SICKLE CELL DISEASE CARRIER SCREENING
Briefing Paper Workgroup Update
SACHDNC September 16, 2010 – Washington, DC

Briefing Paper Purpose

- Apprise Secretary of HHS of new rules and practices concerning screening of college athletes for Sickle Cell Trait(1)
- Discuss the impact of the policies and practices related to SCT screening of college athletes on the pubic health system
- Recommend appropriate responses and actions by HHS

1. The term Sickle Cell Trait (SCT) to be used throughout the report/recommendations

Workgroup Members and Chairs

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Briefing Book Organization

Section 1: Introduction and Background

Section 2: Research findings and reports on Health Outcomes of Sickle Cell Trait

Section 3: Impact of the Sickle Cell Trait Screening Rule of the National Collegiate Athletic Association on affected populations, public health, health care systems, and other stakeholders.

Section 4: Recommendations of SACHDNC to the Secretary, U.S. Department of Health and Human Services on Screening of Student Athletes for Sickle Cell Trait

Topics Covered in Briefing Paper

- National and global prevalence of Sickle Cell Trait (SCT)
- Effects of SCT on health
- Unexpected deaths in athletes and military recruits with SCT
- Recommendations of athletic associations on screening athletes for SCT
- General issues related to screening people for SCT
- Recommendations of the Committee

Background: Prevalence and Global Distribution

Worldwide > 300 million people with SCT

- Highest Global Prevalence Rates
  - 15% Sub-Saharan Africa (800 million total population)
  - 0-44% India - pockets in various tribal groups
  - 1-20% Middle East
  - 1-10% Caribbean
- USA: 1.31% in newborns

Background: Prevalence and Global Distribution

Worldwide > 300 million people with SCT

- Countries with High Numbers of SCT persons
  - Nigeria: > 30 million
  - India > 20 million
  - Congo, DR > 16 million
  - Brazil > 9 million
  - Tanzania > 6 million
  - Kenya > 5 million
  - Ghana > 4 million
  - Saudi Arabia > 4 million
  - USA > 4 million

Major impact of SCT on public health, military, or sports, if present, not likely to be missed in these countries

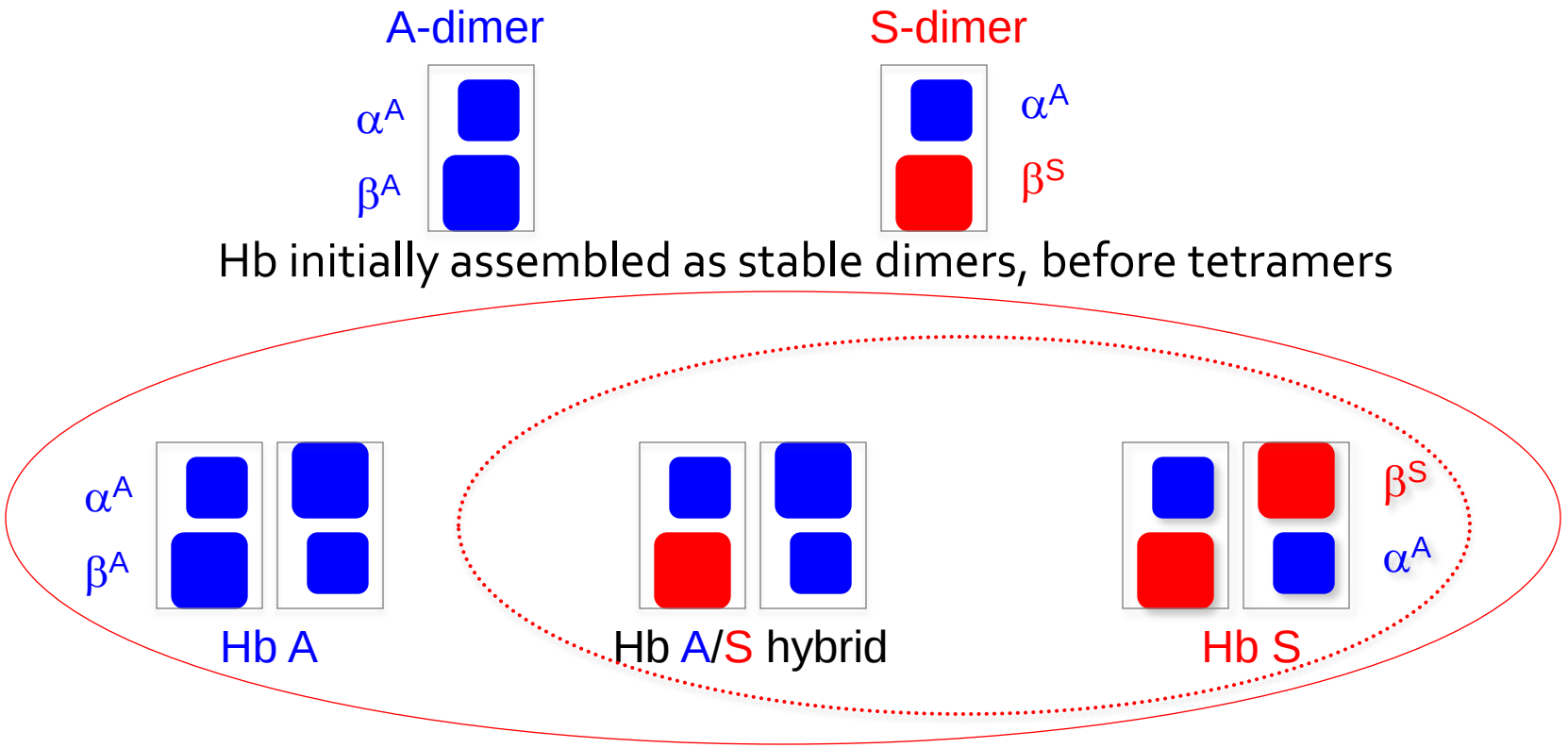
Background: Definition of Sickle Cell Trait

