

Stroke In Children

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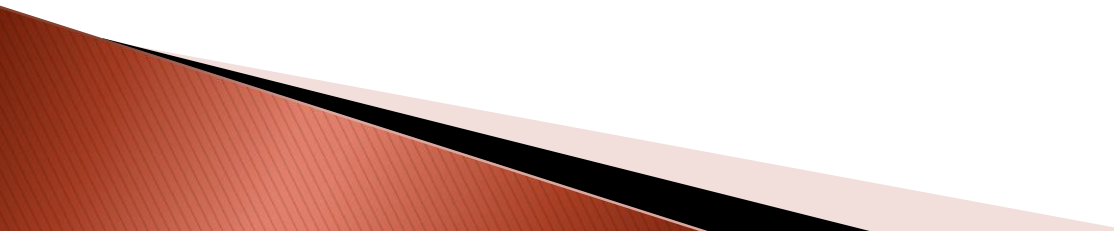
University
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Disclosures

- ▶ None

Objectives

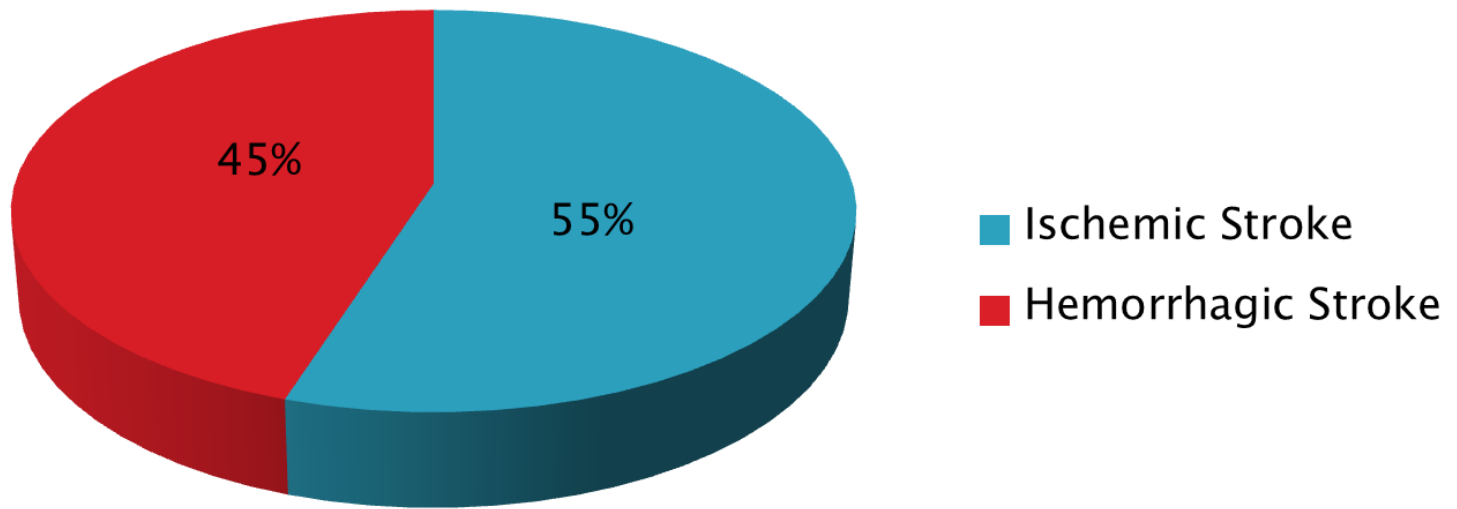
- ▶ Understand the definitions and terminologies used in childhood stroke
 - ▶ Recognize the age-specific clinical presentations and mimics of childhood stroke
 - ▶ List common risk factors and initial diagnostic work-up required to confirm the diagnosis
 - ▶ Review current treatment approaches, and
 - ▶ Appreciate the long term outcome of childhood stroke
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Pediatric Stroke

Stroke occurring anytime between in-utero (20 weeks gestation) to 18 years of age.

- **Childhood Stroke:** Stroke occurring over 28 days of postnatal life to 18 years of age.
- **Perinatal Stroke:** Stroke occurring anytime between 20 weeks gestational age and 28 days of postnatal life.

Pediatric Stroke



deVeber G, Peds Neurology 2019, Ferriero DM et al. AHA, Stroke 2019

Epidemiology

▶ Overall Annual Stroke Incidence

- 3 – 25/100,000 children/year in developed countries
- Highest in the perinatal period, 25–30% of all strokes, 1/2700–5000 live births/year

Hemorrhagic Stroke

- 1 to 1.7 in 100 000 children/year, common in neonates at least 1 in 6300 live births

Ischemic Stroke 1 – 2/100, 000 children

- AIS: Children 1.2 – 8/100,000 children/year
Neonates 10.2 – 29/100,000 or 1/4000 live births/year
- CSVT: 0.67/100,000 children/year, 43% neonates, over half one year old

Ischemic Perinatal Stroke (IPS)

- ▶ A group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization between 20 weeks of fetal life through the 28th postnatal day confirmed by neuroimaging or neuropathologic studies.

*NICHD-NINDS Perinatal Stroke Workshop
Pediatrics 2007; 120: 609-616*

Categories of IPS

Following three sub-categories were suggested:

- ▶ **Fetal ischemic stroke** diagnosed before birth by using fetal imaging methods or in stillbirths on neuropathology
- ▶ **Neonatal arterial ischemic stroke** diagnosed after birth and on or before the 28th postnatal day (including in preterm infants)
- ▶ **Presumed perinatal ischemic stroke or PPIS** diagnosed in infants in whom it is presumed but not certain that the ischemic event occurred sometime between the 20th week of fetal life through the 28th postnatal day.

