Starvation, Death and Destruction: The Battlefield of AVN

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Speaker's Disclosure Statement

- I have no industry relationships to disclose
- I will discuss off-label use of medications

Objectives

1. Identify factors that contribute to the development of AVN in children with hematologic or oncologic disorders
2. Discuss treatment options for AVN

Different Names, Same Game

- Avascular necrosis
- Osteonecrosis
- Aseptic osteonecrosis
- Atraumatic necrosis
- Ischemic bone necrosis

- Death of bone tissue due to lack of blood supply
- Bone is a living tissue that requires blood

Pathophysiology

- Normal bone growth
  - Break down: Resorption of old bone by osteoclasts
  - Build: Formation of new bone by osteoblasts
  - AVN = Breakdown faster than repair
- Pathophysiology of AVN
  - Decrease blood supply to bone (ischemia)
  - Infarction and necrosis of bone and marrow cells
  - Tiny breaks/collapse of bone components
  - Destruction and collapse of joint
  - Mechanical failure

Risk Factors

- Sickle cell disease
- Steroids (ALL, HCST)
- Orthopedic disorders
- Trauma
- Lupus
- Infection
- Coagulation disorders
- Gaucher disease
- Renal transplant
- Radiation therapy
- Malignancy
- Biphosphonate use

Sickle Cell Disease and AVN

- AVN of the femoral head
  - Most common cause during childhood
  - 2-4.5 cases/100 patient-years
  - Overall prevalence = 10%
  - 50% of patients with Hemoglobin SS disease by age 33
- Natural history
  - 80% of affected hips are painful
  - AVN results in permanent loss of motion, limb-length discrepancy, and gait dysfunction

ALL Risk Factors for AVN

- Corticosteroids
- Age >10 years (girls 10-14 and boys >15), but not adults
- Race (white>black; non-Hispanic>Hispanic)?
- Female sex?
- High body mass index/obesity, especially at diagnosis?
- Elevated lipid levels?
- Genetic polymorphisms?
- Other chemotherapy agents: Asparaginase, cyclophosphamide and high dose methotrexate?

Steroid Therapy and AVN

- Exact pathogenesis unknown; proposed mechanisms
  - Alteration in circulating lipids → microemboli in arteries supplying bones
  - Stimulate bone marrow fat cells to increase in size/numbers → blocks venous flow
  - Effect vascular endothelial cells and smooth muscle cells → stasis → increased intraosseous pressure → necrosis
- Often multi-joint involvement
- Most cases diagnosed within 1 year of starting treatment, but may occur many years later

Steroid Therapy and AVN

- CCG 1961 for high risk ALL
  - 21-day continuous vs alternate week dexamethasone (AWD) in delayed intensification
- 143/2056 patients developed symptomatic AVN at 377 skeletal sites resulting in 139 surgeries
- Overall incidence = 7.7% at 5 years
  - 1-9 years: 1%; 10-15 years: 9.9%; >16 years> 20%
- Continuous vs AWD
  - Rapid early responder females>16 years: 17% vs 44%
  - Rapid early responder males>16 years: 8% vs 35%

Steroid Therapy and AVN

- COG 2032 for high risk ALL
  - 14-day dexamethasone vs 28-day prednisone in induction
  - Continuous dexamethasone for <13 years vs alternate week dexamethasone (AWD) for ≥13 years in DI
  - Dexamethasone vs prednisone pulses in maintenance
- Study amended twice due to high AVN rates
  - AVN rate at 18 months (on treatment!) = 28% for 10-12 year olds receiving continuous dexamethasone in DI
  - #1: Patients>10 years to receive prednisone in induction
  - #2: All patients to receive AWD dexamethasone in DI and prednisone during maintenance

Age and AVN

- Maturing bones of adolescents, especially long bones that have late epiphyseal closure and contribute to pubertal growth, appear to be most susceptible
  - Epiphyseal closure results in elevated intraosseous pressure, especially if steroid-induced fat-cell hypertrophy, reducing blood flow to bones leading to marrow ischemia and ultimately necrosis?
  - Excessive metabolic activity in growth plates and bones during pubertal growth spurt make them more susceptible to hypoxic effects?
  - Increased end-organ susceptibility caused by a markedly increased growth rate and hormonal changes?

