Sickle Cell in Athletes

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Education Objectives

- Review how sickle cell is inherited
- Review sickle cell pathology process
- Review screening and diagnostic tests for sickle cell disease and trait
- Review common symptoms seen in athletes and differentiate them from other processes
- Review management of sickle cell crisis
“Sickle Cell Trait is not a disease”

- Life expectancy is the same between sickle cell trait and unaffected individuals
- Calling it a disease potentially will
  - Affect the ability of 2.5 African Americans from getting life insurance, health insurance, hired
  - Impact the participation/livelihood of 6.7% of NFL players who are sickle cell trait positive
- But there does seem to be a risk for active individuals
  - This was first identified in military recruits
    - 28 times more likely to have an exercise related death (thankfully this is still a small number)
Let’s try to get some perspective

<table>
<thead>
<tr>
<th>Football Fatalities 2000-2008</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>High School</td>
</tr>
<tr>
<td>Direct</td>
</tr>
<tr>
<td>Indirect</td>
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</table>

- Direct – fatal head and neck injuries incurred during participation
- Indirect – fatal systemic failure as a result of exertion with participation (heat, cardiac, sickle cell)

ANNUAL SURVEY OF FOOTBALL INJURY RESEARCH 1931 – 2008 (NCCSI)

- Participation rates
  - ~ 1,500,000 high/middle school players/year
  - ~ 75,000 collegiate players/year (NCAA, NAIA, NJCAA)
Cause of Non-Traumatic Death
NCAA Football
All Divisions 2000-2009...

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Exertional Sickling Deaths in College Football

- 1974 Colo., ran 800 m
- 1985 Ark., ran ¾ mile
- 1986 Miss., ran 1 mile
- 1987 Ind., ran 1200 m
- 1989 Utah, ran ¾ mile
- 1990 NM, ran 800 m
- 1992 Ga., ran 1000 m
- 1995 Ariz., ran 900 m
- 2000 Tenn., ran 800 m
- 2001 Fla., 1 hr. mat drill
- 2004 Ohio, ran ~10 min
- 2005 Mo., 1 hr. field drill
- 2006 Tex., ran 1600 yds
- 2008 One in Fla., one in NC
- 2009 NC, ran 500 yds

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More than 70,000 people have sickle cell disease.

Sickle cell disease occurs in 1 in every 500 African American births.

2.5 million people have sickle cell trait.

1 in 12 African Americans has sickle cell trait (8%)
  - 96% of all cases of sickle cell trait

1 in 2000 non-African-Americans has sickle cell trait (0.046%)
  - 4% of all cases of sickle cell trait
Virginia Numbers

- **Sickle Cell Disease**
  - 3700 cases of sickle cell disease
  - 75 babies born every year with sickle cell disease
  - 1 in 325 African-Americans have sickle cell disease
    - (< 1% identified in other ethnic groups)

- **Sickle Cell Trait (Carriers)**
  - >155,000 Virginians are sickle cell trait/carriers
  - 1 in 12 African-Americans
  - 2000 births every year

- **Bottom Line:** there is more sickle cell trait and disease in Virginia than the national average
Where in Virginia?

Sickle Cell Disease in Virginia

- Eastern VA - King's Daughters 49%
- Central VA - VCU 23%
- Northern VA - INOVA Fairfax 19%
- Western VA - UVA and Carilion 9%
How is sickle cell passed from one generation to the next?

- Autosomal Recessive inheritance pattern
How is sickle cell passed from one generation to the next?

- **Autosomal Recessive inheritance pattern**
  - This means that both boys and girls can carry the trait (AS)
  - This means that the trait can run through a family without anyone ever inheriting the disease (SS)
  - This means that someone can inherit other hemoglobin problems along with the sickle cell trait
    - Hemaglobin CS
    - Hemaglobin S beta thalassemia
Is there any good reason to have sickle cell trait?

- Sickle trait is associated with increased survival in areas with endemic malaria (Selective Advantage)
- Sickle cell is “malarial” more than it is racial
  - Sicily 4% carrier rate; 12% of Northern Greeks and Turkey
So what actually is going on with sickle cell disease?

