Sickle Cell Disease and TCD: Hematologist Perspective

Paul R Gordon MD
Sickle Cell Disease

Epidemiology

- Most prevalent inherited disorder in AA
- Origin in Africa at least 5 mutational events
- βs expanded through selective pressure from plasmodium falciparum (survival advantage)
- Incidence parallels incidence of malaria
- βs spread geographically by commerce, slave trading, and migration
Sickle Cell Disease

In USA:

- Homozygous SS is 0.14%
- Heterozygous AS 8.6%
- 2000 new cases per year
- About 100,000 cases of SCD in the USA
- 10-20% will have severe phenotype

Motulsky AG NEJM 1973
Pathophysiology

Molecular sickling

- **De-oxygenation:**
  - β⁶: Mutant valine at position 6
  - Abnormal interaction with α and β
  - Deoxygenated HbS insoluble
    - β⁶ valine: β hydrophobic pocket: β70 β73 β84 β85
  - EM: HbS fibers parallel to long axis of cell
  - Distorted cellular milieu/membrane
  - Down stream organ infarction and clinical manifestation
Sickle Cell Disease

**Definition:** \( \beta_s \)

- **Genotype:** GAG to GTG → Hb\( \beta \) (glu6val)
- **Phenotype:** multigenetic: pleiotropic and epistatic genes
- **Secondary events** → inter-individual differences in clinical manifestation

**Modifier genes**

- **Adherence proteins:** vWF lamatin
- **Red cell receptors:** CD36 α4β1
- **Endothelial integrins:** ICAM-1 VCAM-1
- **WBC adherence**
- **↑ TNF IL-1 → ICAM-1 VCAM-1 expression**
- **RBC membrane permeability (Gardos channel)**
Sickle Cell Disease

Infection
- S Pneu < 4yrs
- 20% meningitis
- 15% death
- 15% recurrence
- 37% PCN
  Adamkiewicz J Peds 2003

CNS event
- Stroke
- 105% HbSS
- 50-100% recur
- Mortality 25%
  Frempong Blood 1998
- 17% Silent Infarct
  Stein AJNR 2003

HbS POLYMER

Veno occlusive crisis
- Bone infarction/pain

Splenic Sequestration

Acute chest syndrome
- 29.2% CCSSD
  ACS → mortality
- Death/hospitalization
- SCLD/Pul HTN
  Castro Blood 1994
  Vichinsky NEJM 2000

Chronic illness
- Organ failure
- SCLD/Pul HTN
- Renal failure
- Rep hospitalization

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CNS event
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Stroke in SCD

- One of the most common and devastating complications of SCD.

- 10 percent of children with HbSS will have overt strokes.

- HbSC and HbSβ-thalassemia infrequently have overt CNS events.

- Adverse motor and cognitive sequelae.

- Transient ischemic attack (TIA) often precedes stroke.

- 20 to 35 percent of children with HbSS have silent cerebral infarcts (SI).

- SI can cause cognitive decline and predispose to additional SI and to overt strokes.


Stroke in SCD

- Stroke
  - Generally secondary to stenosis or occlusion of the ICA or MCA.
  - May be precipitated by ACS, parvovirus infection, or other acute events.
  - Recurrence rates 46-90%.


- Primary prevention/Secondary prevention
  - TCD
  - Chronic transfusion program
  - Hydroxyurea
  - Hematopoietic stem cell transplantation

Stroke in SCD

- Trans Cranial Doppler (TCD)
  - Lesions of blockage of the ICA and MCA can be detected by TCD ultrasonography
  - Correlates with stenosis on angiography and subsequent stroke
  - Blood flow velocity is inversely related to arterial diameter
  - Stroke prevention trial in sickle cell anemia (STOP)


Stroke in SCD

- STOP Trial
  - Randomization of SCD with abnormal TCD
  - Transfusion vs standard of care
  - Primary Prevention
  - Time averaged mean of the maximum velocity of blood flow in the MCA and ICA (TAMMV)
  - Normal(<170 cm/sec) conditional (170-200 cm/sec) or abnormal (>200)
  - >200cm/sec at least 40% chance of CNS event
  - Abnormal for X2 TCD
Stroke in SCD

- Prophylactic PRBC transfusion after abnormal TCD reduced the incidence of stroke from 10%/y to <1%/y
- The STOP study led to recommendations for TCD screening and prophylactic transfusion for children with abnormal velocities on ultrasonography.
- PRBC transfusion leads to the reduced risk of stroke
  - Iron over load
  - Alloimmunization
  - Cost
  - Social impact

- STOP 2
- Switch Trial  Ware R, Blood. 2012 Apr 26;119(17):3925-32
- Twitch Trial  Ware R, Lancet. 2016; 387: 661–670
### TABLE 3. Characteristics of the 11 Patients Who Had Cerebral Infarctions.*

