Stroke and Little Folk

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Disclosures

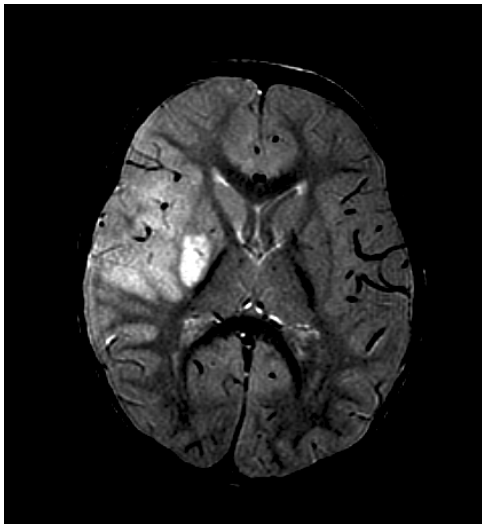
- No financial disclosures

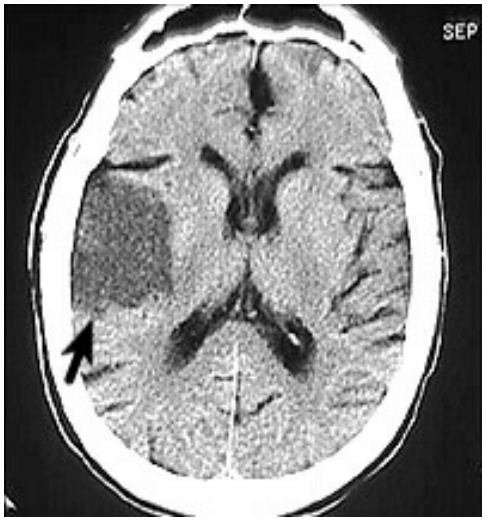
4 yo “previously healthy” male presenting with acute onset headache with L sided facial droop and weakness.

Exam: T 37.3 *although notes report that he was febrile at some point to 101F;* BP 95/58, HR 117, RR 22

Neurologic Exam

- Mental Status: Awake, says "head" when asked about pain, gives thumbs up on right to command.
- CN: PERRL 5mm -> 3mm, right gaze preference, L UMN facial weakness
- Motor/Sensory: moderate left hemiparesis with antigravity movement of arm spontaneously and leg to stimulus. Left-sided neglect.



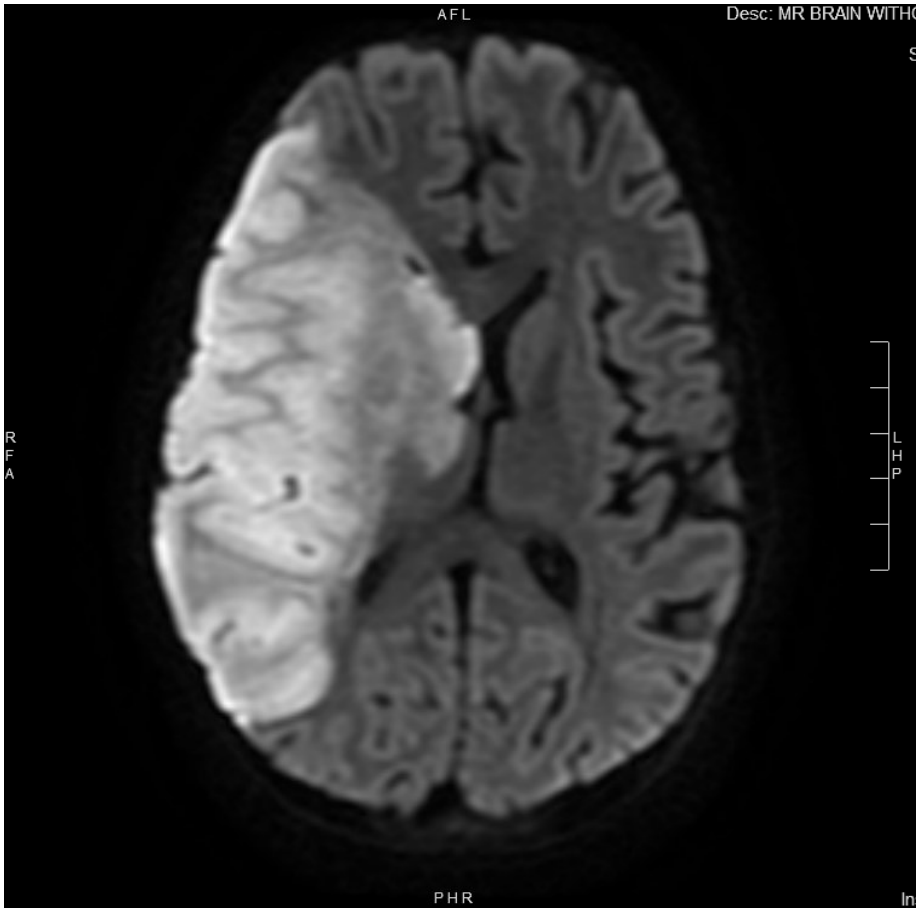


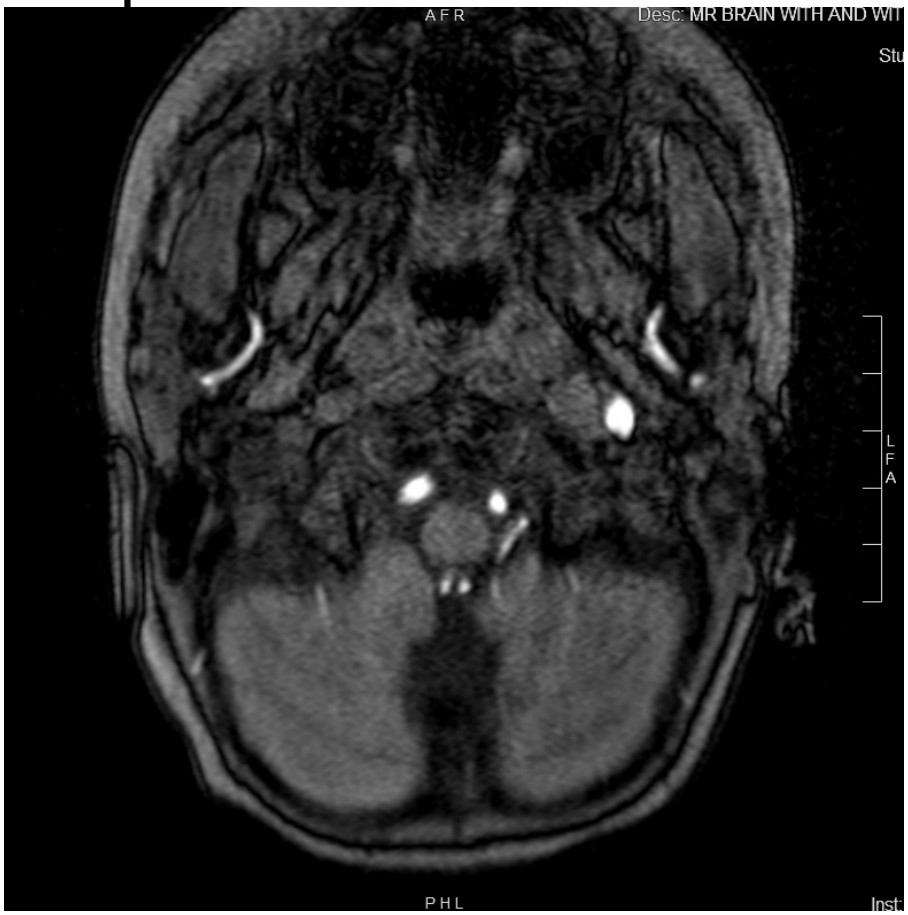
Hyperacute Pediatric stroke imaging:

- **MRI/MRA (preferred, <13 years)**
  - *Sensitive for acute ischemia*
  - *Diffusion restriction positive within minutes, remains bright 7-10 days*
  - *MRA for larger vessel occlusion*

- **CT/CTA/CT perfusion (≥13 years):**
  - *Insensitive for early ischemia*
  - *Hypodensity seen after 6-12 hours*
  - *Sensitive for hemorrhage*
  - *CTA for large vessel occlusion*
  - *Perfusion adds tissue at risk*

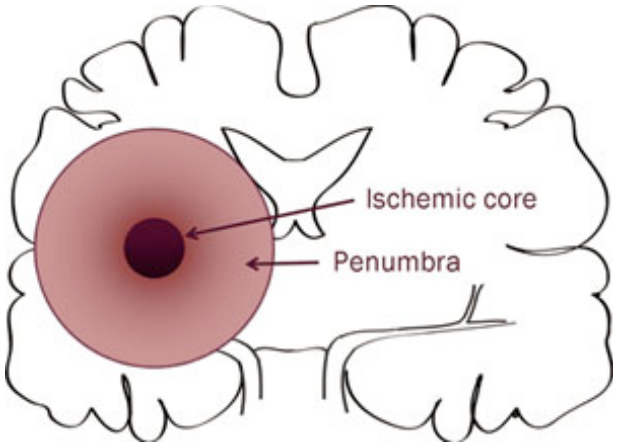
4 yo “previously healthy” male presenting with acute onset headache with L sided facial droop and weakness.





Childhood arterial ischemic stroke

- > 28 days of life
- 3,000/year in the United States
- **Includes ischemic and hemorrhagic**
  - Adult: estimated 80% of strokes ischemic
  - Children: estimated 50% of strokes ischemic
- Arterial stroke:
  - Embolic
  - Thrombotic
  - Small vessel
- After occlusion of a vessel:
  - irreversibly injured core infarct
  - larger “penumbra” of brain tissue with diminished blood flow, which infarcts over time (hours)

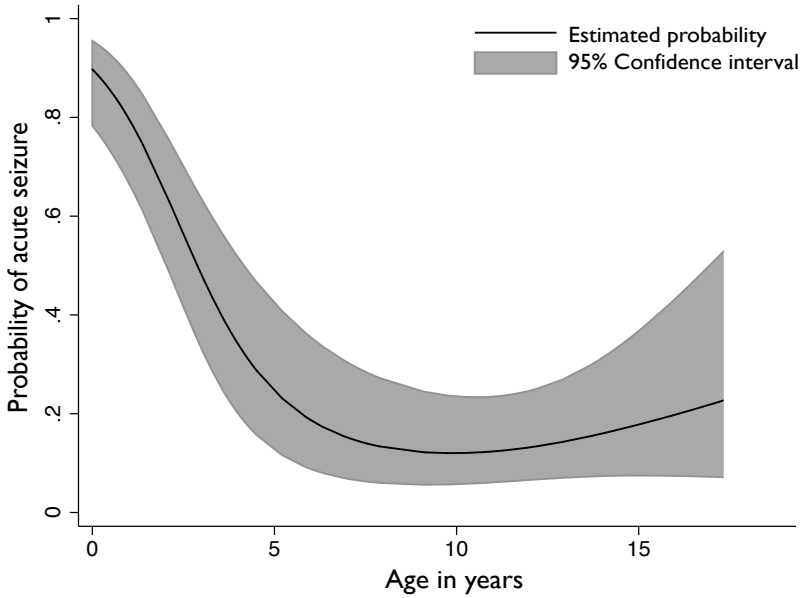


Acta Pharmacologica Sinica (2011) 32: 861–872

Childhood arterial ischemic stroke

Presentation:

- **focal neurologic deficits (most common):**
  - **hemiparesis, hemifacial weakness**
  - **speech and language**
  - **vision disturbance**
  - **ataxia**
- Altered mental status, headaches (30%), acute seizures (30%)
- Timing of deficit onset
  - Abrupt: 51%
  - Progressive over hours: 36%
  - Waxing/waning: 13%
- Most frequent affected artery is the MCA



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Etiologies of Childhood Stroke:

- Cardiac
  - Congenital ht dz
  - Bacterial endocarditis
  - Rheumatic ht dz
  - Arrythmias
- Vascular disease
  - Transient Cerebral Arteriopathy
  - Moyamoya
  - Arterial dissection
  - FMD
- Hematologic
  - Sickle cell dz
  - Leukemia
  - Polycythemia
- Hypercoaguable state
  - Aquired: sepsis, nephrotic syndrome, liver failure, SLE, anti-phospholipid syndrome, cancer
  - Inherited: protein c/s deficiency, AT III deficiency, Factor V Leiden, MTHFR, prothrombin 20210
- Infection
  - Meningitis/encephalitis
  - Chicken pox
- Drugs
  - Cocaine
  - OCP's
  - Chemotx (L-asp)
- Metabolic/Genetic
  - Homocystinuria
  - Fabry's
  - Organic acidemias
  - Majewski's Osteopdysplastic Primordial Dwarfism, type II
  - Collagen vascular (e.g., Ehlers-Danlos)
- Neurocutaneous d/o's
  - Neurofibromatosis
  - Tuberous sclerosis
  - PHACE syndrome

Childhood Arterial Ischemic Stroke

Large vessel arteriopathy

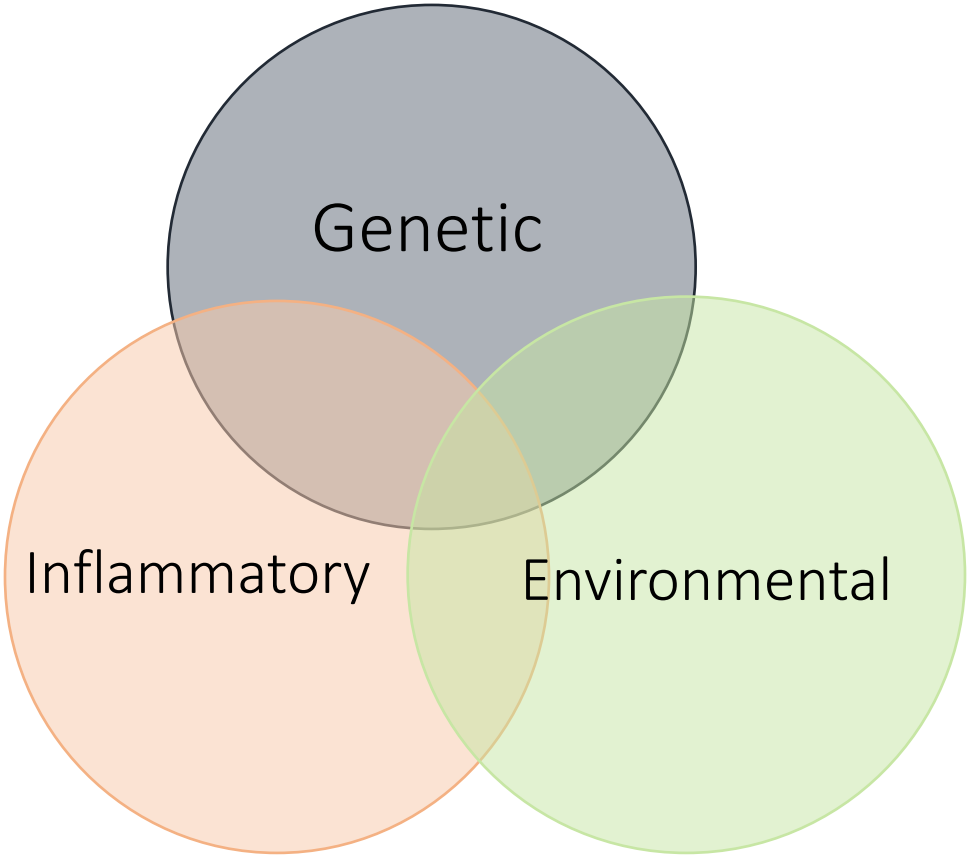
- **Acquired:**
  - Extracranial Dissection
  - Moyamoya
  - Vasculitis
  - Reversible Cerebral Vasoconstriction Syndrome
  - Transient cerebral arteriopathy
  - Rotational vertebral injury
- **Congenital/genetic**
  - PHACE, Sickle cell anemia, ACTA2

