Ischemic Stroke in Children

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Funding – I have NIH grants to study:
• Hemorrhagic Stroke in Children – K23NS062110
• Stroke Prevention in Sickle Cell Disease – R21NS080639
Epidemiology of Perinatal Stroke

• Definition: perinatal = between 20 weeks gestation and 28 days of life
• Prevalence: ~ 1:3,000 births (33/100,000)
• Gender difference: 75% boys
• Most common location for ischemic stroke = middle cerebral artery territory (MCA), Left > Right
  – Blood flow through the heart goes across the foramen ovale into the Left side of the heart and the up the Left > Right internal carotid artery to Left MCA
  – Suggests embolic cause for most perinatal stroke
• Recurrence risk over 5 years ~ 2%
  – All recurrences were in kids with congenital heart disease.
Newborn with Seizures at 24 Hours of Life
Clinical Presentation of Acute Arterial Ischemic Stroke in Newborns N=46

• Prospective cohort of term neonates with acute arterial ischemic stroke diagnosed on MRI within first 28 days of life

Presenting Symptoms:
• **Seizures** - 41/46
• Apnea - 2/46
• Lethargy - 1/46
• Incidental - 2/46 stroke diagnosed on neuroimaging study ordered for another reason
• Note – no children with hemiparesis as a newborn!
  – Hemiparesis apparent at 4-5 months of age

Wustoff et al. Pediatrics 2011
Epidemiology of Childhood Stroke

Childhood Stroke
2-3/100,000*

Hemorrhagic Stroke
1.1/100,000

ICH
0.8/100,000

SAH
0.3/100,000

Ischemic Stroke
1.2/100,000

*Incidence rate is per 100,000 child-years.

Overall, childhood stroke is as common as brain tumor in childhood!!

Differential Diagnosis of Acute Hemiparesis in Children:

Why is CT not enough?

- Complex migraine = hemiplegic migraine
- Focal seizure with focal weakness after seizure (Todd’s Paralysis)
- Stroke – Ischemic/Hemorrhagic
- Other focal brain pathology

Stroke Mimics can include:
- Encephalopathy related to hypertension, intracranial infection, tumor, drug toxicity, pseudotumor cerebri, inflammatory disease, epilepsy

Etiology of Ischemic Stroke in Older Kids: Think Embolic or Arteriopathy

- **Arteriopathy** – present in 60-80% of Children
  - **Arterial Dissection (25%)**, also Focal cerebral arteriopathy, Moyamoya, post-infectious, HIV, Varicella, etc
- **Cardioembolism (25-35%)**
- **Sickle Cell Anemia (HbSS)**
  - 10% will have a *clinical stroke* by age 20
  - 20% more will have a *silent infarct*
- Hypercoaguable state
- More unusual causes… vasculitis, pregnancy, metabolic disorders, cerebral sinus venous thrombosis
- **Idiopathic (5–15%)**
Etiology of Hemorrhagic Stroke in Kids

- Arteriovenous Malformations (#1 = Vascular)
- Cerebral Cavernous Malformation
- Aneurysm
- Coagulation or platelet dysfunction
- Moyamoya
- Hereditary Hemorrhagic Telangetasia
- Cerebral Sinus Venous Thrombosis
- Tumor
- Idiopathic

Hemorrhagic strokes are nearly 50% of strokes in children…
Causes & Risk Factors: Lessons from Registries

- Sites: 46 centers, 10 countries, (43% of cases from US)
- Enrollment: N=3099 from 1/2003-1/2012, age birth – 19 yrs, arterial & venous ischemic stroke
Arterial Ischemic Stroke Risk Factors: International Pediatric Stroke Study
N = 676 (2007 data)

- Arteriopathy 53%
- Cardiac disorders 31%
- Infection 24%
- Acute head and neck disorders 23%
- Acute systemic conditions 22%
- Chronic systemic conditions 19%
- Prothrombotic states 13%
- Acute systemic conditions 22%
- Chronic head and neck disorders 10%

