III B.SC BIOCHEMISTRY

CLINICAL BIOCHEMISTRY (16SCCBC9)

SEMESTER: VI

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GOUT AND HYPERURICEMIA

Gout is a common inflammatory arthropathy characterized by painful and swollen joints resulting from precipitating uric acid crystals. Decreased renal excretion and/or increased production of uric acid leads to hyperuricemia, which is commonly asymptomatic, but also predisposes to gout. Acute gout attacks typically manifest with a severely painful big toe (podagra) and occur most often in men following triggers such as alcohol consumption. Acute gouty attacks are treated with nonsteroidal anti-inflammatory drugs (e.g., naproxen or indomethacin), while management of chronic gout includes lifestyle modifications and possibly allopurinol to control hyperuricemia.

Epidemiology

- Sex: ♂ > ♀ (3:1)
- Age of onset: 30–60 years
- Prevalence: ~ 8 million people in the US
- Higher incidence in African Americans

Etiology

Gout

- Deposition of urate crystals into joints
- Hyperuricemia predisposes to gout
- Associations:
    - Diabetes mellitus
    - Hypertension
    - Hypercholesterolemia, hypertriglyceridemia
    - Anemia

Acute gouty arthritis is not always associated with elevated serum uric acid levels; it can also occur when serum uric acid is normal!

Hyperuricemia

- Uric acid is an end-product of purine metabolism that is renally excreted.
- Insufficient excretion or increased production of purines leads to hyperuricemia, possibly triggering a gout attack.
- May be primary or secondary.
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Primary hyperuricemia

- Idiopathic extracellular supersaturation of uric acid
- No history of comorbidities or medications that affect uric acid formation or excretion

Primary hyperuricemia is aggravated by poor dietary habits!

Secondary hyperuricemia

- Decreased uric acid excretion (most common)

    - Medications (e.g., pyrazinamide, aspirin, loop diuretics, thiazides, niacin)
    - Chronic renal insufficiency; lead nephropathy
    - Ketoacidosis (e.g., due to starvation, diabetes mellitus) and lactic acidosis
- Increased uric acid production
    - High cell turnover (e.g., tumor lysis syndrome, hemolytic anemia , psoriasis, myeloproliferative neoplasms, chemotherapy, or radiation)
    - Enzyme defects (e.g., Lesch-Nyhan syndrome, phosphoribosyl pyrophosphate synthetase overactivity, von Gierke disease)
    - High-protein diet
    - Obesity
- Combined decreased excretion and overproduction: high alcohol consumption

Pathophysiology

- Uric acid has poor water solubility, even under physiological conditions. Factors that trigger urate crystal deposition include:
    - ↑ Uric acid levels
    - Acidosis
    - Low temperature (e.g., cool peripheral joints)
- Crystalline arthritis: supersaturation of uric acid in extracellular fluid → intraarticular uric crystal precipitation (coated by IgGs) → phagocytized by polymorphonuclear cells → release of inflammatory mediators and enzymes → local joint inflammation
- Chronic effects: repeated attacks → aggregations of urate crystals and giant cells (tophi) → deformities and arthritis

Clinical features

Asymptomatic stage

- Hyperuricemia with no symptoms
- May last up to 20 years or even longer

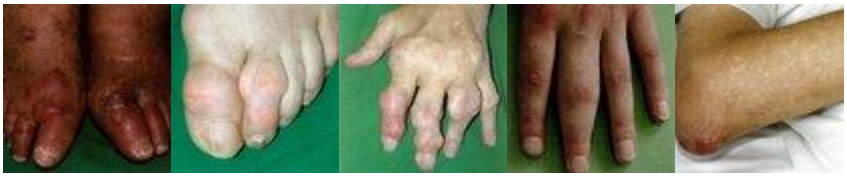
Acute gouty arthritis

- Triggers: anything that leads to hyperuricemia
- Arthritis: usually monoarticular during first attacks
    - Acute severe pain with overlying erythema, decreased range of motion, swelling, and warmth; possible fever
    - More likely to occur at night, typically waking the patient
    - Symptoms peak after 12-24 hours; regression may take days to weeks.
    - The recovering joint may present with desquamation of the overlying skin.
- Locations: Peripheral small joints in the lower extremities are especially affected.
    - Podagra: metatarsophalangeal joint (MTPJ) inflammation of the big toe is the most common site)
    - Gonagra: inflammation of the knee
    - Chiragra: inflammation of finger joints, esp. metacarpophalangeal joint of the thumb
    - Others: ankle and tarsus, other toe joints, wrist, elbow

Chronic gouty arthritis

- No longer common
- Progressive joint destruction

- Tophi formation
    - Multiple painless hard nodules with possible joint deformities
    - Bone tophi: urate crystal deposition in bones (e.g., elbows, knees, extensor surfaces of forearms)
    - Soft tissue tophi: urate crystal deposition in the pinna of the external ear, subcutis, tendon sheaths, or synovial bursas
- Renal manifestations with uric acid nephrolithiasis and uric acid nephropathy



