Sickle Cell Disease

**Introduction**
- Many advances in both basic science and treatment have come about in sickle cell disease over the last 20 years.
- We recognize sickle cell disease as a group of complex genetic disorders leading to potentially life-threatening multi-organ damage.
- Understanding the genetics and pathogenesis of the disease has led to many treatment approaches and decreased both morbidity and mortality.

**Historical Review**
- Sickle cell disease was known long before the medical profession recognized it in 1904 (red cells of a sick dental student from Grenada).
- James Herrick described red cell as “sickled shaped” in 1910.
- 1927: Hahn and Gillespie correlated sickling with low oxygen.
- 1940: Deoxygenated cell altered hemoglobin structure (Sherman).
- 1948: Janet Watson noted few sickle cell in newborns/fetal hemoglobin.
- 1948: Pauling and Itano noted sickle hemoglobin was different and SCD was first disorder related to a protein abnormality.

**Historical Review**
- 1956: Ingram and Hunt sequenced Hbg S (glutamic acid to valine) and thus predict SCD (first genetic disorder whose molecular basis was known).
- 1984: BMT cured the disease.
- The Human Genome.
Normal Vs. Sickle Red Cells

- **Normal**
  - Disc-Shaped
  - Deformable
  - Life span of 120 days

- **Sickle**
  - Sickle-Shaped
  - Rigid
  - Lives for 20 days or less

What Is Sickle Cell Disease?
- An inherited disease of red blood cells
- Affects hemoglobin
- Polymerization of hemoglobin leads to a cascade of effects decreasing blood flow
- Tissue hypoxia causes acute and chronic damage

Overview of Sickle Cell Disease
- SCD due to hemoglobin SS presenting with hemolytic anemia and vaso-occlusion.
- Affects 1 in 500 African Americans
- Hispanic (Caribbean, C.America and S. America) have 1 in 2000
- 8 % of African American with trait
- Endemic malaria
- Found worldwide
Historical Distribution of Hemoglobin Variants

Hemoglobin S
Hemoglobin C
Hemoglobin D
Hemoglobin E
Malarial Regions of Africa and Asia
Alpha thalassemia occurs in all these regions as well

Overview of Sickle Cell Disease
- 15% deaths by age 20
- Median male survival – 42; female 48
- 25-30 years less than average AA life expectancy
- Male / Female 1:1
- Symptoms at 6 months
- Hemoglobin SC, Sickle B-Thal and HPFH

Pathophysiology of SCD
- All sicklers have same genetic mutation
- Thymine substitutes for adenine in DNA of B-globin gene
- Valine replaces glutamic acid in position 6 of protein
- Recessive trait
- Final product of mutation is Hgb S

Why Do Cells Sickle?
- Glutamic acid is switched to valine
- Allows the polymerization of sickle hemoglobin when deoxygenated

Pathophysiology of SCD
- Long helical polymers form, causing red cell deformity
- Deformed sickle cells occlude vessels, cause vascular damage and ultimately end organ ischemia and damage
- Influence of fetal hemoglobin and oxygen extraction
- Hgb F: no polymers and decrease concentration of Hgb S
Hemolysis and Vaso-occlusion

**Hemolysis:**
The anemia in SCD is caused by red cell destruction, or hemolysis, and the degree of anemia varies widely between patients. The production of red cells by the bone marrow increases dramatically, but is unable to keep pace with the destruction.

**Vaso-occlusion:**
Occurs when the rigid sickle shaped cells fail to move through the small blood vessels, blocking local blood flow to a microscopic region of tissue. Amplified many times, these episodes produce tissue hypoxia. The result is pain, and often damage to organs.

