Pediatric Stroke

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A whole different problem

- Atherosclerosis and modifiable factors are not relevant issues
  - Populations at risk include neonates, children with congenital heart disease, patients with disorders of mitochondrial metabolism

- Presentation subtle, course stuttering, diagnosis typically delayed

- Differential diagnosis much broader

- Clinical trials for mechanical thrombolysis, anticoagulant and antiplatelet therapies not available
Suspicion of stroke

- Obstacles to evaluation
  - Victims of pediatric stroke typically ill
  - Delay in seeking care
  - Lack of history, transport without observer
  - Sleeping patient
  - Limited ability to comprehend, cooperate

- Differential diagnosis
  - Focal seizures
  - Hemiplegic migraine
  - Medication ingestion / substance abuse
Spectrum of disorders

- Perinatal stroke
  - Arterial stroke
  - Cerebral venous sinus thrombosis

- Acute arterial stroke
  - Congenital heart disease
  - Thromboembolic stroke
  - Arterial vasculopathy
  - Disorder of coagulation / fibrinolysis
  - Sickle cell disease

- Carotid dissection

- Metabolic stroke-like events

- Hypotensive stroke (watershed infarcts)
Confirmation of stroke

- CT perfusion and angiogram, including imaging of vessels of neck
- MRI and MR angiogram as second choice
- Catheter cerebral angiography
  - Suspected arterial dissection
  - Further evaluation of vasculitis of medium-sided vessels
  - Planning for revascularization with moyamoya disease
Treatment

- Mechanical thrombectomy
  - Risk/benefit data not available in children
  - Better natural outcome in children than adults
    - In brainstem stroke, 8% vs. 39% mortality
    - 60% good outcome vs. 70% poor outcome

- Thrombolytic therapy
  - Candidates rarely identified with 4.5 hr for intravenous tPA or 6 hr for intra-arterial tPA
  - Risk/benefit ratio not studied in children
  - Complication rate is higher in children; outcome without tPA more favorable in children than in adults
  - For ages 2–17, consider IV tPA 0.9 mg/kg within 3 hr of known onset
    - For significant hemiparesis, aphasia, LOC
    - Parental approval for off-label use
Anticoagulant therapy

- No good randomized, controlled data in children
- Used for dissection, cardio-embolic stroke, but not sickle cell disease
- Unfractionated heparin (UFH) preferred with high risk of hemorrhagic complication, when invasive procedures planned, when rapid reversal needed
- CT performed 3 days after initiation; if no hemorrhage UFH switched to low-molecular-weight heparin (LMWH)
- 4% risk of symptomatic hemorrhagic complication
- Practices vary widely; IPSS document use in 43%
Treatment

- Antithrombotic treatment Balance of hemorrhagic risk and risk of recurrence or extension of infarction
  - Consensus that some level of antithrombotic therapy beneficial
  - Appropriate in congenital heart disorders
  - Appropriate in arterial dissection

- No evidence of efficacy for anticoagulation
  - Intracranial hemorrhage in 4%
<table>
<thead>
<tr>
<th><strong>ETIOLOGY</strong></th>
<th><strong>THERAPY</strong></th>
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<tbody>
<tr>
<td>Perinatal stroke</td>
<td>No antithombolysis unless CHD or prothrombotic</td>
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<tr>
<td>Uncorrected CHD</td>
<td>LMW heparin / warfarin or aspirin</td>
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<tr>
<td>Corrected CHD</td>
<td>Aspirin</td>
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<tr>
<td>Moya-moya disease</td>
<td>Aspirin, revascularization</td>
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<tr>
<td>Other arteriopathy</td>
<td>Initial LMWH then LMWH or warfarin or aspirin</td>
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<tr>
<td>Idiopathic arterial ischemic stroke, no residual stenosis</td>
<td>Initial LMWH/aspirin, then aspirin 2 - 5 years</td>
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<tr>
<td>Inherited prothrombotic</td>
<td>Initial LMWH then warfarin</td>
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<tr>
<td>Postvaricella angiopathy / med-large vessel vasculitis</td>
<td>LMWH/aspirin +/- immuno-suppression when stenosis</td>
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<tr>
<td>Sickle cell disease</td>
<td>Chronic transfusion, aspirin</td>
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Delivery of care