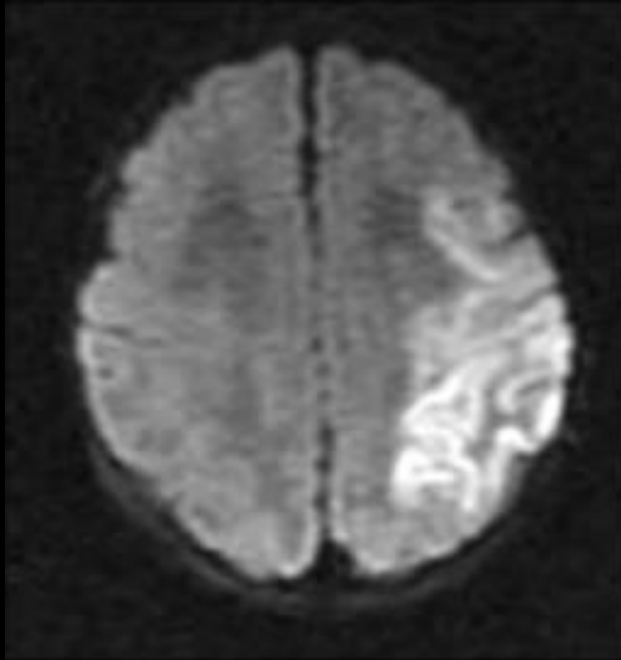
NICHD-NINDS Perinatal Stroke Workshop Pediatrics 2007

Neonatal Arterial Ischemic Stroke (NAIS)

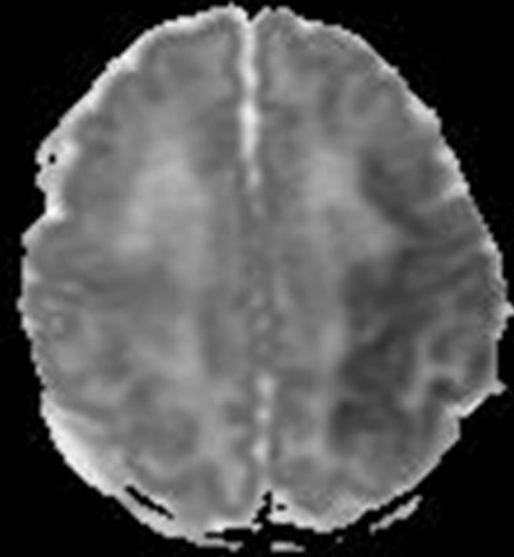
- ▶ Acute presentation in the neonatal period (0–28 days)
 - Seizures, mostly focal in >80%, typically after 24 hours
 - Hemiparesis / monoparesis, in about 10% –20%
 - Irritability, lethargy, vomiting and decreased level of consciousness less common, > 30%
- ▶ Presence of acute or sub acute infraction on neuroimaging

Neonatal Ischemic Stroke

DWI

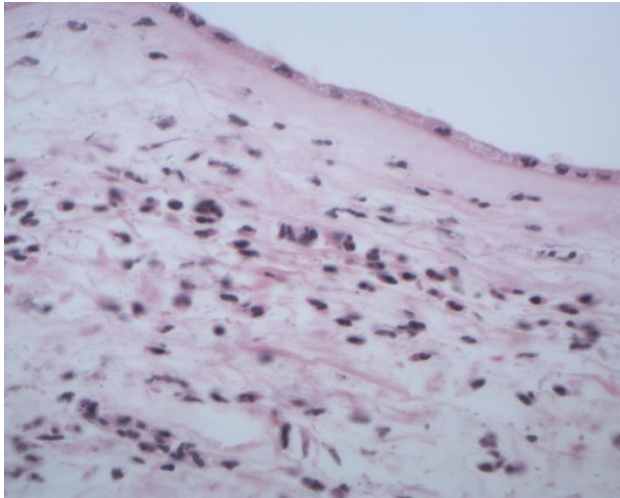


ADC

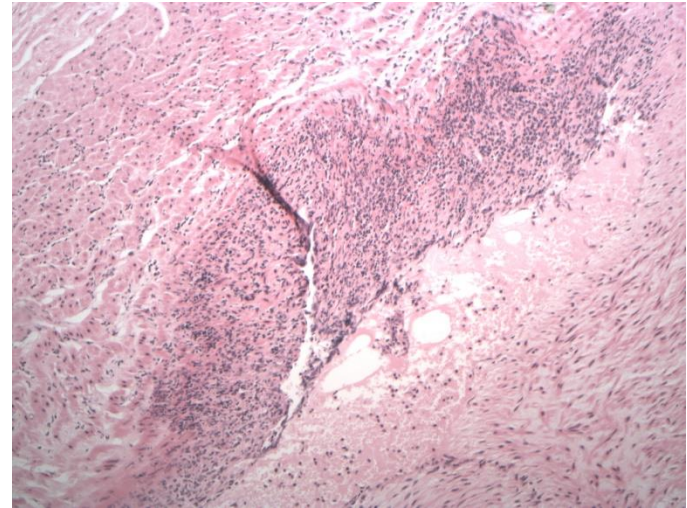


Term baby with focal, right-sided, tonic-clonic seizures at 3 days of life

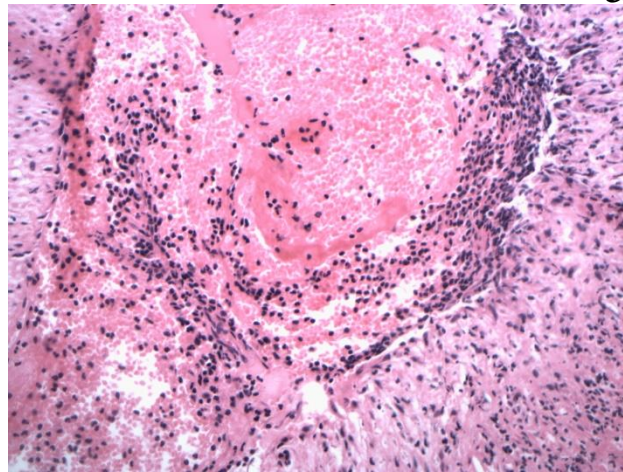
Placental Histopathology



Neutrophilic infiltrate within the amnion and chorion



Inflammatory material within the placental & umbilical vessels



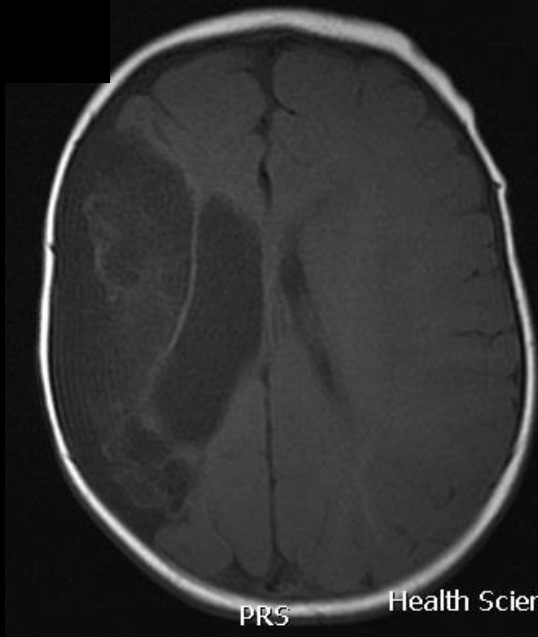
Layering of fibrin, inflammatory & red blood cells (lines of Zahn) - a thrombus

Presumed Perinatal Ischemic Stroke (PPIS)