Cardiac disease

- **Acquired:**
  - Patent Foramen Ovale
  - Cardiomyopathy
  - Endocarditis
  - Valvular disease
  - Arrhythmia
- **Congenital/genetic**
  - Congenital Heart Disease
- **Inflammatory**
  - Lupus

Thrombophilias, non-vascular strokes, cryptogenic strokes

- Causes of childhood stroke are heterogeneous, difficult to classify, multifactorial

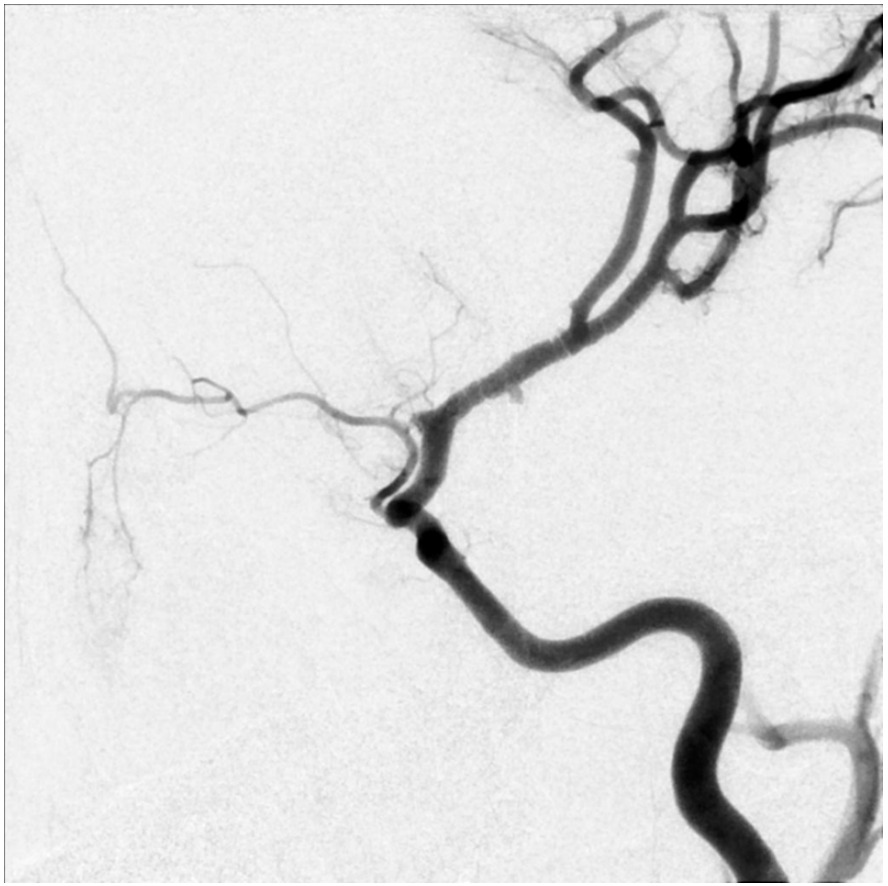


Arteriopathy – Focal cerebral arteriopathy

- Focal Cerebral Arteriopathy (FCA) – unilateral stenosis and/or irregularity of the large intracranial arteries of the anterior circulation
- predominant underlying mechanism that accounts for majority of pediatric stroke (18-64%)
    - FCA-dissection type: intracranial arterial dissection, typically in the setting of trauma
    - FCA-inflammation type:
        - Transient cerebral arteriopathy (TCA)
        - Moya-Moya
        - Genetic or syndromic
    - FCA-undetermined

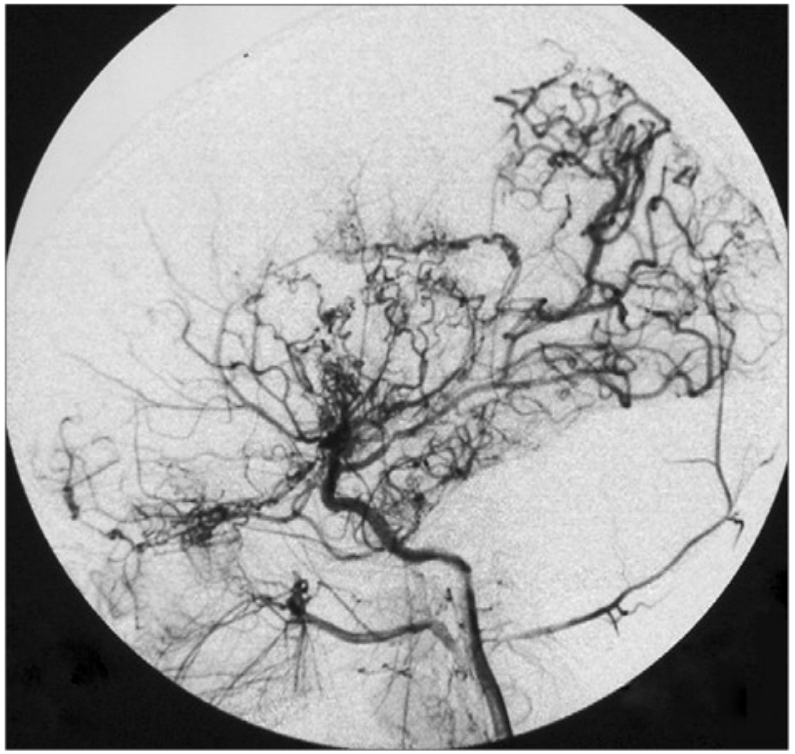
Arteriopathy – Transient cerebral arteriopathy

- Location: involving the junction of distal internal carotid artery and its proximal branches (MCA and ACA)
- Clinical course: stereotyped, monophasic natural history characterized by frequent early progression (for days to weeks), plateau with nonprogression by 6 months, and subsequent improvement in some with complete resolution in a minority