- A Pediatric Code Stroke team?
  - Response time of physicians to ED
  - Qualified professional to interpret CT/CTA studies
  - Patient management? ED, hospitalist, neurosurgeon, intensivist, resident, pediatric neuro-hospitalist
  - Complexity of standardized protocol
  - Time constraints, evidence for administration of tPA
  - Suitable facility for intensive monitoring and care
  - Transportation of patient, delay in treatment
  - Practicability at both ends for tele-stroke oversight

- Use of Pediatric NIH Stroke Scale
Further consideration

- Perinatal stroke
- Cerebral venous sinus thrombosis
- Congenital heart disease
- Thromboembolic disease
- Cerebral arteriopathy
- Mitochondrial stroke-like events
Perinatal stroke: overview

- No preventative strategies
- Risk factors and presentation overlap with hypoxia-ischemia
- Prothrombotic tendencies in pregnancy, but thrombophilia rarely sole etiology
Perinatal stroke: clinical

- Commonly begins with focal seizure, often presenting >12 hours after birth
  - MCA distribution most commonly
  - Seizure control / prognosis a function of underlying global hypoxia-ischemia

- Associated with subtle hemiparesis (corticospinal innervation is bilateral at birth)
  - With deterioration of control on the good side
  - Constraint-induced movement therapy (CIMT) may help shift control to impaired hemisphere
  - Bimanual therapy combined with CIMT to induce motor learning in the brain
Perinatal stroke: evaluation

- Placental disease provides source of emboli
  - Association with chorioamnionitis / placental inflammation

- Thombophilia evaluation after age 6 weeks
Perinatal stroke: evaluation

**Maternal conditions**

- Acquired or inherited hypercoagulability
- Genetic disorders (Factor V Leiden, anticardiolipin)
- Autoimmune disorders (SLE)
- Hypertension in pregnancy (pre-eclampsia)
- Intrauterine infection
- Inflammatory disorders
- Trauma to mother
- Prenatal substance abuse (cocaine)
Perinatal stroke: evaluation

<table>
<thead>
<tr>
<th>Placental disorders</th>
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<tr>
<td>Fetal thrombotic vasculopathy</td>
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<tr>
<td>Thrombosis (maternal surface)</td>
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<tr>
<td>Emboli from thrombotic sites (fetal surface)</td>
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<td>Inflammatory mediators from infection</td>
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### Perinatal stroke: evaluation

#### Fetal Conditions

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<td>Hydrops fetalis</td>
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<td>Multiple gestation / polyhydramnios</td>
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<td>Twin-twin transfusion syndrome</td>
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<td>Intrauterine growth restriction (IUGR)</td>
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Perinatal stroke: evaluation

**Neonatal Conditions**

- CNS or systemic infection
- Polycythemia with hyperviscosity
- Extracorporeal membrane oxygenation (ECMO)
- Cardiac anomalies / R-to-L shunting
- Catheterization
- Sources of paradoxical emboli
- Genetic disorder of hypercoagulability
- Vascular anomaly
Perinatal stroke: outcome

- Deficits become gradually apparent over time
  - Cerebral palsy in 30 – 70%
  - Epilepsy at 6 months in 20 – 50%
  - Involvement of cerebral cortex, basal ganglia and internal capsule predicts hemiparesis

- Up to 90% ultimately become ambulatory

- Stroke recurrence risk is negligible
Cerebral venous sinus thrombosis

- Subtle in context of HIE and seizures
- Greater identification with MRI and MRV, although findings subtle
- May affect bilateral deep gray and white matter
- Presumed in term infants with IVH, especially with thalamic injury
- Mechanical factor of occipital compression of superior sagittal sinus when supine
- Thrombus progression in 5% with anticoagulation and in 30% without
Congenital heart disease

- Continuing risk since corrective surgery is often multi-step process, in part based upon need for growth
- Increased risk for extended time even after full correction