HCST and AVN

- AVN after allogeneic transplant
  - Nested case-control study; AVN (160)/control (478)
  - Median time to develop AVN: 14 months
  - Risk factors
    - Age ≥ 5 years at time of transplant
    - Female gender
    - Myeloablative conditioning regimen
    - Chronic GVHD
  - Decreased risk
    - Nonmalignant disease
    - Reduced-intensity conditioning regimens for malignant disease

Li, X., et al. (2014). Biology of Blood and Marrow Transplantation, 20 (4), 587-592.

HCST and AVN

- AVN after allogeneic transplant
  - St. Jude Children's Research Hospital prospective study post-transplant
  - 30% of patients developed AVN of knees and/or hips
  - 45% of lesions had at least 30% epiphyseal involvement
  - Median time to develop AVN: 12.3 months
  - Risk factors
    - >10 years old at time of transplant
    - AVN on MRI prior to transplant
  - Knees most frequent site, but hips had greater severity
  - Some regression and resolution of pre-HCST AVN

Sharma, S., et al. (2012). Bone Marrow Transplantation, 47 (8), 1067-1074.

Facts to Mull Over …

- On CCG 1961, patients with AVN had a 17.6% *better* event-free survival than patients without AVN
- Asparaginase allergy is associated with a *lower risk* of AVN
  - Concomitant asparaginase treatment is associated with higher plasma exposure dexamethasone; so patients with asparaginase allergy received lower systemic exposure to asparaginase

Presentation

Clinical Symptoms

- Pain is the most common presenting symptom
  - Often described as throbbing, deep, or intermittent
  - May be referred to other areas (eg femoral head lesions may be felt in groin, thigh or buttocks)
  - Symptoms usually start with just weight bearing, then progress to at rest
- Affected joints may be asymptomatic
- Inflammatory symptoms (swelling) generally absent
- Sudden severe onset of pain concerning for joint collapse

Physical Examination

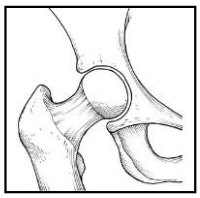
- Limp
- Antalgic gait
- Restricted ROM
- Tenderness around bone
- Joint deformity
- Muscle wasting

Imaging and Staging

What Modality is Best?

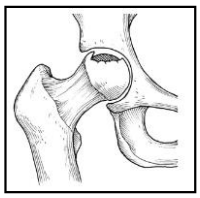
- X-ray: Doesn't identify early changes; may remain normal for months after symptoms first appear
- MRI: Most sensitive and specific method
- CT: Used to assess extent of disease and calcification; clearly shows articular deformity and bone collapse
- Bone scan
  - More sensitive than X-ray, less sensitive than MRI
  - Increased uptake mainly due to increased activity of osteoblasts (bone formation)

Staging I



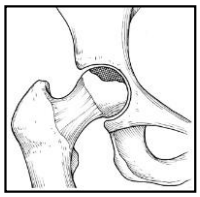
- X-ray: Not detectable
- MRI: Slight bone marrow edema or effusion; joint effusion most commonly appears in the knees
- Bone scan: Increased uptake mainly due to increased activity of osteoblasts (bone formation)

Staging II



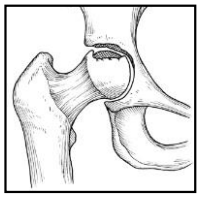
- X-ray: Mixed osteopenia (bone mineral density lower than normal) or sclerosis
- MRI: Evidence of lesion, abnormality in bone tissue
- Bone scan: Increased uptake

Staging III



- X-ray and MRI: Bone collapse of joint appears imminent

Staging IV



- X-ray and MRI: Collapse of joint

Seek and You Will Find

St. Jude's Total XV Therapy

- Symptomatic AVN usually diagnosed first year of therapy
- 17.6% symptomatic AVN at 6-12 months from diagnosis
- 53.6% asymptomatic AVN at end of therapy
- 25% of patients with asymptomatic MRI changes early in treatment (by week 10) went on to develop symptoms, but
- Most symptomatic patients had mild-moderate symptoms, and only a minority required surgical treatment

Kawedia et al, 2011. Blood, 117 (8), 2340-2347.