- Globin composition of Hb A: $\alpha^{A}_{2}\beta^{A}_{2}$

  Hb S: $\alpha^{A}_{2}\beta^{S}_{2}$

- We inherit one β–globin gene from each parent
- Inheritance of normal β^{A}-(hemo)globin gene from one parent and β^{S}- sickle (hemo)globin gene from the other
- Each red cell in a person with sickle cell trait contains both hemoglobins A and S, always more A than S, hence the designation AS
- "Excess" Hb A inhibits Hb S polymerization and red cell sickling, under normal physiologic conditions

Pathology of Sickle Cell Trait
Assembly of Globin Tetramers



- Hb S and Hb A/S hybrid polymerize on deoxygenation
- "Excess" Hb A inhibits Hb S and Hb A/S polymerization and red cell sickling

Pathology of Sickle Cell Trait
In vitro

- Inducible polymerization and red cell sickling
  - low O2, low pH
  - bases for sickling and solubility screening tests
- Altered Filterability
  - Failure in leukoreduction filtration in CPD
- Increased whole blood viscosity
- Increased red cell rigidity
- AS cells infected with malaria have increased splenic clearance and may have enhanced sickling potential

Pathology of Sickle Cell Trait
In vivo

- Sickling inducible experimentally by strenuous exercise under ambient high temperature and water deprivation
- No hemolysis, no anemia, no reticulocytosis
- Normal red cell morphology; no sickle forms on peripheral smear
- No pattern of acute vasoocclusive events typical of sickle cell disease
- Hyposthenuria – thought to be caused by loss of renal concentrating ability due to loss of vasa rectae in high osmolar, low pH, renal medulla

Pathology of Sickle Cell Trait

The U.S. Veterans Study, 1979 *(Heller, et al., NEJM,1979)*

65,154 consecutively admitted, black male patients in 13 VA hospitals

- Overall frequency of SCT was 7.8 per cent
- Inpatient records of 24,616: 18,294 with no abnormal Hb, 4,900 AS, and, 1,422 AC - reviewed.