Diagnostics

- Arthrocentesis
    - Indications
        - New-onset acute gout attack
        - If past suspected gout attacks were not confirmed via polarized light microscopy
    - Polarized light microscopy findings: needle-shaped, negatively birefringent monosodium urate crystals
    - Synovial fluid: WBC > 2000/μL with > 50% neutrophils
- Laboratory tests
    - ↑ Serum uric acid levels
    - Typical in acute attacks: ↑ WBC and ↑ ESR
    - Testing for ↑ renal uric acid may be indicated in some cases (see extra information for more details).
- Imaging
    - Ultrasound

        - "Double-contour" sign representing hyperechoic monosodium urate crystals covering hyperechoic bone contour
        - Tophus (a mixture of hyperechoic and hypoechoic structures)
    - MRI
        - Excellent measure to detect tophi formation
        - Method of choice to detect spinal involvement
    - CT: can detect bone erosions as well as tophi
    - X-ray
        - Acute gout attack: not useful, as early changes cannot be detected
        - Chronic gout: radiopaque soft tissue , punched-out lytic bone lesions with spiky periosteal appositions

Pseudogout (CPPD)

- Short description: paroxysmal joint inflammation due to calcium pyrophosphate crystal deposition (calcium pyrophosphate dihydrate)
- Epidemiology
    - Sex: ♂ = ♀
    - Age of onset: adults > 50 years of age
- **Etiology**
    - Mostly idiopathic (primary form)
    - Secondary form: joint trauma, familial chondrocalcinosis, hyperparathyroidism, hemochromatosis, gout, hypophosphatemia
- **Clinical presentation**
    - Often asymptomatic

- Acute (pseudogout attack): monoarthritis (rarely oligoarthritis), mostly affecting the knees and other large joints (e.g., hips, wrists, and ankles)
- May become chronic (can affect multiple joints)
  - Osteoarthritis with CPPD (most common form of symptomatic CPPD): progressive joint degeneration with episodes of acute inflammatory arthritis typical of pseudogout attacks

- **Diagnosis**
  - Arthrocentesis should be performed, especially in acute cases.
    - Polarized light microscopy: detection of rhomboid-shaped, positively birefringent CPPD crystals
    - Synovial fluid findings: 10,000-50,000 WBCs/μL with > 90% neutrophils
  - X-ray findings: cartilage calcification of the affected joint (chondrocalcinosis)
    - Fibrocartilage (meniscus, annulus fibrosus of intervertebral disc) and hyaline cartilage (joint cartilage) may be affected.
  - Test for hypercalcemia (esp. hyperparathyroidism).
  - Serum uric acid levels are normal.
- **Treatment**
  - Asymptomatic cases do not require treatment unless there is an underlying condition (e.g., hyperparathyroidism).
  - Symptomatic treatment (similar to gout)
    - Best initial treatment: NSAIDs
    - Alternatives: colchicine or intra-articular corticosteroids
  - Arthroscopic lavage may also be considered
  - Possible joint replacement

Treatment

Acute gout attack

- NSAIDs (e.g., indomethacin, naproxen, ibuprofen)
    - Indications: patients who cannot tolerate oral glucocorticoids or colchicine
    - Initiate as soon as symptoms occur.
    - Discontinue 2–3 days after symptoms resolve.

The use of aspirin in acute gout attacks is contraindicated as it inhibits uric acid excretion, thereby delaying the cessation of symptoms.

- Colchicine: inhibition of microtubule polymerization → inhibits phagocytosis of urate crystals, leukocyte activation and migration, and cell chemotaxis.
    - Indications: patients who cannot tolerate NSAIDs (e.g., patients with chronic kidney disease or gastrointestinal ulcers) or oral glucocorticoids
    - Prophylaxis: prevents flares of acute or recurrent gouty attacks in patients beginning uricosuric agents (e.g., probenecid) or xanthine oxidase inhibitors (e.g., allopurinol)
    - Side effects: diarrhea, nephrotoxicity, and myelosuppression
- Oral glucocorticoids (e.g., prednisolone)
    - Indications: no response or contraindications to NSAIDs and colchicine
    - Dose should be tapered gradually (over the course of 2 weeks)
- Intra-articular corticosteroids
    - Indications: particularly with single-joint involvement
    - Fewer systemic side effects compared with oral corticosteroids
- Local ice therapy may help relieve pain.
- Rest the affected joint to avoid recurrence.

Proton pump inhibitors should be given to patients being treated with both NSAIDs and glucocorticoids to avoid gastrointestinal ulcers.

Chronic gout

General measures

- Weight loss (if applicable)
- Purine-restricted diet (e.g., low-protein diet)
- Reduce alcohol consumption
- Sufficient/high fluid intake
- Close management of diabetes and blood pressure
- Consuming dairy products, vitamin C, and coffee can lower levels of uric acids and therefore prevent gout.

Medical therapy

- **Indications:**
  - Recurrent gout (e.g., more than 2 gout attacks per year)
  - Uric acid nephropathy
  - Tophi development
  - Serum uric acid > 9 mg/dL
- **General approach:**
  - Delay initiation of urate-lowering medication until ~ 2 weeks after an acute attack has resolved
  - Despite their therapeutic effect, urate-lowering medications may trigger or prolong an acute gout attack.

- Urate-lowering drugs should be combined with colchicine