Pediatric Stroke
(Another reason kids aren’t just little adults.)

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Disclosure

- I have no relationships with commercial companies to disclose.
- I will be discussing off-label use of medications in children.
  - FDA
    - “There are no adequate and well controlled studies on heparin or coumadin in pediatric patients.”
    - “Safety and effectiveness of lovenox in pediatric patients has not been established.”

Learning Objectives

- Understand the most common causes of acute ischemic stroke in children
- Plan the diagnostic evaluation of a child with acute ischemic stroke
- Identify indications for anticoagulation or antiplatelet therapy in pediatric acute ischemic stroke

International Pediatric Stroke Study

- Mission:
  - To perform international collaborative research aimed at understanding, preventing, and improving outcomes in pediatric stroke.
  - The ultimate mission of the IPSS is to expand knowledge on childhood stroke through publications.
- Started 2003
- 219 Centers
- 54 Countries
- 5151 patients
  - 1800 neonates
  - 3500 children
- 18 publications

Cases

- 8 month old well child check. Parents report patient is left-handed.
- 3 year old with sickle cell disease awoke from nap with slurred speech.
- 15 year old passed out and awoke with left sided facial droop and right-sided weakness.
- What do these cases have in common?

Pediatric Acute Ischemic Stroke (AIS)

- Perinatal Stroke
  - 28 weeks to Birth
- Neonatal Stroke
  - Birth to 28 days of life
- Childhood Stroke
  - 29 days to 18 years
- Adult Stroke
  - >18 years
Perinatal/Neonatal Stroke
- Incidence 1:2800-1:5000
  - 87% present in 1st week of life
  - Only 30% with focal neurologic findings
  - 17 times more common than childhood stroke
  - 50-70% of congenital hemiplegic cerebral palsy

Risk Factors
- Maternal Factors
- Perinatal Factors
- Vasculopathy
- Birth Trauma and Asphyxia
- Infection
- Congenital Heart Disease (20%)
- Inherited Thrombophilia (20%)

Are neonates more likely to bleed or to clot?
- Quantitative and qualitative differences exist between preterm and term neonates and children
- Neonates have the highest risk of thrombosis compared to infants/children
  - Platelets – same number, hyporeactivity
  - VWD elevated
  - Factors 2, 5, 7, 9, 10, 11, 12 – low
  - Factor 8 high
  - ATIII, Prot C, Prot S low
  - Plasminogen quantity and function low
  - Shorter bleeding time and TEG

Childhood AIS
- Annual incidence 1.2-8:100,000 children
- Mortality 3%
- Long term neurologic sequelae = 70%
- Risk of recurrence 7-20% (highest in arteriopathies)

Etiology of Pediatric Strokes
- 24% idiopathic
- Cardiac Abnormalities
- Sickle Cell Disease
- Arteriopathies
- Thrombophilia
- Genetic Disorders
- Sympathomimetic Drugs

Cardiac Abnormalities
- 25-28% of Childhood AIS attributed to congenital or acquired cardiac source
  - Reported as leading cause in most studies
  - Cardio-embolic phenomenon
- Cyanotic and complex congenital heart disease have greatest risk
  - 1/3-1/4 of events occur peri-procedurally
- A few studies report increased prevalence of inherited or acquired thrombophilias
  - 12 fold inc risk stroke in cardiac patients with two or more prothrombotic disorders
Sickle Cell Disease

- Cerebral vasculopathy
  - Most common in SCD-SS patients
  - Incidence 10% Overt stroke by age 20
  - Incidence 20% Silent stroke by age 20
- Acute stroke therapy
  - Exchange transfusion (automated superior to manual)
- Primary stroke prevention
  - Transcranial Doppler Ultrasound (TCD) Screening
  - Chronic Transfusion Therapy = 92% decrease in rate of stroke in pts with abnormal TCD
- Secondary stroke prevention
  - Chronic transfusion therapy

Arteriopathies

- Second most common cause of AIS
- 2011 IPSS report of 676 children with AIS
  - 53% with arteriopathy (included SCD)
    - 24% focal cerebral arteriopathy
      - Associated with preceding viral infection
      - Subtype of FCA = 7% post varicella infection
    - 22% moyo moyo
    - 20% arterial dissection
    - 12% vasculitis
      - Arteriopathies most common in ages 5 to 9
  - 2011 IPSS report of 676 children with AIS
  - 53% with arteriopathy (included SCD)

Thrombophilia

- 2011 IPSS report
  - 13% with identified prothrombotic risk factor
    - 77% with single risk factor
    - 23% acquired thrombophilia
    - 8% heterozygous FVLeiden
    - 24% elevated Lipoprotein (a)
  - 2% identified with adult risk factors
    - Hypertension (9); hyperlipidemia (3); diabetes (1)
  - Independent versus permissive risk factor?