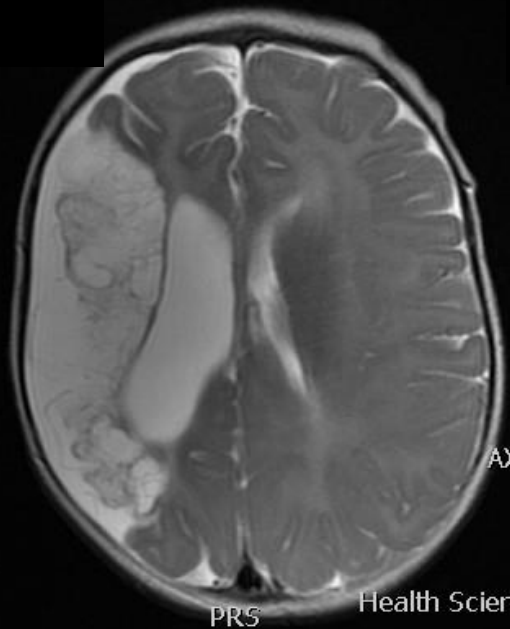
- ▶ Delayed presentation – Almost all
 - Pathological handedness
 - Other focal deficits: Awkward gait, difficulty walking or failure to achieve developmental milestones
 - Seizures typically focal – in later years of life
 - Incidental finding on neuroimaging
- ▶ Acute presentation – Rare
 - Seizures
 - Hemiparesis / monoparesis – very rare
- ▶ Presence of old infarction corresponding to an arterial territory on neuroimaging

Presumed Perinatal Ischemic Stroke (PPIS)

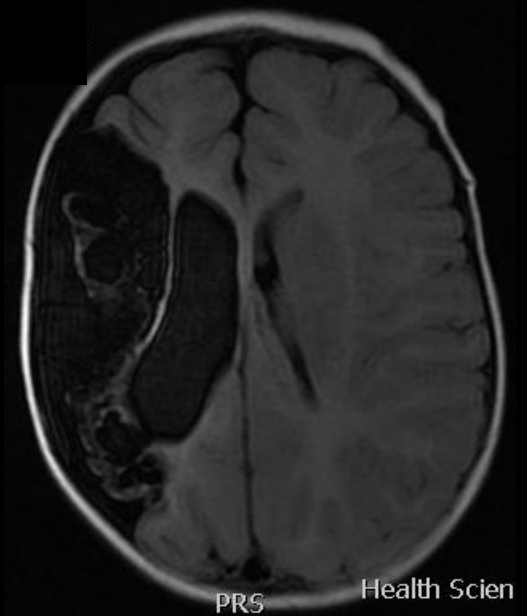
MRI Brain: Axial T1



Axial T2



Axial FLAIR



6 months old girl with infantile spasms and right hand dominance

Perinatal Ischemic Stroke

Etiologies & Risk factors

▶ Maternal Factors

- Infection
- Thrombophilia, including antiphospholipid antibodies
- Pre-eclampsia
- Cocaine use
- Smoking
- History of infertility

▶ Placental Factors

- Placental Infarction
- Abruptio/ Insufficiency
- Chorioamnionitis

▶ Obstetrical Factors (Mother & Infant)

- Arterial injury during delivery due to head and neck mechanical trauma
- Need for resuscitation or low Apgar score at 5 minutes

▶ Fetal/Infant Factors

- Congenital heart disease – up to 24%
- Infection – Meningitis, sepsis
- Thrombophilia – uncommon, unless strong maternal/family history

Childhood Arterial Ischemic Stroke

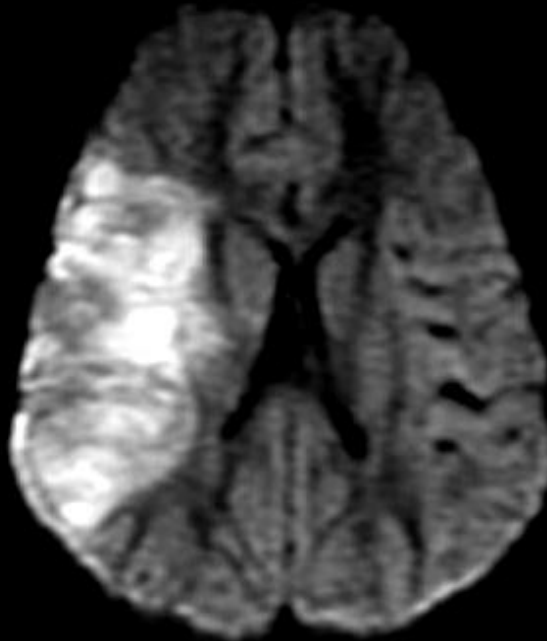
(Non-neonates)

