Crystalline Arthropathies: Gout

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Crystalline Arthropathies

- **Gout** – monosodium urate (MSU)
- **Pseudogout** – calcium pyrophosphate dihydrate (CPPD)
- **Calcium hydroxyapatite (HA)**
- **Calcium oxalate (CaOx)**
Gout

Henry William Bunbury, 1815
Gout

- James Gillray – 18th century artist, famous for his political and social satire.
Gout

- Men >> Women
  - Men: dramatic rise in urate levels at puberty
  - Women: gradual increase, maximum levels after menopause
    - Estrogen promotes uric acid excretion

- Older age
  - 9% of men >80 years have gout

- Increased prevalence in African Americans
Urate Metabolism

- Uric Acid: weak acid, most commonly exists as urate

- Solubility in joint fluid influenced by many factors:
  - Temperature – 1st MTP
  - Nidus for crystal formation – OA
  - Dehydration – nocturnal onset
Urate Metabolism

Diet

Purine intake contributes significantly to blood uric acid; about 1/3 of total urate

Synthesis

10% patients are over-producers

Excretion

90% patients are under-excreters
Urate Metabolism: Synthesis

From Primer on Rheumatic Diseases, 13th ed.
Urate Metabolism: Over-Production

- Salvaged purine from increased cell turnover
  - tumor lysis, psoriasis, hematologic malignancies
- Inborn error of metabolism (PRPP synthetase or HPRT)
  - X-linked traits
Stages of Classic Gout

Asymptomatic Hyperuricemia

Acute Intermittent Gout

Chronic Tophaceous Gout (Advanced Gout)

Symptom-free Intercritical Periods
Asymptomatic Hyperuricemia

- **Hyperuricemia**: serum urate > 2SD above mean value (gender & age-matched)
  - ULN 7.0-8.0 mg/dL
  - Serum urate > 6.8 mg/dL exceeds soluble concentration of MSU
- Common: up to 40% population
- Hyperuricemia causes:
  - 90% - underexcretion
  - 10% - overproduction
Vast majority will never develop gout or complications

Risk of developing gout increases with urate levels:

- Urate 7-8 mg/dL – 3%
- Urate >9 mg/dL – 22%
Hyperuricemia: Link to Obesity and Insulin Resistance

- Weight reduction is associated with a decline in urate levels
  - Lower de novo purine synthesis
- Exogenous insulin reduces renal excretion of urate
  - Increased urate reabsorption URAT1 exchanger
  - Stimulation of Na+ dependent co-transporter in PCT
Stages of Classic Gout

- Asymptomatic Hyperuricemia
- Acute Intermittent Gout
- Chronic Tophaceous Gout (Advanced Gout)
- Symptom-free Intercritical Periods
Acute Intermittent Gout

“He goes to bed and sleeps well, but about two a clock in the morning, is waked by the pain, seizing either his great toe, the heel, the calf or the ankle. This pain is like that of dislocated bones, with the sense as it were of cold water, poured upon the membranes of the part affected; presently shivering and shaking with a feverish disposition. Pain is first gentle, but then comes to its height, resembling a violent stretching or tearing of ligaments, sometimes a gnawing of a dog. Such a quick and exquisite pain, that it is not able to bear the weight of the cloths upon it, nor walking in the chamber.”

Thomas Sydenham, 17th century physician, who wrote of his personal experiences with gout
Acute Intermittent Gout

- Usually occurs after decades of asymptomatic hyperuricemia
- Rapid development of warmth, swelling, erythema and pain
  - May resemble cellulitis
- Escalates over 8-12 hours
- Systemic symptoms are common
Acute Intermittent Gout

- Monoarticular
- Podagra ("foot trap") is initial presentation in 50% patients
  - Occurs eventually in 90% of patients
- Lower extremity predominant disease
  - Exception – little old ladies on diuretics
  - Gout likes to go to areas of damage
- Typically self limited; resolves within 1-2 weeks
Podagra
Acute Intermittent Gout

Provocative Factors

- Sudden change in serum urate level
  - Trauma (even minor) – rapid efflux of free water from the joint → sudden increase in synovial fluid urate concentration
  - Alcohol – accelerated breakdown of ATP → acute rise in uric acid production
    - Beer – contains guanosine, which is catabolized to uric acid
    - Beer >>> liquor >> wine
  - Severe medical illness – increased degradation of ATP
Acute Intermittent Gout

Provocative Factors (continued)

- **Diet** – purine rich foods
  - Organ meats, red meat, pork, shrimp, scallops, tuna
  - Spinach, mushrooms, asparagus, beans/lentils
- **Drugs** – due to rapid change in urate levels
  - Allopurinol – destabilize microtophi during rapid change in serum uric acid concentration
  - Thiazides – selectively interfere with urate excretion at PCT
  - ASA – low dose (<2 g/d) impairs uric acid excretion, but hi doses cause uricosuric effect
Acute Intermittent Gout

Provocative Factors (continued)

- Drugs contributing to hyperuricemia:
  - Under-excretion
    - Thiazides, furosemide, insulin, ?beta-blockers
  - Urate re-absorption
    - Pyrazinamide, low dose salicylates
  - Urate over-production
    - Cytotoxic drugs, ?warfarin
- Drugs that enhance excretion:
  - probenecid, losartan, high-dose salicylates
Acute Intermittent Gout