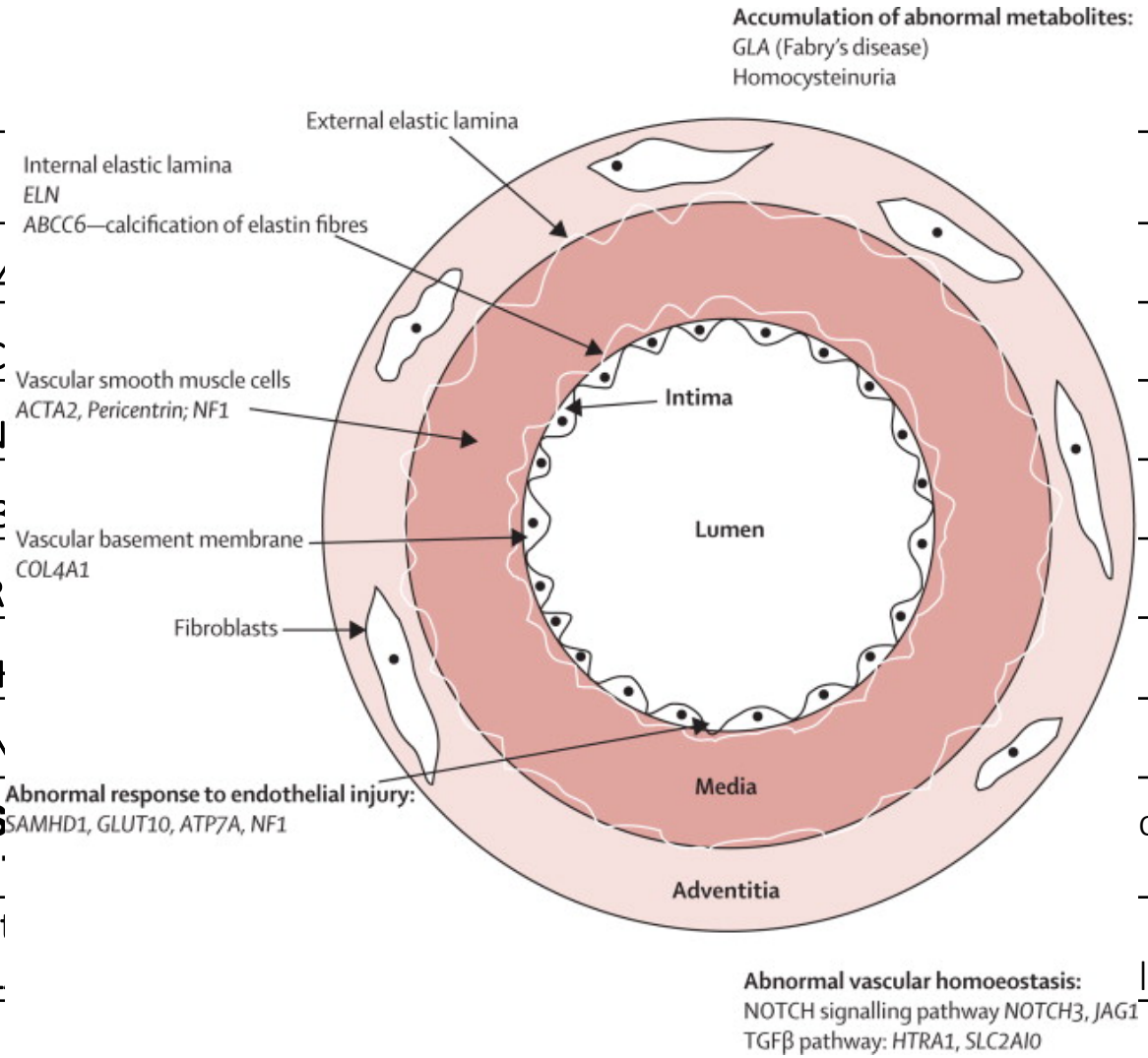


Arteriopathy – Moyamoya

- slow, progressive (usually bilateral) steno-occlusive changes of intracranial ICAs involving ACA and MCA
- Bimodal age distribution: accounts for ~ 6% of childhood arterial ischemic stroke
- High prevalence of TIA and silent infarction.
  - single center cohort study of 54 children, TIAs occurred in 70% and acute AIS in 48%
  - Imaging at time of initial diagnosis showed evidence of silent infarct in 52% *(Amlie-Lefond et al., 2015)*
- Treatment:
  - Medical: ASA, high salt diet, fludrocortisone, midodrine, avoid anti-hypertensives
  - Surgery:
    - Direct: STA-MCA bypass
    - Indirect: EDAS, EMS



Arteriopathy—Genes and disorders…



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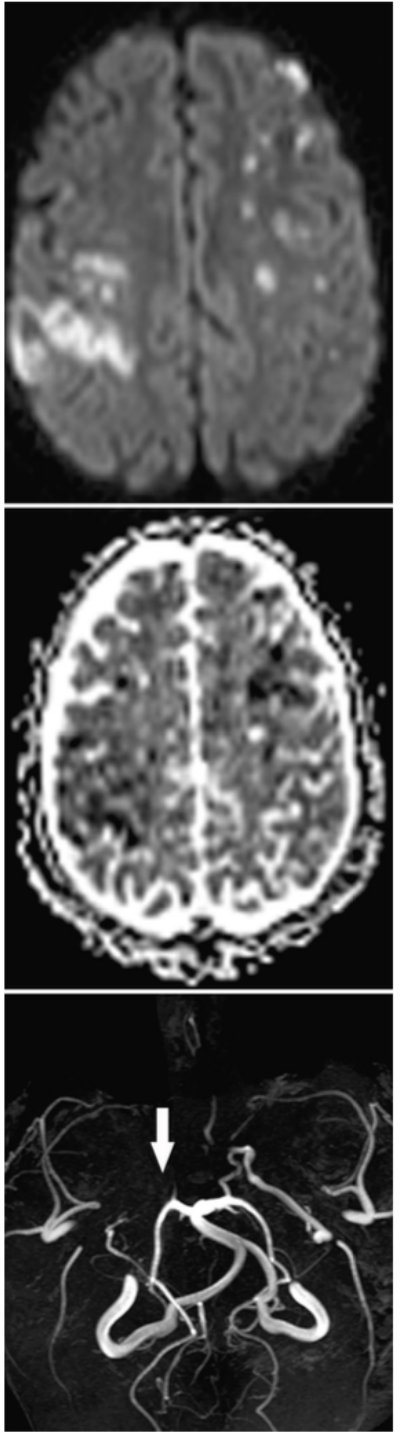
Paediatric stroke: genetic insights into disease mechanisms and treatment targets Volume 10, Issue 3, 2011, 264–274

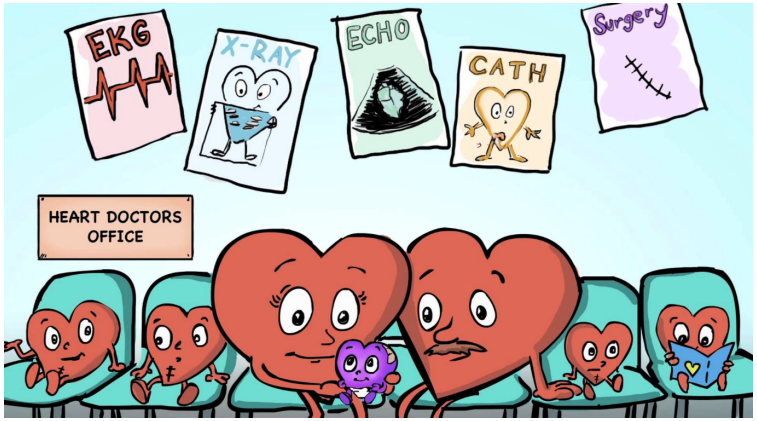
Hematologic—Sickle Cell Disease

- 11% of homozygous SCD children have a stroke by age of 20
- 200 fold increased risk of stroke (strongest risk factor)
- Pathophysiology: thrombi, hyperplasia of internal elastic membrane and scarring of the media
- **Stroke Prevention Trial in Sickle Cell Anemia (STOP):**
  - Transcranial doppler (TCD): identifies children with SCD who are at high risk for stroke (time-averaged mean blood flow velocities in ICA or MCA >200 cm/sec)
- Txt: chronic RBC transfusion reduces the risk of first stroke by **90%**



Cardiac

- Cardioembolic stroke accounts for ~ 30% of all childhood stroke
  - Congenital heart Disease
  - Procedure related events: Berlin Heart EXCOR VAD, ECMO, Fontan, and cardiac cath
  - Endocarditis
  - Acquired heart disease: PFO, arrhythmia, cardiomyopathy



Exam: T 37.3 *although notes report that he was febrile at some point to 101F;* BP 95/58, HR 117, RR 22

- Awake, says "head" when asked about pain, gives thumbs up on right to command. PERRL 5mm -> 3mm, right gaze preference, L UMN facial weakness, moderate left hemiparesis with antigravity movement of arm spontaneously and leg to stimulus. Possible left neglect.