Complications of Sickle Cell Disease

- Anemia associated with hemolysis, splenic sequestration and aplastic crisis
- Infections with encapsulated organisms (10-30% mortality)
- Acute Chest Syndrome (fluids and sedation)
- Vaso-occlusive / Pain crises / dactylitis
- Strokes in 11% of sicklers, TIA and silent infarcts

Clinical Presentation

- Fever / infection
- Chest pain
- Fatigue and anemia
- Headaches / weakness / sensation changes
- Priapism
- Abdominal and bone pain / muscle aches

Fever and Infection

- Fever > 38.5°C (101°F) is an EMERGENCY
- Basic laboratory evaluation:
  - CBC with differential and reticulocyte count, blood, urine, and throat cultures, urinalysis, chest x-ray
  - Parenteral broad-spectrum antibiotic (e.g. ceftriaxone) immediately after blood draw and before other procedures such as chest x-ray
  - Observe after antibiotics with repeat vital signs

Indications for hospitalization & continued IV antibiotics:

- Child appears ill
- Age < 1 year
- Any temperature > 40°C
- Laboratory values:
  - WBC > 30,000/µL or < 5,000/µL
  - Platelet < 100,000/µL
  - Hb < 5g/dL
- Other complications such as splenic sequestration or acute chest syndrome

Splenic Sequestration

- Hemoglobin SS
  - Incidence increased: 6 and 36 months
  - Overall incidence about 15%
- Hemoglobin SC
  - Incidence increased: 2 and 17 years
  - Mean age 8.9 years
  - Can occur in adolescence and adulthood
  - Incidence about 5%
Splenic Sequestration
- Sudden trapping of blood within the spleen
- Usually occurs in infants under 2 years of age with SS
- Spleen enlarged on physical exam, may not be associated with fever, pain, or other symptoms
- Hemoglobin more than 2 g/dL below baseline, often with relative thrombocytopenia
- Severe sequestration crisis can be fatal within a few hours.

Treatments For Splenic Sequestration
- Intravenous fluids
  - Maintain vascular volume
- Cautious blood transfusion
  - Treat anemia, sequestered blood can be released from spleen
- Spleen removal or splenectomy
  - If indicated

Health Maintenance
Special studies
- Brain: Transcranial doppler ultrasonography, MRI/MRA
- Lungs: Pulmonary function tests, Echo cardiogram for pulmonary hypertension
- Neurologic: Neuropsychological testing

Pulmonary complications in SCD
- Primary pathologic processes are infection, bone marrow infarction, fat emboli as well as rib and sternal infarcts and pulmonary edema
- ACS most common pulmonary problem

Acute Chest Syndrome
A leading cause of death in sickle cell disease
Clinically:
- Acute onset of fever, respiratory symptoms, new infiltrate on chest x-ray
Causes
- Infection
- Fat emboli
- Lung infarct
Treatment
- Hospitalize
- Antibiotics (broad spectrum plus macrolide)
- Oxygen
- Analgesics
- Bronchodilators
- Simple or exchange transfusion

Pulmonary hypertension
- Retrospective studies estimate prevalence of pulmonary hypertension in SCD patients to be 20-40%
- Hemolysis, chronic anemia and transfusion were predictive
- Prospective study: elevated TR jet velocity > 2.5 m/sec on ECHO in 30% of 62 children > 6 years with Hgb SS and SBT
- Risk factors: increase reticulocyte count,
- low O2 saturation and high platelets
- Right heart catheterization is now required for definitive diagnosis of pulmonary hypertension
Pulmonary hypertension
- Definitive diagnosis require right heart cath, but plasma level of brain natriuretic peptide (BNP) and six-minute walk test may help identify
- BNP > 160pg/ml was sensitive, specific and had positive predictive value in detecting pulmonary hypertension
- Supportive care with transfusions to maintain Hgb S < 20 % and Oxygen therapy
- Clinical trial with prostacyclin and agents to reduce PA pressure are needed
- Sildenafil stopped in July due to increased sickle cell crisis

Obstructive Sleep Apnea
- Upper airway obstruction during sleep due to adenoid and tonsillar enlargement
- 1/3 of SCD patients/ snoring
- Hypoxemia on sleep studies and improve with T & A
- Compliance poor with CPAP

Hydroxyurea to reduce red cell hemolysis may be of benefit.
- 10 children with elevated TRV on echo treated with HU decreased TRV, improved hemoglobin concentration and O2 saturation
- Survival decreased in children and adults with SCD and pulmonary hypertension, each 10mmHg rise in mPaP associated with 1.7-fold increase in mortality, median survival 26 months

