Pediatric stroke: assessment and management

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UPMC Stroke Update.
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4 yr-old girl with pneumonia who developed left hemiparesis

- Day 1 transferred from OSH for worsening pneumonia (LLL then LLL + RUL while on antibiotics); walked during day
- Day 2: clingy, wanted her mom to carry to bathroom, irritable with manipulation of left arm
- Day 3: concerns about left hemiparesis, neurology consulted;
- Diagnostic possibilities?
Pediatric stroke: neurologic differential diagnosis (VITAMINS)
- (V) asacular
- (I)nfectious
- (T)oxic, trauma
- (A) utoimmune
- (M) etabolic
- (I) diopathic
- (N)eoplasms
- (S)eizures, (p(S)y)ch
4 yr-old girl with pneumonia who developed left hemiparesis: neuro consult

- Recurrent URI sx for 2 weeks
- Hospitalized for at least 7 days before brain attack; Family denied recent trauma
- **PE:**
  - T38.7 119/81 P130 RR 30 cried but consoled;
  - crusted eyes,
  - Right gaze preference persistent with oculocephalic stimulation
  - left hemianopsia,
  - left facial droop and dense left hemiparesis
- **Labs:** Adenovirus (+); influenza A/B (-)
4 yr-old girl with pneumonia who developed left hemiparesis: DWI
4 yr-old girl with pneumonia who developed left hemiparesis

- Tortuous verts
- No mural hematoma on T1 Fat Sat
- No clear dissection
- Etiology of stroke?
- Further eval?
4 yr-old girl with pneumonia who developed left hemiparesis

- Tortuous verts
- No hematoma on T1 Fat Sat
- Access to trampoline at grandfather’s house
R V1, V2 vertebral artery dissection
4 yr-old girl with pneumonia who developed left hemiparesis

- Likely remote neck trauma on trampoline
- Hypoxemia
- Hypotension with illness
- Hypercoagulable state with illness
Pediatric stroke: clinical challenges

- Differences between adult and pediatric stroke
- Risk factors in pediatric stroke
- Categories of clinical presentation
- Clinical challenges
  - Delays in presentation
  - Delays in detection of stroke by healthcare providers
  - Differential diagnosis and stroke mimics
- Current evaluation and management
- Status of thrombolysis pediatric stroke
Definitions

• Pediatric brain attack: focal brain dysfunction of apparently abrupt onset
• Pediatric stroke: ischemic injury and death of neurons due to occlusion of blood supply or hemorrhage into brain parenchyma.
Pediatric stroke distinctives

- Incidence of 3-6 per 100,000 person-years (Agrawal et al, 2009)
- Almost 25% perinatal
- Many perinatal strokes only detected at 6 months of age when mild hemiparesis detected.
- In childhood hyperlipidemia and hypertension rarely important

Hemorrhagic vs. ischemic stroke

Adults: 85% ischemic infarct, 15% hemorrhagic


Hemorrhagic stroke

• Causes of hemorrhagic stroke in children?
Hemorrhagic stroke (Jordan et al, 2008)

- HMO database: 116 nontraumatic childhood hemorrhages in 2.3 million children 1993 to 2003
- Etiology
  - Arteriovenous malformation 31%
  - Unknown etiology 25%
  - Cavernous malformations 15%
  - Medical etiologies 14%
  - Cerebral aneurysms 13%
  - Brain tumors 2.5%

Stroke database results: International pediatric stroke study group, Jan 2003 to Aug 2007 (Mckay et al for the IPSS, 2011)

- 676 children between 1 month and 18 yrs of age 
  arterial ischemic stroke
- 341 neonates (age<29 d) with stroke 
  (hemorrhagic, ischemic, cerebral sinovenous thrombosis CVST)
- 170 children with cerebral venous sinus thrombosis (CVST)