SCT had no effect on:

- average age at hospitalization or death
- overall mortality
- length of hospitalization on medical and surgical wards, or,
- frequency of any diagnosis

SCT was positively associated with:

- essential hematuria
- pulmonary embolism (1.5 % of "AA" vs. 2.2 % of AS, $p < 0.001$)

Pathology of Sickle Cell Trait
Clinical manifestations

A. Renal
   - Urine concentrating defect (hyposthenuria)
   - Gross (unilateral) hematuria
   - Asymptomatic bacteruria (pregnancy)
   - Pyelonephritis
   - Autosomal dominant polycystic kidney disease
   - Renal medullary carcinoma

B. Venous thromboembolism
   - GATE study (Austin, et al., Blood, 2007) confirmed VA Study
   - SCD associated more with arterial thrombosis

C. Splenic infarction at high altitude

D. Exercise / Heat related sudden death

Pathology of Sickle Cell Trait

Exercise / Heat-related Sudden Death: Military

Kark Report, NEJM, 1987

All deaths among 2.1 million enlisted recruits during basic training in the U.S. Armed Forces in 1977 to 1981 were classified from autopsy and clinical records as: non-sudden - sudden explained - unexplained by preexisting disease.

Recruits	AS	No Hb S
"Black"	37,300	429,000
"Non-Black"	1,300	1,620,000

Total no. Exercise-Related Deaths: 41

50% from Exertional Heat Illness (EHI); 50% idiopathic sudden death. Rhabdomyolysis predominant form of EHI.

Pathology of Sickle Cell Trait

Exercise / Heat-related Sudden Death: *Military*

Kark Report, NEJM, 1987

Death / 100,000	"Black" AS	"Non-Black" AS	"Black" no Hb S	Non-Black no Hb S
Sudden unexplained	32.2 (12/37,300)	0 (0/1,300)	1.2 (5/429,000)	0.7 (1/1,620,000)
Sudden explained	2.7	0	1.2	0.5
Non-sudden	0	0	0.7	1.1

Relative risk of Sudden Death, AS vs. no Hb S:

"Blacks" 27.6 (95% CI 9-100; P < 0.001);

All 39.8 (95% CI 17-90; P < 0.001).

Pathology of Sickle Cell Trait

Exercise / Heat-related Sudden Death: Military

Kark, Follow-up Study: Prevention of Heat Illness (1)

Intervention:

Stricter rules for prevention of EHI were instituted including

- direct observation that recruits drank the amount of water recommended, and,
- wet bulb black globe temperature index measured every 30-60 minutes.

Kark JA, et al : Prevention of Exertional Heat Illness protects recruits with sickle cell trait from exercise-related death. SRGL, Sickle Cell Disease Program, NIH web site, Dec 16, 1999 (abstr). Cited at: http://sickle.bwh.harvard.edu/sickle_trait.html

Pathology of Sickle Cell Trait

Exercise / Heat-related Sudden Death: Military

Kark, Follow-up Study: Prevention of Heat Illness (2)

Participating centers trained 2.3 million recruits (40,000 with AS)

Deaths: AS recruits: Predicted - 15; Actual - 0

non-AS: Predicted - 19; Actual - 11

Non-participating centers trained 1.2 million recruits:

Deaths: No significant difference, predicted vs. observed (14 each), regardless of Hb type

Kark JA, et al : Prevention of Exertional Heat Illness protects recruits with sickle cell trait from exercise-related death. SRGL, Sickle Cell Disease Program, NIH web site, Dec 16, 1999 (abstr). Cited at: http://sickle.bwh.harvard.edu/sickle_trait.html

Pathology of Sickle Cell Trait
Exercise / Heat-related Sudden Death: Sports

- Single cases mostly reported in mass media since 1960s
- Basis of hemoglobin diagnosis usually unclear
- Association of sickling usually based on autopsy finding of sickled red cells in tissues
- Most cases suggest heat-related illness and rhabdomyolysis, similar to cases in military recruits
- College football most common sport involved
- Events typically in pre-season or off season training drills, many on first day
- Unlike military, no large epidemiologic study; no trial of simple interventions to reduce risk of heat-related illness

Pathology of Sickle Cell Trait
Participation in Competitive Sports

Point: Counterpoint

Sickle cell trait should/should not be considered asymptomatic and as a benign condition during physical activity

Point:
Daniel Le Gallais, et al.: *J Appl Physiol 103: 2137–2141, 2007*

Counterpoint:

Philippe Connes, et al.: *J Appl Physiol 103:2138-2140, 2007.*

Larger studies support Point; small or anecdotal cases support Counterpoint.

NCAA and Sickle Cell Trait
Case of Lloyd II

Index Case:

- Dale Lloyd II, a former football student-athlete at Rice University, 19, collapsed after 16, 100 yd sprints, on Sep 24, 2006
- died one day later

- Autopsy: death caused by "acute exertional rhabdomyoloysis secondary to sickle cell trait."