Childhood Arterial Ischemic Stroke

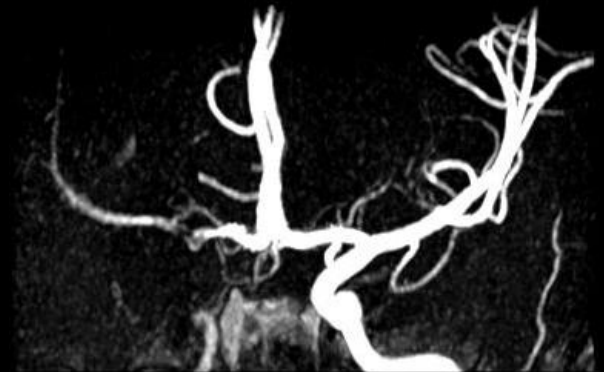
Axial CT Scan



Axial Diffusion MRI



MRA



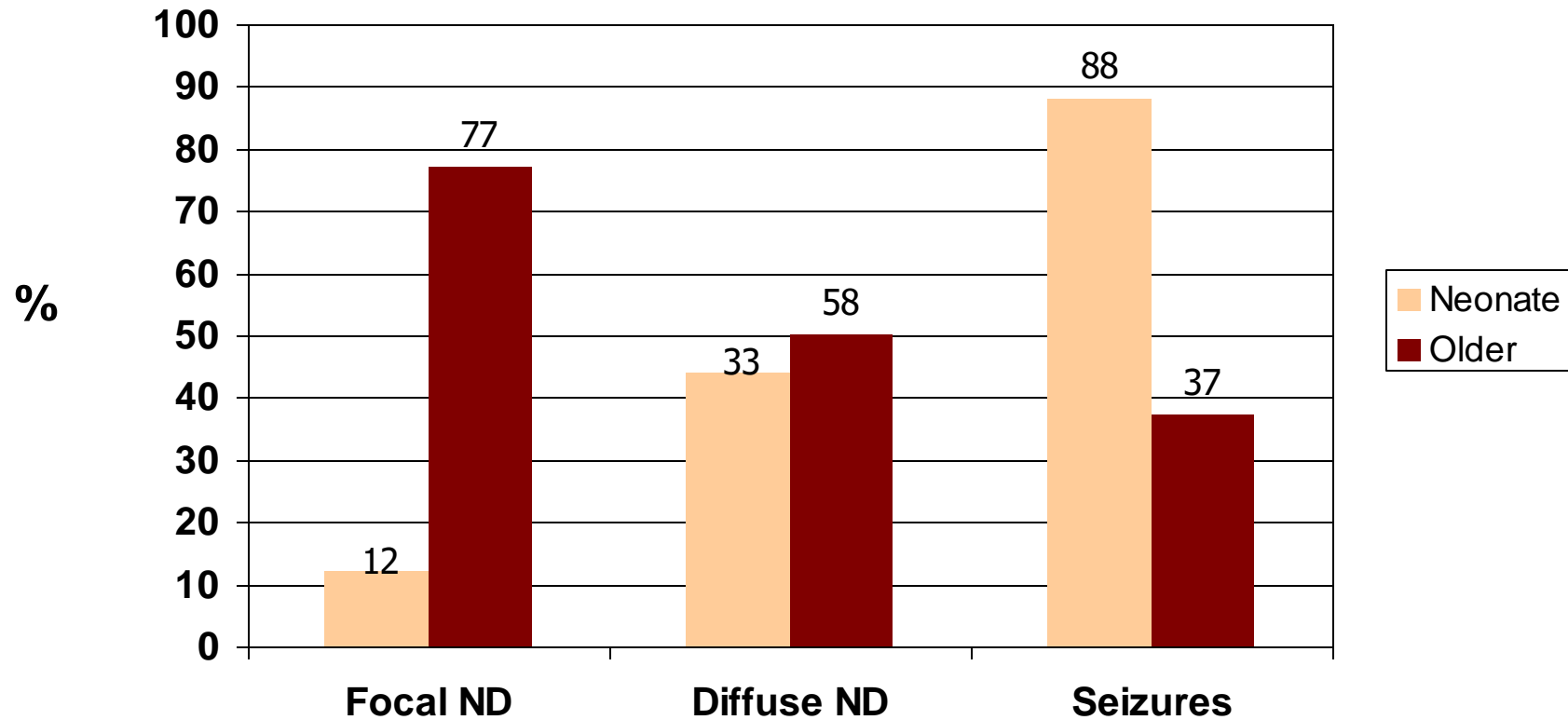
3 yr-old girl with left sided focal seizures, weakness and slurred speech

Clinical Presentation

Infants and Older Children

- ▶ Any sudden neurological deficit – 70%
 - Hemiparesis with or without facial weakness
 - Speech problems
 - Sensory deficits
 - Any other motor deficits: ataxia, balance problems
- ▶ Seizures, often focal – > 45%
- ▶ HA, fever, altered level of alertness – > 50% children
- ▶ Preceding TIA may have occurred in ~30%

Clinical Presentation



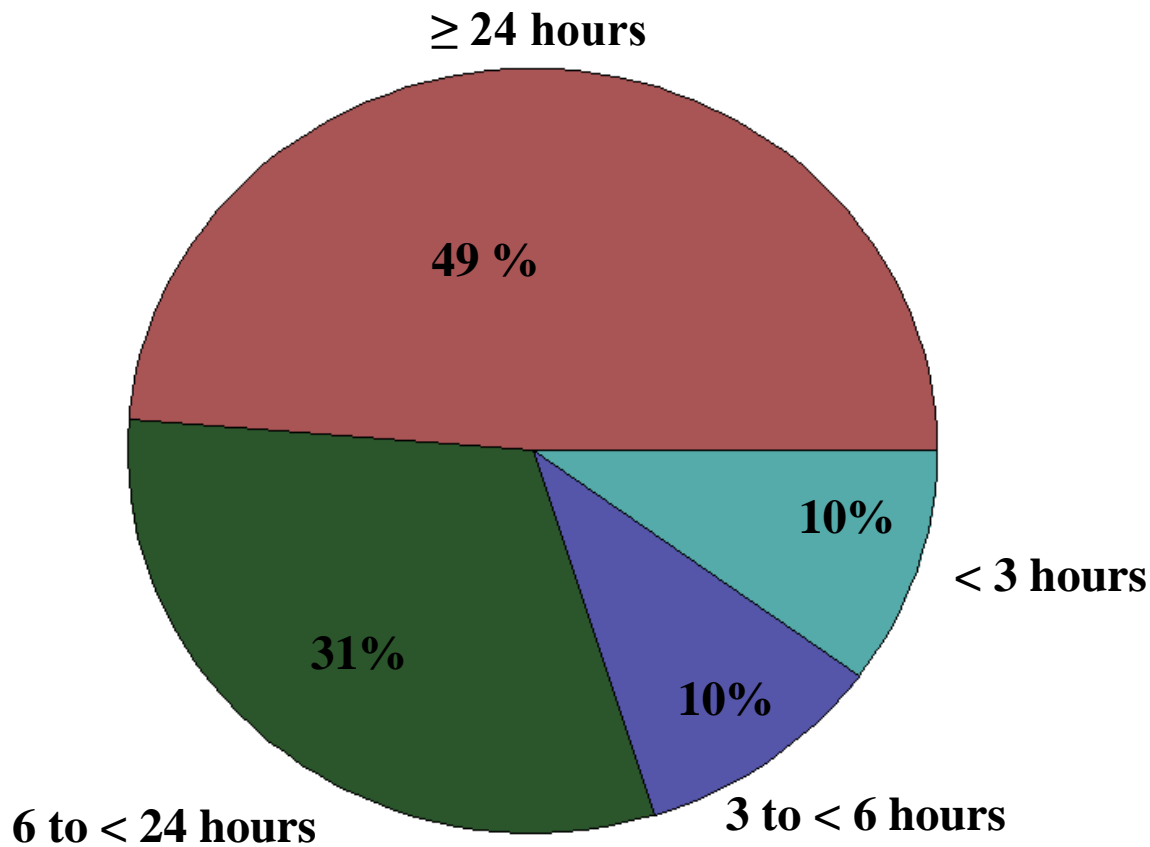
Challenges in Childhood Stroke

- ▶ Presentation
 - Non focal presentation (seizures, lethargy, headache)
 - Age related, non-specific, inability to report subtle symptoms
 - Less than 25% present within 3–6 hours
 - Limited exam in irritable young children
- ▶ Infrequent in children – decreased awareness/Misconception...
“Does not occur in children”, “benign in nature”
- ▶ Delay in considering stroke as a possibility, in children presenting with focal neurological deficits

