PEDIATRIC SICKLE CELL DISEASE

Discovering New Horizons

Peter A Lane, MD
Professor of Pediatrics
Emory University School of Medicine
Director, Sickle Cell Disease Program
Children’s Healthcare of Atlanta
PEDiatric Sickle Cell Disease (SCD)

Disclosures

Hydroxyurea not FDA approved for use in children

Clinical Research Funding to CHOA SCD Program:

• NIH
• FDA
• CDC
• PCORI
• Pfizer
• Global Blood Therapeutics
• Sancillo
• Novartis
PED diATRIC SICKLE CELL DISEASE
Discovering New Horizons

• Brief Overview of SCD
  ➢ History
  ➢ Pathophysiology
  ➢ Clinical manifestations
  ➢ Genetics and inheritance

• Horizons: Old and New
  ➢ Improved surveillance for SCD
  ➢ Ongoing development of innovative therapies
  ➢ Assessing effectiveness of care
  ➢ Ensuring access to and delivery of optimal care to all
PEDiatric sickle cell disease (SCD)

Objectives

• Review the history, pathophysiology, and clinical manifestations, and genetics of SCD
• Understand the incidence, demographics and mortality of SCD in Georgia
• Review progress in the development of innovative therapies for SCD
• Review current efforts to deliver optimal care to all
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SICKLE CELL DISEASE
The First Molecular Disease

1910 Herrick: First description of sickled cells
1927 Hahn and Gillespie: Oxygen-dependency of sickling
1949 Pauling, et al: Electrophoretic abnormality of HbS
1951 Neel: Autosomal recessive inheritance
1957 Ingram: Single amino acid substitution
1961 Specific mutation identified (β6 glu → val)
**Sickle Hemoglobin (Hb S)**

Point mutation in β-globin: β6 (Glu → Val)

Most common hemoglobin variant worldwide

Sickle cell trait (AS)
- 7-8% Africans Americans
- Hispanic, Mediterranean, Middle East, Caribbean, India, Central & South America

≥ 100,000 persons with SCD in US, millions worldwide

Deoxy-Hb S polymerizes
- Damages RBC → hemolysis
- Vaso-occlusion and tissue injury

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SICKLE CELL DISEASE
Clinical Manifestations of Hemolysis

- Chronic anemia
- Jaundice
- Cholelithiasis
- Aplastic crisis
- Decreased energy / exercise intolerance
- Growth and pubertal delay
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SICKLE CELL DISEASE

**Hemolysis**

**Vasoocclusion**

**Acute Events**
- Pain
- Splenic sequestration
- Infection
- Acute chest syndrome
- Stroke
- Priapism

**Chronic Organ Damage**
- Splenic dysfunction
- Chronic pain
- Lung disease
- Neuro-cognitive
- Pulm hypertension
- Nephropathy

**Treatment Complications**
- Medication toxicity
- Iron overload
- RBC alloimmunization
- Other iatrogenic

**Psychosocial Complications**
- Absence from school & work
- ↓ Academic achievement
- ↓ Readiness for transition
- Stress, depression, ↓ self esteem

↓ Quality of Life
Morbidity
Early Death
High Cost
SICKLE CELL DISEASE
Complex Progressive Chronic Vasculopathy

Hb S polymerization
RBC dehydration
RBC membrane damage
Decreased RBC deformability
Abnormal RBC-endothelial adherence
Endothelial cell activation and injury
Chronic inflammation
Hypercoagulability
Nitric oxide depletion 2o hemolysis
Sickle Cell Anemia: Autosomal Recessive Inheritance

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## SICKLE CELL DISEASE

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Approx % of U.S. Patients</th>
<th>Hemolysis</th>
<th>Vasoocclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb SS</td>
<td>65</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Hb SC</td>
<td>25</td>
<td>+</td>
<td>++ / +++</td>
</tr>
<tr>
<td>S β⁺ thalassemia</td>
<td>7</td>
<td>+</td>
<td>+ / ++</td>
</tr>
<tr>
<td>S β⁰ thalassemia</td>
<td>2</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>SD, SO, SE, SLepore</td>
<td>1</td>
<td>Varies</td>
<td>Varies</td>
</tr>
</tbody>
</table>

*Each genotype characterized by largely unpredictable and widely variable phenotype*
SICKLE CELL DISEASE