### Arterial Ischemic stroke risk factors (IPSS, 2011)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Frequency (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriopathy: focal arteriopathy, moyamoya, dissection, post-varicella)</td>
<td>53</td>
</tr>
<tr>
<td>Cardiac :CHD, acquired heart disease, post cardiac surgery</td>
<td>31</td>
</tr>
<tr>
<td>Infection: meningitis etc.</td>
<td>24</td>
</tr>
<tr>
<td>Acute head and neck disorders: head/neck trauma, pharyngitis, Surgery, otitis media</td>
<td>23</td>
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<tr>
<td>Acute systemic conditions: fever, sepsis, shock, dehydration, acidosis</td>
<td>22</td>
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<tr>
<td>Chronic systemic conditions: Sickle cell disease, hematologic malignancy, iron deficiency, indwelling catheter</td>
<td>19</td>
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<tr>
<td>Prothrombotic states: protein S, C defic.; acquired thrombophilia, MTHFR, elevated lipoprotein A, PT20210A, Factor VL,</td>
<td>13</td>
</tr>
<tr>
<td>Chronic head and neck disorders: migraine, brain tumor, VP shunt, AVM, aneurysm</td>
<td>10</td>
</tr>
<tr>
<td>Atherosclerosis related: IDDM I, hypertension, hyperlipidemia</td>
<td>2</td>
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</tbody>
</table>
Stroke presentations

• Hemorrhagic vs ischemic
  – Headache, vomiting more common with hemorrhagic
  – Long delay in diagnosis more common with ischemic than hemorrhagic stroke (Gabis et al, 2002)

• Cerebral sinovenous thrombosis
  – Spectrum of clinical presentation overlaps with arterial ischemic and hemorrhage strokes
    • Headache, seizures, vomiting, lethargy or drowsiness

Delays in diagnosis of pediatric stroke

- Delays in presentation in adult stroke have led to underutilization of thrombolytics
- Long time lag to first clinician contact (Gabis et al, 2002):
  - Mean of 14.3 hrs for hemorrhagic stroke
  - Mean of 42.8 hrs for ischemic stroke
Delays in diagnosis of pediatric stroke

- Physician awareness in arterial ischemic stroke (Srinivasan et al, 2009)
  - Focal signs didn’t lead to quicker diagnosis
  - Average time from clinical onset to diagnostic confirmation: 24.8 hrs
  - 75% of patients seen with 3 hrs
  - Stroke mimics likely to important contributors to delay

Pediatric stroke mimics?
Stroke mimics

• What percentage of adult brain attacks are stroke mimics?
• What are the adult stroke mimics?
• What percentage of pediatric brain attacks are stroke mimics?
Stroke mimics: pediatric vs. adult  (Mackay et al, 2014)

• A brain attack was defined as focal brain dysfunction of apparently abrupt onset.
• symptoms required for inclusion:
  – weakness,
  – sensory disturbance,
  – speech disturbance,
  – visual disturbance,
  – altered conscious state, unexplained collapse,
  – first febrile or afebrile seizure,
  – headache with other symptoms
  – dizziness or unsteadiness.
• Brain attack in 301 out of 101000 ED presentations

Stroke mimics: pediatric vs. adult (Mackay et al, 2014)

- Pediatric brain attack: 8 most common final diagnoses:
  - migraine in 28%,
  - seizures in 15%,
  - Bell palsy in 10%,
  - **ischemic or hemorrhagic stroke** in 7%,
  - Conversion disorders 6%
  - Syncope 4.7%
  - Encephalopathy 3%
  - CNS demyelination 2%

- Meta-analysis of adult brain attack: 8 most common diagnoses:
  - **Ischemic or hemorrhagic stroke** in 73.1%
  - Seizure or epilepsy in 4.3%
  - Migraine in 2.4%
  - PNS mononeuritis in 2.1%
  - CNS tumor in 2.1%
  - Syncope in 1.7%
  - Psychiatric in 1.5%
  - Cord lesion in 0.9 %

Mackay et al (2014)
Mimics of childhood stroke  (Shelhaas et al, 2006)

