Pediatric Stroke: A Rare Disorder with a Lifetime of Disability

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Learning Objectives

After the presentation, the participant should be able to:

• Understand the epidemiology in addition to the short- and long-term burden of pediatric stroke (‘Debunking the myths’)

• Identify common pediatric stroke presentations

• Describe the initial assessment and stabilization

• List elements of the work-up for stroke etiology, secondary prevention and rehabilitation
Pediatric Stroke Myth #1: Kids don’t have strokes

• Incidence of pediatric acute ischemic stroke is 1.2-13/100,000
• Pediatric stroke rates in GCNK region: 4.4/100,000

**Incidence of young adult stroke (18-55) 6.6-11.4/100,000
Pediatric Stroke Myth #2: Kids recover better than adults

http://sites.bu.edu/ombs/2018/02/15/how-is-the-brain-plastic/
Pediatric Stroke Myth #2: Kids recover better than adults

- Prospective study of 95 children (1 mo – 16 years) and 154 young adults (16-45 yrs)

Pediatric Stroke Myth #2: Kids recover better than adults

- Mortality: 14% in children; 7% in young adults
  - Median survival time for those that died
    Children: 5 months (IQR 14 days – 3 yrs)
    Young adults: 4 days (IQR 4 days – 3 years)

- Children exhibited more behavioral disturbances
- Young adults felt the stroke effected their everyday life more

Pediatric Stroke Myth #3: There is nothing to be done for kid strokes

- NOT TRUE!!!

- There is a general increase in the use of thrombolysis, particularly in the adolescent population

- Interventional therapy is being increasingly used in pediatric patients

- These therapies have little to no evidence base beyond case series and expert opinion in the pediatric population (for now…)
Pediatric stroke is divided into two distinct populations

Neonatal: 20 weeks gestation – 28 days of life
Childhood: 29 days – 18 years

Neonatal Stroke

### Risk Factors for Perinatal Arterial Ischemic Stroke

<table>
<thead>
<tr>
<th>Type of Risk Factor</th>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Maternal</td>
<td>Thrombophilia, Infertility, Prolonged rupture of membranes, Preeclampsia, Smoking, Intrauterine growth retardation, Infection, Maternal fever</td>
</tr>
<tr>
<td>Fetal</td>
<td>Thrombophilia, Congenital heart disease, Arteriopathy, Hypoglycemia, Perinatal asphyxia, Infection, Need of resuscitation, Apgar score of &lt;7 at 5 minutes</td>
</tr>
<tr>
<td>Placental</td>
<td>Chorioamnionitis, Placental infarcts, Placenta weighing less than tenth percentile</td>
</tr>
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</table>

- **Incidence ~13/100,000**
- **2nd most common cause of perinatal seizures**
  - as many as 94% have acute symptomatic seizures
  - Epilepsy will occur in 11% NAIS and 19% PPAIS
- **Mortality 0.16/100,000**
- **Recurrence risk 1-2%**
Childhood Stroke

Common Etiologies:

• Cardioembolic - 20% of childhood strokes
  - TTE
  - If negative, TEE or cardiac MRI

• Cervicocephalic arterial dissection (CCAD) – 7-19%
  - MRA with T1* Fat Sat; CTA; DSA

• Arteriopathy (Not including SCD) – 27-48%
  - MRA, CTA, DSA

• Hypercoagulable work-up
  - will be abnormal in 30-50%

Other Considerations:

• Autoimmune vasculitidies
  - SLE, cPACNS

• Genetic/Metabolic
  - Sickle cell anemia, CADASIL, Fabry’s dz
  - homocysteinuria, MELAS
  - EDS, FMD, Marfan’s, COL4A1,
  - Loeys-Dietz syndrome
Recognition is key…

The median time from symptom onset to diagnosis in pediatric stroke is **24 hours**

**In-hospital delays account for most of this time**
7 yo male presents to the ED with concern for seizure activity

- LSN 20:30; Time to ED 21:20
- Left gaze deviation; Right motor response ‘decreased’ on initial evaluation
- Left face twitching 15-20 min – ativan and fosphenytoin given, gaze deviation and facial twitching resolve
- Time to Head CT 21:40 – Normal imaging
- GCS 11 after medication and Head CT, but moving all extremities equally
Presentation of pediatric stroke/TIA: Raising the Index of Suspicion

- Stuttering onset of symptoms
- Seizures
- Headaches
- Ataxia
- ‘Classic’ stroke symptoms (hemiparesis, speech abnormalities, hemisensory loss, visual changes, etc.)

