TCD in Sickle Cell Disease

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TCD in Sickle Cell Disease

Outline
- Review importance of SCD and stroke
- TCD helped identify high risk
- The STOP Study
- Putting TCD into practice for SCD

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Background
- About 80,000 with severe SCD in USA
- Stroke is frequent complication of SCD
- 11% stroke prevalence by age 20
- Mostly large artery territorial infarctions
- 75% are ischemic infarctions
- Average age of stroke victims 4 years
- Frequent occlusions of d-ICA, MCA

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Background
- Nature of occlusions still not clear
- Seems to involve inflammatory vasculopathy
- Possible role for plasma free hemoglobin released by hemolysis, and effect on Nitric Oxide
  Adams RJ, Arch Neurol 2007;64:1567-74

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Background
- Ischemic infarctions more common in kids
- Hemorrhages more common in adults
- Hemorrhage often SAH; can be ICH in deep structures such as thalamus
- Many hemorrhages related to “moya-moya” changes from earlier occlusions/strokes
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Silent Infarctions

- New methods (MRI) show about 20% rate of silent infarctions (SI) in SCD patients
- Increased risk of SI if lower HCT, history of seizure, lower painful event rate, higher WBC count
- SI associated with cognitive deficits and poor school performance


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Silent Infarctions

- Children with SI had 2X > school problems
- 80% with SI had clinically significant cognitive deficits, 35% deficits in academic skills
- SI on MRI more frequent in girls < 6 yrs, boys until age 10
- SI smaller, less in frontal or parietal lobes

Schatz J, et al, Neurology 2001;56:1109-11

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Silent Infarctions

- Children with SI have increased incidence of new stroke (1.03/100 pt-yrs), and new or more extensive SI lesions (7.06/100 pt-yrs) vs. those without SI (0.54/100 pt-yrs)
- Chronic transfusion decreases risk of new SI or stroke, but risk/benefit unclear
- CBF by CASL MRI has inverse correlation with cognitive function in SCD children

Pegelow CH 2002
Strouse JJ, et al, 2006

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Transfusions

- Transfusions known to reduce stroke rate but cannot be uniformly applied
- Financial analysis shows $9828-50,852/pt-yr for SCD with chronic transfusion
- If chelation needed, mean $39,779/pt-yr
- Cost of chronic transfusion Rx for SCD approaching $400,000/pt-decade

Wayne AS, Blood 2000

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Background

- Lacked marker of high risk to guide Rx
- TCD shown feasible in SCD patients
- MFV in SCD higher than normal children
- TCD readily ID’d intracranial lesions
- TCD changes shown to identify
- Risk could be stratified based on TCD mean velocities


Transcranial Color Duplex Sonography in SCD
Right MCA: Normal
Transcranial Color Duplex Sonography in SCD
Left MCA: “Normal per STOP”

Transcranial Color Duplex Sonography in SCD
Left T-ICA: Abnormal 192 cm/s Vmean

Transcranial Color Duplex Sonography in SCD
Right T-ICA: Abnormal 240 cm/s Vmean

MR-A in Sickle Cell Disease
5 year old without symptoms
MR-A unremarkable

MR-A in Sickle Cell Disease
Now age 9 with tight MCA stenosis
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Normals in SSD Children

- Normal velocities higher due to age/anemia
- MCA Vmax 168 +/- 38 cm/s
- MCA Vmean 115 +/- 31 cm/s
- ACA Mmax 138 +/- 34 cm/s
- ACA Vmean 94 +/- 28 cm/s
- Abnormal 2 SD above these normal values

Adams RJ et al, 1989

Accumulation of stroke in SCD with normal, conditional, or abnormal TCD results

40% stroke in 3 years for abnormal group

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The STOP Study

- STOP was a multi-center, randomized, controlled clinical trial testing whether TCD screening, followed by transfusions could prevent first stroke in patients with SCD ages 2-16 (vs. standard clinical care)
- First study to use TCD as inclusion criteria for multi-center effort

