Crystal Arthritis

Gout

- Gout results from deposition of monosodium urate MSU monohydrate crystals in and around the tissues of joints causing attacks of acute inflammatory arthritis
- Gout is associated with hyperuricemia : serum uric acid levels greater than 6.8 mg/dL
    - Purine's metabolic end product is uric acid and it's normal level is 4-6.8 mg/dl
    - Uric acid levels do not correlate with the attack severity
    - Acute attacks may occur with normal levels
- The risk of gout and acute gouty attacks are strongly correlated to the degree of hyperuricemia however it is not a sufficient causative factor for the development of gout
    - Only about 20% of hyperuricemic patients develop gout (crystallization) during their lifetime which marks the step to clinical symptomatic gout
    - Asymptomatic hyperuricemia may last up to 10 years
- Hyperuricemia can be primary (idiopathic) or secondary (more common)
- Causes of secondary hyperuricemia
    - Decreased uric acid excretion : most common cause
        - Renal insufficiency : most common cause of hyperuricemia
        - Metabolic acidosis
        - Postmenopausal women
        - Hyperparathyroidism and hypothyroidism
        - Drugs : NSAIDs / aspirin / loop diuretics / thiazides
        - Alcohol consumption (ethanol)
    - Increased uric acid production
        - PRPP Synthetase overproduction (which synthesizes purines)
        - Lesch Nyhan syndrome : HGPRT deficiency which converts purines to other substances like alanine aka salvage pathways
        - Malignancies and Tumor lysis syndrome
        - Hemolytic anemia
        - Chemotherapy and radiation
        - Obesity and sleep apnea
        - Vitamin B12 deficiency
        - Hypertension, high cholesterol & triglycerides
- Renal underexcretion is the cause for 90% cases of hyperuricemia followed by uric acid overproduction
- Gout is more common in men (estrogen is a protective factor)
- Hyperuricemia occurs much more frequently in transplantation patients using cyclosporine than in the normal population
- Pathogenesis : prolonged hyperuricemia leads to tissue deposits of MSU crystals (microtophi) form in the synovium and on the cartilage
- Triggers of urate crystal deposition : high Uric acid levels / acidosis / low temperature (cool

peripheral joints)

- During an acute attack - microtophi break apart shedding a large number of MSU crystals into the joint space and activating synovial macrophages and fibroblasts that phagocytize the crystals - this leads to the activation of a cytosolic multiprotein complex NALP3 inflammosome - release of IL1 and inflammatory mediators
- Clinical Features of Acute gout attack
    - Triggers for acute attacks : sudden increase in uric acid after consumption of purine rich foods or alcohol / trauma / surgery / diuretics use / dehydration / stress
    - Severe sudden pain with erythema, swelling, warmth and decreased range of motion usually in 1 joint especially in the first ever attack (Asymmetrical distribution is common if more than one joint is affected)
    - Symptoms typically occur at night waking the patient
    - Symptoms peak after 12–24 hours and regress over days to weeks
    - Fever might be present
    - Tenosynovitis, bursitis and cellulitis may accompany
    - The most commonly involved joint is the first metatarsophalangeal joint (Podagra) followed by ankle
    - The patient is asymptomatic between attacks
- Clinical features of Chronic Gout
    - Develops 10 or more years after the onset of acute attacks due to untreated hyperuricemia
    - The pathognomonic feature of chronic gout is the tophus, a palpable painless nodular collection of MSU crystals in soft tissues (like ear pinna or tendons) & joints
    - These tophi lead to progressive joint destruction, joint deformities, chronic arthritis and dactylitis
    - Renal symptoms
        - Uric acid nephrolithiasis with low urine pH
        - Uric acid nephropathy : acute obstructive uropathy mainly seen with tumor lysis syndrome
- Diagnosis
    - Synovial fluid analysis is the gold standard for diagnosing gout
    - Aspirated synovial fluid appears cloudy, analysis shows inflammatory cells (neutrophils) and gram staining is negative
    - MSU Crystals are needle shaped, negatively birefringent and may be intracellular
    - Serum uric acid is not a diagnostically reliable test during acute flares since it may be normal or even low
    - Other tests like ESR, CRP and WBC are b elevated
    - Xray
        - Chronic gout : well defined punched out juxtaarticular erosions characterized by a sclerotic rim and overhanging edges are seen on xray (rat bites) : Uric acid is radiolucent
        - Acute gout : normal

