Pediatric Stroke: Impact and Morbidity

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Disclosures

• No disclosures or conflict of interest
Overview

- Epidemiology
- Etiology/Risk factors
- Clinical Presentation
- Morbidity
- Recurrence
- Treatment and Rehabilitation
- Conclusion

“A large number of cases of infantile cerebral palsy are caused by the same factors that bring about the majority of cases of cerebral paralysis of adults: tearing, embolism, and thrombosis of cerebral vessels.”

Sigmund Freud, 1897
Epidemiology

Case 1: Elijah
Introduction

• Pediatric stroke is a heterogeneous disorder and a major cause of morbidity in the pediatric population
• 5-year recurrence risk is \(~20\%\)
  – <3% for neonatal stroke if no underlying etiology
• Children with cerebrovascular abnormalities are at the highest risk of recurrence
• Cerebral arteriopathies may account for up to 30-50% of childhood stroke in otherwise healthy children
Overview of Childhood Stroke

• Male > female
  – Largely but not fully explained by trauma

• Blacks > whites
  – Not accounted for by sickle cell alone

• Ischemic slightly ≥ hemorrhagic

• Among the top 10 causes of death in children
  – 7 – 28 % of children with stroke die

• > 50% of survivors develop some neurological or cognitive deficit or impairment

Incidence: Arterial Ischemic Stroke

• Children: 3-6/100,000 children/year
  – This translates into ~3000-5000 strokes/year

• Neonates: 20 – 30/100 000 live births/year
  – This translates into ~1:4000 live births
  – Population-based epidemiologic study from Switzerland using MRI confirmation of neonatal arterial ischemic stroke showed a higher incidence of 1:2300 live births
  – 90% within the first week

• Cerebral sinovenous thrombosis: 41/100 000 live births/year
Mean age of childhood presentation of AIS is ~ 4-6 years

GENDER FOR AIS PATIENTS
58% (324) of neonates male
59% (760) of infants and children male

Etiology
Childhood Cerebral Vasculopathies

• Childhood cerebral arteriopathies include well established entities such as arterial dissection, moyamoya, dissection, and vasculitis

• Most children however have isolated unilateral focal stenosis of large intracranial vessels – so called focal cerebral arteriopathy (FCA) of childhood

Arteriopathy Subtypes Among 277 Children With AIS and Arteriopathy Diagnosed on Vascular Imaging¹

<table>
<thead>
<tr>
<th>Arteriopathy</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCA</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>Moyamoya (primary or secondary)</td>
<td>62</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>

Clinical Significance of Cerebral Arteriopathies in Childhood Stroke

• Among children with stroke, arteriopathy has emerged as the predominant underlying mechanism, causing 53% of cases\(^1\)

• Cerebral arteriopathies may account for up to 64% of childhood stroke in otherwise healthy children\(^2\)

• Predictors of arteriopathy\(^1\):
  – Early school age (5 to 9 years)
  – Recent upper respiratory infection
  – Sickle cell disease

\(^1\) Amlie-Lefond et al. Circulation 2009;119:1417-1423

Clinical Presentation
Neonatal AIS: Clinical Presentation

- Focal seizures in a well infant >12 hours of life
- Neonatal encephalopathy
- Diffuse neurological signs
- Focal neurological deficits uncommon
- Late presentation:
  - Motor asymmetry
  - Early hand preference

Kirton et al. Arch Neurology 2010

AIS Clinical Presentation
N = 917 Neonates and Children

- Total
- Neonate
- Older

deVeber and Kirton for CPISR, Child Neurology Society 2006
Infarct Characteristics

- Middle cerebral artery: >80%
- Left side: ~60%
- Posterior circulation: 10-15%
- Multifocal: 15-30%
- Hemorrhagic transformation: 10-20%
- Arterial abnormalities: ~20-30%

Childhood AIS: Clinical Presentation

- Most common presenting feature:
  - Hemiparesis 45-100%
- Onset of deficit:
  - Abrupt 51%
  - Progressive over hours 36%
  - Waxing/waning 13%
- Seizures as presenting feature: 26%
- Cerebellar strokes
  - Mild symptoms, but potentially fatal
  - Mistaken for gastroenteritis
  - Red flags: vomiting w/o fever, ataxia, diplopia
Case 2: Madelyne

- MM born at term following uneventful pregnancy
- Development normal up until about 4-6 months of life
  - Not rolling to left side as well as right
  - Reaching better with right hand
- Reassured until 8 months of age, family and PMD noted preferential use of right hand and keeping left hand clenched
Case 2

- Examination showed normocephalic, well appearing young girl
- Very strong, dominant right side. Reaching into left field with right arm. Transferring from right to left not vice versa.
- Increased tone left arm > leg. No significant facial asymmetry. Increased reflexes and Babinski on the left
- Clinical Diagnosis: Left hemiplegia
  - DDx: Right cortical MCA infarct; Right neuronal migration disorder

Outcomes:
- Mild-moderate left hemiplegia
- Normal cognition and development
- No seizures to date
Neonatal AIS: Long Term Outcomes

• Motor = Hemiplegic CP: ~90%
• Epilepsy: ~30%
• Learning / cognitive: ~30%
• Language: ~30%
• Psychiatric / Behavioral: ~30%
• Vision: <20%
• Recurrence: <1%
Imaging is key to diagnosis and prognosis.