Recurrent vascular and lung parenchymal insult are greatest risk for sickle cell chronic lung disease
- SCCLD develop as early as age 20, lung dysfunction can be rapid and death within 7 years
- Start with chest pain and mild reductions in FVC and TLC, progress to diffuse interstitial fibrosis and poor O2 saturation, finally to prolonged chest pain, severe pulmonary fibrosis, hypoxemia at rest and elevated pulmonary artery pressure at rest

Sickle Pain Is Unique: A Life-long Pain Experience

Doctors have the means at hand to relieve the suffering of millions of Americans. Why aren't they doing it?
**Pain Management**

- Morphine Sulfate now being used in higher dosing IV, IT and as a nebulized agent
- Toradol
- Dilaudid
- Fentanyl patch
- Non-pharmacologic adjunctive therapy

**DEPENDENCE vs ADDICTION**

- **Physical dependence**
  - Physiological Problem
  - Expected response to chronic opioid administration
    - Characterized by onset of acute withdrawal syndrome upon cessation of opioid or administration of antagonist
    - Downward titration is necessary to prevent symptoms
      - Decrease dose 10-20% daily and step
  - Addiction
    - Psychological Problem
    - Behavior pattern of drug abuse
      - Craving, overwhelming involvement in obtaining drug, using it for other than pain control, using drug despite negative physical, social, legal, or psychological consequences

**Chronic Pain**

- Pain lasting >3 to 6 months
- Patients should receive comprehensive psychologic and clinical assessment
- Treatment
  - Analgesics
  - Hydroxyurea
  - TENS units
  - Relaxation techniques
  - Physical and occupational therapy

**Bone Disease Diagnosis and Treatment**

- Avascular necrosis of hips and shoulders
  - Index of suspicion
    - Persistent hip or shoulder pain
    - Plain film or MRI
- Treatment
  - Conservative
    - NSAID’s and 6 weeks of rest off affected limb
    - Physical therapy

**Screening AVN**

- Avascular Necrosis
  - Hip Films
  - Hip MRI
  - Grading of AVN
    - Grade I: MRI
    - Grade II: Film/MRI
    - Grade III: Film
    - Grade IV: Film
    - Grade V: Film
  - No grade for AVN of the shoulder
Strokes
- Leading cause of death in children and adults
- 0.6 to 0.76 per 100 patient years during first 20 years of life, mostly Hgb SS
- 300 times higher than children without SCD
- Ischemic strokes in children 2-9 years old

Stroke
Any acute neurologic symptom other than mild headache, even if transient, requires urgent evaluation.
- Historically 8 to 10% of children with SS
- “Silent Stroke” in 22% of children with hemoglobin SS

Treatment: Chronic transfusion therapy to maintain sickle hemoglobin at or below 30%

STOP 1 Trial
- 130 children, all > 200cm/sec on at least two studies
- Observation vs prophylactic transfusion (<30% Hgb S)
- Early termination with 1 to 10 infarction rate in transfusion group
- Also reduced risk of silent strokes
- TCD between age 2-4 is effective for screening stroke risk (AA Neurology)

Strokes
- Risk factors include prior TIA’s, low steady state Hemoglobin, ACS (recent or recurrent), elevated systolic BP
- TCD: time averaged mean velocity in large intracranial vessels
- > 170cm/sec worrisome
- >200 cm/sec high risk even before MRA lesions noted
Silent Strokes

- MRI/MRA study: 65 neurologically intact children with SCD age 1-6, 18 had silent infarcts (28%)
- Occlusion or stenosis of large intracranial arteries
- Hemiparesis, dysphasia, gait disturbance and change in level of consciousness replace by memory issues and poor school performance (cognitive changes)

Stroke

- Intracranial hemorrhage
  - More common in adults
- Sequela overt and "silent strokes"
  - Paralysis: overt stroke
  - Neuropsychologic changes: both overt and silent strokes
    - Visual-spatial impairment
    - Impaired memory
    - Poor impulse control

