Crystal Arthropathies

Ayesha Iqbal, M.D.

- Gout – Monosodium urate
- CPPD – Calcium pyrophosphate dihydrate crystal deposition
- Basic Calcium Phosphate Dz – Hydroxyapatite

Objectives

- Brief review of etiology and pathophysiology
- Recognize predisposing factors
- Review diagnostic criteria and evaluation
- Select appropriate treatment

Gout

- Gout is an inflammatory arthritis resulting from deposition of monosodium urate crystals in joints and other connective tissue structures

Epidemiology

- Most common inflammatory arthritis in men
- Prevalence in US: 3.9% (~8 million)
- ↑ incidence and prevalence worldwide
- Male to female – 4:1

Hyperuricemia and Gout

Humans have inactivated the Uriscase gene which degrades uric acid to water soluble Allantoin.

- Hyperuricemia is defined as levels >2 standard deviations above nL
  - 6.8 mg/dl in men.
  - 6.0 mg/dl in women.
- Solubility of MSU is 6.8 mg/dl

Rare before puberty and in premenopausal women
Hyperuricemia and Gout

- **Hyperuricemia is a risk factor for gout**
  - Prevalence: 2.3 - 41.3%
  - Less than 20% get gout
  - ↑ incidence of gout with ↑ serum uric acid (SUA) levels.
  - The annual incidence rates for gout
    - 0.1% at SUA levels less than 7 mg/dl
    - 0.5% at SUA levels between 7 - 8.9 mg/dl
    - 4.9% at SUA levels above 9 mg/dl

Hyperuricemia - Mechanism

- Decreased excretion of Uric acid: 80-90%
- Overproduction of Uric acid: 10%
  - Lesch-Nyhan Syndrome: Hypoxanthine-guanine phosphoribosyl transferase deficiency (HGPRT)
- Combined Mechanism
  - Lesch-Nyhan Synd: Young boy with arthritis (gouty), kidney stones, abnormal involuntary movements, self injury/mutilation

Predisposing factors

- Ethanol consumption
- Diet: High purine diet, high fructose beverages
- Obesity
- Metabolic syndrome
- Acute illness, Post - Op
- Renal insufficiency
- Hypertension
- Chronic lead toxicity- Saturnine gout

Predisposing factors

- Drugs: Diuretics, low dose salicylates, β- Blockers, Pyrazinamide, Ethambutol, Cyclosporine, tacrolimus, Insulin
  - Strong disease association – CKD, Metabolic syndrome, HTN, CAD

Pathophysiology

- Not completely understood
- Better idea about the inflammatory response
  - MSU crystals undergo phagocytosis by macrophages which stimulates a cyopyrin inflammasome (NLRP3), this induces release of pro-inflammatory cytokines (IL-1β, IL-6,8 and TNF)
  - These cytokines lead to recruitment and activation of leukocytes resulting in signs of inflammation in acute gouty arthritis

Clinical manifestations

Classic presentations in the natural course of urate deposition disease:

- Asymptomatic Hyperuricemia
- Acute gouty arthritis
- Intercritical gout or interval gout
- Chronic gout:
  - Tophaceous
**Acute gouty arthritis**
- Sudden intense inflammation, severe pain, redness, swelling, warmth and disability
- First attack: 4th-6th decade in men
- Monoarticular in 80-90% cases
- Polyarticular in 3-14%
- 1st MTP commonly involved- 50%
- Fever, leukocytosis and ↑ inflammatory markers
- Self-limited

**Intercritical Gout**
- Asymptomatic periods in between acute attacks
- Approx 70% will have a second attack in 2 years
- 10% never have a recurrence
- Over time, attacks are less explosive, polyarticular, and take longer to resolve

**Chronic Gout**
- Approx takes 12 years between initial attack and development of chronic arthritis in untreated patients
- Pain free intercritical periods are rare
- Tophi: Collections of MSU crystal core in connective tissues enclosed by granulation tissue
- Joint destruction
  - Confused with other inflammatory arthritides

**Chronic Tophaceous Gout**
Cyclosporine induced tophaceous gout

Diagnosis

- Mostly on the clinical basis of:
  - An acute monoarthritis
  - Hyperuricemia
  - Dramatic improvement of articular symptoms in response to Colchicine
- Accuracy ↑ with typical presentation
- Definitive diagnosis: demonstration of MSU crystals in synovial fluid or from tophi

  - Aspiration! Aspiration! Aspiration!

