Avascular Necrosis
and other bone problems

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SCAGO Learning for Life – April 2012
Objectives

- What is Sickle Cell Disease
  - How it causes problems
  - Effect of genes

- Normal Bones

- Avascular Necrosis

- Osteoporosis

- Bone infections
What is Sickle Cell Disease?
Dense RBCs

- Less deformable
- More HbS
- More hemolysis – lower Hb

Protects against AVN
What Bones Look Like

The skeleton is one of the largest organs in the body.
Bone Strength

- The strength of bone is determined by its composition and structure
  - Bone must be stiff and able to resist deformation, thereby weight bearing
  - Bone must also be flexible and able to absorb energy by deforming without cracking
  - Bone must also be light to facilitate movement

90% mineral - stiff for sound transmission

40% mineral - flexible for head butting
What Happens to Bones in SCD?

- Bone marrow expansion from increased RBC production
- Growth of marrow elsewhere in the body extramedullary haematopoiesis (EMH)
- Infarction of marrow & trabecular bone pain episodes fat emboli
- Avascular Necrosis
- Osteoporosis
- Infection of bone or joints osteomyelitis, septic arthritis
Increase in BM Activity

Normal

Sickle Cell Disease
New Marrow Tissue Forming in the Body

Front View

Side View
Bone Ischemia

Dactylitis
- most common 6mth-2yrs (<6yrs)
- 18-45% of children
- <2yrs = bad prognosis

Spinal Collapse
Avascular Necrosis

Also called:

- Osteonecrosis
- Aseptic necrosis
- Ischemic necrosis
- Osteochondritis dissecans

Reduced blood supply to bone leading to the death of bone and marrow cells, and eventual mechanical failure.
Reduced blood supply, increased pressure in the bone, mechanical stress

1. Interruption of blood circulation within bone
2. The adjacent bone area becomes engorged
3. Bone loses minerals
4. Thinning of bone
5. Collapse or fracture
How common is AVN?
27% in children
40% of patients have AVN by 35yrs
Does not appear more common in “elderly” but depends on imaging technique

Which joints are affected?
- Shoulders or Hips
  50% of pts with an affected hip will have both hips involved
  75% of pts with an affected shoulder will also have hip AVN

A wider area of bone is affected in SCD compared to other causes of AVN
How does AVN present?

- Pain in joint
  - on movement
  - when weight bearing (hips)
  - can be felt in groin, thighs or buttocks

- Reduced movement of joint

- May be found when imaging for other reasons
  - 50% of pts with hip AVN have no symp
  - 80% of shoulders asymptomatic

- Xrays often normal initially

- The process is progressive, resulting in joint destruction within 3 to 5 years if left untreated
  - 95% of stage-I hips became symptomatic within 3 years and 86% experience collapse
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no symptoms, normal x-ray and MRI</td>
</tr>
<tr>
<td>1</td>
<td>normal x-ray, abnormal MRI</td>
</tr>
<tr>
<td>2</td>
<td>abnormal x-ray, cysts and sclerosis</td>
</tr>
<tr>
<td>3</td>
<td>subchondral collapse, crescent sign</td>
</tr>
<tr>
<td>4</td>
<td>flattening of the head</td>
</tr>
<tr>
<td>5-6</td>
<td>degenerative joint disease - arthritis</td>
</tr>
</tbody>
</table>
X-ray of the Left Hip

- Joint space narrowing
- Articular sclerosis
- Patchy lucency or cysts
- Flattening of the femoral head
MRI of the Left Hip

- Near complete involvement of:
  - femoral head
  - femoral neck
  - upper femur to the mid-diaphysis

- But minimal collapse of the femoral head
Stage 4 AVN of Left Hip
Normal hip
The goal is to preserve the joint for as long as possible

3 options:
- Conservative management
- Joint preserving procedures
- Joint replacement
Conservative Treatment

- bed rest
- physiotherapy
- partial weight bearing with crutches
- weight bearing as tolerated
- analgesics (Tylenol, NSAID, opiate)
- slow removal of the dead bone by bisphosphonate drugs may be beneficial

This approach is generally ineffective at stopping it getting worse
Joint Preservation

Artificial joints last <10yrs, so alternatives to delay need for replacement...

- Core decompression
  reduces pressure in bone, improves blood flow
  relief of pain
  no effect on delaying collapse of joint
  New techniques?

- Bone marrow grafting
  injecting BM cells to encourage new bone growth

- Osteotomy
  redistribute weight bearing forces to healthy bone
Core Decompression
Joint Replacement

- Older, less active patients
- >30% of the joint affected
- If collapse of joint

30% of patients will need revision within 5yrs
Current Studies

ClinicalTrials.gov

No active research in this area

UHN: MSC from bone marrow to improve growth of bone after core decompression
Previous Studies

121 SCD patients with asymptomatic AVN of the hip followed for 14 years:

- 84% of stage 0 hips became symptomatic
  61% experienced collapse

- 95% of stage 1 hips became symptomatic within 3 yrs
  86% experienced collapse

- All stage 2 hips became symptomatic within 2 yrs
  and all collapsed

- 75% of patients in the study had intractable pain and required surgery


### Table: Criteria for Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria for Staging</th>
<th>At Initial Visit</th>
<th>At Final Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Hip at risk with normal radiographic and magnetic resonance imaging findings</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>I</td>
<td>Abnormal magnetic resonance imaging findings, normal radiographic findings</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>Abnormal radiographic findings with sclerotic or cystic changes in the femoral head but no crescent line</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>III</td>
<td>Abnormal radiographic findings with a crescent sign with femoral head flatting of ≤1 mm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>Collapse of the femoral head of &gt;1 mm without joint-space narrowing</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>Joint-space narrowing</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>VI</td>
<td>Advanced degenerative changes</td>
<td>0</td>
<td>42</td>
</tr>
</tbody>
</table>