- Lloyd did not know he had sickle cell trait

- Family sued Rice, former coach Todd Graham, the NCAA and two nutritional supplement companies for "wrongful death"

NCAA and Sickle Cell Trait
Case of Lloyd II: NCAA Response (1/2)

As part resolution Lloyd family, the NCAA agrees to:

- Amend its Sports Medicine Handbook Guideline 3c to state that while Sickle Cell Trait screening is normally performed on all U.S. babies at birth, some student-athletes may not know if they have the trait.

- Donate $50,000 to the Sickle Cell Disease Association of America in the name of Dale Lloyd II, to provide awareness, education and screening for Sickle Cell Trait in the athletic population.

NCAA and Sickle Cell Trait
Case of Lloyd II: NCAA Response (2/2)

- Contribute $10,000 to the Dale Lloyd II Scholarship Fund.
- Prepare an educational video about Sickle Cell Trait to appear on the NCAA website and make it available to member schools.
- Stress a point of emphasis on the Sports Medicine Handbook Guideline 3c in regular preseason communication with media prior to the 2009 football season and in the football rules book.

Current NCAA Rule

April 2010: Division I Legislative Council Rule

- Division 1 student-athletes
  - must be tested for sickle cell trait,
  - show proof of a prior test, or,
  - sign waiver releasing an institution from liability if they decline to be tested.
- Rule to take effect 2010-2011 academic year
- NCAA rule follows recommendation of National Athletic Trainers' Association (NATA) that "institutions should carefully weigh the decision to screen"

NATA Training Guidelines (1/2)
The Athlete with Sickle Cell Trait

1) Slow build up; paced progressions, longer periods of rest and recovery between repetitions.

2) Preseason and year-round strength and conditioning; exclude from mile runs, serial sprints, etc.

3) Cease activity with onset of symptoms

4) Set own pace.

NATA Training Guidelines (2/2)
The Athlete with Sickle Cell Trait

5) Adjust work/rest cycles for environmental heat stress

b. Emphasize hydration

c. Control asthma

d. No workout if an athlete with sickle trait is ill

e. Watch closely the athlete with SCT who is new to altitude. Modify training, and have supplemental oxygen available

6) Educate and encourages athletes with sickle cell trait to report any symptoms immediately

Screening College Athletes for SCT
Social and Ethical Issues Discussed

1. Impact on Newborn Screening Programs
2. Choice screening tests
3. Need for proper counseling pre and post-testing
4. Privacy of health information (HIPAA)
5. Inadequacy of athletic departments to provide proper management of screening and counseling
6. Discrimination based on Genetic Information (GINA)

SACHDNC Recommendations (1/3)

1. All individuals should have the opportunity to find out their risk for various medical disorders, including their carrier status for genetic conditions such as sickle cell disease.

2. Genetic testing should not be a pre-requisite for participation in sports.

1. Evaluation and testing for sickle cell disease and other genetic conditions should take place within the individual's medical home. That evaluation should include counseling regarding the implications of the information for the individual and assurance of the privacy of genetic information.

SACHDNC Recommendations (2/3)

4. As part of the individual's medical evaluation for participation in organized sports, all potential athletes should be given education on safe practices for prevention of exercise and heat related illnesses.

5. Athletic programs should apply universally, simple measures successfully used to prevent exercise and heat-related death in military recruits.

SACHDNC Recommendations (3/ 3)

6. The Secretary of Health and Human Services, instruct SACHDNC to work with the SCDAA, relevant federal agencies, athletic associations, community based and health care professional organizations to develop guidelines and educational resources about screening for sickle cell trait in all persons, including athletes.

7. The National Institutes of Health and the Centers for Disease Control and Prevention conduct and support research to ascertain if some athletes with sickle cell trait are at increased risk of exercise-related sudden death.

Relevant activities

- Framing the Research Agenda for Sickle Cell Trait meeting, June 3-4, 2010 (NIH)
- Bonham VL, Dover GJ, and Brody LC: Screening Student Athletes for Sickle Cell Trait — A Social and Clinical Experiment. N ENGL J MED 363;11 NEJM.ORG SEPTEMBER 9, 2010, 997
- SCDAA Annual Convention, September 21-24, 2010: Session devoted to Sickle Cell Trait