PART ONE
- Osteoarthritis
- Rheumatoid arthritis
- Seronegative Spondyloarthropathies

PART TWO: THIS LECTURE
- Crystal induced arthropathies
- Polymyalgia Rheumatica
- Fibromyalgia
- Benign Tumors of the Joints
OBJECTIVES

- Describe the pathogenesis of gout.
- Describe the pathogenesis of calcium pyrophosphate deposition disease.
- Discuss the diagnostic findings of calcium pyrophosphate deposition disease.
- Compare and contrast gout, calcium pyrophosphate deposition disease, and basic calcium phosphate diseases.
- Compare and contrast the characteristics of tenosynovial giant cell tumors and synovial chondromatosis.
- Know the treatment approach for tenosynovial giant cell tumors and synovial chondromatosis.

CRYSTAL INDUCED ARTHROPATHY

- Gout
  - Monosodium urate monohydrate
  - Pseudogout
    - Calcium pyrophosphate dihydrate
    - Basic calcium phosphate
  - Inflammatory arthritis
  - Episodic and acute
  - Acute can occur
  - Crystals ingested by monocytes leading to recruitment of neutrophils

CRYSTAL ARTHROPATHY: EPIDEMIOLOGY

- Gout
  - 3% of general population
  - 0.5 million
  - Males >> Females
  - Age 65 and older 4.9%
  - Males 7% vs Females 3%
  - Ages 20-49 years 0.9%
  - Chronic hyperuricemia
    - 8.8 mg/dl
  - Women protected by uricosuric effect of estrogens
  - Additional risk factors: obesity, metabolic syndrome, diet (high purine diet, fructose), medications (thiazide diuretics & low dose aspirin)
**GOUT**

- Supersaturation of uric acid
- Crystal formation
- Crystals activate immune system
  - Trigger complement cascade which recruits neutrophils
  - Phagocytosis by monocytes activates intracellular inflammasome
  - Inflammasome activation leads to increased IL-1β


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**GOUT: HYPERURICEMIA**

- Overproduction or underexcretion
- Overproduction accounts for 10%
- Underexcretion by kidneys accounts for most causes
- Only 20% of hyperuricemic patients develop gout


PMCID: PMC3247913 

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3247913/

**URATE SYNTHESIS PATHWAY**
CLINICAL DIAGNOSIS

- Acute inflammatory arthritis
  - “Attack” or “Flare”
- Usually monarticular
  - Can be oligo or polyarticular
- Podagra
  - Acute involvement of 1st MTP
- Resolves in days to weeks
- Repeated attacks
  - Characteristic erosions (x-ray)
- Tophi
- Definitive diagnosis: demonstration of crystals on polarized microscopy


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Analyzer
Compensator
Polarizer

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URATE CRYSTALS

TOLPHI

XRAY: GOUTY EROSION
CALCIA PYROPHOSPHATE DEPOSITION DISEASE (CPPD)

- AKA Pseudogout
- Calcium pyrophosphate dihydrate crystals
  - Acute presentations similar to gout
  - Podagra not characteristic of pseudogout like it is with gout
  - Knees & wrists more involved. Elbows, shoulders, ankles
  - Inflammatory signs not always as severe as in gout
  - Chondrocalcinosis on x-ray imaging
  - Neither sensitive nor specific
  - Presentations
    - Asymptomatic (chondrocalcinosis on x-ray but no symptoms)
    - Acute
    - OA with CPPD (pseudoa with chondrocalcinosis—"pseudoOA")
    - Chronic CPP crystal inflammatory arthritis ("pseudoRA")

CPPD EPIDEMIOLOGY

- More common in older individuals
- Prevalence difficult to measure
  - Chondrocalcinosis: 55-55 years old: 4%, 80-84 years old: 18%, >85 years old: 27%
- Secondary Causes: hemochromatosis, hyperparathyroidism, hypophosphatemia, hypermagnesemia
  - Most are sporadic
  - Familial cases: very rare
CHONDROCALCINOSIS

- Calcium crystal deposition in menisci of the knee & triangular cartilage of the wrist
- Radiographic description, not a clinical presentation
- Observed in 20-85% of crystal proven CPPD, varying with age and joint examined
- Does not correlate with degree of symptoms


CALCIUM PYROPHOSPHATE CRYSTALS

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CPPD CRYSTALS IN CARTILAGE

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**CPPD TREATMENT**

- **Acute CPPD**
  - Similar to treatment for acute gout
  - NSAIDs, oral steroids (prednisone), steroid injection if appropriate, colchicine
  - Frequently, anti-IL1 therapy (anakinra)
- **Osteoarthritis with CPPD**
  - Similar to that for OA alone
- **Chronic CPP crystal associated inflammatory arthritis**
  - NSAIDs, low dose colchicine
  - In some cases, methotrexate, hydroxychloroquine
  - There is no equivalent to chronic urate lowering therapy used in gout

**A WORD ON BASIC CALCIUM PHOSPHATE CRYSTALS**

- Umbrella term for many crystals
  - Hydroxyapatite, octacalcium phosphate, trimetaphosphate, magnesium whitlockite
- Deposits in joints and soft tissue
  - Tendons, intervertebral discs, joint capsules, synovium, cartilage
- Close association with osteoarthritis?
  - Found in knee synovial fluid in 30-60% of subjects with knee OA
  - Presence correlates with severity of degenerative changes & joint effusion
- **Milwaukee shoulder**
  - Hydroxyapatite associated destructive arthritis
  - Elderly females with destruction of rotator cuff & glenohumeral joint
  - Monarticular but can be bilateral
  - Occasionally involves knees, hips, elbows, wrists

