Sickle Cell Trait and Its Controversies

3rd Annual Sickle Cell Disease Symposium
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Shrewsbury, MA

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Chief Medical Officer (2008 – 2012)
Sickle Cell Disease Association of America (SCDAA)
Controversy & Confusion
Sickle Cell Trait Misinformation

- Screening
- Insurance Injustice
- Social Humiliation
- Sports Ban
- Clinical Mismanagement
- Employment Exclusion
- Selective Abortion
- Coroner's truth?
Highly Quoted Literature

- Elliott Vichinsky: “Renal medullary carcinoma is a rare and aggressive tumor that is seen almost exclusively in young patients with sickle cell trait”

- Charis Kepron, Gino Somers, Michael Pollanen: “Sickle Cell Trait Mimicking Multiple Inflicted Injuries in a 5-Year-Old Boy”

- Nigel Key, Vimal Derebail: “During exercise, Sickle Cell Trait appears to be a risk factor for sudden death and rhabdomyolysis, particularly when the exercise is intense, and is performed at high altitude"

- Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong, Y: “Complications associated with sickle cell trait: a brief narrative review”

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Sickle Cell Trait

- Hb AS genotype.
  Hb S <50%  Hb A >50%

- Normal CBC with no anemia, hemolysis undetectable

- Microscopic sickling significant in the loops of Henle of the renal medulla, occasionally in the spleen, and in the drainage of vitreous humor post-trauma

- Reversible sickling is detectable and increases during exercise

- Large population studies show normal survival and slight increased admission for hematuria
Formation of Deoxygenated Hb S Polymers

- Deoxygenated Hb S polymer forms more rapidly with hypoxemia, high temperature, high 2,3 BPG

- High risk for specific sites: arterioles in the renal papillae, vessels of the spleen
Clinical Complications Proven to Be Associated with Sickle Cell Trait

- Age-related loss of maximal urinary concentration, episodic hematuria, mild increase in UTI of pregnancy
- Altitude & exercise related splenic infarction
- Traumatic hyphema
- Renal medullary carcinoma
- ? Reports of increased Venous Thromboembolism (VTE)
  Heller ’73, Austin ’07
- Unexpected exercise-related death in recruits and young athletes
What are the risks of having sickle cell trait?

Splenic Infarction - a risk for organ damage

Ryan Clark who has Sickle Cell Trait loss both his spleen and gallbladder when he played at the the Denver Broncos's 5,280-foot-high Sports Authority Field
What are the risks of having sickle cell trait?

Eye problems

- Hyphema - collection of blood in the eye
- Glaucoma
What are the risks of having sickle cell trait?

Kidney/Urinary Tract problems

- Isothenurias with loss of maximal renal concentrating ability (dilute urine)
- Hematuria (blood in urine) secondary to renal papillary necrosis
- Renal medullary carcinoma in young people (ages 11 to 39 years)
- Bacteruria (urinary tract infection) in women
4 million with Sickle Cell Trait in the US
300 million Worldwide

Same Genetic Mutation, Different Genetic Disease Phenotype

By: Ingrid Lobo, Ph.D. (Write Science Right) © 2008 Nature Education
Citation: Lobo, I. (2008) Same genetic mutation, different genetic disease phenotype. Nature Education 1(1)

Three individuals carry the same disease-causing mutation; two suffer from the disease but exhibit different symptoms, while the third is completely unaffected. Why?

- Why predominately strenuous exercise?
- Why predominately football?

- Modifier genes
- Environmental factors
- Allelic variation
- Complex genetic and environmental interactions
Exercise Induced Heat Illness and Death
Hemoglobin S and Rates of Exercise-Related Death Unexplained by Preexisting Disease – Military Recruits

<table>
<thead>
<tr>
<th>Black Recruits*</th>
<th>with Hb AS</th>
<th>without Hb S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>37,300</td>
<td>429,000</td>
</tr>
<tr>
<td>Rate/10^5 p*yrs</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>227</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Relative Risk = 30

(95% CI = 11 to 84) (p-value <10^-6)

Advice to People with SCT

- After becoming well conditioned, risk of unexpected exercise-related death is much less, but still significant.

- The same precautions should be taken to avoid heroic effort, to remain conditioned for any task, and to follow sensible procedures to minimize risk of Exertional Heat Illness (EHI) at all times.