Retrospective analysis of the **Face Arm Speech Test (FAST)** and the **Recognition of Stroke in the Emergency Room (ROSIER)** tool in true pediatric stroke cases were positive in 78% and 81%, respectively. Yock-Corrales, *et al.* **BMC Pediatrics** 2011, 11:93
But what about the stroke mimics?

- Seizure with Todd’s Paralysis
- Complex/Familial Hemiplegic Migraine
- Stroke-like episodes
  - Sturge-Webber Syndrome
  - Mitochondrial Disorders
  - Alternating Hemiplegia of Childhood

**Emergent MRI may be necessary to sort this out**
Assessment of Pediatric Stroke – PNIHSS¹

- NIHSS² is a validated assessment tool that can be utilized by trained medical personnel (physician, nurse) from a variety of sub-specialties (neurologist, internal medicine, EM, etc.)

- Facilitates communication between providers for patient care in addition to a standardized scale for clinical trials

- Pediatric NIHSS¹ validated for use in 2011 – only validated for use by trained child neurologists (requires a toy and knowledge of early childhood development in patients <6 years)

- Both have been shown to be the most important predictor of a favorable outcome³,⁴

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Clinical Case Continued

- Patient was dispositioned to the PICU for observation for new onset seizure with status epilepticus

- Continued to have waxing and waning mental status during 36 hour observation in ICU
  - Neurology consultation documents mild dysarthric speech, but no other focal deficits
  - Routine EEG 24 hours after presentation normal
  - Nursing documentation of neurochecks remains ‘non-focal’

- Transferred out to neurology floor – soon after, had an episode of vomiting
  - Would only arouse to noxious stimulus
  - Found to have acute right face, arm and leg weakness with ‘slurred speech’
~1 hour after acute change

- MRI demonstrates acute ischemic changes
- MRA does not show vasculopathy changes

~11 hours after acute change
Fibrinolysis in Pediatric Stroke (rtPA)

• Not FDA approved for stroke treatment in persons <18 years of age

• TIPS trial (multi-center NIH funded trial designed to assess safety and efficacy of rtPA in pediatric stroke) stopped after having enrolled only one patient in 4 years

• Recent retrospective reports demonstrate that rtPA use in pediatric stroke is increasing from 5.2/1000 children to 9.7/1000 children
  - Treated children tended to be older (mean age: 13.1 years versus 8.1 years)
  - The majority of this increase is taking place at non-children’s hospitals

• Use in pediatric patients recommended to be done in the setting of a clinical trial

• However, current off-label use should, at minimum, follow current AHA/ASA Guidelines for rtPA administration and strict monitoring criteria post administration

1) Rivkin, MJ et al., Stroke (2015); 46:880-885
2) Alshekhlee, A et al. Pediatric Neurology (2013); 49:313-318
3) Gross, H; Guilliams, KP; Sung, G Neurocrit Care (2015); 23:S94-S102
Interventional Therapy

In 2012:

- Recommendations for interventional therapy in pediatric stroke was based on 34 case reports utilizing either IA rtPA or clot retrieval
  - Mean time to recannalization 14 hours (2-72 hours)
  - 12/34 Complete recannalization; 13/34 Incomplete recannalization
  - Complications in 10/34 (ICH 8/34; Symptomatic ICH 1/34)
  - Class IIb recommendation

- At centers with experienced pediatric angiographers, interventional therapy for pediatric AIS with proximal artery occlusion may be considered