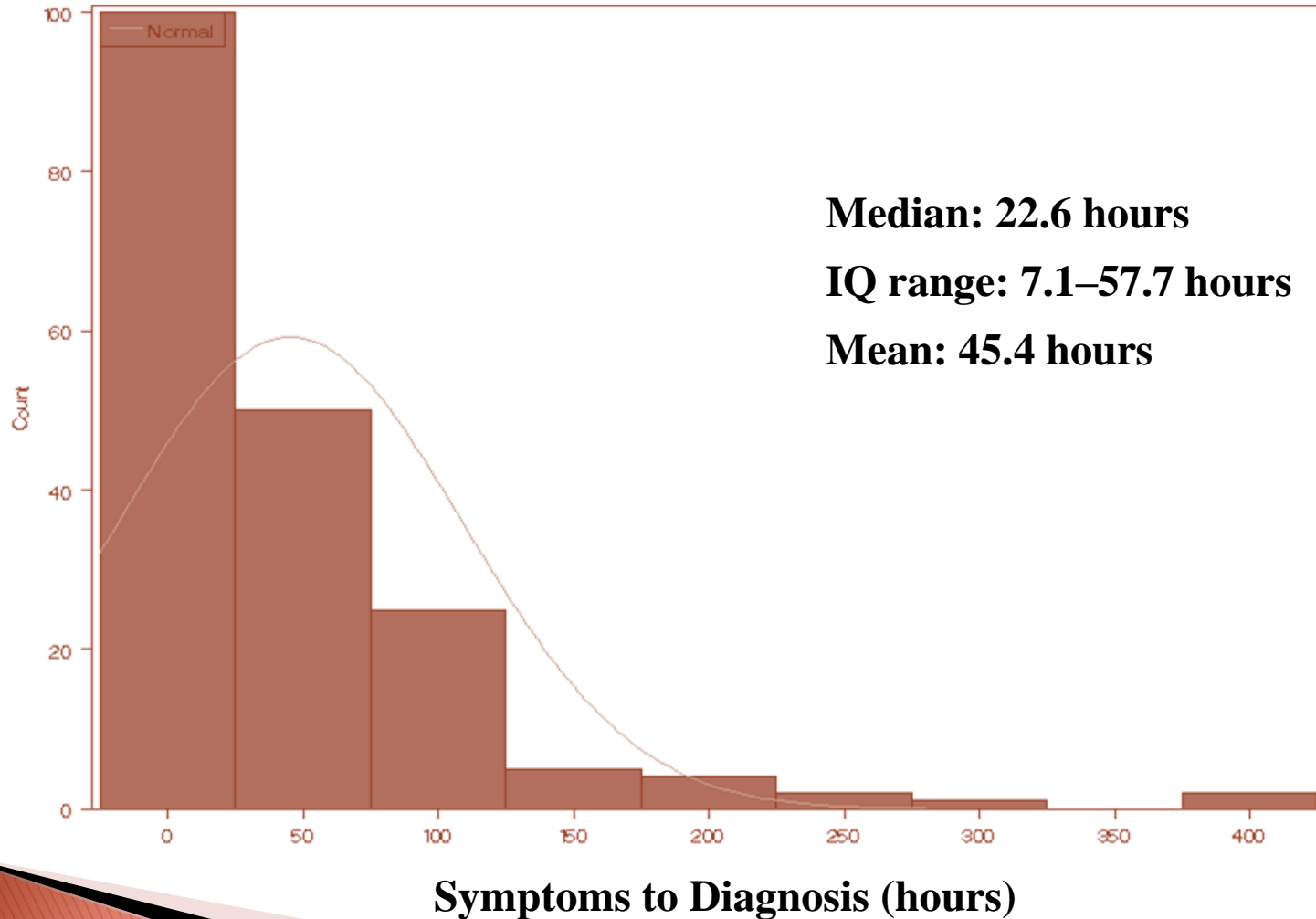
Challenges in Childhood Stroke

- ▶ Existence of various *Stroke Mimics*, that are common in children
 - Seizures with ictal or post-ictal Todd's paresis
 - Hemiplegic migraine
 - Focal demyelination, abscess, tumors
 - Intracranial infection, trauma
 - Non organic somatoform disorder
- ▶ Neuroimaging access challenges:
 - Availability of urgent CT/MRI
 - Need for anesthesia

Total Delay to Diagnosis in Childhood AIS (N=189)



Total Delay to Diagnosis in Childhood AIS (N=189)



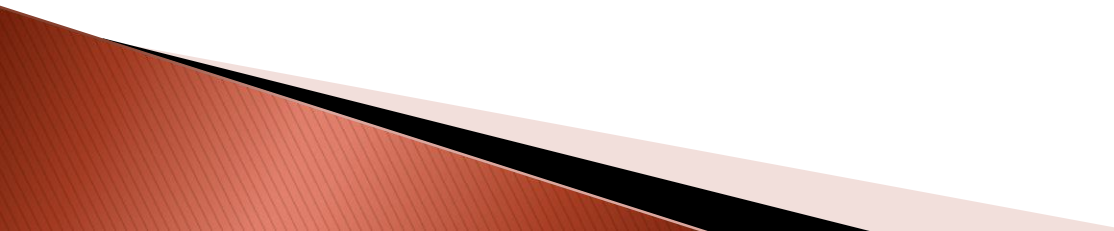
Delay to AIS Diagnosis in Children

- ▶ Diagnosis of AIS was missed in over 40%.
- ▶ 10 – 30% of children have had a ‘missed’ preceding TIA

Rafay et al, Stroke 2008

***Even if the diagnosis is made, underlying causes and risk factors are complex, poorly understood and differ from those in adults.

Etiologies & Risk Factors

- ▶ Many associations, risk factors and causations described with childhood stroke
 - ▶ Majority have multiple or overlapping risk factors, up to 50%
 - ▶ Idiopathic, in up to 30%
- 

Etiologies & Risk Factors

▶ Major three

- Arteriopathies – over 50%, including infectious and traumatic
- Cardiac disorders – up to 30%, cyanotic HD, perioperative, procedure related, ASD/PFO
- Prothrombotic states & disorders – 18 – 22%, Acquired > congenital