Stroke and Hydroxyurea

- Manipulation of fetal hemoglobin
- 35 patients with SCD and stroke and transfusions discontinued
- 42 months on Hydroxyurea, hgb 9.2g/dl, hgb F 19%, no iron overload.
- Seven recurrent stroke, 4 non compliant with hydroxyurea
- Rate of recurrence per 100 patient years with hydroxyurea and overlapping transfusion was favorable to chronic transfusion therapy alone
- Second study with MTD hydroxyurea and monitoring with TCD showed overall incidence of new strokes of 0.5 events per 100 patient years of observation
- Terminated by NHLBI after 14/41 SCD patient assigned to stop reverted to high stroke risk by TCD and two others had actual stroke
- TCD good for risk determination before and after transfusion therapy

Stopping transfusions?

- Treat for minimum 30 months with Hgb S <30 % for 20 months
- TCD normalizes
- No prior stroke or moderate arterial lesions on MRA was evaluated
- Terminated by NHLBI after 14/41 SCD patient assigned to stop reverted to high stroke risk by TCD and two others had actual stroke
- TCD good for risk determination before and after transfusion therapy
Treatment Options
- The Basics: Antibiotics, Pain meds, Hydration and Transfusions have changed
- New directions of therapy towards prevention, early detection and preventing organ damage
- Penicillin / Vaccines
- Newborn Screening and death risk
- Exchange transfusions for ACS, priapism and sequestration

Hydroxyurea stimulates fetal hemoglobin and decreases white cell counts
- Multicenter Study on Hydroxyurea (1992)
- Terminated early
- Sicklers with half as many pain crises
- Longer periods between crises
- Few ACS, less hospitalizations and less transfusions with little side effects

Bone Marrow Transplantation replaces defective cells
- HLA identical sibling
- GVHD and graft failure (prior transfusions)
- Limited sibling matches
- CURE!

Hematopoietic cell transplantation
- Potentially cure for sickle cell disease
- Clinical course variable
- Prognostic factors are lacking
- Advanced disease concerns
- Transplant related mortality

Hematopoietic Cell Transplantation
- Sibling donors <25%
- Siblings with Sickle trait acceptable
- Belgium studies: overall and DFS 96 and 89%
- Cytoxan/busulfan, no TBI vs non-myeloablative therapy
- Center for International Blood and Marrow Transplant Research 67 patient between 1989-2002
Hematopoietic Cell Transplantation

- Average age 10 years (2-27) stable or improved MRI of brain
- Linear growth improved
- 3 of 26 developed GVHD
- 81% bone marrow was source for stem cells
- Five year Overall and DFS were 97% and 85%
- Only 9 patients (13%) recurrence of SCD

Early Transplants better overall survival and DFS
- Lower rates of death, engraftment failure, mixed chimerism and relapse (7/36)
- Goal of alternative donors, non-myeloblastic conditioning and umbilical cord offer potential improvement

Hematopoietic Cell Transplantation

Treatment Options

- New and perhaps experimental approaches are many.
- Erythropoietin (EPO) stimulates red cell production and fetal hemoglobin synthesis (Livingston, 1994) delivered via adenovirus vector.
- Arginine butyrate stimulate fetal hemoglobin, side effects, IV and short half-life

Gene Therapy
- Proof exist that it is possible to correct genetic defects in the blood by correcting damaged RNA
- Correcting RNA will allow for the removal of the sickle defect from patients born with the disease
- How this can be accomplished is still very much experimental

Gene Therapy

Adolescents and Transition of Care

- Young adults (>20 years) with frequent pain crises at greatest risk for early death
- Barriers to care for young adults
  - Lack of adult SCD providers
  - Loss of medical coverage
  - Developmental (level of independence, denial of chronic illness)
  - Ineffective coping skills (passive versus active)

Adolescents and Transition of Care

- Develop explicit plan for transition
- Team approach- pediatric and adult providers, social work, school/vocational staff, support groups
- Plan gradual transition (start 1 year before)
- Continue communication between pediatric & adult providers after transition
Conclusions

- While our knowledge of the genetics of sickle cell disease is extensive, more is needed to reach our goal of curing this terrible disease.
- These are exciting times and the sky truly is the limit!!!