Lipoprotein (a)*

- Prothrombotic risk factor
  - Atherogenesis
  - Hypofibrinolysis due to plasminogen inhibition
- 10 fold increased risk of recurrent AIS
  - **“lipoprotein little a”**

Evaluation & Treatment of Pediatric AIS

Evaluation

- Neuroimaging
  - MR
    - Brain, Angiography, Venography
  - CT angiography
  - TCD (sickle cell disease)
- Echocardiogram
Laboratory Testing

**Acute Testing**
- Anti-phospholipid antibodies
  - Anti-β2 GPI
  - Lupus Anticoagulant
  - Anti-Cardiolipin
- D-dimer
  - Primarily in cardiac patients

**Long-term Testing**
- Inherited risk factors
  - Protein C/S activity
  - AT III
  - FVL
  - Prothrombin 20210
  - Fasting Homocysteine
  - Lipoprotein (a)
- Repeat D-dimer

Treatment of Stroke in Kids

- No RCT of acute stroke treatment in kids (except for SCD)
- Treatment recommendations are largely from consensus guidelines
  - American Heart Association (AHA), American College of Chest Physicians (ACCP), Royal College of Physicians (RCP)

Treatment

- ACCP, 9th ed.
  - Antithrombotic Therapy in Neonates and Children
  - Last updated 2011
    - Next update waiting for data on newer anticoagulant therapies
    - Defined methodology and grading with evidence

- Acronyms
  - VKA – Vitamin K antagonist (coumadin)
  - UFH – unfractionated heparin
  - LMWH – low molecular weight heparin (enoxaparin)
  - ASA – Aspirin
  - tPA – tissue plasminogen activator

Guidelines for Neonatal AIS

- For neonates with first AIS, in the absence of cardioembolic source, suggest supportive care over anticoagulation or ASA. (Grade 2C)
- For neonates with first AIS and documented cardioembolic source, suggest UFH or LMWH. (Grade 2C)
- For neonates with recurrent AIS, suggest anticoagulation or ASA therapy.

Guidelines for Pediatric AIS

- For children with AIS, with and without thrombophilia, recommend UFH, LMWH or ASA until dissection and embolic causes are excluded (Grade 1C)
- For children with AIS, once dissection and embolic causes excluded, recommend ASA for minimum 2 years vs no antithrombotic therapy. (Grade 2C)
- For children with AIS, recommend against TPA or mechanical thrombectomy outside of research. (Grade 1C)
Guidelines for Cardio-embolic AIS

• For AIS secondary to cardio-embolic cause, suggest LMWH or VKA for at least 3 months. (Grade 2C)

• For AIS secondary to cardio-embolic causes due to right-to-left shunts (PFO), suggest surgical closure. (Grade 2C)

Guidelines for Dissection

• For AIS secondary to dissection, suggest therapy with LMWH or VKA for at least 6 weeks. (Grade 2C)

• Ongoing treatment based on radiologic assessment on degree and extent of stenosis.

Guidelines for Arteriopathies

• For acute AIS due to non-moyamoya vasculopathy, recommend UFH, LMWH, or ASA for 3 months compared to no treatment at all.
  – Ongoing therapy guided by repeat imaging.

• For children with acute AIS secondary to Moyamoya, suggest ASA over no therapy.
  – Suggest referral to center to consider revascularization.

Acute Therapy for AIS in Kids

- tPA
  • No interventional trials using tPA in the hyperacute phase of childhood AIS.
  • AHA recommends against due to safety concerns.
  • Unclear guidelines for adolescents who meet adult criteria.
  • IPSS Thrombolysis in Pediatric Study

Barriers to Research

• Sub-acute presentation common in neonates

• Median time to diagnosis of childhood AISi = 24-35 hours much longer than 3-8 hour interval for acute intervention

• Vulnerable population/Parental Consent
Prognosis

- Increased risk of recurrent stroke:
  - Abnormal cerebral vasculature on initial imaging
  - Progression of intracranial arteriopathy on subsequent imaging
- Long-term neurologic outcomes:
  - Fever
  - Younger age
  - Larger volume of area affected
  - Cortical involvement = poor functional outcome

Summary

- Peak incidence of stroke bimodal
  - Perinatal/neonatal and adults
- Very few children present with adult risk factors (2%)
- Therapeutic recommendations are based on consensus
- Research in pediatric stroke is needed
- IPSS has laid the framework for multi-center therapeutic trials

Questions

Off-Label Use of Medications in Children

- 20% of FDA approved medication have a pediatric label.
  - Pediatric Research Equity Act (PREA) 1998
    - New drugs must have plan to include children or explain why not included.
    - Drug companies get an extra 6 months of exclusive marketing if they also include children in their studies.

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