Assess predisposing factors

- Labs
  - SUA:
    - May be normal in acute attacks
    - SUA level needed to monitor therapy
  - Renal uric acid excretion:
    - Age of onset before 25
    - FH of early onset gout
    - Nephrolithiasis
  - Inflammatory markers: non specific

- Imaging
  - Non specific in early and acute gout
  - Typical features may be seen in chronic gout

- Synovial fluid analysis

Synovial Fluid Analysis

- Microscopy:
  - Cell counts: 5,000 – 100,000 (Inflammatory)
  - Neutrophilic predominance
  - Light microscopy
    - Needle shaped MSU crystals
    - Compensated polarized light microscopy:
      - Intracellular MSU crystals
      - Needle shaped
      - Strong negative birefringence
      - Acute attack: Sensitivity 85%
      - Inter-critical period: Sensitivity 70%
        (Extracellular Crystals)

  - Septic arthritis should always be ruled out by a gram stain and culture in these situations

Plain microscopy

Compensated polarizing

Yellow when parallel to Z’ axis
**Imaging**

Plain Radiography
- **Acute Gout:**
  - Non specific
  - Soft tissue swelling
- **Chronic Tophaceous Gout:**
  - Tophi
  - Punched out erosions with sclerotic borders and overhanging edge

*High resolution USG, dual energy CT can diagnose earlier disease.*

**USG - Crystal deposits**

**Double Contour**

**USG - 1st MTP**

**Diagnosis**

- Differential diagnosis:
  - Infection:
    - Septic arthritis
    - Cellulitis
    - Septic bursitis
  - Other crystal induced arthropathies
  - Other inflammatory arthropathies
    - Rheumatoid arthritis
    - Spondyloarthritis
  - Trauma

- *Inflammatory monoarthritis and elevated uric acid not always gout*
Treatment

Therapeutic aims:
- To terminate the acute attack promptly
- To prevent recurrences of acute gouty arthritis
- To prevent or reverse complications of the disease

Treatment options vary
- Acute gouty arthritis
- Prophylaxis
- Chronic gout

2012 ACR Gout Guidelines

Assess benefits and risks of treatments
Cost-effectiveness not assessed

Grades of evidence supporting recommendations
Level A: supported by multiple (more than 1) randomized clinical trials or meta-analyses (20%)
Level B: supported from a single randomized trial, or non-randomized studies (30%)
Level C: consensus opinion of experts, case studies, or standard of care (50%)

Acute gouty arthritis

Pharmacologic:
- NSAIDS
- Colchicine
- Steroids
- IL-1 inhibitors

Step up or combination therapy can be used (C)

Non Pharmacologic:
- Co morbid risk reduction
- Assess and manage drug interferences
- Education

NSAIDS: (A)
- Traditionally Indomethacin has been used
- Various NSAIDS have showed similar efficacy and tolerability within the class
- ADR: GI irritability, HTN, fluid retention, headaches, rash, hypersensitivity, renal failure

Colchicine: (A)
- Use within 24 hours of acute attack (C)
- FDA approved:
  - 1.2mg orally once followed by 0.6mg
  - EUAR recommendation:
  - 0.6mg orally two or three times per day
  - Dose adjustments for renal and severe hepatic impairment
  - New FDA recommendations: caution concurrent use CYP3A4 inhibitors and P-glycoprotein
- ADR: GI discomfort, diarrhea, BM suppression, Rhabdomyolysis, Dermatoses, Peripheral neuritis