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Methods for STOP Study

- Sickle Cell or Sickle Thal, age 2-16
- TCD by standard protocol & instrument (Nicolet/EME TC-2000)
- Sonographers trained in protocol
- Centralized blinded reading at MCG
- Sampling at 2 mm intervals
- Called NL, Conditional, Abnl, Inadequate
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Methods for STOP Study
- >200 cm/s in ICA or MCA on two studies
- Studies one week to one month apart
- Randomized to standard care or transfusion
- Transfusion target of <30% Hgb S
- Ongoing transfusions q 3-4 weeks
- Primary study endpoints of stroke or ICH

Results for STOP Study
- TCD screening of 1,934 children
- Overall, 9.7% abnormal studies
- Higher % abnormal in younger patients
- 79 initially normal, later turned abnormal
- Of 266 abnormal, 85% abnormal on repeat
- Finally, 130 children enrolled

Results of STOP Study
- Cohort of 130 with 60 boys, 70 girls
- Mean age 8.3 years
- 63 to transfusion Rx; 67 to standard care
- Initial Hgb/HCT slightly lower in Rx group
- No other baseline differences

29 potential events in 23 patients
Adjudication confirmed 11 events in the control group, and 1 in the Rx group
One event was ICH
Statistically significant (p<0.001) with 92% relative risk reduction
If ICH excluded, still p=0.002

NIH Clinical Alert issued and rec’d TCD screening of SCD patients age 2-16

Adams RJ, Arch Neurol 2007;64:1571
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**STOP Study Caveats**
- 10 patients dropped out of Rx group
- 9 in Rx group got allo-immunization
- When Rx to >250ml/kg, chelation required for high ferritin levels (>2500 mg/l)
- No answer for how long Rx required
- STOP 2 showed reversion to abnormal study and stroke risk when transfusion D/C’d

**Applying Results**
- Don’t do if patient asleep, just aroused, acutely ill, febrile, or agitated
- Confirm repeat study in 1-4 weeks
- Screen q 6-12 months in younger patients
- One screening not sufficient due to variability
- 18 month rate of conversion from conditional to abnormal reported at 23% (Hankins JS, et al 2008)

**Practical Application**
- Utilization of TCD for screening in SCD appears to be less than optimal
- Suggested only about 50% eligible patients get yearly screenings
- High no-show/cancellation rates
- Missed appts (20-80%); must overbook

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**Applying Results**
- Similar TCD instrument, training, method/protocol, and criteria
- Search MCA & ICA at 2 mm increments
- Study all segments but MCA (85%) and dICA (12%) where Vmax found
- Optimize signal; use highest reading for time averaged mean max velocity

**Practical Application**
- HbSC TCD velocity cut points are lower
- 98 percentile cut point was 128 cm/s
- Stroke risk remains in adults with SCD, but TCD not as predictive in adults with SCD, and cannot be used for risk stratification in adults
  Valadi N et al, 2006
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**Practical Application**
- ACA velocities important also
- ACA MFV >170 cm/s confers increased risk of stroke, after adjustment for ICA/MCA
- Normal ICA/MCA, high ACA gives 10X risk
- If ICA/MCA abnormal, still 2X risk
- Few stroke events in ACA territory
  

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**Criteria for linear transducers**
- Lower velocities found to be up to 10% lower than studies with non-imaging probes
- May need to lower cut points to closer to 160-165 for conditional, and 185 for significant stroke risk, rather than 170 and 200 per the STOP Study.
  
  Bulas D, 2005
  Bulas DI, et al, 2000

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**Conclusions**
- Stroke with SCD is preventable
- TCD/TCCD identifies high risk patients and can guide use of Rx
- STOP is “home run” for stroke prevention
- NIH rec’s TCD for all SCD age 2-16
- Not effective screen in adults
- Must educate physicians, patients, insurers
- Needs collaborative team effort

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**Applying Results: TCCD**
- Many use TCCD or TC Power Duplex for intracranial testing
- Most use zero angle of insonation, assume correlations with conventional TCD acceptable for MCA, d-ICA, ACA
- Recent suggestion that TCDI with angle correction acceptable
  

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**Questions Remain**
- Mechanism of high velocity (stenosis vs hyperemia)?
- Mechanism of Rx effect?
- Correlations with MRA, CTA?
- How long to Rx?
- Would higher cut point be better?

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