**Source:** American College of Rheumatology Image Library
POLYMYALGIA RHEUMATICA

- Autoimmune disorder
- Pain and stiffness in proximal joints and muscles
  - Shoulders and hips, neck muscles can be affected
- Constitutional symptoms: fatigue, malaise, anorexia, low-grade fever, weight loss
- Encountered in patients with Giant Cell Arteritis
  - discussed in Dr Gierut's lecture on vasculitis
- Not to be confused with polymyalgia
  - Autoimmune, inflammation of the skeletal muscles, predominantly proximal muscles


- Age 50 years and older, 2/3rds females
- Incidence rates increase with age
- Highest incidence rates in northern Europe, Scandinavian countries
- Highest incidence rates are from UK: 84/100,000 person-years
- Etiology—still unclear
  - Circulating monocytes/macrophages releasing IL-6
- Laboratory findings: increased ESR, CRP, IL-6
  - no serologies/antibodies like in rheumatoid arthritis or systemic lupus erythematosus
- Treatment:
  - Corticosteroids (prednisone)
  - Steroid sparing agents in selected cases (Methotrexate)
Classically characterized by chronic widespread pain & ≥11 tender points
- Rule out organic and mechanical causes of pain
- Not an autoimmune inflammatory condition
- Chronic widespread pain found in 5-15% of the population
- 1.5 times more likely in women
- Pathogenesis: unclear, complex and multifactorial
  - "stressors" can act as triggers—sensitivities, physical trauma, emotional stress
  - Risk factors: female gender, worry or expectation or chronicity, lack of control of the stressor, intensity of the initial symptoms, latency following stress
- Management: minimize chronic stressors (physical and emotional), restorative sleep
  - Pharmacologic: tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (fluoxetine), antiepileptic drugs (gabapentin, pregabalin)
TENOSYNOVIAL GIANT CELL TUMOR

- Most common benign neoplasm of the synovium
- Associated with translocation fusing the promoter of the collagen 6A3 gene to the coding sequence of M-CSF (macrophage colony stimulating factor)
- Diffuse TSGCT
  - Previously known as pigmented villonodular synovitis
  - Involve joint synovium
  - Monoarticular arthritis with recurrent swelling
  - Erosions develop
  - Knees in 80%, hip, ankle
  - Clustered mass of red brown hide, finger-like projections and nodules
- Localized type: circumscribed and contained
- Microscopic for both: resemble synoviocytes, and multiple hemosiderin-laden macrophages, osteoclast-like giant cells

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TENOSYNOVIAL GIANT CELL TUMOR

- Localized TSGCT
  - Giant cell tumor of tendon sheath
  - Painless mass involving wrist and finger tendon sheaths
  - Most common soft tissue tumor of the hand
  - Erosions in 15%
- Treatment surgical excision

https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B9781437717815000209?scrollTo=%23s0290
SYNOVIAL CHONDROMATOSIS

- Multiple nodules of hyaline cartilage within subsynovial connective tissue
- Can undergo enchondral ossification
- Osteochondromatosis
- Unclear whether it is a metaplastic or neoplastic process
- Benign and does not metastasize
- Joint pain, swelling, stiffness, crepitance
- Limited motion with locking or grating sensation on movement
- Knee most commonly affected
  - Hips, elbows, shoulders, and ankles
- Treatment: surgical excision of involved synovium & removal of loose bodies


CASE #1

- 53 year old female presents with 2 month history of joint pain and swelling
- Joints involved: bilateral 2nd-3rd metacarpophalangeal joints and wrists, right 4th proximal interphalangeal joint, left elbow and right knees
- Pain is worse in the morning, accompanied by stiffness lasting 3-4 hours
- Additional symptoms: fatigue, and occasionally subjective low grade fevers
- Medications tried: acetaminophen (did not help), ibuprofen (gives partial relief)
CASE #2

- 62 year old male presents to Emergency Department for acute onset right knee pain and swelling that began 2 days ago
- Symptoms began that morning with severe pain, patient unable to bear any weight
- Has never had these symptoms before, but did have an episode of pain and swelling in left forefoot 4 years ago which was also severe, but resolved in 3 days
- Pain is currently not improving
- No fevers or rash. No sick contacts. No other symptoms
- Started a new medication 1 month ago for hypertension, but cannot recall the name
- On exam, knee is red, hot, and exquisitely painful
**CASE #3**

- 71 year old female with over 10 years of pain in multiple joints
- Joints involved: multiple hand joints but worst at the proximal and distal interphalangeal joints, also at lower back and both knees
- Cannot tell if they get swollen, but she has noted bony nodules at her fingers, and cannot put rings on her fingers anymore
- Has had increasing difficulty with making a full grip in both hands
- Mother had similar problems with her hands
- Uses acetaminophen with partial relief

**CASE #5**

- 23 year old male with 6 months of lower back and upper buttock pain
- Now with right knee pain and stiffness
- Morning stiffness lasts 1 hour
- Minimal swelling, which is worse with extensive activity
- Tenderness to palpation at both sides of the upper buttock area, no tenderness at the right knee, but it is mildly swollen and warm to touch
- No history of rashes or gastrointestinal complaints
- No recent infections
CASE #6

- 30 year old female with 2 weeks hand pain and swelling
- Accompanied by morning stiffness lasting 45 minutes
- No fevers or chills, and not other joint pain
- Ibuprofen gives temporary relief
- No rashes or gastrointestinal complaints
- She is a kindergarten teacher