Family testing for Carriers *

Individuals at risk
• Sickle cell trait (AS)
• Hemoglobin C trait (AC)
• β thalassemia
• Other hemoglobin variants

Laboratory testing
• Hemoglobin electrophoresis, HPLC
• CBC / MCV
• Quantitation of A2 & F if MCV low or low normal

*Provided by Sickle Cell Foundation of Georgia at reduced or no cost
SCD SURVEILLANCE IN GEORGIA
The GA RuSH & PHRESH Projects

• Funded by NIH and CDC (one of 7 states)
• Surveillance to estimate the number of individuals with SCD
  ➢ Age, SCD genotype
  ➢ Demographics
  ➢ Healthcare utilization
  ➢ Morbidity and mortality
• Partners
  ➢ Georgia Department of Public Health
  ➢ Georgia Health Policy Center, Georgia State
  ➢ SCD Center at Grady
  ➢ SCD Program at Children’s Healthcare of Atlanta
  ➢ SCD Program at Georgia Reagents University
  ➢ Sickle Cell Foundation of Georgia

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Public Health Surveillance for SCD in Georgia

NIH/CDC RuSH Grant: (2010-2012)
• One of 7 states funded to conduct surveillance for SCD and thalassemia

CDC PHRESH Grant: (2012-2014)
• Only state (of 7) funded for continued SCD surveillance

Georgia CDC Transfusion Complications Grant: (2014-2019)
• Only state funded to characterize and reduce complications of blood transfusions in SCD & thalassemia

CDC Foundation Grant (2016)
• Extend SCD surveillance to include 2004-2014
## Surveillance for SCD in Georgia 2004-2008

*Results of CDC-funded RuSH Project*

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Confirmed SCD</th>
<th>Probable SCD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn Screening</td>
<td>730 (17%)</td>
<td>98</td>
<td>828</td>
</tr>
<tr>
<td>GA Regents Univ</td>
<td>1,218 (28%)</td>
<td>14</td>
<td>1,232</td>
</tr>
<tr>
<td>Grady</td>
<td>1,661 (39%)</td>
<td>2</td>
<td>1,663</td>
</tr>
<tr>
<td>CHOA</td>
<td>1,908 (45%)</td>
<td>242</td>
<td>2,150</td>
</tr>
<tr>
<td>Medicaid/CHIP</td>
<td></td>
<td>1,993</td>
<td>1,993</td>
</tr>
<tr>
<td>State Health Benefit Plan</td>
<td></td>
<td>215</td>
<td>215</td>
</tr>
<tr>
<td>Hospital administrative data</td>
<td></td>
<td>2,147</td>
<td>2,147</td>
</tr>
<tr>
<td><strong>De-duplicated Total</strong></td>
<td><strong>4,288</strong></td>
<td><strong>3,011</strong></td>
<td><strong>7,299</strong></td>
</tr>
</tbody>
</table>
Surveillance for SCD in Georgia 2004-2008
Results of CDC-funded RuSH Project

Key Findings

- 7,299 cases of SCD in GA
  - 4,288 confirmed
  - 3,011 probable

- 53% ≥ 20 years of age

- 65% in ATL metro area

- Limitations of ICD-9 codes in administrative databases
  - 12% with ≥ 1 SCD ICD-9 code did not have SCD
## Care Providers for SCD Patients in GA

<table>
<thead>
<tr>
<th>Provider Specialty</th>
<th>Outpatient Visits</th>
<th>Percentage of Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Medicine</td>
<td>52,890</td>
<td>19%</td>
</tr>
<tr>
<td>Family Practice/General Practice</td>
<td>48,161</td>
<td>17%</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>40,554</td>
<td>14%</td>
</tr>
<tr>
<td>Hematology</td>
<td>31,512</td>
<td>11%</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>16,976</td>
<td>6%</td>
</tr>
</tbody>
</table>

Population: Medicaid all-cause outpatient visits 2004-2008 for confirmed and probable cases of SCD

Data from Georgia Registry and Surveillance for Hemoglobinopathies (RuSH)
Hospital Encounters by Age for SCD*

* For individuals who had at least one ER or in-patient encounter in 2004-2008

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Data from Georgia Registry and Surveillance for Hemoglobinopathies (RuSH)
Age at Date of Death in SCD

