Sickle Cell Disease: Where are we?

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Outline

• Hunter-Gatherer to Settler
  – Pre-Malaria Era
• Malaria Selective Pressure
• Genetic Epidemiology
• Pathophysiology of SCD
• Morbidity and mortality patterns
• Contributions from Nigeria
• Nigerian SCD Network
• Priorities
Origins of Man - Hunter/Gatherer
(~10,000 BC)
Agricultural Revolution - Neolithic (3,000 – 500 BC)

Infections became endemic & transmission rate increased
Malaria

• Protozoal disease transmitted by the anopheles mosquito
• Prehistoric man suffered from the disease
• Probably originated in Africa and accompanied human migration to the Mediterranean, India and South East Asia
• Today about 500 million people are exposed and 2-3 million die annually
Malaria Transmission Rate

• Population density of hunter/gatherer so low that malarial parasites could not maintain the high endemicities and transmission rates that occur among high-density tropical agriculturalists

• It is also among the latter that the highest frequencies of Hb variants are found (Livingstone 1989)
  – Balanced polymorphism from advantage conferred by heterozygotes against malaria complications
King Tut, 14th Century Pharaoh

- Had osteonecrosis
- Walked with a cane
- Died at age of 19 years
- Believed to have SCD
Distribution of Malaria and HbS
Selective Effect of Malaria on the S Trait
INCREASED SICKLING OF PARASITISED ERYTHROCYTES AS MECHANISM OF RESISTANCE AGAINST MALARIA IN THE SICKLE-CELL TRAIT

Lucio Luzzatto, E.S. Nwachuku-Jarrett, S. Reddy

Severe Malarial Infection in a Patient with Sickle-cell Anaemia
Adelola Adeloye, L. Luzzatto, G. M. Edington


Abnormal haemoglobins in the Sudan savanna of Nigeria. I. Prevalence of haemoglobins and relationships between sickle cell trait, malaria and survival.

Fleming AF, Storey J, Molineaux L, Iroko EA, Attai ED.
Williams T, Obaro S. Trends in Parasitology 2011
Multicentric Origin on $\beta^S$ Mutation

Nagel & Ranney, 1990
Pathophysiology of Sickle Cell Disease (Steinberg 1999)
Secondary organ damage

- Silent infarction
- Elevated tricuspid regurgitation
- Cardiomyopathy
- Priapism
- Osteonecrosis
- Ulcers
- Retinopathy
- Functional asplenia
- Iron overload
- Cholelithiasis
- Renal failure
- Microalbuminuria
Cause of death
children versus adults

<20 years of age, n = 46

≥20 years of age, n = 186

Powars et al Medicine 2005
Mortality in African SCD Patients

- Garki study\textsuperscript{10}
- Kilifi study\textsuperscript{41}
- Barclay (1971)\textsuperscript{46}

Increases in Life Expectancies of Patients With Sickle Cell Disease

Source: National Heart, Lung, and Blood Institute.
Increases in Life Expectancy of Patients with Sickle Cell Anemia in the U.S.
SCD is a Public Health Issue

• Enabling Act of parliament
  – National Policy
• Game Changers
  – Counseling & health education
  – Newborn screening
  – Penicillin prophylaxis
  – Hydroxyurea
  – Transcranial Doppler
    • Chronic transfusion to prevent stroke
Predictive Value of TCD in SCD Stroke

The graph shows the probability of remaining stroke-free over time for different TCD flow rates. The x-axis represents time in months, ranging from 0 to 35. The y-axis represents the probability of remaining stroke-free, ranging from 0.4 to 1.

- The blue line represents flow rates of < 170 cm/s (Normal).
- The blue line with dashes represents flow rates of 170–199 cm/s (Conditional).
- The red line represents flow rates of ≥ 200 cm/s (Abnormal).

The p-value is 0.0001, indicating a statistically significant difference in the probability of remaining stroke-free between the different flow rate categories.

Hydroxyurea
suggested modes of action

- HbF induction
- Cell count reduction
- Reduces cell adhesion
- Reduces haemolysis
- Induces NO release

Ware R. Blood. 2010
Hydroxyurea overall survival

Patients receiving hydroxyurea (n = 131)
10-year survival: 86%
p = 0.001

Patients not receiving hydroxyurea (n = 199)
10-year survival: 68%

Voskaridou et al. Blood 2010
Hydroxyurea response per genotype

Reduction in mortality was observed across HbSS and HbSβ₀ groups, but not in HbSβ⁺ patients.
Transfusion in SCD
increasing use...

