Sickle Cell Disease and the Brain

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Disclosure

• Nothing to disclose
Outline

• Signs and symptoms of stroke
• Epidemiology of stroke
• Treatment and prevention of stroke
• Chronic transfusion and stroke
  – STOP and STOP2 studies
• Hydroxyurea as an alternative
  – SWiTCH and TWiTCH studies
• Uncertainties in the diagnosis and management of Silent Infarct
  – SIT study
• Discussion
What is stroke?

- Sudden loss of blood circulation to an area of the brain
- Corresponding loss of neurological function
- Ischaemic
  - Large artery
  - Small vessel
  - Cardioembolic
- Haemorrhagic
- Transient Ischaemic Attack (TIA)
  - Temporary loss of blood circulation
  - Symptoms usually resolve in 24 hours
Brain Anatomy
LATERAL SURFACE OF CEREBRUM SHOWING AREAS OF FUNCTIONAL LOCALIZATION

- Generalized & Coordinated Movements
- Skilled Movements
- Tactile Sensation
- Stereognosis
- Proprioception
- Sensory Combination and Interpretation
- Visual
- Reading
- Verbal (Speech & Interpretation)
- Auditory Memories
- Musical
- Visual Memories
- Fear
- Memories
- Bodily Reaction
- Emotional Reaction
- Writing
- Intellect
- Judgement
- Reflection
- Creative Thought
- Activation
- Adverse Movements
- General Movements

*Note: Anterior parietal (postcentral sulcal) artery also occurs as separate anterior parietal and postcentral sulcal arteries.
Anatomy of a Stroke

http://www.ajnr.org/content/27/4/728/F2.large.jpg
Signs and Symptoms of Stroke

- One-sided weaknesses and/or sensory changes (numbness, tingling)
- Loss of balance
- Vision loss
- Slurring of speech
- Seizures
- Typically one or few symptoms predominates
Spectrum of SCD Complications

These mechanisms are not mutually exclusive

Hemolysis, endothelial dysfunction
- Precapillary arteriole
- Smooth muscle cells
- Erythrocyte
- Endothelial cells
- Arg → NO → O2
- NOS
- XO
- NO → ET-1

Viscosity, vaso-occlusion
- Capillary
- Postcapillary venule
- Monocyte
- Platelets
- αβ;
- VCAM-1

Decreased NO bioactivity
- Pulmonary hypertension
- Leg ulceration
- Priapism
- Stroke

Increased vaso-occlusion
- Pain crisis
- Acute chest syndrome
- Osteonecrosis
Natural History of Cerebral Vasculopathy in SCD

Adams RJ. Big strokes in small persons. Arch Neurol. 2007 Nov;64(11):1567-74
Risk of Hemorrhagic and Infarctive Stroke Changes with Age

Measurement of Transcranial Doppler Velocity Via Ultrasonography

- Standard of care
- Ultrasound Doppler aimed at the MCA
- Measures peak velocity of blood flow
- High velocity = stenosis and vasculopathy (like a narrowed garden hose)
- > 200 cm/s (= abnormal) associated with 40% risk of stroke within 3 years
- Performed annually
- From the time when the baby can lay still (~ 2 years-old) until the bone window closes (early/late teens)

Adams RJ. Big strokes in small persons. Arch Neurol. 2007 Nov;64(11):1567-74
Epidemiology of CVA in SCD

High TCD → Stroke → Low TCD → STOP, STOP2 → High TCD

10% Stroke
90% Cohort studies
STOP Study Design

• Patients:
  – SCD patients (SS, S/β0 thal), Age 2 to 16
  – Transcranial Doppler Velocity > 200 cm/s
  – No history of stroke

• Study design:
  – Randomized to transfusion vs. no transfusion (standard of care)
  – Transfusion target: pre-transfusion HbS < 30%, Hb < 120, Hct < 0.360
  – Patients can achieve target by simple or exchange transfusion

• Primary end-point:
  – cerebral infarction and hemorrhage, diagnosed by MRI

STOP Study Results

<table>
<thead>
<tr>
<th></th>
<th>Transfusion</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>No stroke</td>
<td>62</td>
<td>56</td>
</tr>
</tbody>
</table>