Mackay M, Ann Neurol 2011;69:130–140
Arteriopathy Subtypes Among 277 Children with AIS

<table>
<thead>
<tr>
<th>Arteriopathy</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>FCA*</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>Moyamoya (primary or secondary)†‡</td>
<td>61</td>
<td>22</td>
</tr>
<tr>
<td>Arterial dissection†</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Sickle cell disease arteriopathy</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Postvaricella angiopathy</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Other§</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Unspecified vasculopathy</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

*Includes TCA (n=11).
†Excludes children with sickle cell disease.
‡One subject with moyamoya and dissection.
§Fibromuscular dysplasia (n=2), atherosclerosis (n=1), vessel hypoplasia (n=2), HIV vasculopathy (n=1), Sturge Weber (n=1), Susac syndrome (n=1), penetrating trauma (n=1), and cervical artery ligation (n=1).

What are these?
Why So Much Interest in Arteriopathy?

- Population-based study
  - Children 1 month to 18 years
  - 5-year cumulative recurrence rate = 19%

- Children without arteriopathy had no recurrences

- With vascular abnormality, 5-year cumulative recurrence rate = 66%
## Predictors of Arteriopathy

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 d–4 y</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>5–9 y</td>
<td>2.04 (1.25–3.34)</td>
<td>0.004</td>
</tr>
<tr>
<td>10–14 y</td>
<td>1.12 (0.68–1.86)</td>
<td>0.647</td>
</tr>
<tr>
<td>15–19 y</td>
<td>1.10 (0.61–1.97)</td>
<td>0.749</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td></td>
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<tr>
<td>Cardiac disease</td>
<td>0.37 (0.24–0.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>3.06 (1.27–7.39)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Recent infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.34 (0.13–0.88)</td>
<td>0.026</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0.27 (0.05–1.36)</td>
<td>0.112</td>
</tr>
<tr>
<td><strong>URI</strong>*</td>
<td>2.36 (1.05–5.27)</td>
<td>0.037</td>
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*Includes sinusitis and otitis media.

Amlie-Lefond et al. *Circulation* 2009
Vascular Effects of Infection in Pediatric Stroke (VIPS)

NIH/NINDS-funded multicenter cohort study
PIs: Heather Fullerton, UCSF; Gabrielle DeVeber, Toronto
Data coordinating center: IPSS data core, Toronto

Hypotheses:

1) Infection can lead to childhood arterial ischemic stroke by causing vascular injury.

2) Resultant arteriopathy and inflammatory markers predict recurrent stroke.

Prospectively enroll 350 children (1 month – 18 years) with AIS and collecting extensive infectious histories, blood, urine and serum samples
Pediatric Stroke Alert – Vanderbilt

• Child with stroke like symptoms for < 48 hours

• tPA is NOT the major issue, but stroke diagnosis will prompt an acute change in management and monitoring

• Pediatric Stroke Alert Page by ED or PCICU
  – Page notifies pediatric neurology on-call resident, peds stroke attending, PICU, MRI tech and On-call Radiologist
Immediate Management / Initial Supportive Care for All Strokes

**Goals:** Improve Cerebral Perfusion/Oxygenation + Minimize Cerebral Metabolic Demands

- **EXAM:** Assess level of consciousness, motor, and language function carefully
  - Get an exam you can follow serially (i.e. PedNIHSS)

- Hourly GCS x 8+ hours

- Isotonic **IV fluids**

- Head of bed **flat** for best cerebral perfusion unless ICP is of significant concern – then **30 degrees**

- Normothermic, normoglycemic

- Oxygen if sats not > 95%
Urgent Stroke Imaging in Kids

• Order **emergent** non-contrast brain MRI
  – An abbreviated MRI sequence to confirm acute stroke and assess for hemorrhage
  – **Kids with symptom(s) within the last 48 hours** or if stroke will cause dramatic management change

• **Head CT misses 60% of pediatric strokes**

• **VCH Radiology has a protocol for this study**
  – DWI/ADC, GRE for blood (labelled T2-FFE), T1 and T2 axial (MRA can be added)