Labs:

- BMP wnl
- AST/ALT: 3446/1643; Alk phos 78
- WBC 4.5
- Initial Hb 2.4 → corrected 5
- Initial INR 1.9 → corrected 1.4

- CRP 1.5, Procalcitonin 5.93; LDH 19529
- CSF: WBC 1, RBC 0

- RVP Positive for Parainfluenza 1 and 3
- Rapid Flu negative

Diagnostic Evaluation

PRELIMINARY LABS:

BASIC LABS: CBC, platelets, PT/PTT, electrolytes, BUN/CR, glucose, type and screen

IMAGING:

- MRI Brain
- MRA brain and neck with vessel wall imaging

CARDIAC/OTHER

- EKG
- Echo with bubble

Diagnostic Evaluation

THROMBOPHILIA:

- Protein C & S
- Antithrombin III
- Lupus anticoagulant screen
- Lipoprotein (a)
- Factor V Leiden
- Prothrombin
- MTHFR

(PRN) METABOLIC:

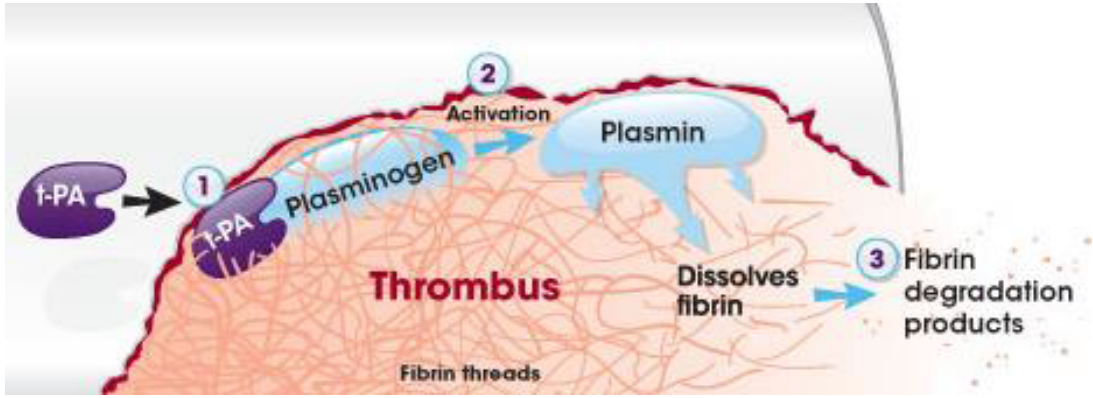
- Urine organic acids
- Lactate
- Pyruvate
- Plasma amino acids
- MELAS mutation
- CSF lactate

(PRN) VASCULITIS

- ESR, CRP
- ANA
- RPR
- Lupus anticoagulant screen
- C3, C4, VW Ag
- More extensive imaging

t-PA (alteplase, Activase®)

- Recombinant Tissue Plasminogen Activator, Thrombolytic
- Indication: management of acute ischemic stroke
  - Administer within ~4.5 hours of documented stroke onset
  - Not FDA approved in patients < 18 years of age
- **Mechanism of action: binds to fibrin, converts plasminogen to plasmin to result in clot lysis**



Challenges for child tPA protocol

- Ethics of treating children with potentially risky therapy
- Risk of symptomatic ICH after treatment with tPA
- Effects of developmental hemostatic differences btwn. adults and children (affect dosing, safety, and efficacy)
- tPA dose for children
- Frequency and type of neuroimaging used in initial and follow up scans

Thrombolysis in Pediatric Stroke (TIPS)

- NIH funded phase 1 clinical trial to determine safety and pharmacokinetics of intravenous tPA in children 2-18 yo within 4.5 hours of AIS and diagnosed on MRI
- Primary aim: Determine safety, best dose, and feasibility of treatment with intravenous (IV) tPA of children who
- Secondary Aim: pharmacokinetics of tPA in children and assessment of the 90-day clinical outcome among treated patients
- Consensus opinion: when intravenous tPA considered in children, adult dose of 0.9 mg/kg can be used.

*** Study was closed due to low enrollment ***

Rivkin et al., 2015

Exclusion criteria for IV t-PA

1. Significant edema or midline shift on head CT
2. Symptoms suggestive of subarachnoid hemorrhage or verified by CT scan
3. Prior intracranial hemorrhage from an untreated source
4. Sustained SBP> 185 mm Hg, diastolic > 110 mm Hg or aggressive treatment to lower BP
5. Any condition or circumstance in which the treating physician assesses that rtPA treatment would pose a significant hazard
6. Coma, severe obtundation, fixed eye deviation with complete hemiplegia
7. Minor or isolated stroke symptoms (NIHSS <4)
8. INR > 1.7 or suspected/known coagulopathy
9. Low molecular weight heparin within 24 hours or PTT>40 secs due to unfractionated heparin.
10. Platelet count < 100,000; hematocrit < 25%; serum glucose < 50 or > 400 mg/dL
11. Prior stroke or head injury within the preceding 3 months
12. Arterial puncture at a noncompressible site or lumbar puncture within 7 days
13. Major surgery or serious trauma within prior 14 days
14. Known intracranial neoplasm, AVM, or aneurysm
15. Presumed septic embolus
16. History of pericarditis, ventricular thrombus or aneurysm related to MI in previous 3 months
17. Pregnancy

Endovascular stroke treatment

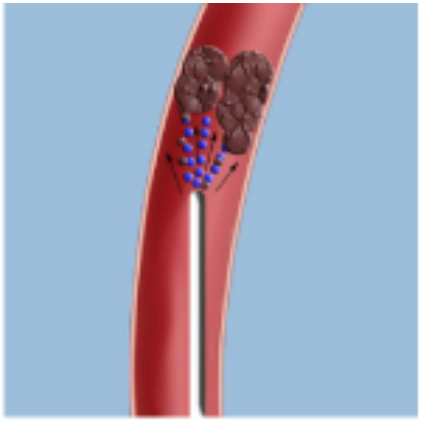
Goals:

- Removal of clot
- Restore blood flow to ischemic brain
- Save brain tissue at risk that has not yet died

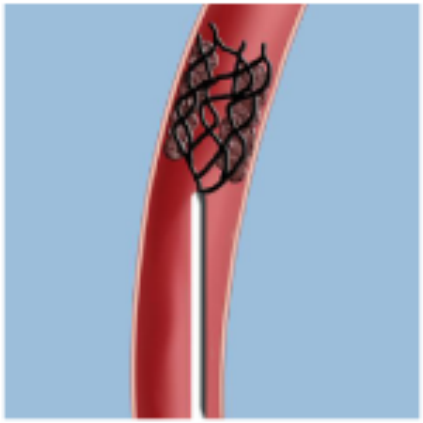
In Adults:

- **DAWN:** 6-24 hours after onset can be beneficial in adults with NIHSS >10 and core infarct volume <30 mL or NIHSS >20 and core infarct volums < 51 mL

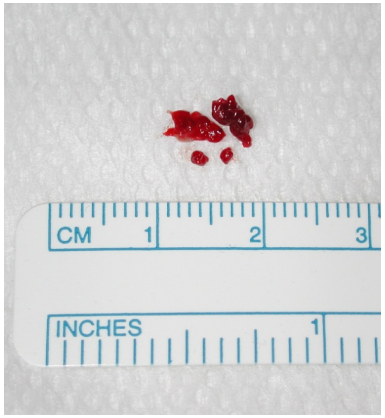
- **DEFUSE 3:** Benefit with thrombectomy in extended window (6-16 hours after onset)



Intra-arterial thrombolysis



Stent retriever device



Internal Medicine Journal, 28 JUL 2015, pages 798-805

What about children?