Management

Can AVN Reverse?

- Study of symptomatic AVN in children with ALL
  - 40% had complete resolution of symptoms at 5 years
  - 24 patients with radiology follow-up: 25% partially or completely reversible lesions, 54% stable lesions, 21% progressive lesions
- Study of femoral head AVN in 48 children with ALL
  - >10 years (40 children): 19 progressed to joint collapse and required total hip replacement; 21 had no improvement at end of monitoring
  - <10 years (8 children): none required hip replacement; 4 had significant improvement at end of monitoring

Treatment

- Goals
  - Stop progressions of bone damage
  - Reduce pain
  - Improve function of the affected joint
- Considerations
  - Age (maintaining skeletal growth, need for multiple surgeries)
  - Extent, stage and location of damage
  - Health of patient
  - Risk for recurrence of malignancy

Non-Surgical Management

- Inconsistent and limited success in preventing disease progression
- Restrict weight-bearing exercise
- Physical therapy
- Medications: lipid-lowering drugs, anticoagulants, vasodilators, bisphosphonates, traditional Chinese medications
- Electromagnetic stimulation
- Hyperbaric oxygen

Surgical Management

- Joint preserving procedures
  - Core decompression (open necrotic area of the bone to relieve pressure and stimulate re-vascularization)
  - Bone grafts or bone marrow (cell based therapy)
  - Oosteotomy (remodel/re-align)
  - Arthrodesis (fuse)
- Joint replacement (arthroplasty)

Core Decompression

- Pre-collapse of joint
- Single 8-10 mm core into necrotic lesion, or small diameter multiple 3 mm cores
- Pain relief
- Reduce intraosseous pressure
- Create open area for new blood vessels to grow
- Enhance new bone growth
- 70-80% success rate at 5 years

Novais, E.N., et al. (2015). Journal of Pediatric Orthopedics, 35 (8), 810-815/

Core Decompression and ABMI

- Autologous bone marrow implantation to induce bone repair in femoral head
- Procedure
  - 60-120 mL bone marrow aspirated from anterior iliac crest
  - Concentrated to 15 mL of bone marrow cells
  - Multiple small core drillings in the femoral epiphysis
  - Concentrated marrow slowly injected into the femoral head
  - 24 hour admit for hydration and pain management
  - No cast or brace; 2 month touch down weight-bearing on crutches

Core Decompression and ABMI

- Pediatric trial (Novais et al)
  - 11 patients with SCD, 14 hips
  - >90% decreased pain, >80% decreased progression to joint collapse
- Adult trial (Daltro et al)
  - 89 patients with SCD
  - Historically 70% to 90% without intervention progress to collapse/osteoarthritis requiring arthroplasty within 5
  - Only 3.4% did not achieve good results
  - No collapse of femoral head in 60-month follow up

Novais, E.N., et al. (2015). Journal of Pediatric Orthopedics, 35 (8), 810-815.
Daltro, G.C., et al. (2015). Stem Cell Research & Therapy, 6 (110). 1-18.

Osteotomy

- Rotates necrotic portion of bone away from the weight-bearing surface, redistributing the weight-bearing force to the articular cartilage that is supported by healthy bone
- Prolonged post procedure recovery includes extended restricted weight-bearing until healing occurs

Arthroplasty

- Late stage when joint is destroyed (collapsed or severe arthritis)
- Damaged bone is removed and replaced with an artificial joint, usually with plastic or metal parts

Case Studies