• Hope to avoid sedation and **short protocol takes < 10 minutes**
Pediatric NIH Stroke Scale

• Document a PedNIHSS in kids 2-17 years and regular NIHSS in 18+ years

• PedNIHSS – **Major Modifications from Adults:**
  – LOC: Instead of Month and Age
    • Ask – “How old are you?”, “Where is Mommy?”
  – LOC: Instead of grip
    • “Show me/touch your nose”
  – Ataxia
    • “Reach for toy and kick leg”
  – Language
    • Name pediatric images on stroke cards, observation if < 6 years

PedNIHSS is Reliable and Valid for Children Ages 2 and Up

www.pednihss.com
Pocket Guide

Ichord R. et al. Stroke 2011
Example of Modifications for Young Children

**LOC Questions**

The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues. Modified for children, age 2 years and up. A familiar Family Member must be present for this item: Ask the child "how old are you?" Or "How many years old are you?" for question number one. Give credit if the child states the correct age, or shows the correct number of fingers for his/her age. For the second question, ask the child "where is XX?", XX referring to the name of the parent or other familiar family member present. Use the name for that person which the child typically uses, e.g. "mommy". Give credit if the child correctly points to or gazes purposefully in the direction of the family member. Omit this item for infants age 4 months up to age 2 years.
American Heart Association
Guidelines for Pediatric Stroke Published in 2008

AHA Scientific Statement

Management of Stroke in Infants and Children
A Scientific Statement From a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young

E. Steve Roach, MD, FAHA, Chair; Meredith R. Golomb, MD, MSc; Robert Adams, MD, MS, FAHA; Jose Biller, MD, FAHA; Stephen Daniels, MD, PhD, FAHA; Gabrielle deVeber, MD; Donna Ferriero, MD; Blaise V. Jones, MD; Fenella J. Kirkham, MB, MD; R. Michael Scott, MD, FAHA; Edward R. Smith, MD
Diagnostic Evaluation of Ischemic Stroke: Head, Neck, Heart, Blood

- **MRI/A Brain** – “Stroke protocol with diffusion” perfusion preferred, Heme sequence– for blood!, MR Venogram

- **Image of NECK vessels** – MR Angiography or CT Angiography, NOT ultrasound

- **Echo** – Trans Thoracic Echo with bubble study

- **Coag Evaluation**
Thrombolysis in Children?

Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study

Catherine Amlie-Lefond, Gabrielle deVeber, Anthony K Chan, Susan Benedict, Timothy Bernard, Jessica Carpenter, Michael M Dowling, Heather Fullarton, Collin Hovinga, Adam Kirton, Warren Lo, Khaled Zamel, Rebecca chord, for the International Pediatric Stroke Study

Note: alteplase = tissue plasminogen activator (tPA)

Study showed that a Publication Bias Exists – best tPA cases are reported… and that 2- 3% of children with strokes in USA and Canada were receiving tPA.

Thrombolytic Therapy For Acute Stroke

PEDIATRIC ISSUES

- Many stroke mimics in kids, migraine, seizure, etc
- Need to confirm a stroke exists BEFORE tPA
- Correct tPA dose in children?
  - Literature suggests children may need more tPA than adults
  - Literature also suggest that kids bleed more when given tPA for other indications (peripheral thrombosis, etc)
- Risk/Benefit ratio
  - Kids recover well from stroke – will they see the same benefit that adults do from tPA?
Safety and dose-finding study of intravenous (IV) tPA in children with acute AIS ages 2-17 years

Determine the maximal safe dose of intravenous (IV) tPA within 4.5 hours from onset of acute ischemic stroke
  – This is time since last seen normal

Three doses (0.75, 0.9, 1.0 mg/kg) for children

Must have PedNIHSS of ≥4 (significant deficit)
  • MRA or CTA to confirm partial or complete vessel occlusion prior to tPA
Conclusions on tPA in Kids