John Kark, MD
The NCAA’s Mandatory Policy
What are the risks of having sickle cell trait?

Heat related illness

- Environment-based work-rest cycles
- Heat acclimation monitoring
- Guidelines for hydration
- Rapid detection of and treatment for heat illness
- June 2009 - NCAA Committee on Competitive Safeguards and Medical Aspects of Sports adopted recommendation that its member colleges and universities test student athletes to confirm their SCT status.

- April 2010 – NCAA Division II Legislative Council decided that effective from the 2010-2011 academic year, all incoming Division I student athletes must be tested for SCT, show proof of a prior test or sign a waiver releasing the institution from liability if they decline to be tested.
Genetic Information is Private – Right?
- Protection of the rights of the individual
- Privacy
- Protection against actions of a discriminatory nature
- Stigmatization
- Prevention from participation in competitive sports
- Families are not able to obtain newborn screening results
- Student athlete born before newborn screening implemented
GENETIC INFORMATION IS CONFIDENTIAL?

Title I of the Genetic Information Nondiscrimination Act (GINA) of 2008, prohibits genetic discrimination in Health Insurance

Illegal for health insurance providers to use or require genetic information to make decisions about a person's insurance eligibility or coverage.
GENETIC INFORMATION IS CONFIDENTIAL?

Title II of the Genetic Information Nondiscrimination Act of 2008 (GINA), prohibits genetic information discrimination in employment

Illegal to discriminate against employees or applicants because of genetic information.
GENETIC INFORMATION IS CONFIDENTIAL?

Don’t alarm but cautiously explain:

• Insurers have denied people health insurance for having sickle cell trait
  - What are your state’s pre-existing condition laws?
  - Individual insurance policies carry the highest risk of denial

• Are there employers in your state who have denied people jobs because of having sickle cell trait or other genetic conditions?
  - Small employers carry the highest risk for employment barriers
Where are the Newborn Screening Results
WHO SHOULD BE SCREENED FOR SICKLE CELL TRAIT OUTSIDE OF NEWBORN SCREENING?

Weren’t You Screened as a Newborn?

Rescreening & Cost

Current newborn screening infrastructure does not maintain newborn sickle cell trait screening results that can be readily accessed on a need to know basis.
WHO SHOULD KNOW IF THEY HAVE SICKLE CELL TRAIT?

Athletes

Recruits

Everyone
WHO SHOULD BE SCREENED FOR SICKLE CELL TRAIT OUTSIDE OF NEWBORN SCREENING?

• All expectant couples and those planning to have children should be offered the option to test for gene mutations that cause sickle cell disease

• People with a family history of sickle cell disease

• People with a family history of thalassemia

• People with a family history of sickle cell trait
Medical Societies
ASH Policy

ASH does not support testing or disclosure of sickle cell trait status as a prerequisite for participation in athletic activities. ASH believes that current scientific evidence does not justify this requirement. It is also not consistent with good medical practice or established principles of public health ethics. Screening for sickle cell trait should be voluntary and should take place in a setting that ensures privacy and is performed by a knowledgeable provider who is able to offer comprehensive counseling.

ASH recommends the implementation of universal interventions to reduce exertion-related injuries and deaths, since this approach can be effective for all athletes irrespective of their sickle cell status. Universal interventions are used successfully by organizations like the U.S. Army and the Brazilian military. Until the NCAA requires universal interventions, student athletes remain at risk for suffering from significant heat stress/exertion-related injury or death. Participation in athletics can be made safer with these measures, thereby rendering screening for and disclosure of sickle cell trait status unnecessary.

ASH believes that the NCAA Division I policy, as currently written and implemented, has the potential to harm the student athlete and the larger community of individuals with sickle cell trait. The NCAA policy attributes risk imprecisely, obscures consideration of other relevant risk factors, fails to incorporate appropriate counseling, and could lead to stigmatization and racial discrimination.