- Using the Kids Database from 2012 – interventional therapy was used in ~1% of pediatric stroke cases

- A more recent meta-analysis looking at the safety and efficacy of 1º versus 2º (post-thrombolysis) mechanical thrombectomy in pediatric patients demonstrate that there was no difference in the safety or efficacy of the two techniques
### Anticoagulation/antiplatelet therapy after pediatric AIS –
**Recommendations from American College of Chest Physicians**

<table>
<thead>
<tr>
<th>Stroke Etiology</th>
<th>Anticoagulation/ Antiplatelet</th>
<th>Timing</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>UFH OR LMWH OR ASA</td>
<td>Immediate</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Re-stroke on ASA</td>
<td>Clopidogrel OR UFH OR LMWH</td>
<td>At time of new symptoms</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Cardioembolic†</td>
<td>LMWH (transition to warfarin)</td>
<td>Immediate (VKA 14 days)</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Cervicocerebral Arterial Dissection†</td>
<td>UFH OR LMWH (transition to warfarin)</td>
<td>Immediate (VKA 14 days)</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Non-Moya-Moya Vasculopathy†</td>
<td>UFH OR LMWH (transition to warfarin)</td>
<td>Immediate (VKA 14 days)</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Moya-Moya</td>
<td>ASA</td>
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</tbody>
</table>

†Decision will be made based upon both etiology and infarct size/risk of hemorrhage

**Strong recommendation to involve a trained hematologist in the care of the pediatric stroke patient**

Risk of Hemorrhage with Anticoagulation after Pediatric Ischemic Stroke

Safety of Anticoagulants in Children with Arterial Ischemic Stroke

• Best data in children: Prospective cohort study of 215 children with AIS; 123 received anticoagulation therapy (ACT) for a minimum of 24 hours within 7 days of diagnosis
  - UFH: (No loading dose), titrated to PTT = 60-85 sec, or anti-Xa 0.35-0.7 Units/mL
  - LMWH: 1 mg/kg/dose BID (goal anti-Xa 0.5-1.0 Units/mL at 4 hours post-dose)
  - warfarin: 0.2 mg/kg/day titrated to INR = 2-3

• 83% of patients in ACT group initiated therapy within 72 hours of diagnosis

• ICH occurred in the following:
  No therapy/ASA only: 12/75 (16%)
  ACT: 14/123 (11%); 9 were asymptomatic, 5 were symptomatic, No ICH related mortality

• Efficacy has yet to be established in children
Work-up of the Case

- Patient had a TTE that was negative for PFO or vegetations; F/U TEE also negative
- CTA – No vascular abnormalities suggestive of vasculopathy or vasculitis in the neck or major vessels from the Circle of Willis
- ESR 8 and CRP 1.6 on day of stroke
- Hypercoagulable work-up: Protein C deficiency secondary to critical illness
- Metabolic work-up (Lactate/Pyruvate, SAA, UOA, acylcarnitine profile): WNL
- VZV Ab: Neg; Mycoplasma IgM and IgG + (consistent with his pneumonia 3 weeks ago)
DSA gives the diagnosis...

7 days after presentation ~4 months after presentation

Transient Cerebral Arteriopathy
(aka: Focal Cerebral Arteriopathy)
Transient Cerebral Arteriopathy

- Unilateral focal/segmental stenosis or occlusion involving the distal ICA and initial segments of ACA or MCA\(^1\)

- Non-progression of symptoms beyond 6 months\(^1\)

- Hypothesized to be a post-infectious phenomenon\(^2\)
  
  Risk factors: 1) infection in the week prior to infarction (OR 6.3) 
  2) undervaccination (OR 8.2) 
  3) African-American race (OR 1.9) 
  4) Rural residence (OR 3.0)

- 25% risk of stroke recurrence within 1 year\(^3\)

- Retrospective studies suggest possible role for steroids\(^4\)