- **Hemoglobin**
  - Protein inside red blood cells that carries oxygen to tissues and carries carbon dioxide away
  - Made of four subunits each able to carry one oxygen
    - 2 alpha
    - 2 beta
  - Sickle Cell is caused by an abnormal Beta chain gene
So what actually is going on with sickle cell disease?

- **Making a hemoglobin molecule**
  - **Grab two alphas and two betas**
  - **Sickle cell disease** – all betas are abnormal “S” subunits
    - Each hemoglobin molecule will have:
      - Two normal Alphas + two abnormal “S” Betas
  - **Sickle cell trait** - % of betas are abnormal “S” subunits
    - Some hemoglobin molecules will have:
      - Two normal Alphas + two normal Betas
      - Two normal Alphas + two abnormal “S” Betas
      - Two normal Alphas + one normal Beta + one abnormal “S” Beta
So what actually is going on with sickle cell disease?

- In low oxygen states
  - The abnormal “S” beta unit warps and allows for cross linking to occur between the abnormal “S” beta units
  - If enough cross linking occurs the red blood cell will become stiff and arc shaped
Sickling Situations

- **Low Oxygen Environments**
  - High altitude situations (over 4000 feet)
    - Airplane flights
    - Cities over 4000 – Boulder, CO; Denver, CO; Bozeman, MT; Colorado Springs, CO; Laramie, WY; Lees-McRae College, Banner Elk, NC
    - Cities close to 4000 – Boone, NC (3400); Missoula, MT (3209)
    - Above 4K feet at rest – 2% of red cells are sickled
Sickling Situations

- Decreased oxygen delivery
  - Poorly functioning lungs
    - Bronchitis, Pneumonia, Common Cold, Asthma
  - Alterations in blood oxygen carrying ability
    - Pre-practice dehydration
      - Hangover
      - Not sufficiently replenishing from day before
        - WBGT > 75 during preceding 24 hours
    - During practice dehydration
      - Environmental heat stress
        - WBGT > 75 at practice time
        - Heat retaining clothing
  - Fever
  - Iron deficiency anemia

- Alterations in blood delivery
  - Organs that have blood redirected away from them during maximal exercise
    - Kidneys, spleen
Sickling Situations

- Increased oxygen usage
- Increase in environmental heat stress
- Sustained high intensity activity above conditioning level
  - In exercise to exhaustion at sea level 1% of total red cells will sickle
- Obesity with poor exercise fitness level
- Inadequate sleep
- Fever
Sickling Situations

- Often a combination of several factors
  (the least important of which is the level of exercise)
  1\textsuperscript{st} or 2\textsuperscript{nd} day of spring training (over weight and un-conditioned)
  + Warmer than expected day
  + “spring cold” with cough and recent fever
  + Repetitive timed runs (5 x 100 yd sprints)
  = sickle cell crisis/hospitalization/acute renal failure
Exertional Sickling Deaths in College Football

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So What happens in the body with a sickled red blood cell?

- Normal red blood cells
  - Normal red blood cell (RBC)
- Abnormal, sickled, red blood cells (sickle cells)
  - Sickle cells blocking blood flow
  - Cross-section of sickle cell
  - Sticky sickle cells
  - Abnormal hemoglobin form strands that cause sickle shape
Where does Sickle Cell Trait affect an Athlete?

- Kidney
- Spleen
- Muscles
Where does Sickle Cell Trait affect an Athlete?

- **Kidney**
  - Can affect individual nephrons and cause slow decrease in function over years
  - Can affect cluster of nephrons acutely
    - Kidney infarct
    - Microscopic or gross hematuria
Sickle Cell Crisis in a Kidney

- **Symptoms**
  - Flank pain
    - Not increased or decreased by changing position
    - Not able to palpate tender muscle
    - CVA tenderness to percussion
  - Nausea
  - Blood in urine
Sickle Cell Crisis in a Kidney

Return To Participation

- Wait until gross and microscopic hematuria resolves (visual check and urine dipstick check)
- Make sure kidney lab work is normalized (BUN, Cr)
- Gradual increase in activities over 1 week before allowing full participation
Where does Sickle Cell Trait affect an Athlete?