ASH strongly supports increased biomedical and population-based research on sickle cell trait as it relates to exertion-related illness, as well as other clinical conditions. New knowledge derived from research should benefit individuals with sickle cell trait and help inform public policy.
PRESS RELEASE
American Medical Society for Sports Medicine
For Immediate Release Jan 26, 2012

AMSSM Statement on Sickle Cell Trait

FOR IMMEDIATE RELEASE (Jan. 26, 2012)

LEAWOOD, Kan. - On January 26, 2012, the American Society of Hematology (ASH) released a position statement calling for the reversal of the 2010 NCAA policy for mandatory screening of all Division I athletes for sickle cell trait (SCT).

SCT has been associated with cases of exertional sudden death in NCAA athletes, in particular in African American football players. While rare, these tragic deaths appear to be largely preventable through education, implementation of safety guidance on heat acclimatization and hydration, adherence to appropriate strength and conditioning programs, and effective emergency action planning. Team physicians play a key role in educating athletes, coaches, and college medical staff regarding safety precautions in athletes with SCT, as well as other conditions that may affect safe participation.

The AMSSM notes that the NCAA policy provides all athletes with education on SCT as well as the option to opt out of the process of screening, without any penalty to participation. The AMSSM also agrees with ASH in supporting universal preventive measures to make participation in sports safer for all athletes. We strongly support increased laboratory and clinical research to promote evidence-based practice in this complex and controversial area.

The AMSSM looks forward to working with both the NCAA and ASH on this important issue. As a leading sports medicine organization, AMSSM is fully committed to protecting the health and safety of college athletes.
The Unintended Consequences of the NCAA Sickle Cell Screening Policy

Posted by Matt Wood on May 8, 2012 in Ethics, sports medicine

By Matt Wood

In 2006, Dale Lloyd II, a 19-year-old freshman football player at Rice University, collapsed during a conditioning workout and died the next day. His death was linked to complications from sickle cell trait, or having one of the genes that causes sickle cell disease.

In two separate surveys published in *Pediatrics* and the *Clinical Journal of Sports Medicine*, Ross and her colleagues asked pediatricians and sports medicine providers about the NCAA policy. More than 70 percent of both groups supported targeted screening for African American athletes in all NCAA divisions. At the same time, a majority of both groups also expressed concerns about discrimination against athletes with sickle cell trait. These answers seem to contradict each other. If providers were concerned about discrimination they wouldn’t support targeted screening versus screening all athletes, or they wouldn’t support the screening policy at all.
Sickle Cell Trait Screening in Athletes: Pediatricians’ Attitudes and Concerns
Joy Koopmans, Lucy A. Cox, Holly Benjamin, Ellen Wright Clayton, and Lainie Friedman Ross

...National Collegiate Athletic Association (NCAA) adopted a recommendation that all Division...respondents about their awareness of the NCAA policy and whether they supported universal...white. Almost half were aware of the NCAA policy, with highest awareness in members...
Controversy & Confusion
ADVOCACY