- 41% of all patients received ≥ blood transfusions in 10 years
- Increasing % of transfused patients (from 17.8% to 23.9%)
- Increase due to exchange transfusions and acute pain treatment
- More “indications”: renal failure, ulcers, lung disease, priapism

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Recent publications from Nigeria
Prevalence of Sensorineural Hearing Loss In Nigerian SCD Patients

  - Studied children 6 – 15 years old; found prevalence of 21.5%

  - Studied children 6 – 19 years; found prevalence of 13.4%

- Aderibigbe, Ologe and Oyejola *J Natl Med Assoc* 2005; 97:1135
  - Studied adult patients 16 – 48 years; reported prevalence of 4.3%

  - Studied children 4 – 15 years; found a prevalence of 3.8%
Stroke and Neurological Problems

  – In a 15-year review of children with stroke in a teaching hospital, among 31 case, 27 (87%) had SCD, all Hb SS with 1 HbSC
  – This was a frequency of 5.4% of patients being followed in the hospital
  – The mean age at first stroke was 6.8 years
  – Of the 7 patients that had CT, 5 had infarction and 2 hemorrhage

• Kehinde et al J Natl Med Ass 2008
  – Questionnaire study of ~600 SCD patients and equal number of controls
    • 76% of SCD and 32% of controls had neurological manifestations
      – Among children: stroke, febrile seizures and headaches
      – Among adolescents and adults: paraplegia, epileptic seizures and sensory neuropathies
Proteinuria among Adult Nigerian SCD Patients

- studied 200 adult patients
  - Serum electrolytes/urea and eGFR in addition to 24 hour urine for proteinuria
  - 28% had significant proteinuria
    - Among the males with proteinuria, 50% had chronic renal disease
Avascular Necrosis

• Akinyoola et al Nig Postgrad Med J 2007
  – Retrospective study of 416 patients in Ile-Ife
  – 340 SS and 76 SC
  – 66(15.9%) had clinical and radiological evidence of AVNFH
    • 80% were SS
    • 60.3% presented with stage IV disease
Gallstones in Nigerian SCD Patients

- Bojuwoye et al Trop Doc 2006
  - 100 patients aged 15 – 50 years
  - Overall prevalence of 28%
  - 15 -19 years 8%
  - 20 – 24 years 14%
  - 25 – 29 years 3%
  - 30 – 34 years 2%
  - 35 – >39 years 1%
    - +ve association with BMI, SS crises, reticulocyte, serum total bilirubin, AST and ALT

- Durosinmi et al Afr J Med Sci
  - Among adults (18 – 50yrs), found prevalence of 24.2%

- Nzeh and Adedoyin Ped Radiol 1989
  - Among children (2-16 years), found a prevalence of 4.8%
Nigerian SCD Network

• Established in 2010

• Brings together Nigerian SCD experts both in the country and in the Diaspora including physicians, scientists, social workers, NGOs and patients (currently ~120 members)
Objectives

- Document activities of SCD-related groups in the country
- Uniform management and counseling guidelines
- Pursue the establishment of a national SCD policy
- Liaise with internal and external funding agencies to promote training, research and care
- Establish partnerships and collaborations with external centers of excellence (within and outside Africa)
- Organize workshops and conferences within the country
Working Groups

• Education, Guidelines and Protocols
• National SCD Policy
• Research (Infections, Hydroxyurea, Natural History, Phenotypic characteristics/diversity)
• Newborn Screening
• Finance and Publicity
Achievements

• National policy on non-communicable diseases (NCD) - 2010
  – Incorporating SCD policy
• Position paper presented by the Nigerian President at the 2011 UN Summit on NCDs
• Informational, educational and counseling (IEC) materials and management guidelines for SCD have been produced
• Advocacy for the provision of pneumococcal vaccines for children under the EPI
• Adaptation of the NIH parents’ handbook for Nigeria
• Registry of dedicated SCD clinics in the country
• Pilot newborn screening schemes have been established in several states of the country
• Six model comprehensive SCD centers are being established in the country by the Federal Government (Lagos, Abakiliki, Keffi, Kebbi, Gombe, Bayelsa)
• A comprehensive Bill for an Act for the Prevention, Control and Management of SCD is now before the National Assembly.
Collaborations

• Several partnerships are already active in different parts of the country involved with research and other projects including the following:
  – Sickle cell cohort study
  – Infection surveillance (Michigan State University)
  – Pilot newborn screening programs (King’s and Guy’s Hospitals, London, University of Chicago, Connecticut State Public Health Department and US Association of Public Health Laboratories,)
  – Genomic studies (H3Africa, African Pharmacogenomics network, Sickle CHARTA)
  – Educational grants (FIOCRUZ Foundation, Bahia, Brazil)
• Close contact with the Global SCD Network
Training
Counselling
Blood sampling
Dedicated SCD Clinics/Centers in Nigeria
### Table 1. Characteristics of Clinics and Common Practices

<table>
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<th>No.</th>
<th>Clinic*</th>
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<th>Adult/Peds</th>
<th>~No. of patients</th>
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<th>Database (Y/N)</th>
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<th>Penicillin (Y/N)</th>
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**Table 2. Facilities Available in the Different Clinics/Hospitals**

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Immediate Priorities

• Capacity building
  – Training and updating physicians
    • Workshops and conferences
    • MSc (UCL), Masters & Doctorates (Brazil)
  – Laboratory technicians
  – Counselors

• Data collection
  – Streamlined and uniform data collection in all center
  – Central point

• Liaison with FMOH, State governments and other stakeholders
  – Policy
  – Guidelines and management protocols
  – Act of parliament
ANPA Potential Contributions

• Act as SCD advocates
  – Government, parliament, NGOs etc
• Sponsorships
  – Training at different levels
  – Workshops
  – Conferences
• Expert consultations and teaching
• Donation of equipment
  – HPLC
  – TCD
  – Computers

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Thank you