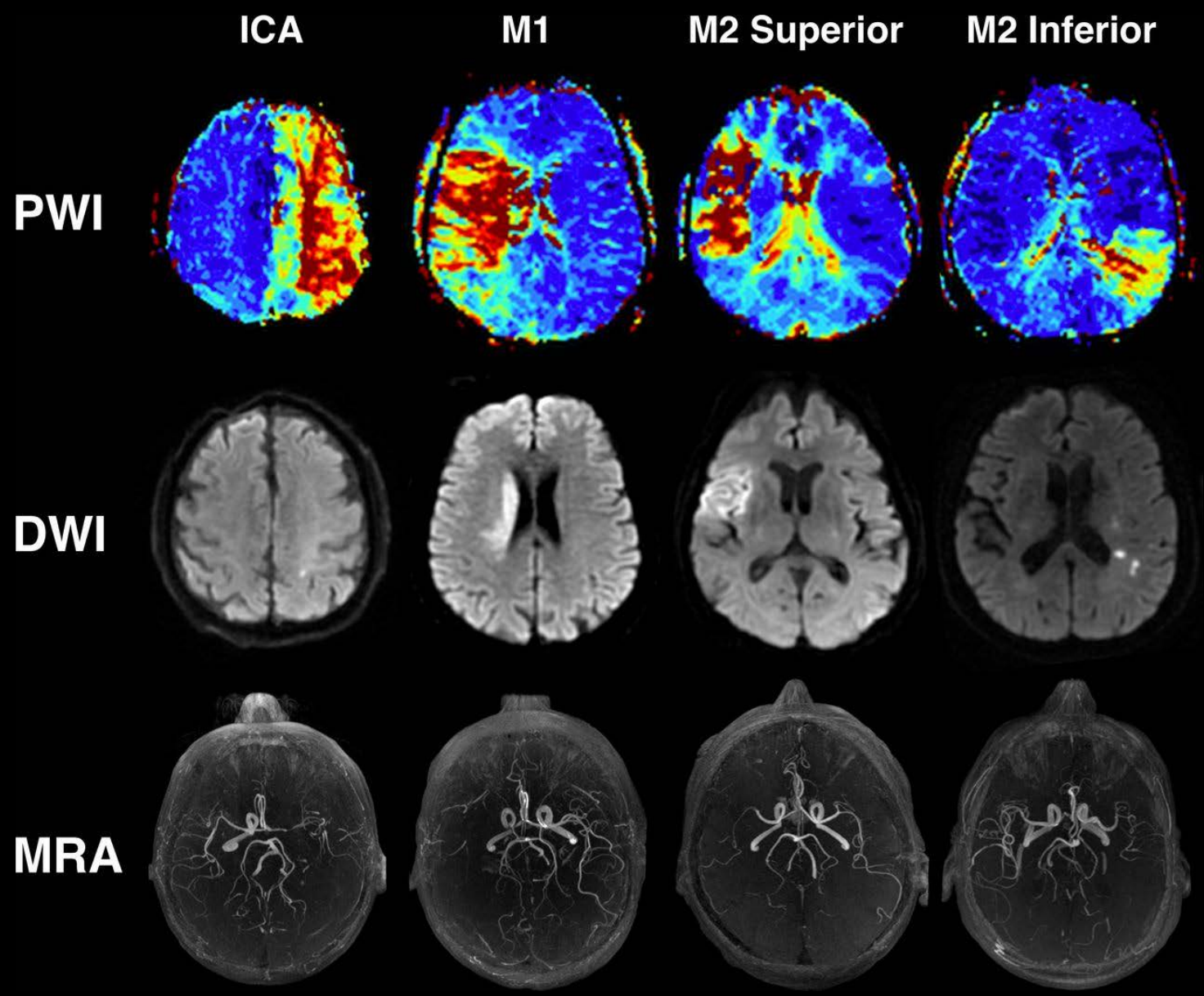
Childhood Stroke and Embolectomy: Can we extrapolate?

