Ischemic Stroke in Children

Lori Jordan M.D., Ph.D.
Director, Pediatric Stroke Program
Vanderbilt University School of Medicine
Nashville, Tennessee

DISCLOSURES
Lori Jordan M.D., Ph.D.

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• 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.

Epidemiology of Childhood Stroke

Childhood Stroke 2-3/100,000*  
Hemorrhagic Stroke 1.0/100,000  
SAH 0.1/100,000  
ICH 0.8/100,000  
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!!

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

Newborn with Seizures at 24 Hours of Life
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 (2-15%)

Etiology of Hemorrhagic Stroke in Kids

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

Hemorrhagic strokes are nearly 50% of strokes in children...

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>Subtype</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Arteriopathy</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>Moyamoya (primary or secondary)††</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>Vascular</td>
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<td></td>
</tr>
<tr>
<td>Sickle cell disease arteriopathy</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Prothrombotic 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>
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</tbody>
</table>

Includes TIA (n=11), includes children with sickle cell disease, includes sudden with myocardial infarction and dissection, vascular involvement associated with moyamoya and dissection, arteriovenous malformation (n=5), moyamoya (n=1), arterial hypertension (n=1), sickle cell disease (n=1), Sturge-Weber syndrome (n=1), moyamoya (n=1), symptomatic group (n=1), and cerebral arterioanomaly (n=1).

What are these? Amlie-Lefond et al. Circulation 2009

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
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>OI (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>2.04 (1.25-3.34)</td>
<td>0.001</td>
</tr>
<tr>
<td>1.12 (0.81-1.55)</td>
<td>0.647</td>
</tr>
<tr>
<td>1.19 (0.81-1.73)</td>
<td>0.246</td>
</tr>
<tr>
<td>Recent infection</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.34 (0.13-0.86)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0.27 (0.10-0.74)</td>
</tr>
<tr>
<td>UEB</td>
<td>2.76 (1.05-7.27)</td>
</tr>
</tbody>
</table>

*Includes inpatient and outpatients.

VIPS Study

Vascular Effects of Infection in Pediatric Stroke (VIPS)

NHINNDS-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, ped's 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

Example of Modifications for Young Children

American Heart Association Guidelines for Pediatric Stroke Published in 2008

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

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?

**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


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

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

1. AHA website on Pediatric Stroke. [Link](http://www.strokeassociation.org/STROKEORG/AboutStroke/StrokeInChildren/StrokeInChildren_UCM_309543_SubHomePage.jsp)
   See also the AHA Pediatric Stroke Fact Sheet. [Link](Google).


*Google* Vanderbilt Pediatric Neurovascular Center to find our website. [Link](http://www.childrenshospital.vanderbilt.org/neurovascular)