• 143 patients referred for stroke team evaluation
  – Newborn to 18 yrs, mean age of 10.5 yrs.
  – 79% ultimately diagnosed with stroke syndromes
  – 30 (21%) patients with stroke mimics
    • Benign: 11
    • Not benign: 19

# Mimics of childhood stroke

(adapted from Shelhaas et al, 2006)

<table>
<thead>
<tr>
<th>Benign</th>
<th>Not benign</th>
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<tbody>
<tr>
<td>migraine</td>
<td>Neonatal seizure</td>
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<tr>
<td>psychogenic</td>
<td>Posterior reversible encephalopathy syndrome</td>
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<tr>
<td>musculoskeletal</td>
<td>Metabolic stroke</td>
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<tr>
<td>delirium</td>
<td>Epilepsy (new diagnosis)</td>
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<tr>
<td>Periodic hypertensive episodes</td>
<td>Postictal paralysis</td>
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<tr>
<td></td>
<td>Acute Disseminated Encephalomyelitis</td>
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<td></td>
<td>Tumor</td>
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<td></td>
<td>Cerebellitis</td>
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<td></td>
<td>Drug Toxicity</td>
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<td></td>
<td>Idiopathic intracranial hypertension</td>
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<tr>
<td></td>
<td>Subdural empyema</td>
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<tr>
<td></td>
<td>Arteriovenous malformation</td>
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<tr>
<td></td>
<td>Moyamoya</td>
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<td>Intracranial abscess</td>
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Pediatric arterial ischemic stroke

• Common symptoms and signs?
Pediatric arterial ischemic stroke: mode of presentation (IPSS, 2011)

- **Focal signs:** 82%
  - Hemiparesis
  - Speech disturbance
  - Visual disturbance
  - Other: cerebellar signs, cranial neuropathies, sensory signs, higher cortical

- **Diffuse signs:** 64%
  - Reduced consciousness
  - Headache
  - Papilledema
  - Vomiting, dizziness, vertigo

- **Seizures:** 31%

Which patients with new onset seizure need imaging?
Stroke presenting as seizure

- Lateralized tonic-clonic activity based on injured and epileptic cortex
- Eye deviation and head turn away from side with brain injury and seizure activity
- Seizure accompanied by post-ictal deficit that doesn’t resolve quickly is suspicious for intracranial processes including stroke (AAN, 2001)

Lateralizing signs in infant seizures
(Loddenkemper et al, 2004)

- Reliable signs of focal activity
  - Focal clonic activity
  - Unilateral spasms
  - Focal tonic activity
  - Unilaterally directed nystagmus
  - Postictal hemiparesis
  - ***tonic eye deviation unreliable
Seizures as presenting symptoms with acute arterial ischemic stroke

• CHOP stroke registry 2005-2008: 60 Patients presenting with stroke between 2 months and 18 yrs (Abend et al, 2011)
  – (13) 22% presented with seizure (10 focal, 3 nonfocal)
  – All had focal deficits accompanying seizure
    • Hemiparesis (100%)
    • Mental status change (38%)
    • Visual deficit (23%)
    • Dysarthria or aphasia (15%)
    • Ataxia (8%) (1)
  – Children <=3yrs: 7.7 fold greater risk of seizure at presentation, compared to older children

• Riley Hospital for Children, 1989-2005: children <1 yr more likely to present with seizures (Zimmer et al, 2007)
Acute pediatric brain attack: initial management

- Priorities?
- First steps?
- Principles?
Acute pediatric brain attack: initial management

- Glucose check: avoid significant hyperglycemia or hypoglycemia, potentially detrimental in hemorrhagic and ischemic stroke (Wiener et al, 2008)
- Euvolemia
- Blood pressure: No evidenced based guidelines
  - In adults with ischemic stroke, permissive hypertension (MAP <130)
- Cerebral aneurysm: more aggressive BP control

Acute pediatric brain attack evaluation: imaging

- One acute stroke MRI/MRA protocol
  - DWI/ADC
  - T2 FLAIR
  - ASL
  - MRA brain
  - SWAN (to make sure not bleed)