• Developmental hemostasis makes dose of tPA for stroke in kids unclear
• NIH-funded Phase I, dose-finding and safety study for tPA is in progress
• 20 sites; Vanderbilt is the only center in TN
  – TIPS = Thrombolysis in Pediatric Stroke

• tPA use is currently experimental in kids
  – Just as in adults, consider and document contraindications for tPA, especially in older adolescents
AHA Guidelines: Ischemic Stroke Treatment

- **Anticoagulation** is useful for long-term anticoagulation of children with a substantial risk of recurrent cardiac embolism, cervical arterial dissection and selected hypercoagulable states (Class I, Level of Evidence C)

- **Aspirin** is a reasonable option for the secondary prevention of AIS in children whose infarction is not due to SCD and in children who are not known to have a high risk of recurrent embolism or a severe hypercoagulable disorder (Class IIa, Level of Evidence C)
  - ASA dose of 3 to 5 mg/kg/day is reasonable (Class IIa, Level of Evidence C) up to maximum of 325mg daily.
Recent Pediatric Stroke Alert Case 1

• 10-year-old boy with sickle cell anemia (HbSS) with sudden onset of left face and arm weakness 2 hours ago
• Rapid transport to VCH, Stroke Alert paged
• In ED, alert but restless
• Only able to hold still for 3 minutes for acute MRI but 2 key sequences obtained
• Sedation deferred given risk in this situation
Acute MRI Shows a Small Right Parietal Stroke That Would Have Been Missed by CT

Rapid transfer to PICU for exchange transfusion, standard of care for acute stroke in sickle cell anemia.
AHA Guidelines: Sickle Cell Anemia

Class I Recommendations

- **Primary Prevention**: Periodic RBC transfusions for abnormal TCD >200 cm/second based on time averaged maximum velocity in the MCA (STOP I, Adams et al. *N Eng J Med* 1998;339:5-11)


Class II Recommendations

- **Acute Treatment**: Exchange transfusion for acute ischemic stroke to reduce Hb S to <30% of total Hb
- Hydroxyurea if transfusion not feasible
- Consider bone marrow transplant
- Revascularization as last resort in SCA
Recent Pediatric Stroke Alert Case 2

• 3 year old who awoke crying with left hemiparesis, face, arm, leg lasting 30 minutes

• In ED, normal exam for 2300 and fussy child

• Evaluation?

• Does this child need to be admitted?

• Sounds like a TIA…
A Surprise: Midline Mass

Increased intracranial pressure, worse when supine for nap…
Don’t ignore stroke-like symptoms in kids
Recent Pediatric Stroke Alert Case 3

• 7-year-old healthy boy plays football with his brother, then seems quiet, pale. Seems off balance and to be saying very little (says “night Mom”) at 1930pm.

• The next morning, has right face and arm weakness and can’t say any words. Looks scared. Follows commands.

• EMS is called and radios VCH ED that they have a child with a possible stroke at 0705am.

• Peds ED at 0720am, PedsNIH stroke scale = 5.
Urgent MRI

Acute ischemia on DWI and ADC images
MRA

- Had MRA – looked embolic
- CTA no dissection in neck
- Conventional angiogram – fine
- Echo – normal, no PFO
- Hypercoag work up - normal

MRA with cut off/occlusion of arterial branch
Conclusions

• Consider stroke in any child with a hemiparesis or aphasia, especially those with risk factors
  – Help avoid delays in diagnosis! Educate staff at your hospital!

• Think about methods to support cerebral perfusion
  – Fluids = first line
  – Thrombolytics and clot retrieval devices are experimental (use will be rare even when studied)

• Don’t sedate
  – Follow neuro exam for worsening and/or cerebral edema

• Teach families of children at higher risk about stroke symptoms with FAST mnemonic (FACE-ARM-SPEECH-TIME)
References/Further Reading


See also the AHA Pediatric Stroke Fact Sheet. (Google).


“Google” Vanderbilt Pediatric Neurovascular Center to find our website. http://www.childrenshospital.vanderbilt.org/neurovascular