AHA/ASA Guidelines in 2015: Endovascular thrombectomy can be considered for some acute AIS patient < 18 yo

- **Over 35 cases of recanalization therapy in pediatric AIS have been reported, most with successful outcome.**

- **Special Considerations:**
  - Smaller arteries
  - Weight based limitations for radiological contrast/radiation exposure
  - Arteriopathies that cause AIS (introducing catheter to acutely inflamed artery or chronically stenosed cerebral arteries)

Hyperacute Stroke in children:

- Anterior Circulation

Age Range	IV tPA*	Endovascular Treatment*
≥ 13 years	4.5 hours	Discuss
≥ 1 year - < 13 years	Do not use	Discuss
< 1 year	Do not use	Do not use

- Basilar Artery Thrombosis

Age Range	IV tPA*	Endovascular Treatment*
≥ 13 years	4.5 hours	Discuss
28 days - < 13 years	Do not use	Discuss

*Time from stroke ictus (last seen normal). Strict time limit for IV tPA; increased hemorrhage risk outside of time windows. *Does not apply to children with sickle cell disease.*

Ischemic stroke *mimics* in children

ED providers correctly diagnose stroke in ~60% of children, giving ~40% of cases an incorrect initial diagnosis of stroke mimic

- **Complicated Migraine/Migraine with Aura**
  - Neurologic symptoms with headache
- **Bell's Palsy**
- **Post-ictal Todd's Paresis**
  - Persistent neurologic symptoms after a seizure
- **"The stomach flu"**
  - Cerebellar stroke: nausea and vomiting
  - Ataxia unnoticed because child in bed
- **Other:** brain tumor, demyelinating disease, encephalitis, TBI, syncope, intoxication, psychogenic disorders

Delays and Challenges: Diagnostic tools and strategies used in adults to distinguish stroke from stroke mimics have limited utility in children, with sensitivity ~60%.

(Mackay et al., 2017; Braun et al., 2006)

Considerations for clinical practice:

Medical Education:

- Develop programs of education to improve knowledge and skills in diagnosis and emergency management of pediatric stroke for frontline providers **(pediatricians, emergency physicans, and EMTs)**
- Education for **subspecialty providers** who care for populations at high risk of stroke: **(cardiologists, hematologists, cardiac intensivists, nursing, and pediatric intensivists)**

Research:

- Develop and validate bedside clinical assessment methods to ID stroke with improved sensitivity and specificity
- Better imaging techniques for early and accurate diagnosis
- Define modifiable stroke risk factors to incorporate into screening, early diagnosis, and prevention in children with heart disease.

Acute Management of Childhood AIS

Considerations for clinical practice:

- ICU monitoring for at least 24 hours after stroke.
- Glucose
  - Hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia.
  - -Goal: 140-180 mg/dL
- Hyperthermia (>38°C) should be identified and treated.
- Seizure Management
- Caution in children with intracranial vascular stenosis such as moya moya and FCA. Avoid HYPOTENSION.
- Decompressive hemicraniectomy
- Children with large-volume infarcts (more than ½ MCA territory) should consider early prophylactic hemicraniectomy w/in first 24 hours.

Controversies and Knowledge Gaps

Controversies:

- Setting for treatment: should treatment occur only in centers with pediatric vascular neurologist?
- Hemicraniectoym management
- Blood pressure management

Knowledge Gaps:

- Determining timing and appropriate candidates for hemicraniectomy
- Appropriate BP treatment
- Appropriate treatment of hypo/hyperglycemia

Summary

- Children have strokes
- Neuroimaging (particularly diffusion weight MR) is keystone for diagnosis of pediatric stroke and other investigations might be considered according to clinical presentation.
- There is wide range of underlying systemic factors that contribute to childhood stroke including: sickle cell disease, cardiac disorders, genetics, trauma, and major infections
- Arteriopathy is the predominant underlying mechanism causing stroke.
- Hyperacute therapies exist including tPA and endovascular retrieval.
- Management includes normothermia, normotension/hypertension?, seizure management, and hemicraniectomy
- Stroke mimics are much more common including seizure, post-infectious cerebellitis or migraine

A little more about our “previously healthy” patient:

- PMH: unimmunized, has only seen his pediatrician twice
- ROS: Fatigue with behavior changes (clinging to Mom, did not want to go to school) x 1 month. Past week w/ increased fatigue, nausea, and emesis with decreased PO. + Dry cough, tactile fevers. Sister w/ recent URI.
- Medications: None
- FH: No stroke, seizures or known hyper-coaguability.
- SH: lives with Mom and two older siblings in Ukiah

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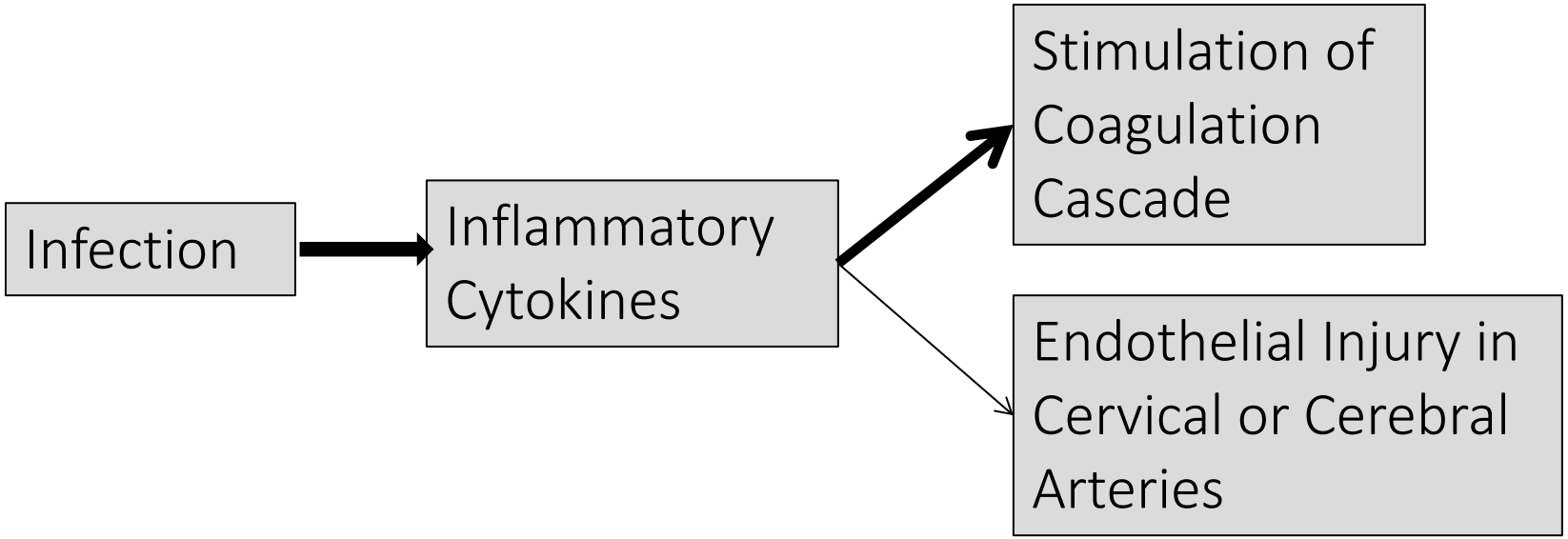
INFECTION