- **Spleen**
  - Infarct
    - Severe pain in left flank and side
      - Not better or worse with movement
      - Can not feel sore muscle
      - Pain radiates up to left shoulder blade
      - Pain worse with deep breath (splinting)
  - Nausea and Vomiting
  - Associated with left pleural effusion, atelectasis in left lower lobe of lung

- **Back up of blood flow – enlargement**
- **Identified by examination and ultrasound or CT scan**
Sickle Cell in the Spleen
Altitude seems to be the biggest risk for spleen

- 15 cases have occurred during airplane flights
- 24/32 (75%) cases have occurred in white or Mediterranean heritage sickle cell trait individuals

General recommendation – avoid sustained exercise

> 7000 feet
Sickle Cell in the Spleen

- **Return To Participation**
  - Usually self resolving in 10-21 days
  - RTP managed much like splenomegaly associated with mononucleosis
    - Resolution of palpable spleen
    - Normal spleen on ultrasound or CT scan
    - Normal blood work (CBC, Platelets)
  - Gradual increase in activities over 1 week
Where does Sickle Cell Trait affect an Athlete?

- **Muscles**
  - Affects large muscle groups that get used the most in sports – Legs

- **Symptoms**
  - Muscle pain and WEAKNESS
  - Progressive muscle involvement
    - Abs, arms, diaphragm
  - Can occur 2-3 minutes into exercise
Sickle Cell Crisis in the Muscles

- **Muscles**
  - **Mild** – pain and weakness which can recover in a few seconds to minutes
  - **Severe** – muscles can ‘infarct’ and start to die which releases:
    - Muscle enzymes - Rhabdomyolysis
    - Acidosis – cardiac arrhythmias (sudden death)
    - Kidney failure – dying muscles release myoglobin which sludges in kidneys and causes them to fail (delayed death)
Sickle Cell Crisis in the Muscles

- **Return To Participation**
  - Minor spell (mild pain and weakness that self resolves in seconds to minutes)
    - Wait 30 minutes after symptom free
      - Allows time for hydration efforts to get into circulation — HYDRATE
      - Allows time for oxygenation to get throughout the circulation — GIVE OXYGEN
  - After severe spell (rhabdo with kidney failure)
    - Wait for kidney function to return to baseline (BUN, Cr)
    - Wait for muscle enzyme levels to return to baseline
    - Gradual increase in activities over 1-2 weeks
  - Permanently disqualified from returning to participation if severe spell included any of the following:
    - Creatinine > 6.0
    - CPK > 27,000
    - Vision loss or focal neurologic changes with spell (sickling spell in brain or eyes)
How can you tell what caused your athlete to collapse?

<table>
<thead>
<tr>
<th></th>
<th>Sickling Collapse</th>
<th>Cardiac Collapse</th>
<th>Heat Cramp / Collapse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When</strong></td>
<td>Early in practice or after sprints</td>
<td>Anytime</td>
<td>Late in practice</td>
</tr>
<tr>
<td><strong>Warning Signs</strong></td>
<td>No clear prodrome symptoms</td>
<td>No clear prodrome symptoms</td>
<td>Feel tingling/twitching</td>
</tr>
<tr>
<td><strong>Overall Symptoms</strong></td>
<td>Slump to ground with weak / wobbly muscles</td>
<td>Collapses more than slumps</td>
<td>Hobbles off field or falls because of tight muscle</td>
</tr>
<tr>
<td><strong>Pain pattern</strong></td>
<td>Moderate ‘heart attack’ ache / pain in muscles</td>
<td>No pain in muscles</td>
<td>Severe and burning pain</td>
</tr>
<tr>
<td><strong>Muscle pattern</strong></td>
<td>Muscle progressively becoming weaker / flaccid</td>
<td>Muscles flaccid</td>
<td>Muscle contracted tight like a rock</td>
</tr>
<tr>
<td><strong>Alertness</strong></td>
<td>Normal Level of consciousness</td>
<td>Loss of Consciousness or decreased level or seizures</td>
<td>Normal level of consciousness but can progress to decreased level with heat stroke</td>
</tr>
<tr>
<td><strong>Sidelines Care</strong></td>
<td>Pull from participation, Oxygen if available and activate 911 + apply AED if symptoms not immediately better</td>
<td>Activate and initiate ABCD’s of emergency cardiac care</td>
<td>Stretch and massage muscle and administer oral fluids</td>
</tr>
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Treating a Sickle Crisis
NATA consensus statement 2007