Steroids: (A)
- Unable to tolerate NSAIDs / colchicine
- NSAIDs contraindicated
- Suboptimal response
- Rapidly effective
- Caution in diabetic patients
- ADR: Hyperglycemia, Infection, Fluid retention, Osteoporosis, Cataracts, Psychosis
Acute gouty arthritis

Steroids:
- **Intra-articular:**
  - Used for monoarticular and oligoarticular arthritis
  - Infection must be ruled out
- **Orally:**
  - 30-40 mg once a day, tapered over 2 weeks
  - Unable to tolerate PO
- **Parenteral:**
  - Low dose colchicine (0.6-1.2mg/day) prevents rebound flares (B)
  - Do not initiate or change Urate lowering therapy during an acute attack

Treatment Chronic Gout

- **Pharmacologic:**
  - **Urate lowering therapy:**
    - Xanthine oxidase inhibitors
    - Uricosuric agents
    - Uricase
    - Others
  - **Prophylactic agents:**
    - Colchicine
    - NSAIDs

Urate Lowering Therapy

- **Indications**
  - 2 or more major attacks per year (A)
  - Tophaceous gout (A)
  - Nephrolithiasis (C)
  - Renal uric acid excretion more than 1100 mg/dl (C)
  - CKD stage 2 and greater (C)
- **SUA level less than 6.0 mg/dl needed for prevention of acute attacks**
- **SUA around 5.0 mg/dl required for resorption of tophi**

Urate Lowering Therapy

- **Allopurinol (A)**
  - Blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid
  - Mean effective daily dose is 300 mg
  - Initiated at 100 mg/day, titrated up every 2-4 weeks to maintain the desired antihyperuricemic effect
  - SUA levels fall within 2 days of treatment and reach stable levels in 1-2 weeks
  - Dosage to be adjusted in renal insufficiency

Adverse reactions:
- Precipitate acute gouty arthritis
  - w/ colchicine prophylaxis
- Rash: 3 - 5%; 0.1% can progress to AHS (severe exfoliative dermatitis, ARF)
- Leukopenia
- Thrombocytopenia
- Drug fever
- Vasculitis
- Interstitial nephritis
- Drug interactions especially 6-mercaptopurine and Azathioprine

HLA-B*5801 screening in high risk population (Han Chinese, Koreans with CKD 3 and Thai descent)
Febuxostat (A)
- Non-purine, selective inhibitor of Xanthine oxidase
- No dose adjustments in mild - mod renal and hepatic impairment
- 80-120mg per day
- ADR- Acute flare, ↑ LFTs
- Use contraindicated with 6-MP, azathioprine and theophylline

**Urate Lowering Therapy**

**Uricosuric agents:**
- **Probenecid (B)**
  - Start 250 mg BID, titrated every few weeks to a maintenance dose of 500-1000 mg 2-3x/daily
- **Losartan (B)**
  - An angiotensin II-receptor antagonist has been shown to have a modest uricosuric effect in a study of hypertensive patients by Wurzner et al.

**Urate Lowering Therapy**

**URAT-1 (Urate-anion exchange transporter) inhibitor – Lesinurad**
- Increases uric acid excretion
- Approved in combination with Xanthine Oxidase Inhibitors for treatment of difficult to treat hyperuricemia in Gout
- Nephrotoxicity noted when used alone.
- Contraindication:
  - CrCl less than 30ml/min, ESRD, Dialysis, Kidney transplant, Tumor Lysis synd and Lysch-Nyhan synd
New Treatments

- **IL-1 Beta Inhibitors**
  - NLRP3 inflammasome implicated in inflammatory response to gout crystals
  - Role – Acute and Chronic active gouty arthritis
    - Anakinra: IL-1 receptor antagonist
    - Rilonacept: IL-1 alpha and Beta soluble receptor antagonist
    - Canakinumab: fully human monoclonal antibody
      - SC administered
      - Role in treatment of acute flare and possibly prophylaxis
      - Rejected by FDA, approved by EU for acute treatment