<table>
<thead>
<tr>
<th>RuSH Dx Level</th>
<th>Observations</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>268</td>
<td>136</td>
<td>37.55</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>Probable</td>
<td>280</td>
<td>208</td>
<td>44.99</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>548</td>
<td>344</td>
<td>42.05</td>
<td>41</td>
<td>50</td>
</tr>
</tbody>
</table>

SCD not listed on death certificate in 55% of cases!
SCD Mortality in Georgia
*CDC-RuSH Surveillance Project (7,299 patients)*

SCD not listed on death certificate in 55% of cases!
DEVELOPMENT OF INNOVATIVE THERAPIES

Expanding Specific Therapy for SCD
- Hydroxyurea *
- Red blood cell transfusions *
- Stem Cell (Bone Marrow) Transplantation *
- Gene Therapy *
- Stroke prevention *

Developing new therapies for prevention of complications
- Glutamine – Recently FDA approved
- GBT440 – Phase IIa
- Omega 3 Fatty acids – Phase II

Developing new therapies for treatment of complications
- IV Rivapansel for treatment of severe pain – Phase III
- IV Arginine for treatment of severe pain – phase II

* Discussed in depth by others today
Objective:
- To expand the number of health professionals able and willing to provide care for persons with SCD

Target audience:
- PCPs, other health care professionals

Contents:
- Health Maintenance
- Management of Acute Complications
- Management of Chronic Complications
- Hydroxyurea Therapy
- Blood Transfusions


Sickle Cell Disease Program
Children’s Healthcare of Atlanta

• Largest in US (1,876 active patients in 2016)
• Comprehensive clinics, ED and inpatient services
  ➢ Egleston
  ➢ Scottish Rite
  ➢ Hughes Spalding
• Multidisciplinary SCD teams on all 3 campuses
  ➢ Hematologists, nurse practitioners, nurses, social workers, psychologists, child life specialists, chaplains
• NBS Follow-up Program
  ➢ Confirmatory testing in CHOA lab
  ➢ Initial outpatient consultation
  ➢ Subsequent coordination of care with PCP
Comprehensive Care for SCD (1)

• Newborn screening and diagnosis
• Patient and family education
• Health maintenance services
  ➢ Age-specific primary care
  ➢ Penicillin and immunizations
  ➢ Prevention and treatment of organ damage
  ➢ Psychosocial and other supportive services
  ➢ Genetic services
• Treatment of acute complications (eg pain, infection)
• Psychosocial and other supportive services
Comprehensive Care for SCD (2)

- “Specific” Therapy for SCD – treatment to directly impact the abnormal sickle red blood cells
  - Hydroxyurea – improves the function (health) of the patient’s red cells
  - Chronic blood transfusions – replaces abnormal red cells with normal red cells
  - Bone marrow transplantation – replaces the bone marrow that makes sickle red cells with marrow that makes normal red cells.
SICKLE CELL DISEASE IN GEORGIA
Efforts to Improve Delivery of Optimal Care to All

CDC Foundation Grant (2016)
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Georgia CDC Transfusion Complications Grant: (2014-2019)
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HRSA grants
• SCFG: Improve transition and access to care for adolescents and adults with SCD
• Southeast Regional SCDTDP
  1. Increase number of knowledgeable providers
  2. Enhance support for SCD providers
  3. Increase access to care and transition services

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Reducing complications of therapeutic blood transfusion in sickle cell disease

James Eckman, M.D.
Peter A. Lane, M.D.
Ross Fasano, M.D.

CME/CNE available through CDC
https://www2a.cdc.gov/TCEOnline

INTRODUCTION

Module 1. Use of Blood Transfusion during Acute Illness
Module 2. Delayed hemolytic transfusion reactions
Module 3. Management of Chronic transfusion
Pediatric Sickle Cell Disease

Summary

Major health issue in children and adults across GA
- Multiple SCD genotypes with variable manifestations and severity
- Complex progressive chronic vasculopathy
- Life-threatening acute and chronic complications
- Significant morbidity and early mortality

Significant progress in expanding specific therapies for SCD
- Hydroxyurea
- Blood transfusions
- Bone marrow transplantation
- Gene therapy

Exciting new innovative therapies for prevention and treatment of complications – NIH, FDA, Pharma

Increased efforts to ensure access to optimal care to all – state, regional and national level
Ted Nicolas says the hydroxyurea he takes to lessen the frequency of his sickle-cell anemia attacks has given him more time to spend with his wife, Marie, and baby boy Matteo.

New drugs offer hope to sickle-cell victims