    - Ultrasound : signs of joint inflammation and erosion / uric acid crystals are visualized (double contour sign) / tophi are visualized
    - Dual energy CT for deeper anatomical structures
- Treatment
    - Lifestyle modification : limit alcohol, purine- rich food and lose weight
    - Acute attack : NSAIDs (indomethacin or naproxen) / oral colchicine / glucocorticoids (oral, IV or intraarticular)
    - Chronic gout : Urate Lowering Therapy (3 types) if > 2 attacks per year and if tophi and joint destruction are seen
        - Uricostatic Therapy : first line
            - Xanthine oxidase inhibitors with decrease uric acid production
            - Include Allopurinol and febuxostat
            - Side effects : Rash / Steven Johnson syndrome
        - Uricosuric Therapy
            - Increase renal excretion of uric acid
            - Include Probenecid : not effective in patients with chronic renal failure
            - Side effects : urolithiasis / allergy
        - Uricolytic Therapy
            - Catalyzes the break down of uric acid into other metabolites
            - Includes IV Pegloticase
            - Contraindicated in patients with G6PD deficiency
        - IL1 antagonists like Anakinra
    - Prophylaxis using low dose colchicine or NSAIDs is usually recommended
- Complications
    - Nephrolithiasis
    - Uric acid nephropathy
    - Joint contractures

Pseudogout

- Pseudogout is a heterogeneous disorder that involves the intraarticular deposition of Calcium Pyrophosphate Dihydrate (CPPD) crystals in the hyaline cartilage
- The disease has 2 forms
    - Primary (idiopathic) : affecting old people over 70-80 : most common type
    - Secondary : joint trauma / metabolic abnormalities like hyperparathyroidism and hemochromatosis / familial chondrocalcinosis
- Pathophysiology : The crystals are phagocytized by resident synovial macrophages, activating the intracellular NALP3 inflammasomes leading to recruitment and influx of neutrophils into the joint space
- The most commonly involved areas are the knee menisci and the triangular fibrocartilage of the wrist
- The most common clinical manifestation is a peculiar type of osteoarthritis called

pseudoosteoarthritis : a non inflammatory arthritis involving joints not typically affected by osteoarthritis such as the wrist, shoulder and metacarpophalangeal joints

- Acute pseudogout attacks may be precipitated by trauma, surgery (parathyroidectomy) or severe medical illness
- Attacks are usually monoarticular or oligoarticular similar to an acute gouty attack and if left untreated they may last from a few days to a few months (polyarticular involvement have a more osteoarthritis-like presentation)
- Clinical features
    - Joint warmth, erythema and swelling in and around the affected joint resembling acute gouty arthritis
    - Fever and possibly systemic symptoms
    - Duration of attack is longer than gout but is self limited
- Diagnosis
    - Confirmed by assessing synovial fluid for the presence of intracellular rod or rhomboid shaped crystals, which exhibit weakly positive birefringence (with chondrocalcinosis)
    - A negative synovial fluid analysis does not rule out Pseudogout as CPPD crystals are weakly birefringent
    - Xray will reveal Chondrocalcinosis
    - Elevated ESR and leukocytosis
    - Normal serum uric acid
- There is no effective treatment to remove CPPD deposits from synovium or cartilage
- Treatment
    - Intraarticular glucocorticoid administration
    - NSAIDs
    - Colchicine
    - Systemic steroids
- In patients with frequent attacks, prophylactic daily low-dose colchicine may decrease the attack frequency