www.sicklecelldisease.org

The Nation’s Primary Advocacy Organization for Sickle Cell Disease
Screening athletes for sickle cell trait and subjecting carriers to alternative training regimens, as recommended by the National Collegiate Athletic Association (NCAA) and National Athletes Trainer’s Association (NATA), has not been demonstrated to reduce the incidence of training-related deaths. Nevertheless this approach carries great risk of stigmatization and discrimination against athletes with sickle cell trait. The NCAA mandate for sickle trait screening does not provide adequate assurance of the privacy of genetic information nor protection from the discriminatory use of such information.
Persons with sickle cell trait have been shown to be more vulnerable than those without trait to heat stroke and muscle breakdown (rhabdomyolysis) when subjected to strenuous forced exercise in military training under unfavorable environmental conditions. Follow up studies demonstrated that the incidence of this problem can be reduced in all recruits by avoiding dehydration and overheating during training. Although similar studies have not been conducted in athletes, and exercise-induced rhabdomyolysis occurs in persons without sickle cell trait, concern has been raised as to the vulnerability of athletes with sickle cell trait to rhabdomyolysis during strenuous conditioning regimens. Deaths of healthy young athletes during conditioning are extremely rare, and are associated with sickle cell trait in less than half of the cases. Moreover, in many cases, such deaths are attributed sickle cell trait because of the presence of sickled cells in tissues at autopsy, even though the occurrence of post-mortem sickling is well documented in sickle cell trait and expected with death from any cause.
The SCDA supports the implementation of universal, safe training guidelines for all athletes, and to rigorously educate and improve the capacity of athletic coaches and trainers to recognize signs and symptoms of heat related illness and to provide medical care to athletes who become ill or injured under their supervision. Given the lack of scientific evidence that substantiates a significant correlation between sickle cell trait in athletes and training related sudden death, SCDA does not support screening of athletes for sickle cell trait as a means to reduce heat related illness or death in athletes who are carriers. The commonsense precautions recommended by NATA -- building up exercise intensity gradually, responding to athletes reporting symptoms of physical distress, and avoiding overheating and dehydration -- if applied universally, would make athletic training safer for all and would obviate the need to identify carriers of the sickle cell gene in the athletic setting. Therefore, the need to identify athletes who are carriers of the sickle cell allele in the athletic setting is unwarranted.
Persons with sickle cell trait have been shown to be more vulnerable than those without trait to heat stroke and muscle breakdown (rhabdomyolysis) when subjected to strenuous forced exercise in military training under unfavorable environmental conditions. Follow up studies demonstrated that the incidence of this problem can be reduced in all recruits by avoiding dehydration and overheating during training. Although similar studies have not been conducted in athletes, and exercise-induced rhabdomyolysis occurs in persons without sickle cell trait, concern has been raised as to the vulnerability of athletes with sickle cell trait to rhabdomyolysis during strenuous conditioning regimens. Deaths of healthy young athletes during conditioning are extremely rare, and are associated with sickle cell trait in less than half of the cases. Moreover, in many cases, such deaths are attributed sickle cell trait because of the presence of sickled cells in tissues at autopsy, even though the occurrence of post-mortem sickling is well documented in sickle cell trait and expected with death from any cause.
National Athletic Trainer's Association (NATA) Precautions and Treatment

No sickle-trait athlete is ever disqualified, because simple precautions seem to suffice. For the athlete with sickle cell trait, the following guidelines should be adhered to:

• Build up slowly in training with paced progressions, allowing longer periods of rest and recovery between repetitions.

• Encourage participation in preseason strength and conditioning programs to enhance the preparedness of athletes for performance testing which should be sports-specific. Athletes with sickle cell trait should be excluded from participation in performance tests such as mile runs, serial sprints, etc., as several deaths have occurred from participation in this setting.

• Cessation of activity with onset of symptoms [muscle 'cramping', pain, swelling, weakness, tenderness; inability to "catch breath", fatigue.

• If sickle-trait athletes can set their own pace, they seem to do fine.

• All athletes should participate in a year-round, periodized strength and conditioning program that is consistent with individual needs, goals, abilities and sport-specific demands. Athletes with sickle cell trait who perform repetitive high-speed sprints and/or interval training that induces high levels of lactic acid should be allowed extended recovery between repetitions since this type of conditioning poses special risk to these athletes.
National Athletic Trainer's Association (NATA) Precautions and Treatment

• Ambient heat stress, dehydration, asthma, illness, and altitude predispose the athlete with sickle trait to an onset of crisis in physical exertion.

• Adjust work/rest cycles for environmental heat stress

• Emphasize hydration

• Control asthma

• No workout if an athlete with sickle trait is ill

• Watch closely the athlete with sickle cell trait who is new to altitude. Modify training and have supplemental oxygen available for competitions.

• Educate to create an environment that encourages athletes with sickle cell trait to report any symptoms immediately; any signs or symptoms such as fatigue, difficulty breathing, leg or low back pain, or leg or low back cramping in an athlete with sickle cell trait should be assumed to be sickling.

• In the event of a sickling collapse, treat it as a medical emergency by doing the following:
INDIVIDUAL COUNSELING AND EDUCATION

- Inform individuals of their rights to protection of genetic information
- Inform individuals at risk about family planning, possible health outcomes and participation in sports
- Refer individuals to appropriate health care provider(s)
- Educate individuals on how sickle cell disorders are acquired
- Educate individuals on the difference between sickle cell disease and sickle cell trait
- Educate individuals on appropriate test for sickle cell hemoglobins (i.e. hemoglobin electrophoresis)
- Educate individuals on the type of hemoglobins that can result in sickle cell disease
- Educate individuals on family planning options (i.e. invitro fertilization)
- Educate individuals on the recognition of symptoms of heat related problems