- All trials excluded < 18 year olds
- Risks may be increased (smaller arteries than adults, and more prothrombotic)
- Natural recovery rates in children may exceed risks

  Median acute PedNIHSS = 5
  mRankin score = 0 or 1 in 60% at 3 - 6 months*

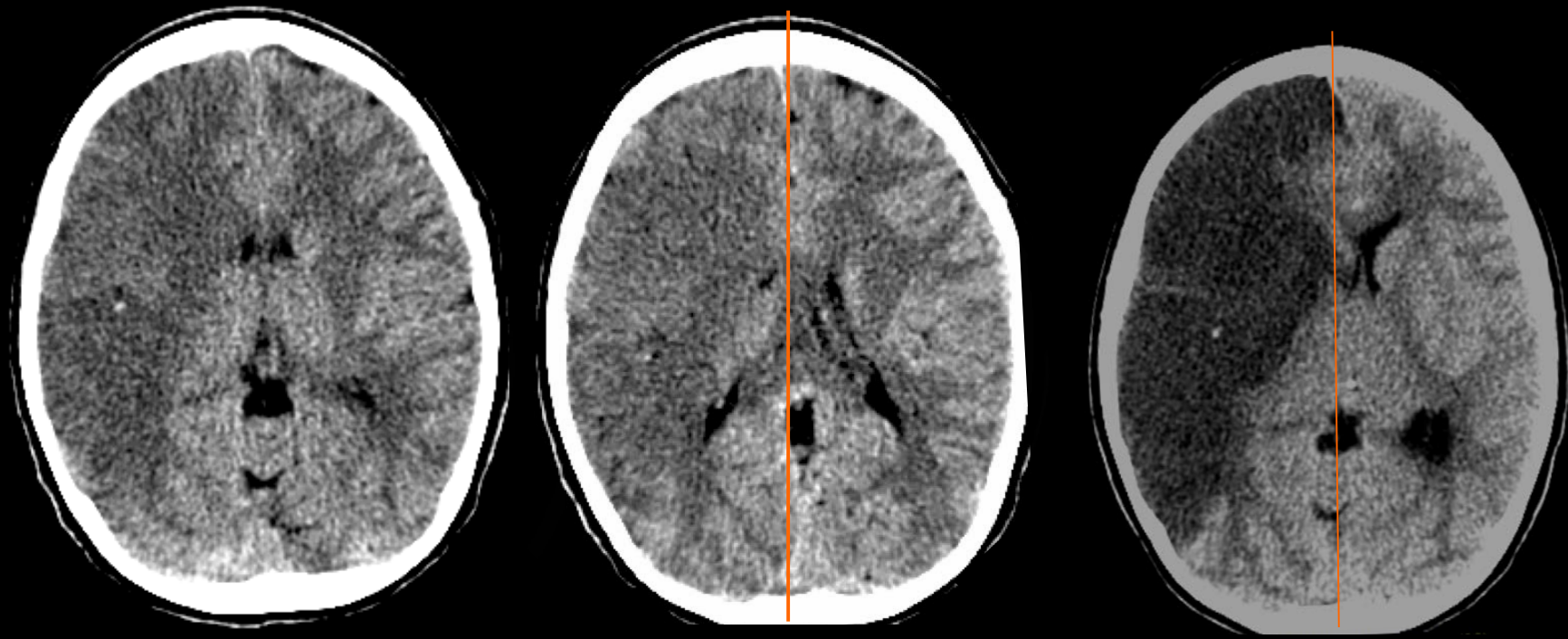
*Bigi et al, Annals of Neurology, 2011

Perfusion Diffusion Mismatch



- Not standard of care in paediatrics
- Unknown risks, unquantified benefit
- Consider in: older teenagers
  therapeutically anticoagulated

Malignant MCA Syndrome



CT 5.5 hrs

12 hrs

40 hrs

Meghan 10 year old girl with headache and
intermittent left focal seizure X 3 h
Right Hemiparesis

Pediatric MMCAI: Rate and Predictors

Among 66 Children (2mo-18yr) with acute MCA stroke at sickkids

Malignant MCA n=12 (18%) vs. No malignant MCA n=54

Predictors	OR (95% CI)	p-value
Seizures within 24 hours	9.06 (1.19, 68.80)	0.0329
Age at stroke	1.45 (1.11, 1.90)	0.0051
NIHSS at presentation	1.34 (1.11, 1.61)	0.0018

Andrade A, Laughlin S et al, in Press 2016, Pediatric Neurology

Thank you!

- Gabrielle deVeber
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- Kelsie Bozinis
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- Mahmoud Slim
- Sujartha
- Zadi
- Alexandra Silver
- Andrea Kassner
- Jackie Leung
- Diagnostic Imaging
- Manohar Shroff
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- Pradeep Krishnan
- Prakash Muthasamy
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- IPSS
- All colleagues, partners

Children and families

International Paediatric Stroke Study Group
IPSS

HEART & STROKE FOUNDATION

SickKids