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at Entry (yr)</th>
<th>Hemoglobin at Entry (g/dL)</th>
<th>Blood-Flow Velocity (cm/sec)</th>
<th>Baseline MRI Lesions</th>
<th>Time from Study Entry to Stroke (mo)</th>
<th>Symptoms</th>
<th>Post-Stroke MRI Lesions</th>
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<tr>
<td>1</td>
<td>5</td>
<td>96</td>
<td>251</td>
<td>Yes left, yes right</td>
<td>14</td>
<td>Left hemiparesis, dysarthria</td>
<td>Yes (worse)</td>
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<td>78</td>
<td>216</td>
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<td>24</td>
<td>Right hemiparesis, aphasia</td>
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<tr>
<td>3</td>
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<td>82/16</td>
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<td>4</td>
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<td>Yes (new)</td>
</tr>
<tr>
<td>4</td>
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<td>92/6</td>
<td>202</td>
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<td>Right hemiparesis, aphasia</td>
<td>Yes</td>
</tr>
<tr>
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<td>246</td>
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<td>Yes (new)</td>
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<tr>
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<td>8</td>
<td>81/16</td>
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<td>14</td>
<td>Right hemiparesis, aphasia</td>
<td>Yes</td>
</tr>
<tr>
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<td>7</td>
<td>89/9</td>
<td>287</td>
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<tr>
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<td>91/7</td>
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<td>Yes left, yes right</td>
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<td>Right hemiparesis, aphasia</td>
<td>Yes</td>
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<tr>
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<td>89/8</td>
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<td>Yes left, yes right</td>
<td>18</td>
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<td>Yes (worse)</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>91/6</td>
<td>203</td>
<td>No left, yes right</td>
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<td>Left hemiparesis, dysarthria</td>
<td>Yes (new)</td>
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<td>No left, yes right</td>
<td>26</td>
<td>Left hemiparesis, dysarthria</td>
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</tr>
</tbody>
</table>

*One patient with left frontal hemorrhage at baseline was excluded. HD denotes hemoglobin, and MRI magnetic resonance imaging.

Values are the highest time-averaged mean velocity recorded in the middle cerebral artery or internal carotid artery during the confirmatory Doppler study.

Signs of atrophy were excluded.

§Patient 11, who was assigned to the transfusion group, had received a transfusion 11½ weeks before entering the study.

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**Figure 1.** Kaplan–Meier Estimate of the Probability of Not Having a Stroke among Patients Receiving Long-Term Transfusion and Patients Receiving Standard Care.

The P value was calculated by proportional-hazards regression analysis. Tick marks indicate the lengths of observation of patients who did not have a stroke. One patient in the standard-care group who had an intracerebral hematoma was excluded from the analysis.
STOP Trial

Margaret T. Lee et al Blood. 2006; 108:847-852)
STOP Trial

- STOP 2
  - Children on transfusion based STOP1 data
  - Randomized to stop vs continue transfusion after 30 months
  - TCD normalized
  - The composite primary end point was stroke or reversion to a result on Doppler examination indicative of a high risk of stroke.

STOP Trial

Figure 2. Kaplan–Meier Estimates of the Probability of No End-Point Event among Patients Assigned to Continued Transfusion or No Continued Transfusion. P values were determined by the log-rank test.

## Recommendations

1. In children with SCA, screen annually with TCD according to methods employed in the STOP studies, beginning at age 2 and continuing until at least age 16.  
   *(Strong Recommendation, Moderate-Quality Evidence)*

2. In children with conditional (170–199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke.  
   *(Strong Recommendation, High-Quality Evidence)*

3. In children with genotypes other than SCA (e.g., HbSβ+-thalassemia or HbSC), do not perform screening with TCD.  
   *(Strong Recommendation, Low-Quality Evidence)*

4. In asymptomatic children with SCD, do not perform screening with MRI or CT.  
   *(Moderate Recommendation, Low-Quality Evidence)*

5. In asymptomatic adults with SCD, do not perform screening with neuroimaging (TCD, MRI, or CT).  
   *(Moderate Recommendation, Very Low-Quality Evidence)*
TCD

- TCD has made a significant impact in standard of care in SCD
- Landmark STOP studies
- NCH-annual TCD’s starting at age 2 until age 16
- Abnormal TCD repeated in 2-4 months
- Prophylactic transfusions started if repeat TCD has Tamm >200cm/sec
- Abnormal TCD refer for SCT
- Now considering Hydroxyurea
NCH Comprehensive Sickle Cell Program

- ~350 patients with Sickle Cell Disease
- NHLBI SCD 2014 treatment guidelines
- Full support team
- Five providers
- BMT-Nemours Jacksonville
- Wright family foundation funding for patient education
- Collaboration across the Nemours enterprise
- Comprehensive sickle cell clinic monthly

NHLBI/NIH-Evidence based management of Sickle Cell Disease Expert Panel report 2014
NCH Comprehensive Sickle Cell Program

To create an environment of mutual partnership with patients and families. To provide comprehensive and compassionate care in order to secure a full and productive life free from the chronic complications of sickle cell disease.
Thank You

Questions