- Alternative: head CT/CTA

- Supplemental: MRA of the neck (w/wo contrast)
  (dissection protocol, T1 fat saturation)

Head CT and susceptibility-weighted MRI in child with hemorrhages accompanying multiple cavernous malformations (adapted from Jordan and Hillis, 2011)

Acute pediatric brain attack: ED labs order set

- CBC and Diff including Platelet (CBC with diff)
- PT with INR, PTT
- Type and Screen
- Sed rate automated, Antinuclear Antibody Titer (ANA, Titer)
- Comprehensive metabolic panel
- Serum glucose
- Lactic acid (Lactate), Pyruvate
- Homocysteine
- Lyme reflex screen
- Thrombotic Risk factor screen (Factor X, dAPC Resistance, ATIII activity, Prot C, Prot S)
- Drug Screen, Basic ED, Blood/urine
- HCG, qualitative serum
Hypercoagulability workup: abnormalities associated with pediatric stroke

- Strong clinical association (Kenet, 2010)
  - Deficiencies of protein S, C, or antithrombin
  - Genetic defects
    - Factor V G1691A mutation
    - Factor II G20210A variant (elevated prothrombin levels)
  - Lipoprotein A: abnormally high level
  - Immunologic abnormalities
    - Acquired antiphospholipid antibodies (serial testing required)
  - Fasting lipid profile
- Need to discriminate transient vs. persistent abnormalities (Trenor and Michelson, 2010)

Acute pediatric stroke evaluation: cardiac

• Appropriate cardiac eval?
Acute pediatric stroke evaluation: cardiac

• Electrocardiogram
• Transthoracic echocardiogram with bubble study
  – Cardioembolic disease
  – Patent foramen ovale
• TEE:
  – suspected endocarditis,
  – Persistent suspicion of PFO
Acute pediatric arterial ischemic stroke management

• Antiplatelet therapy?
• Anticoagulation?
Acute anti-thrombotic therapy

• Antiplatelet therapy: aspirin 1-5 mg/kg/d for at least 2 yrs. (American College of Chest Physicians guideline, 2008)

• Cervicocephalic arterial dissection: 3 to 6 months of anticoagulation with low molecular weight heparin or warfarin followed by aspirin

• Arterial infarct with sickle cell disease: transfusion to lower sickle hemoglobin to <30% (Prengler et al, 2002)
Status of pediatric acute thrombolytic therapy with tPA

- Why can’t we use the adult studies?
Status of pediatric acute thrombolytic therapy with tPA

• Intravenous tissue plasminogen activator (tPA: only in clinical trials (AHA guideline 2008 and American College of Chest Physicians guideline)

• Isolated case reports of success with IV tPA in pediatric stroke

• Comparison: 18 of 687 non-neonatal patients in IPSS database (1999-2007)

Status of pediatric acute thrombolytic therapy with tPA

• Why can’t we use the adult studies?
  – Developmental hemostasis
  – Unique pediatric tools needed for outcome measurement
    • Pediatric NIHSS
    • Pediatric Stroke Outcome Measure (PSOM)
  – How is pediatric coagulation biology different from adults?
Developmental hemostasis (Monagle et al, 2006)

- Endogenous tPA lower in infants and children
- Plasminogen activator inhibitor-1 (PAI-1) binds tPA and inhibits tPA activity
- PAI-1 increased in infants and children
- Increased tPA dose might be needed in children to promote fibrinolysis

Status of pediatric acute thrombolytic therapy with tPA

• Why can’t we use the adult studies?
  – Developmental hemostasis
  – **Unique pediatric tools needed for outcome measurement**
    • Pediatric NIHSS
    • Pediatric Stroke Outcome Measure (PSOM)
PedsNIHSS (Ichord et al, 2011)