- RRR = 0.903

STOP2 Study

• Patients:
  – SCD patients (SS, S/β₀ thal), Age 2 to 16, from STOP study
  – On transfusion for > 30 months with HbS < 30% 2/3 of the time
  – Normal TCD, No stroke
• Study design:
  – Randomized to continued transfusion vs. no transfusion
  – Transfusion target: pre-transfusion HbS < 30%, Hb < 120, Hct < 0.360
  – Patients can achieve target by simple or exchange transfusion

• Primary end-point:
  – Stroke or reversion to abnormal TCD velocities

STOP2 Study Results

<table>
<thead>
<tr>
<th></th>
<th>Transfusion</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/Abnormal TCD</td>
<td>0/0</td>
<td>2/14</td>
</tr>
<tr>
<td>No stroke</td>
<td>38</td>
<td>25</td>
</tr>
</tbody>
</table>

- All strokes or reversion to abnormal TCD velocities occurred within first 10 months
- Both strokes occurred after reversion to abnormal TCD velocities

Chronic Transfusion in SCD
Methods of Transfusion

• Simple “top-up” transfusion

• Exchange transfusion:
  – Automated exchange
  – Manual RBC Exchange Transfusion
Potential Costs with Chronic Transfusion in SCD Patients

- Potential non-infectious risks
- Alloimmunization
- Potential infectious risks (minimal)
- Transfusional iron overload
  - Side effects from iron chelators
- Financial costs to patients (loss time from work, school, etc.)
Alloimmunization in SCD Patients

• Discrepancies between donor pool and recipient ethnicities
• 8 to 47% has been reported
• Dependent on patient age, number of donor units exposed, extent of phenotype matching
• Potential Consequences
  – Delayed hemolytic transfusion reaction (11%)
  – Autoantibody formation

Alloimmunization Examples

RHD and RHCE

- Altered C and e Ag are frequent in Africans
- Cannot be distinguished serologically, but recognized as foreign by the immune system

66% premature stop
19% gene deletion (>90% in Caucasians)

15% RHD-CE-D hybrid
Typed as D- C+
(none in Caucasians)

22% in Africans
Linked with RH-D-CE-D
Typed as D- C+
Ab with C or E like specificities

# Antigen-Matching

- **C/c E/e Kell matched**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 20)</th>
<th>Group B (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of antibodies</td>
<td>31</td>
<td>108</td>
</tr>
<tr>
<td>Common Rh alloantibodies</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 anti-E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 anti-C</td>
</tr>
<tr>
<td>Complex Rh antibodies*</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>11 anti-D (D+ patients)</td>
<td></td>
<td>4 anti-D (D+ patients)</td>
</tr>
<tr>
<td>8 anti-e (e+ patients)</td>
<td></td>
<td>6 anti-e (e+ patients)</td>
</tr>
<tr>
<td>3 anti-C (C+ patients)</td>
<td></td>
<td>20 anti-C or -Ce (C+ patients)</td>
</tr>
<tr>
<td>Other antibodies</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>2 anti-Jk&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>8 anti-K</td>
</tr>
<tr>
<td>1 anti-Fy&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 anti-N</td>
</tr>
<tr>
<td>4 anti-M</td>
<td></td>
<td>6 anti-S</td>
</tr>
<tr>
<td>1 anti-N</td>
<td></td>
<td>1 anti-Js&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 anti-Js&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>4 anti-Jk&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>RH alleles</td>
<td></td>
<td>2 anti-Jk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hybrid <strong>RHD-CE-D</strong> and **RHCE&lt;sup&gt;*&lt;/sup&gt;ce&lt;sup&gt;s&lt;/sup&gt;</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Only altered <strong>RHCE&lt;sup&gt;*&lt;/sup&gt;ce</strong></td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Partial <strong>RHD</strong> and altered <strong>RHCE&lt;sup&gt;*&lt;/sup&gt;ce</strong></td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>
Transfusional Iron Overload

- Impaired growth, infertility (Pituitary gland)
- Hypothyroidism (Thyroid gland)
- Cardiomyopathy, cardiac impairment (Heart)
- Hepatic cirrhosis (Liver)
- Diabetes mellitus (Pancreas)
- Hypogonadism (Gonadal glands)

Hydroxyurea as a Potential Alternative to Transfusion in the Treatment and Prevention of Stroke
Multiple Beneficial Effects of Hydroxyurea for SCD

Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. 2010 Jul 1;115(26):5300-11.
Clinical Studies of Hydroxyurea in SCD

Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. 2010 Jul 1;115(26):5300-11.
SWiTCH