**Childhood AIS: Long Term Outcomes**

- Outcome good
- Depends on underlying risk factors
- More complete recovery than adults
- Central nervous system plasticity
- More effective collateral circulation
- Seizures at presentation and infarct volume > 10% associated with worse outcome
Prognosis

**But** complete recovery uncommon

- Residual hemiparesis
  - 2/3 to ¾ of survivors

- Visual field defects

- Cognitive deficits
  - Mean IQ below population mean
  - Remains within average range
  - Worse if co-existent epilepsy
  - Psychiatric/Behavioral disorders - ~20-60%

- Seizures and Epilepsy

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Left occipital stroke
Case 3. Tim

- TM was a healthy, athletic young boy with normal development until his 11th birthday
- Woke up with headache, right facial droop and dysarthria
- Seen in ER with mild right hemiplegia, including face, dysarthria and aphasia
• MRI with left thalamic infarct

• Work up negative
  – Cardiac, metabolic, LP, autoimmune, hypercoagulable panel, angiogram

• Discharged home without treatment
• Next few weeks was seen 3 times in ER with transient diplopia

• Neurology re-consulted on 3rd occasion
  – Mild VI nerve palsy right otherwise at baseline
  – Repeat MRI – unchanged left thalamic infarct
  – Repeat angiogram …….
Childhood AIS: 5-Year Cumulative Recurrence Risk

- Depends on underlying etiology
- Vasculopathy – highest risk
- Perinatal stroke <3% recurrence risk

Cerebral Arteriopathies and Recurrence Risk

• Arteriopathy is the greatest predictor of recurrence, emphasizing its importance as a treatment target for secondary stroke prevention.

• German study\(^1\) showed a first ischemic stroke in children of vascular origin was significantly associated with having a second stroke (odds ratio 3.9, 95% CI 1.4–10.6).

• Arterial ischemic stroke recurrence risk appears highest in the first 6 months after initial stroke presentation.

\(^1\)Strater R et al, Lancet 2002; 360: 1540–1545

Fullerton et al. Pediatrics 2007
Vasculopathy in Pediatric Stroke (VIPS) Study

- Prospective, case-control study (n = 355)
- Identified risk factors for first childhood AIS including recent infection, under-vaccination, and low socio-economic status
- Only significant risk factor for recurrence was arteriopathy
- 308 (87%) were treated with an antithrombotic medication
- The cumulative stroke recurrence rate was 6.8% at one month and 12% at one year.

Arteriopathy increased the risk of recurrence 5-fold compared to an idiopathic AIS
VIPS Study

- One-year recurrence rate by vasculopathy subtype:
  - Moyamoya – 32%
  - Focal or Transient cerebral arteriopathy of childhood – 25%
  - Arterial dissection – 19%
- Definite arteriopathy in 127 (36%), possible in 34 (9.6%), and absent in 194 (55%)

Vascular Effects of Infection in Pediatric Stroke (VIPS)
Treatment and Rehabilitation
Primary Stroke Prevention

• Sickle cell disease
• Cardiac disease
• Varicella immunization
  – ?Impact on post-varicella angiopathy

Secondary Stroke Prevention

• Efficacy of currently available treatment for secondary prevention of recurrence of childhood AIS is lacking apart from some specific disease entities such as moyamoya
• Given the recurrence risk of childhood AIS is ~15-20%, depending on etiology, this is an important area for future research
Rehabilitation

• As a focal injury in the developing brain, pediatric stroke represents an ideal human model of neuroplasticity
• Child’s rehabilitation needs may change as they grow and develop
• Understanding of developmental expectations and milestones in this age group is imperative

Studies of the upper extremity motor system after stroke illustrate a number of forms of brain plasticity.

Fujii and Nakada (2003) used functional MRI and found that right hand grasping movements produced predominantly left motor cortex activation in a healthy control; but in a typical patient with right hemiparesis, these movements were associated with a shift in motor cortex laterality towards the right hemisphere (double arrow) as well as increased recruitment of left dorsal premotor cortex (single arrow) and bilateral supplementary motor area (arrowhead).