- NIHSS in adult stroke
  - Reliable
  - Good predictive validity when correlated with residual clinical impairment at 3 months
- PedsNIHSS
  - Good inter-rater reliability when administered by neurologist/trainees certified in adult NIHSS
  - Predictive of 3 and 12 month outcome measures (Ichord et al, 2011)
  - Adaptations of LOC questions
  - Adaptation to approach to aphasia

THROMBOLYSIS IN PEDIATRIC STROKE (TIPS)
NINDS Grant #1RO1 NS065818
principal investigator: Catherine Amlie-Lefond MD, U of Washington, Seattle Children’s Hospital
Objectives of TIPS

1. To determine the maximal safe dose of intravenous (IV) tPA among three doses (0.75, 0.9, 1.0 mg/kg) for children age 2-17 years within 4.5 hours from onset of acute AIS.

2. To determine the pharmacokinetics of tPA and its inhibitor, plasminogen activator inhibitor in these children.

3. To measure the 3-month neurological outcome in children treated with IV tPA.
Dose limiting toxicity

1. PH2 (parenchymal hemorrhage within 36 hours after tPA administration involving > 30% of the infarcted area) OR

2. Any intracranial hemorrhage judged to be the most important cause of neurological deterioration (2 or more points change on the PedNIHSS), OR

3. Any hemorrhage that results in the need for transfusion, need to discontinue study drug, surgical evacuation of hemorrhage, or death.
Inclusion criteria

- Age 2 to 17 years inclusive.
- Acute onset of neurological deficit in a pattern consistent with arterial territory ischemia.
- Deficit as defined PedNIHSS score of ≥ 6 that is not improving at the time of tPA administration.
- Time of symptom onset within 4.5 hours of initiation of treatment for IV tPA.
- Children with seizures at or following onset of stroke may be included, as long as the clinical picture is consistent with the documented arterial occlusion.
Inclusion criteria: imaging (part 2)

• Radiological confirmation in one of two ways:
  MRI: acute infarction with restricted diffusion in an arterial territory consistent with the clinical syndrome plus MRA showing partial or complete occlusion in an intracranial artery corresponding to the infarct location, OR
  CT and CT angiogram (CTA): normal head CT or early hypodensity in an arterial territory consistent with the clinical syndrome plus CTA showing partial or complete occlusion in an intracranial artery corresponding to the infarct location.

• Neuroimaging (CT or MRI) with no evidence of intracranial hemorrhage (including HI-1, HI-2, PH-1 or PH-2)
tPA at CHP

• TIPS ended for lack of enrollment
• tPA protocol by adult standards for cardiac patients 18 yr of age and older
• tPA usage in children; expert opinion moving toward TIPS criteria with dose of 0.9mg/kg
A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke


DOI: 10.1056/NEJMoA1411587

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection


DOI: 10.1056/NEJMoA1414905

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke


DOI: 10.1056/NEJMoA1414792
A)-C) Magnetic resonance imaging (MRI) with diffusion weighted sequences confirms acute ischemic infarction in the right fronto-temporal region (restriction marked by rectangle). B)-F MRI 8 hours post treatment reveals reduction in infarcted region.

G) Magnetic resonance perfusion imaging (MRP) indicates markedly reduced blood flow in the right hemisphere.

H) Post thrombectomy
Figure 1. A) Catheter angiography showing occlusion of the right middle cerebral artery. B) Post-treatment follow up of catheter angiography illustrates recanalization of after thrombectomy. C) Magnetic resonance angiogram shows occluded right middle cerebral artery. D) Follow up 8 hours later showing restoration of blood flow.
Pediatric stroke: take-home points

- High index of suspicion needed to rapidly detect pediatric stroke
- Consider imaging in any child with seizure who doesn’t recover in 30 minutes.
- Limited pediatric data; we extrapolate from adult data on many questions
- tPA not standard of care age <18 yrs, but expert opinion leading to consideration of tPA
- If dissection or cardioembolic stroke suspected, start heparin.
- Interventional neurology a consideration for large vessel occlusion