▶ Others

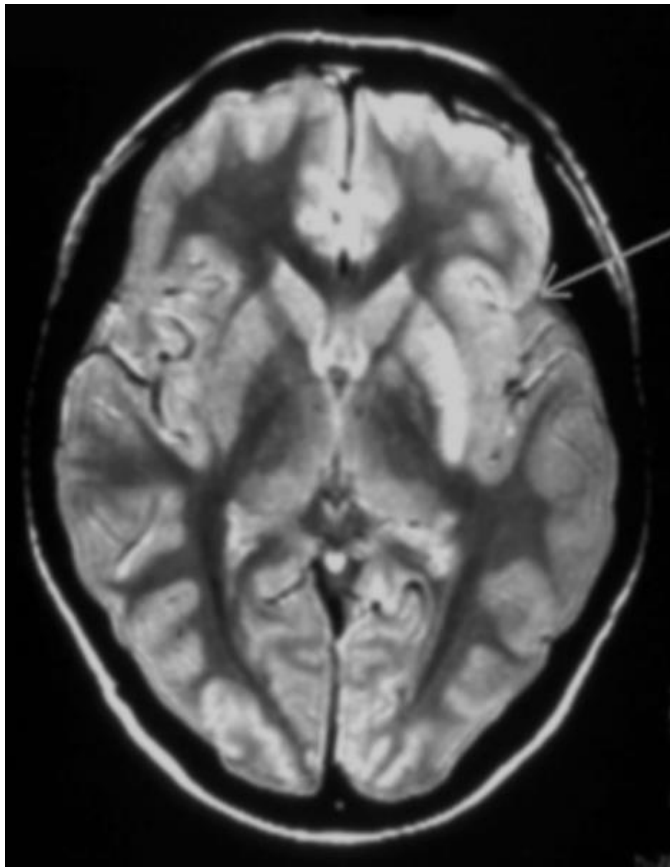
- Infections: Meningitis/sepsis, head and neck infections
- Hematological disorders – anemia, sickle cell anemia – 11% by age 20
- Genetic/metabolic – Homocystinuria, Fabry's, mitochondrial disorders
- Toxins/drugs (e.g. cocaine, radiation)
- Malignancy: (e.g. leukemia, solid tumors)
- Congenital disorders: PHACES, NF1
- Other Emboli: fat, tumor, foreign body, air, amniotic

Arteriopathies in Children with AIS

- ▶ Intracranial focal cerebral arteriopathy (FCA) – 45%
 - Post varicella angiopathy (PVAR) 18%
 - Transient cerebral arteriopathy (TCA) 7%
 - Intracranial arterial dissection – less common
- ▶ Cervical arterial dissection (CAD) – 7.5% – 19%
- ▶ Moyamoya – 6% – 12%
- ▶ CNS vasculitis – 5% – 12%
- ▶ Non specific arteriopathies – 35%

*Ferriero DM et al. AHA, Stroke 2019,
Leung ME & Rivkin M, Peds in Review, 2016*

15 year old girl with sudden onset headache, altered consciousness, right hemiplegia & aphasia and history of head/neck trauma 1 week ago



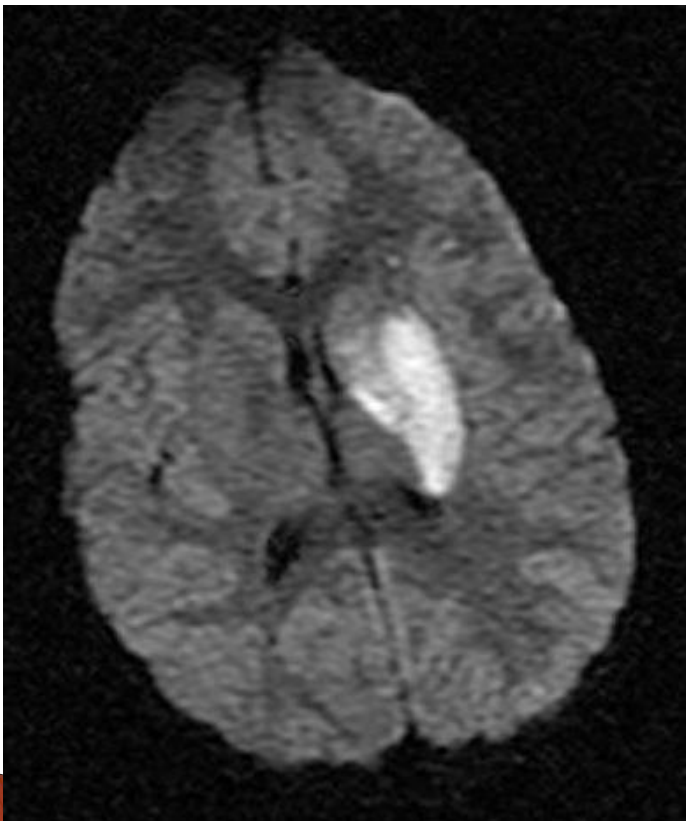
Axial FLAIR MRI



Conventional Catheter Angiogram

8 yrs-old boy with right hemiplegia and h/o chicken pox 6 months ago

Diffusion MRI



Catheter angiogram: LICA injection



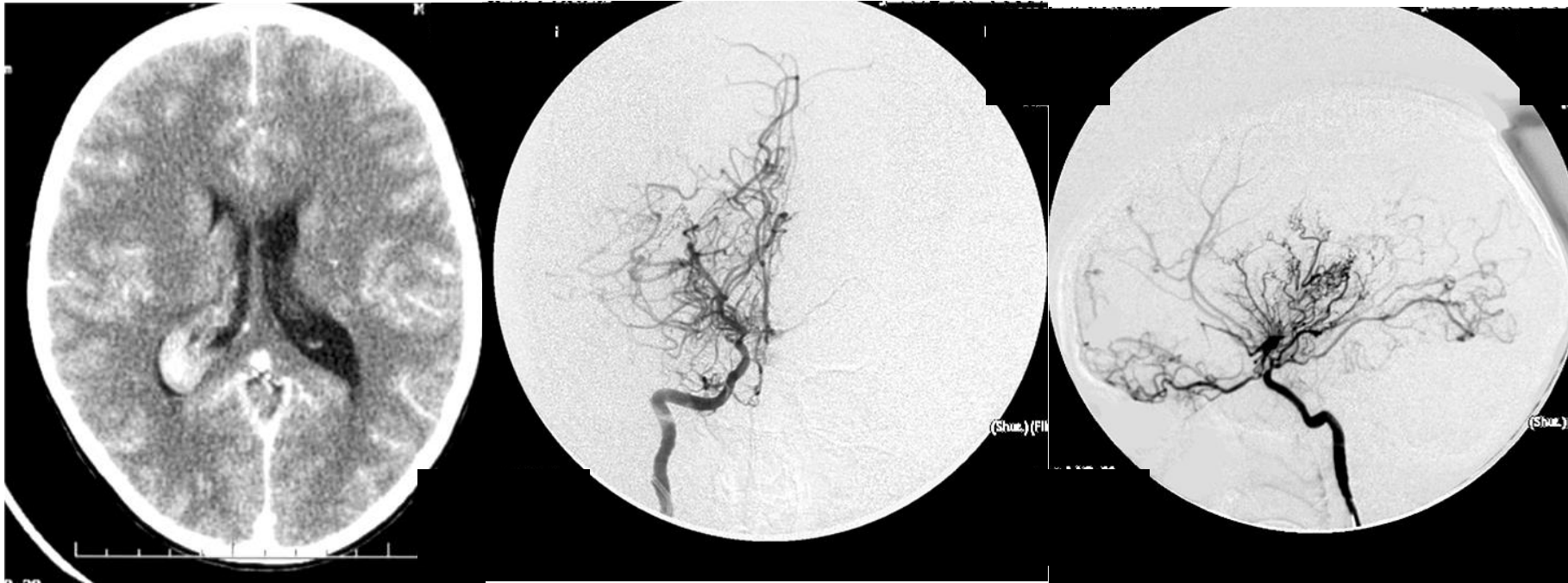
8-yr old boy with severe headache and persisting vomiting