- **Sickle Collapse**
  - Treat as a medical emergency
  - Check vital signs
  - Administer oxygen if available
  - Cool athlete if necessary
  - Altered mental status/declining vital signs
    - Call 911; attach an AED; start high flow IV
  - If transferring to ED
    - Notify EMS and receiving hospital that this is a sickle cell situation and expect explosive rhabdo and metabolic complications

- **Sickle Crisis vs. Exertional Heat Illness**
  - respect both and treat urgently
  - Could be combination – leading to more complicated course
Preventing a Sickle Crisis
NATA consensus statement 2007

- Educate athlete of diagnosis, signs and symptoms of sickle crisis common in sports
- Educate coaching staff, strength/conditioning staff and medical staff of signs and symptoms of sickle crisis and what measures to take in an emergency (assume it is sickling first)
Preventing a Sickle Crisis

NATA consensus statement 2007

- Encourage athlete to maintain fitness level
  - Participate in year round strength and conditioning

- Adjust initial preseason/off-season training
  - Build up slowly with paced progressions
  - Longer periods of rest and recovery
  - Exclude from performance tests (mile run, serial sprints)

- Adjust training based on Ambient heat stress, dehydration, asthma, illness, altitude
  - Increased rest cycles; emphasize hydration; hold if running fever or for respiratory symptoms

- Cessation of activity with onset of symptoms (muscle cramping, pain, weakness, inability to ‘catch breath’
How can you prevent or treat a sickle cell crisis if you don’t know which athletes are at risk?

- All of these recommendations are based on the presumption that you know which of your athletes are sickle cell trait carriers

- NATA consensus statement 2007
  - “Efforts to document newborn screening results should be made during the PPE”
  - “In the absence of newborn screening results, institutions should carefully weigh the decision to screen”

- NCAA press release 6/29/09
  - “Following recommendations from NATA and CAP, the NCAA recommends athletics departments confirm Sickle Cell Trait status in all student-athletes, if it is not already known, during their required medical examinations”
Know your at risk athletes

- Pre-Participation Screening
  - Sickle cell test done on all newborns before discharge from hospital
    - Virginia started doing this in 1989
    - records kept at doctor’s office (sometimes) and at state lab in Richmond
      - Mother’s name, mother’s social security number, gender of baby, date of birth, hospital of birth
    - Many individuals don’t know and don’t have access to their lab report
Know your at risk athletes

Basic screening with Hemoglobin Solubility Test (Sickledex)
if positive – follow up with Hemoglobin Electrophoresis
Know your at risk athletes

- Should you test all athletes?
- Should you test all athletes who do not have newborn lab results?
- Should you only test high risk athletes (African-American, Greek, Turkish, Sicilian, Indian)?
  - This may miss up to 4% of all sickle cell trait carriers
Treatments?

- **Thiocyanate**
  - Can reduce sickling in Sickle Cell Anemia patients
  - No studies on SCT
  - Naturally found in veggies (broccoli and cauliflower)
  - High levels can be toxic

- **Bottom line:**
  - Avoid Herbal preparation
  - Eat your veggies
Bottom Line for Sickle Cell Trait in Athletes

- **Know your athletes**
  - Some sort of screening
  - Make sure all staff/coaches know

- **Know how to prevent spells**
  - You and all coaching staff
  - Educate your coaching/strength staff
  - Modify workouts when oxygen delivery is affected (altitude, heat, pre-season, illness)

- **You can not prevent when you do not know!**
Bottom Line for Sickle Cell Trait in Athletes

- Know how to identify a spell and respond to minor and major spells
  - Educate your coaches/strength staff!
- Know when to allow RTP for a spell
  - Kidney, spleen, muscle
- It is much harder to identify and treat a spell if you do not know your athlete’s status!
References

- NATA Consensus Statement: Sickle cell and the athlete, June 2007. [www.nata.org](http://www.nata.org)