• Phase III multicenter RCT, Non-inferiority
• 30 months, N = 133
• Hydroxyurea + phlebotomy vs. transfusions + chelation
• Composite primary endpoint: stroke recurrence and iron burden
• 12% had recurrent stroke prior to enrollment
• interim data analysis was performed after 1/3
• No difference in LIC
• Stroke recurrence rate: 7/67 vs. 0/66 transfusion + chelation
TWiTCH

• N = 148 planned enrollment (ages 4 to 15)
• SCA + abnormal TCD
• Transfusions + chelation vs. Hydroxyurea + phlebotomy
• Treatment duration: 24 months
• Outcome measurements: LIC, TCD, MRI
TCD Velocities Decrease with Age

**Graph A**: Right MCA velocities (cm/sec) vs. Age (years)

**Graph B**: Left MCA velocities (cm/sec) vs. Age (years)
Neurological Events in SCD

- Increasing morbidity / mortality
- Increasing neuropsychological deficits

- Neuro exam: normal, abnormal
- hemorrhage
- stroke
- high TCD, nl exam, silent infarct
- nl TCD, nl exam, silent infarct
- nl TCD, nl exam, nl MRI
- high TCD, nl exam, nl MRI
Silent Cerebral Infarcts (SCI)

- No signs or symptoms of stroke
- Normal neurologic examination
- Abnormal MRI
- Lack of concordance with TCD velocity
- Definition of abnormal MRI is constantly evolving
  - Improved imaging technologies
  - Different definitions between adults and kids
  - Area under intensive research
- What were classified as SCI previously may had subtle signs of stroke
Epidemiology of SCI

- Constantly shifting definition and lack of consensus amongst researchers
- Patient selection bias (very ill vs. not so ill)
- Lack of longitudinal studies with large number of patients
- Best guess in kids:
  - In adults: 13% in SCA vs. 2% in age- and ethnicity-matched controls without SCA
Risk Factors for SCI

• Low baseline hemoglobin level
• Higher blood pressure
• Male
• May be:
  – History of seizures
  – High white blood cell count
  – SEN $\beta^S$ globin gene haplotype
Anatomic Location of SCI

• (in decreased order of likelihood)
  • Deep white matter
    – Frontal lobe
    – Parietal lobe
  • Basal ganglia
  • Thalamus
  • Temporal lobes
Detection of SCI by MRI
Effects of Silent Cerebral Infarcts

- Lower global intellectual function
- Executive functions
  - selective attention, card sorting, working memory, processing speed
- Visual motor speed
- Coordination
- Visual memory
- Verbal comprehension
- Vocabulary
- Abstract reasoning

- Poor academic achievement
Effects of Silent Cerebral Infarcts

![Bar chart showing proportion of students that required special services or were retained a grade.](chart)
Potential Treatments for SCI

• Currently no therapy has been proven to prevent the occurrence or progression of SCI

• Transfusions
  – reduce the risk of stroke in patients with SCI and abnormal TCD velocities (STOP secondary analysis)
  – Currently being evaluated as an potential option in the SIT study

• Hydroxyurea and HSCT
  – evidence from single arm studies
Silent Cerebral Infarct Multi-center Transfusion (SIT) Trial

- Study hypothesis: monthly prophylactic blood transfusion therapy in children with SCI will result in an 86% reduction in strokes or new or progressive SCIs
- Multi-center randomized-controlled trial (29 sites in US, Canada, UK, and France) over 8.5 years
- Population: Children with history of SCI
- Randomization: blood transfusion or observation x 36 months
- N = 1,880 (planned enrolment)
- Outcome: Strokes, New or enlarged SCI
- Instrument: screening, pre-randomization (baseline), and exit MRI using a designated, prospective imaging protocol

Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease

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Results

• Median age at first stroke 5.4 years-old
• Median duration of follow-up 5.5 years
Progressive Vasculopathy and Silent Infarcts

No Vasculopathy

p = 0.017

+ Vasculopathy
Where to Go in the Post-STOP Era

- Stroke
- Silent infarct
- SIT trial
- What to do?
- Risk of recurrence reduced but not ameliorated
More Questions than Answers

- When to do screening MRI?
- How often should we evaluate SCA patients for SCI?
- Hydroxyurea as a therapeutic option?
- Bone marrow transplantation?
- Gene-therapy?
- Other novel therapeutic agents?
Discussion