Conventional Angiogram

Contrast CT

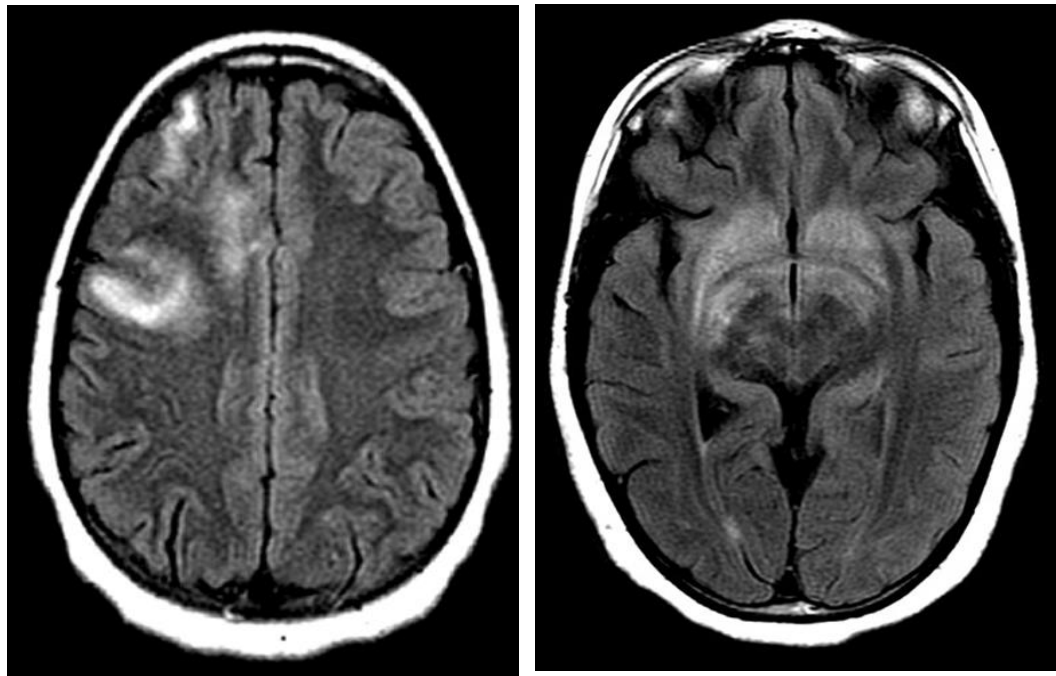
RICA Injection

LICA Injection



10 yrs-old girl with left hemiplegia, hemineglect and memory problems

Axial FLAIR MRI

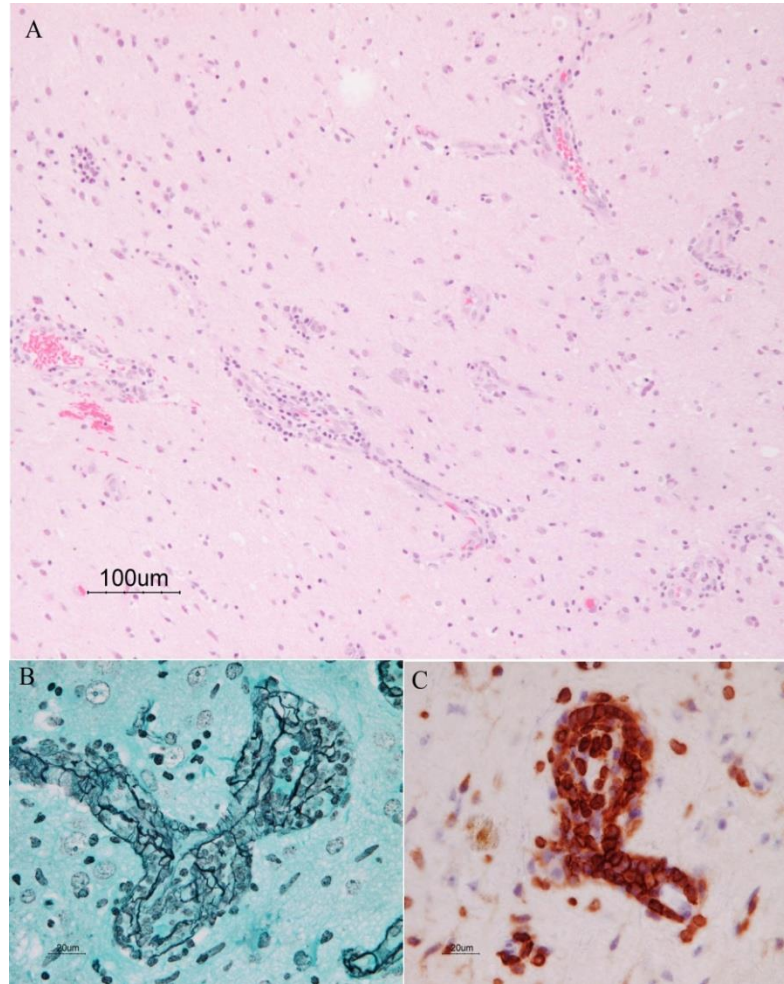


Conventional Angiogram



Rafay et al, CJNS, 2004

Pathology



Diagnosis

- ▶ Clinical suspicion
- ▶ Early and specific neuroimaging

Clinical Suspicion for AIS

- **Personal history**
 - History of trauma, recent infections –history of chicken pox or any other viral exanthem
 - Co-morbid diagnoses such as cardiac disorders, sickle cell disease or other hematologic disorders or syndromes
- **Birth history and maternal history** for perinatal stroke
- **Family history** of early stroke/MI/clotting disorders

Confirmation of Stroke

▶ Parenchymal brain Imaging

- Head CT → misses diagnosis in 15% of children with AIS
- Brain MRI with DWI, FLAIR, GRE or SWI, T1, and T2
 - DWI very sensitive for early cytotoxic edema