Steven C. Cramer et al. Brain 2011;134:1591-1609

Published by Oxford University Press on behalf of Brain 2011.
Botulinum Toxin

- Botulinum toxin A (BoNT-A) injections for spasticity have not been studied specifically for children with stroke
- Good evidence of BoNT-A effectiveness as adjunctive therapy to standard physical and occupational therapy, in improving upper extremity function in children with hemiplegic cerebral palsy

Constraint Induced Movement Therapy

- A growing body of evidence suggests that the inclusion of constraint induced movement therapy (CIMT) and bimanual therapy (BIT) in therapeutic programming may be beneficial for patients with hemiplegia
- Small studies have shown that CIMT is moderately effective in improving use of the stroke-affected upper extremity
Transcranial Magnetic Stimulation

- Based on Faraday Principle
- Rapidly fluxing magnetic field
- Induces current in underlying cortex
- Non-invasive
- Permits focal manipulation of cortical activity

Repetitive Transcranial Magnetic Stimulation

- The rationale of using rTMS as a complementary therapy is mainly to decrease the cortical excitability in regions that are presumed to hinder optimal recovery by low-frequency rTMS delivered to the unaffected hemisphere, while high-frequency rTMS delivered to the affected hemisphere facilitates cortical excitability
- The exact mechanisms of how rTMS works are still under investigation
- There is a growing body of research in stroke patients investigating the effect of rTMS on facilitating recovery by modifying cortical and subcortical networks
Table 1. Costs Differ Based on Age of Stroke, But Do Not Differ Based on Stroke Type.

<table>
<thead>
<tr>
<th></th>
<th>Inpatient cost</th>
<th>Outpatient clinic stroke-related</th>
<th>Total 1-year cost</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 111)</td>
<td>$46,352 ($6,838-958,009)</td>
<td>$1,418 ($0-22,546)</td>
<td>$47,938 ($6,838-958,009)</td>
<td></td>
</tr>
<tr>
<td>AIS (n = 82)</td>
<td>$47,979 ($9,333-958,009)</td>
<td>$1,581 ($0-22,546)</td>
<td>$50,501 ($10,294-958,009)</td>
<td></td>
</tr>
<tr>
<td>CSVT (n = 29)</td>
<td>$33,553 ($6,838-86,106)</td>
<td>$1,152 ($0-13,771)</td>
<td>$34,705 ($6,838-878,831)</td>
<td>NS</td>
</tr>
<tr>
<td>Neonatal (n = 42)</td>
<td>$26,665 ($6,838-86,106)</td>
<td>$1,126 ($0-13,771)</td>
<td>$27,791 ($6,838-874,831)</td>
<td></td>
</tr>
<tr>
<td>Childhood (n = 69)</td>
<td>$64,515 ($9,333-958,009)</td>
<td>$1,652 ($0-22,546)</td>
<td>$66,167 ($10,294-958,009)</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, arterial ischemic stroke; CSVT, sinovenous thrombosis. There was no difference between costs for AIS when compared to CSVT. Costs of neonatal stroke were significantly less than costs of strokes after the neonatal period. Median costs (minimum-maximum) in US dollars.

Table 2. Cost Differences Are Associated With Diagnosis.

<table>
<thead>
<tr>
<th>Associated disease</th>
<th>Inpatient cost</th>
<th>Outpatient clinic stroke-related</th>
<th>Total 1-year cost</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (n = 21)</td>
<td>$117 952 ($29 890-958 009)</td>
<td>$882 ($0-8568)</td>
<td>$118 241 ($31 680-958 009)</td>
<td>³NS</td>
</tr>
<tr>
<td>Vasculopathy (n = 18)</td>
<td>$71 926 ($19 768-323 902)</td>
<td>$4154 ($0-22 546)</td>
<td>$78 211 ($19 768-327 784)</td>
<td>³P &lt; .004</td>
</tr>
<tr>
<td>Systemic (n = 29)</td>
<td>$45 190 ($14 304-861 060)</td>
<td>$1462 ($0-13 771)</td>
<td>$46 652 ($17 304-874 831)</td>
<td>⁴NS</td>
</tr>
<tr>
<td>Idiopathic (n = 19)</td>
<td>$26 375 ($9 333-108 446)</td>
<td>$1587 ($0-7646)</td>
<td>$26 375 ($10 294-112 598)</td>
<td>³P &lt; .001</td>
</tr>
<tr>
<td>Perinatal (n = 20)</td>
<td>$22 315 ($6 838-86 209)</td>
<td>$713 ($0-2794)</td>
<td>$23 405 ($6 838-88 858)</td>
<td>³P &lt; .002</td>
</tr>
</tbody>
</table>

Sickle cell disease (n = 4) | $67 394 ($38 883-256 676) | $2759 ($0-10 458) | $73 509 ($38 883-260 425) | Not compared due to small n

Median costs (minimum-maximum) in US dollars.
³Compared with congenital heart disease.
⁴Compared with vasculopathy.
⁵Compared with systemic disease.
⁶Compared with idiopathic stroke.

Conclusion


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Conclusion

• Increasing awareness and improved neuroimaging has led to increasing incidence of childhood stroke

• Increasing number of children surviving previous lethal diseases which predispose them to stroke

• Need ongoing collaboration and RCT’s to improve diagnosis, prevent primary stroke and recurrence, address optimal rehabilitation therapies, and to improve outcome. Cannot rely on adult data

• Referral and to centers which provide comprehensive pediatric stroke care and evaluation by pediatric neurology stroke experts