### CPPD

- Precipitation of calcium pyrophosphate dihydrate crystals in connective tissue
  - Mostly presents in 6th decade of life
  - Slight predominance in women
  - Mostly asymptomatic

### Etiology and disease associations:

- **Strong**
  - Idiopathic-aging
  - Complication of primary osteoarthritis
  - Mechanical joint trauma or knee meniscectomy
- **Moderate**
  - Familial
  - Systemic metabolic syndromes
    - Hemochromatosis
    - Hyperparathyroidism
    - Hypomagnesemia
    - Dialysis –dependent RF

### Clinical Syndromes

- Asymptomatic with radiological findings-Chondrocalcinosis
- Pseudogout
- Pseudo-rheumatoid arthritis
- Pseudo-osteoarthritis
- Pseudo-neuropathic arthritis

### CPPD

- Chondrocalcinosis
  - Radiographic calcification in hyaline and or fibrocartilage
  - Radiographic surveys demonstrate an age related increase in prevalence
    - 65 - 74 yrs: 15%
    - > 84 yrs: 50%
    - Most are asymptomatic
    - > 50% of these patients have evidence of DJD
    - 25% of these will get pseudogout
**CPPD**

**Pseudogout:**
- Acute attacks of CPPD crystal-induced inflammatory arthritis mimic gout
- Major cause of monoarticular or oligoarticular arthritis in elderly
- Involves large joints - knees, wrist, ankle or MCPs.
- Rarely involves 1st MTP unlike gout
- Self-limited

**Synovial fluid analysis:**
- Elevated WBC count - varies 5,000 - 50,000
- Neutrophilic predominance
- Compensated polarizing microscopy:
  - Rhomboid or rod shaped crystal with faint positive birefringence
  - Acute attack - look for phagocytosed CPPD crystals
  - More difficult to see than urate crystals

**CPPD - SF analysis**

Blue when parallel to the Z’ axis

**CPPD and MSU crystals**

**CPPD - Imaging**

**Conventional radiography:**
- CPPD deposits appear linear radiopaque densities in fibrocartilage and hyaline cartilage
- Areas to focus on - Menisci of knees, triangular discs of distal radioulnar joint and glenoid labra
  - **Large subchondral cysts are a hallmark**
- Joint space narrowing
- Extensive subchondral sclerosis
- Numerous intra-articular bodies
  - Fragmentation of subchondral bone
- Hook osteophytes 2nd, 3rd metacarpal heads
Ultrasound findings

Diagnosis
Aspiration! Aspiration! Aspiration!
- Definitive diagnosis - demonstration of intracellular CPPD crystals
- +/- typical cartilage or joint calcification on imaging
- Screening for associated diseases
  - Serum calcium, phosphorus, magnesium, alkaline phosphatase, ferritin, iron, TSH
- 2nd and 3rd MCP joint osteoarthritis with beak osteophytes and chondrocalcinosis think of hemochromatosis

Treatment
Acute pseudogout
- NSAIDS
- Colchicine
  - 0.6 mg orally two or three times per day
- Steroids
- Joint aspiration
Prophylaxis
- Colchicine
  - 0.6 mg orally twice a day

Summary
- Common inflammatory arthritis
- Easily misdiagnosed
- Aspirate! Aspirate! Aspirate!
Basic Calcium Phosphate Dz

- Hydroxyapatite
- Dz association – OA (70% SF)
- Difficult to detect on SF analysis- non birefringent crystals
- Alizarin red S stain
- Milwaukee Shoulder / Knee Syndrome
  - Intra-articular and periarticular hydroxyapatite crystals
  - Large effusion, minimally inflammatory
  - + joint and surrounding structure destruction
  - + pain