▶ Head and neck Vascular Imaging

- CT angiogram
- MR angiogram – esp. gadolinium enhanced
- MR Fat saturation: for intra-luminal clot in arterial dissection

Investigations for Pediatric AIS

- ▶ Baseline: CBC, PTT, INR, glucose, lytes
- ▶ Inflammatory and Infectious: ESR, CRP, ANA
- ▶ ECG, ECHO +/- TTE with bubble study
- ▶ Thrombophilia work up:
 - Levels: Protein C/S, antithrombin III, plasminogen, fibrinogen, lipoprotein a, homocysteine, APCR, antiphospholipid antibodies, lupus anticoagulant
 - Mutations: FVL and prothrombin gene
- ▶ Placental Pathology in neonatal stroke
- ▶ Transcranial Doppler in Sickle cell disease
- ▶ Idiopathic stroke with positive bubble study – 4 extremity Doppler ultrasound
- ▶ Digital subtraction Catheter Angiogram – in few idiopathic cases

Treatment of Children with Acute AIS

▶ Acute Treatment

- General Supportive measures/Neuroprotective Care
- Hyper acute interventions (Thrombolysis)
- Stroke Prevention –Anticoagulant versus antiplatelet

▶ Long term treatment or Stroke prevention

▶ Stroke Rehabilitation

Neuroprotection Care of Children with Acute Stroke

- ▶ Airway – minority, RSI issues
- ▶ Breathing – avoid high PEEP, pCO₂ changes
- ▶ Circulation – CPP = MAP – ICP
- ▶ Sedation – midazolam
- ▶ Seizures – control promptly, prophylaxis?
- ▶ Temperature – euthermia
- ▶ Glucose – euglycemic
- ▶ ICP – 3–5 days, routine +/- surgery?
- ▶ Aspiration / Nutrition – NG, swallow study

*Ferriero DM et al. AHA, Stroke 2019,
Leung ME & Rivkin M, Peds in Review, 2016*

Pediatric Thrombolysis

- ▶ Hyper acute therapies remain controversial due to lack of adequate feasibility and safety data.
 - Pediatric evidence based on case reports/series
 - IV and IA tPA possibly successful and safe, but biased data
- ▶ Thrombolysis can be considered in select cases – persistent disabling neurological deficits and radiographically confirmed cerebral large artery occlusion.
- ▶ Reasonable to limit to centers with hyper acute pediatric stroke care consideration of this intervention to children meeting certain criteria.

*Ferriero DM et al. AHA, Stroke 2019,
Leung ME & Rivkin M, Peds in Review, 2016*

AIS Prevention

- ▶ LMWH or UFH considered in children for 5–7 days after an AIS, pending further evaluation to determine the cause of the stroke.
- ▶ Anticoagulation with LMWH or warfarin for 3 to 6 months or longer for stroke resulting from cardiac embolism (including neonates) or in individuals with a prior thrombosis or a known prothrombotic disorder.
- ▶ In all other children, maintenance therapy with Aspirin dosed at 3 to 5 mg/kg/day.

(Class IIb, Level of Evidence C)

Ferriero DM et al. AHA Guidelines Stroke 2019

Sickle Cell Disease

- ▶ For primary stroke prevention, annual screening with TCD
 - Children with abnormal TCD – periodic regular transfusions to reduce sickle hemoglobin to 30% or hydroxyurea therapy after 1 year of regular blood transfusions
- ▶ For secondary stroke prevention with confirmed AIS
 - Optimal hydration, correction of hypoxemia and hypotension
 - Regular blood transfusion program to keep the sickle hemoglobin to <30%, with acute AIS <15%
 - Measures to prevent iron overload

(Class I, Level of Evidence A)

- Consider bone marrow transplantation in a clinical trial setting

*Ferriero DM et al. AHA, Stroke 2019,
Leung ME & Rivkin M, Peds in Review, 2016*

Recommendations for Rehabilitation After Pediatric Stroke

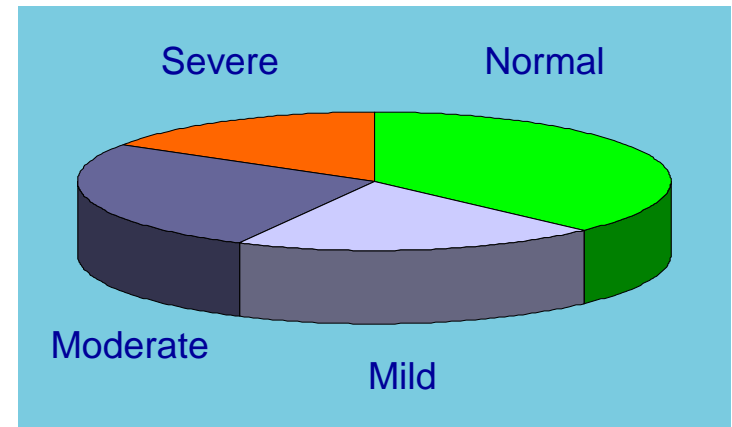
- ▶ Age-appropriate rehabilitation and therapy programs are indicated for children after a stroke
 - Constraint induced movement therapy (*Level of Evidence A*)
- ▶ Psychological assessment to document cognitive and language deficits is useful for planning therapy and educational programs after a child's stroke

(Class I, Level of Evidence C)

Ferriero DM et al. AHA, Stroke 2019

Outcome of Pediatric Stroke

- ▶ Etiology and age dependent
- ▶ Children: 70% have neurological deficits
 - 52 % mild
 - 33% moderate
 - 15% severe
- ▶ Neonates:
 - 68% exhibit cerebral palsy + 1 additional disability in 55%
 - 60% cognitive or speech impairment
 - 40–60% epilepsy
- ▶ Recurrence : 20–33% – <1.2% neonates
- ▶ Mortality: 5–10%, – up to 40% HS



Summary

- ▶ Stroke under-recognized, yet common in children ~ 2–13 /100, 000/year
- ▶ Identified mechanism in ~ 50–80%
- ▶ High recurrence rates ~ 15–33%
- ▶ Presentation and Outcome – etiology and age dependent
 - High morbidity – 70% have neurological deficits
 - Significant mortality in 5–10%
- ▶ Preventable and potentially treatable condition

Suggested Readings

- ▶ *Management of Stroke in Neonates and Children. AHA guidelines. Ferriero DM et al. Stroke 2019*
- ▶ *Stroke in Newborn Infants. Nelson KB, Lynch JK. Lancet Neurol 2004;3:150–158.*
- ▶ *Stroke in Neonates and Children. Brenson–Leung ME & Rivkin M, Peds in Review, 2016*