Infection as a Stroke Trigger



- Infection increases risk of cervical arterial dissection
  (Grau, Arch Neurol 1999; Guillon, Stroke 2003)
- Alternative Explanations:
  - Exposure to vasoactive cold remedies
  - Mechanical forces of coughing/sneezing

VIPS: Vascular effects of Infection in Pediatric Stroke

Prospective study of

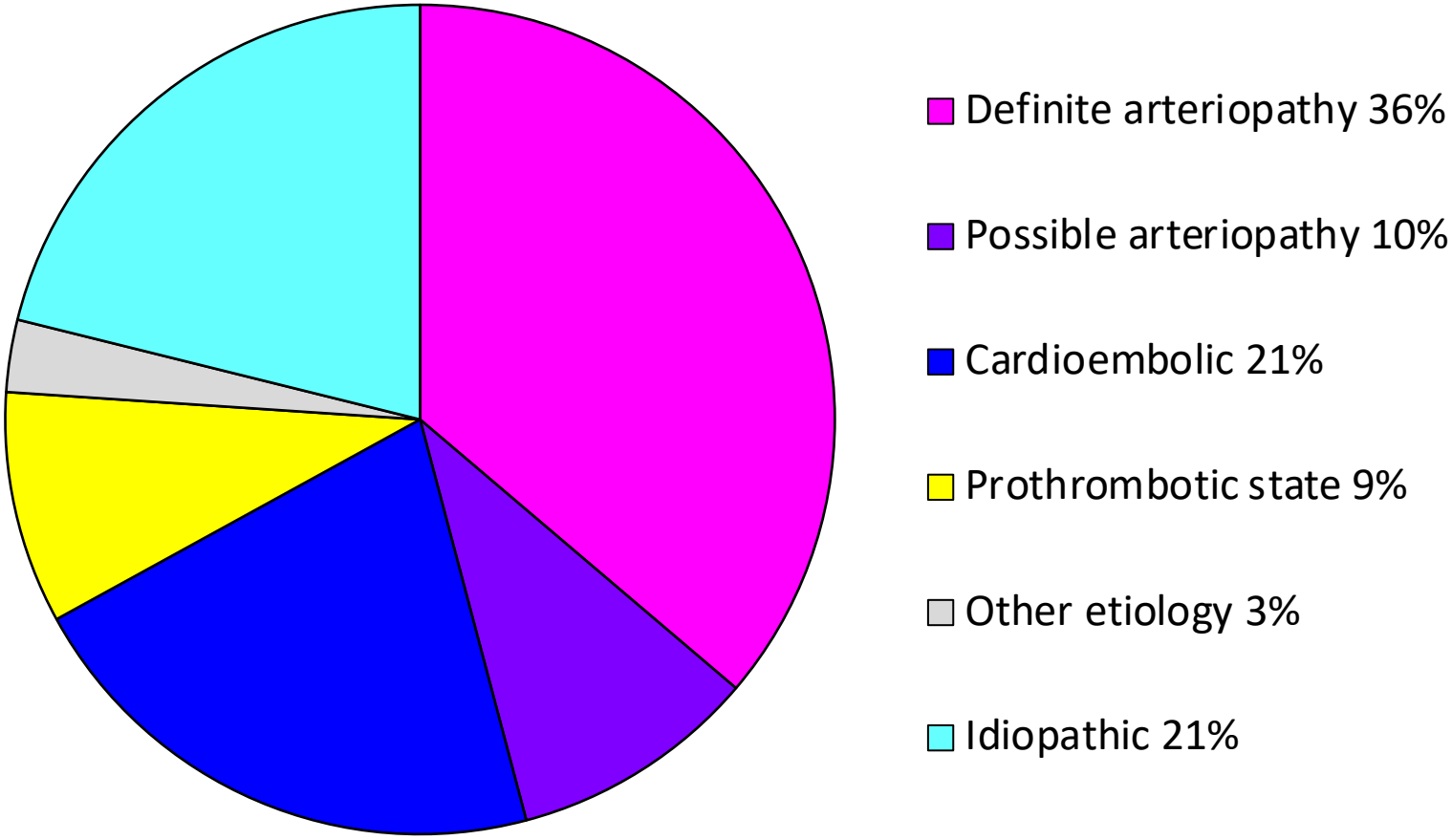
- **355** children with arterial ischemic stroke (AIS)
  - *age 28 days - 18 years*
  - *Enrollment within 3 weeks of stroke ictus*
  - *Minimum brain imaging protocol performed*
  - *Able to provide a blood sample*
- **354** controls
- **37** centers
- **5** continents: North America, South America, Asia, Australia and Europe

Hypothesis: infection transiently increases risk of AIS in children, regardless of stroke subtype

Methods: Case Study Procedures

- Parental interviews performed within 21 days of stroke: prior infections, vaccinations, medications, and family history
- Abstraction of baseline clinical data: stroke presentation, risk factors, and treatment
- Baseline serum samples within 21 days of stroke
- Centralized review of clinical neuroimaging
- Independent classification of arteriopathies with an adjudication process:
  - panel of pediatric stroke neurologists & neuroradiologists

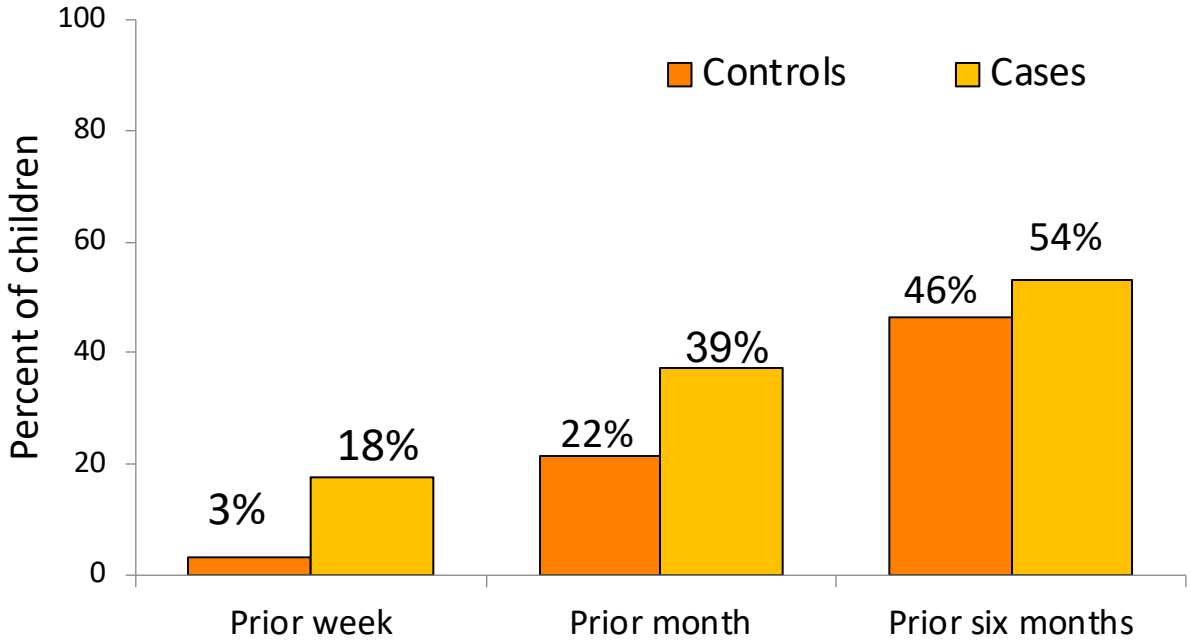
Stroke Subtype



Wintermark, et al, *Stroke* 2014

Results: Clinical Infection

Infection ≤ 1 week prior to stroke/interview date conferred a **6.3**-fold risk of AIS (p<0.0001; adjusted for age).