Hip more likely to worsen if a large section of the femoral head is involved.
215 SCD patients, 42 had symptomatic AVN of the hip:

<table>
<thead>
<tr>
<th></th>
<th>Supportive Care</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pts</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Age</td>
<td>36yrs</td>
<td>30yrs</td>
</tr>
<tr>
<td>Follow-up</td>
<td>14yrs</td>
<td>11yrs</td>
</tr>
<tr>
<td>Severe Pain</td>
<td>34% → 39%</td>
<td>43% → 7%</td>
</tr>
<tr>
<td>Joint function</td>
<td>No change</td>
<td>Improved</td>
</tr>
<tr>
<td>AVN</td>
<td>No change</td>
<td>69% benefited</td>
</tr>
<tr>
<td>Surgery</td>
<td>39%</td>
<td>23%</td>
</tr>
<tr>
<td>Time to surgery</td>
<td>2yrs</td>
<td>7rs</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>19%</td>
<td>58%</td>
</tr>
</tbody>
</table>
## Treatment for avascular necrosis of bone in people with sickle cell disease

### Analysis 1.1. Comparison 1 Hip core decompression and physical therapy versus physical therapy alone, Outcome 1 Pain.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HCD % physical therapy</th>
<th>Physical therapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>NOTSCEA 2006</td>
<td>10/17</td>
<td>13/21</td>
<td>0.95 [0.56, 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

- **Favours HCD % phy therapy**
- **Favours physical therapy**

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**Physical Therapy Alone Compared with Core Decompression and Physical Therapy for Femoral Head Osteonecrosis in Sickle Cell Disease**

Results of a Multicenter Study at a Mean of Three Years After Treatment

Of patients who underwent hip replacement:

- 71% of had >10% blood loss
- 19% had acute chest syndrome or pain
- 15% had fever or infection
- Postoperative surgical complications were reported in 15% of the procedures
  
  bleeding, wound problems, dislocated prostheses

Other Previous Studies

Various forms of protected weight-bearing methods to treat pre-collapse ON of the femoral head (not SCD):

- only 22% had a satisfactory response after 3 years

Study of 36 patients with early stage ON (not SCD):

- surgery was at least 3 times as effective as non-surgical treatments
- in later stages of the disease, non-operative treatment had only 10% success rate

Does Hydroxyurea Help?

- At baseline, 12% of patients had a history of symptomatic AVN.
- During follow-up period: only 1 pt on OHurea therapy presented with AVN compared with 6 patients who did not receive HU.

Indian study of 64 adults with SCD:
46 prescribed OHurea
18 adults did not

- **Hydroxyurea group:**
  73% of pts with early AVN were pain free
  Xray findings normalised
  Advanced AVN did not respond

- 22% in untreated group had improvement in pain only

Hydroxyurea needs to be used early on to be beneficial
Do Transfusions Help?

- No data!
Osteoporosis

*a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequential increase in fracture risk*

- Diagnosis based on bone mineral density measurement by DEXA scan
- Postmenopausal Caucasian women
  - T-score that is > -2.5 = osteoporosis
  - T-score that is > -1.0 = osteopenia

“Low BMD”
Causes of Low BMD

- Bone marrow expansion
- Inadequate physical activity
- Smoking
- Caffeine
- Calcium and vitamin D deficiencies
- Thyroid gland problems
- Diabetes
- Hypogonadism
- Iron overload / Desferal
- Genetic / family history

All of these factors contribute to an imbalance in bone remodelling leading to bone loss
UHN Osteoporosis Data

- High prevalence (76%) of osteopenia in young adults with SCD
  - 50% spine, 31% hip

- Significant Factors:
  - Low BMI, SCD-SS, absence of AVN

- Vitamin D deficiency
  - Very common
  - But does not seem to be a factor
Treatment / Prevention

- Physical activity
- Stop smoking
- Adequate calcium and vitamin D
- Checking of BMD starting in adolescence

Drugs
  - Hormonal replacement
  - Bisphosphonates
  - Hydroxyurea
  - Calcitonin
  - Teriparatide
  - Strontium
  - anti-RANKL (denosumab)
Osteomyelitis

- Most commonly affects the middle of the femur, tibia or humerus
- Salmonella is the most frequent bug
- Increased risk of infection
  - Infarction and dead bone tissue
  - Loss of spleen function
  - Leg ulcers
The clinical presentation of acute bone infarction and osteomyelitis is similar.

Surgical drainage often necessary.

Antibiotic treatment depends on organism and antibiotic sensitivity.

Initially treated with IV followed by oral antibiotics for 6 wks -3 months.

Untreated infection may extend into the joint resulting in septic arthritis.
Summary

- AVN is common
- It is very difficult to treat
- No good alternatives to hip replacement
difficult to comply with prescribed exercise
desire to delay surgery as long as possible
- Chronic pain – huge burden for patients