- Intraoperative variables
  - Duration of cardiopulmonary bypass
  - Duration of deep hypothermic arrest
  - Hematocrit level
  - Management of pH status
Congenital heart disease

- Limited pre-operative neurologic evaluation
  - Impact of CHD on cerebral blood flow during fetal development
  - Few pre-operative brain MRI
  - Delay in development with hypoplastic L heart and with transposition of great arteries → susceptibility to periventricular leukomalacia at all stages

- Disturbances of cerebrovascular regulation
  - Resistance lower with hypoplastic L heart
  - Resistance higher with R-sided obstructive CHD

- Maladaptive neuroplasticity and cerebrovascular autoregulation
Thrombo-embolic disease

- Mechanical thrombectomy
  - Older, larger children
  - Substantial neurologic deficit (Pediatric NIH Stroke Scale 10 – 30)
  - Occlusion of dominant cerebral artery (carotid terminus, MCA M1 segment, basilar or vertebral)
  - MRI diffusion evidence of substantial preservation of brain tissue in relevant territory
  - Under 6 hr for anterior circulation; under 24 hr for posterior circulation
  - Parental consent for off-label use
Cerebral arteriopathy

- Cause of half of childhood strokes: acquired vs. intrinsic
- Acquired: Typically in healthy children with one of two mechanisms
  - (1) Acute arteriopathy with infectious disease
  - (2) Minor head trauma
- Association with iron deficiency
- Basal ganglia stroke with transient cerebral arteriopathy, commonly at junction of distal ICA, proximal MCA and ACA
Cerebral arteriopathy

- **Intrinsic:** Multiple genetic causes of inherent arteriopathies
  - Accumulation of abnormal metabolites (Fabry Disease, homocystinuria)
  - Internal elastic lamina (ELN, ABC C6-calcification)
  - Vascular smooth muscle (NF1, ACTA2, pericentrin)
  - Vascular basement membrane (COL4A1)
  - Abnormal response to endothelial injury (SAMHD1, GLUT10, ATP7A, NF1)
  - Abnormal vascular homeostasis (NOTCH signaling pathway, NOTCH3, JAG1, TGFβ-pathway)

- Moya-moya disease as a chronic arteriopathy
Cerebral arteriopathy: outcome

- Higher incidence of hemiparesis than with perinatal stroke
- Basal ganglia involvement often leads to dystonia after 6 months
- Weaker cognitive performance with younger age and with combined cortical/subcortical involvement
- Stroke recurrence 19%, typically within 1st year
  - Congenital heart disease, arteriopathy predictive
  - Antithrombotic therapy reduces recurrence risk
Mitochondrial stroke-like events

- Acute onset of focal neurologic deficit, movement disorder, or seizures
  - Commonly triggered by infection or dehydration
- Common in MELAS and wide variety of other disorders of OX-PHOS pathway
  - Often suspected, occasionally diagnosed, typically suspect
- Diffusion changes on MRI, not in typical arterial or venous distribution
- Confusing in the context of other simultaneous metabolic decompensation
  - Cardiac arrhythmias or failure, respiratory insufficiency or aspiration, pseudo-obstruction, renal insufficiency, insulin resistance, adrenal insufficiency, electrolyte imbalance
Mitochondrial stroke-like events: treatment

- Guidelines for anticipatory management
  - Pseudo-obstruction a harbinger of stroke in MELAS
- Hydration at 150% maintenance with D10-½NS
  - Monitor renal tubular and adrenal function
  - Dangerous tachycardias, hypoventilation
- Nitric oxide precursors
  - L-arginine 10%, 500 mg/kg bolus with 300 mg/kg/d
  - Consensus for L-citrulline
- Supplements / cofactors
  - Coenzyme Q-10; L-carnitine 50 mg/kg q 6 hr
  - Avoid aspirin, acetaminophen, valproate, propofol
Resources

- Family Guide to Pediatric Stroke
  - www.strokebestpractices.ca

- International Alliance for Pediatric Stroke
  - iapediatricstroke.org