After adjusting for infection in the prior week, neither infection in the prior month or prior 6 months is significant

Fullerton, et al, *Neurology,* 2015

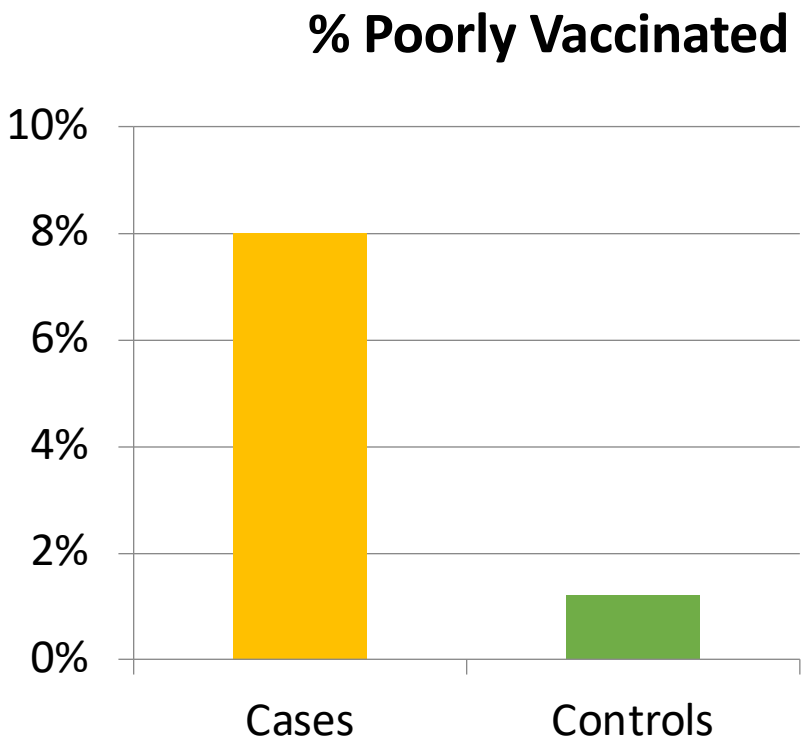
Are childhood vaccinations against infection protective?

Table 3 Exposures to vaccinations among patients with childhood AIS and age-matched controls, measured by parental interview

Characteristic	Cases (N = 355), n/N (%)	Controls (N = 354), n/N (%)	Risk of AIS[a]	
			OR (95% CI)	*p* Value
How many routine vaccines has your child received?				0.001[b]
All expected for his or her age	294/355 (82.8)	320/354 (90.4)		
Most	21/355 (5.9)	22/354 (6.2)		
Some	16/355 (4.5)	2/354 (0.6)		
Few	2/355 (0.6)	0/354 (0.0)		
None	9/355 (2.5)	2/354 (0.6)		
Unknown (missing data)	13/355 (3.7)	8/354 (2.3)		
Composite variable for poorly vaccinated[c] (some/few/none)	27/342 (7.9)	4/346 (1.2)	7.3 (2.5-21)	0.0002[b]
Ever received a routine vaccination against[c]				
MMR	298/355 (83.9)	327/354 (92.4)	0.40 (0.24-0.68)	0.0007[b]
Polio	322/341 (94.4)	338/346 (97.7)	0.42 (0.18-0.98)	0.004[b]
DPT	332/355 (93.5)	344/354 (97.2)	0.43 (0.20-0.93)	0.03[b]
Pneumococcus	255/324 (78.7)	285/322 (88.5)	0.42 (0.26-0.69)	0.0007[b]
Varicella	206/325 (63.4)	258/337 (76.6)	0.51 (0.36-0.74)	0.0003[b]
Meningococcus	211/315 (67.0)	246/323 (76.2)	0.61 (0.42-0.91)	0.01[b]
Hepatitis A	200/317 (63.1)	214/322 (66.5)	0.88 (0.62-1.25)	0.48
Hepatitis B	266/327 (81.3)	263/340 (77.4)	1.3 (0.96-1.01)	0.17
Any vaccinations, prior 6 months	109/341 (32.0)	123/349 (35.2)	0.82 (0.59-1.15)	0.25

Results: Vaccination

Children reported to have had some/few/no routine vaccinations had ***7 times the risk of stroke*** compared to those receiving all or most of their routine vaccinations.



OR (95% CI), p-value

7.3 (2.5, 21), p=0.0002

Adjusted for age and geographic region

VIPS Study

Back to our case….

Labs:

- BMP wnl
- AST/ALT: 3446/1643; Alk phos 78
- WBC 4.5
- Initial Hb 2.4 → corrected 5
- Initial INR 1.9 → corrected 1.4

Further studies:

- CRP 1.5 →15.6
- RVP Positive for Parainfluenza 1 and 3
- Negative: HSV 1&2 Ab, HHV 6 PCR, HIV 1+2, Parvovirus Ab B19; Adenovirus PCR, EBV/CMV PCR & Ab, Babesia Ab, Brucella Ab, Hep Panel
- Mycoplasma IgM 1739 (H), Mycoplasma pneuomoniae DNA negative
- Lipoprotein A 353 (H) (repeat 3 months later: 205 (normal))
- MCV 70 → Iron 22 (ref 22-136); TIBC 343; Transferrin Saturation 6.4, Retic % 0.4;

Iron Deficiency Anemia and Stroke

- Various case control studies suggest association between iron-deficiency anemia (IDA) in healthy children and ischemic stroke.
  - *IDA is significantly more common in stroke patients (53%) vs. control subjects (9%) (Maguire et al., 2007)*
  - *IDA was disclosed in 57.1% of stroke cases with no identified caused compared to 26% of controls. (Azab et al., 2013)*
- Previously healthy children with stroke were 4-10x more likely to have IDA than healthy children without stroke
- Mechanism unclear:
  - *hypercoagulable state directly related to iron deficiency and/or anemia*
  - *Thrombocytosis secondary to IDA*
  - *Anemic hypoxia: mismatch between oxygen supply and end-artery oxygen demand*

- No clot retrevial attempted on the basis of large stroke volume. Additional concern for possible elevated risk for hemorrhage given unknown cause for recent coagulopathy
- After acute period, transferred to inpatient rehabilitation for one month and discharge home with wheelchair
- Started walking on his own 1-2 weeks after discharge. Wheelchair for long distances.
- Developed proximal strength in left shoulder and deltoid / biceps, no distal strength. Needs help with most ADLs, though can feed himself.
- Followed by Neurology – on ASA, will obtain repeat MRI in 1-2 months
- Followed by Hematology "*His anemia was initially thought to be secondary to iron deficiency, however, despite a normal diet and multiple transfusions, he has not had an adequate reticulocytosis and is markedly anemic again. Further, his reticulocyte count has been intermittently elevated and inappropriately low.*"

Summary

- There is wide range of underlying systemic factors that contribute to childhood stroke including: sickle cell disease, cardiac disorders, genetics, trauma, and major infections
- Arteriopathy is the predominant underlying mechanism causing stroke.
- Neuroimaging (particularly diffusion weight MR) is keystone for diagnosis of pediatric stroke and other investigations might be considered according to clinical presentation.
- Minor infection may act as a trigger for childhood arterial ischemic stroke, while routine vaccinations appear protective.
- Previously healthy children with stroke were 4-10x more likely to have iron deficiency anemia than healthy children without stroke