Clinical Case: ICU course after AIS Diagnosis

- UFH gtt discussed, once stroke diagnosed, but felt risk of hemorrhage too high
- He was intubated 12 hours after re-admission to the PICU due to decreasing mental status with hypercarbia
- Neurosurgery consulted, but initially edema managed with hyperosmolar therapy
- Patient MS/neuro exam improved over 24 hours while on HTS, so hyperosmolar therapy discontinued and the patient was extubated
- Patient’s mental status decreases and he begins vomiting; Head CT repeated

86 hours after recognized stroke
Managing Post-stroke Edema –
Borrowing from Adult AHA/ASA Recommendations

- Maximal medical management is reasonable in patients that do not exhibit neurological decline (level of consciousness, ipsilateral pupillary dilatation, brainstem signs)

- Medical management for patients exhibiting neurological decline
  - **Osmotic therapy is reasonable** (Class IIa, L3)
  - Barbiturates, hypothermia and corticosteroids are not recommended (Class III, L3)

- Three prospective randomized trials (DESTINY\(^2\), DECIMAL\(^3\) and HAMLET\(^4\)) demonstrated *improved mortality* with **decompressive hemicraniectomy** performed within the first 48 hrs after symptom onset compared with maximal medical management
  - Pooled analysis showed *improved outcomes* (mRS)

- In the past 8 years, 3 case series in children have shown moderate to good outcomes with DHC after malignant MCA infarction\(^5-7\)

Decompressive Craniectomy after AIS

- Patient re-intubated, bolused with hyperosmolar therapy
- Taken emergently to the OR for craniectomy 88 hrs after apparent stroke event
- ICP able to be well managed and patient has made a moderate functional recovery with mild R hemiparesis, R spasticity, mild dysarthria
The patient survived his acute ischemic stroke

Now what?
Functional Outcomes – Overall promising

- Short-term FU: children, n=94
  - 36% mRS 0
  - 21% mRS 1
  - 12% mRS 2
  - 13% mRS 3
  - 10% mRS 4
  - 9% mRS 5
  - p=0.810

- Short-term FU: young adults, n=151
  - 33% mRS 0
  - 28% mRS 1
  - 20% mRS 2
  - 7% mRS 3
  - 3% mRS 4
  - 5% mRS 5
  - p=0.176

- Long-term FU: children, n=95
  - 27% mRS 0
  - 28% mRS 1
  - 15% mRS 2
  - 16% mRS 3
  - 14% mRS 4
  - p=0.466

- Long-term FU: young adults, n=154
  - 29% mRS 0
  - 25% mRS 1
  - 25% mRS 2
  - 9% mRS 3
  - 4% mRS 4
  - 7% mRS 5
  - p=0.525
Cognitive Outcomes  
Psychosocial  

Functional Outcomes
Cognitive

![Graph showing learning and memory subtest scores](image)

Figure 5. Mean results of learning and memory subtest scores. LL = list learning; MF = memory for faces; MN = memory for names; NM = narrative memory; PM = picture memory; SR = sentence repetition.

Psychosocial

![Bar chart showing SDQ and SSIS & VABS results](image)

Effect on the Parent

- Qualitative study with the parents of children who suffered an AIS
- 6 themes came from the interviews
  - Unawareness of stroke and the brutality of the diagnosis
    * fear (child’s death, recurrence, long-term disability)
    * guilt for missing the signs
  - Lack of information regarding the disease/condition (Why?)
  - Feeling of abandonment after hospital discharge
  - Focus on functional recovery
  - Late awareness of behavioral/cognitive disorders
  - Need for psychological/social support and family adaptation

Take Home Message…

- Children do have strokes – unfortunately the diagnosis is often delayed

- There are things we can do to help improve outcomes acutely - although the evidence for the adult SOC in children is weak or lacking

- Their mortality/functional recovery not significantly different than that of young adult strokes

- While the functional recovery is generally good, the cognitive and behavioral outcomes may cause significant disability

- Care for these patients needs to extend to the whole family
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