- **Intercritical periods** – symptom free periods between attacks
- Interval may initially be years → then attacks become more frequent, longer duration, involve more joints
- MSU crystals can still be identified in the affected joint
Gout in Special Populations

- Women
- Organ Transplant Patients
- Normouricemic Patients
Gout in Women

- May only account for 5% of all gout patients
  - Estrogen promotes UA excretion
- Postmenopausal women
  - 90% of women with gout
  - Diuretics
  - Renal insufficiency
  - Nodal OA
Organ Transplant Patients

- Cyclosporine & tacrolimus induced hyperuricemia
  - Increased urate re-absorption
    - 75-80% of heart transplant patients
    - 50% of kidney and liver transplant patients
  - Gout: 1 in every 6 patients
    - Shorter asymptomatic hyperuricemia phase
    - Rapid tophi development and progression to chronic arthritis
    - Symptoms may be atypical or less dramatic due to chronic steroid use
Normouricemic Gout

- Ensure you have the correct diagnosis (crystal microscopy)
- Serum urate levels may be normal despite chronic hyperuricemia
  - Normal uric acid in 1/3-1/2 of patients during acute attack
  - Shift in uric acid stores
  - Adrenal stimulation, ACTH release → uricosuric effect
- Drugs: ARBs, fenofibrate, high dose salicylates
Stages of Classic Gout

1. Asymptomatic Hyperuricemia
2. Acute Intermittent Gout
   + Symptom-free Intercritical Periods
3. Chronic Tophaceous Gout
   (Advanced Gout)
Chronic Tophaceous Gout
Chronic Tophaceous Gout

- Usually takes about 10 years to develop
- Chronic, persistent pain and inflammation
- Asymmetric polyarthritis
- Tophaceous deposits
Chronic Tophaceous Gout

- Tophi can occur anywhere
  - Ears, knees, olecranon bursae, Achilles
  - Pressure points, nodal OA
  - Renal pyramids, sclerae, valves
Chronic Tophaceous Gout

- **Histopathology**
  - Foreign body granuloma around a core of MSU crystals with macrophages, fibroblasts and lymphocytes

- **Microtophi may be in the synovium**
  - Minor trauma or changes in urate concentration can release crystals and precipitate an attack
Chronic Tophaceous Gout

- Incidence declining
- Takes 11.7 years (ave) to develop a tophus
- Average serum uric acid level 10.3 mg/dL
- Risk factors: early age of onset, 4+ attacks/year, upper extremity involvement, long periods of untreated disease
Chronic Tophaceous Gout
Gout & Renal Disease

- Chronic urate nephropathy
  - MSU crystal deposition in medulla & pyramids
  - Multiple contributing factors – HTN, DM2, CAD

- Acute urate nephropathy
  - Acute renal failure in setting of tumor lysis syndrome
  - Uric Acid:Cr >1.0

- Uric acid nephrolithiasis
  - Occurs in 10-25% of patients with gout
  - May precede development of gout in 40% people
  - Calcium stones still most common
Gout Pathophysiology

- Inflammatory reaction to MSU crystal deposition in synovial tissue, bursae, and tendon sheaths
- Neutrophilic synovitis
- IL-8, IL-1, LT B4, complement, TNF alpha
Gout Diagnosis

- Clinical dx, confirmed with demonstration of MSU crystals in synovial fluid or tophi
  - crystals may still be detected in the synovial fluid between attacks
- Needle shaped, negatively birefringent, intracellular crystals
- Inflammatory synovial fluid: cell count 5,000-80,000
- 24hr urinary uric acid if suspect overproduction
  - > 800 mg suggests overproduction
Gout Diagnosis

- Serum uric acid levels may be elevated, normal or low

Gout Radiographic Features

- Takes many years of chronic disease
- Preserved joint space until very late in course
- Cystic changes
- Well defined erosions
- Punched out lytic lesions with overhanging edges: “Martel’s sign” or G sign
- Soft tissue calcified masses (tophi)
- Juxta-articular osteopenia is minimal/absent
Gout Radiographic Features
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Gout Management

- Treatment of acute attack
- Prophylaxis
- Urate lowering therapy
Gout Treatment – Acute Attack

**NSAIDs**
- No specific NSAID is superior
- Administration as soon as possible after onset of symptoms
- Moderate-high doses
- GI, renal toxicities
- Cardiac safety
Gout Treatment – Acute Attack

Steroids

- Systemic vs. intra-articular injection
- Moderate-large doses are required (30-60 mg/day)
- Taper over 14+ days
- Monitor for toxicities
Gout Treatment – Acute Attack

ACTH

- Effective within hours
- Superior to indomethacin
- Stimulates adrenal glucocorticoid release
- Expensive, not universally available
Gout Treatment – Acute Attack

**Anakinra** (Kineret)

- IL 1 receptor antagonist
- Effective, rapid onset
- Expensive
- Immunosuppression
Gout Treatment – Acute Attack

Colchicine
- No longer recommended as first line agent for treatment of acute attacks
- Relatively long time to suppress attack
- Narrow therapeutic window
- IV colchicine – anaphylaxis
Gout Treatment – Acute Attack

- Never **start** uric acid lowering therapy during acute attack
  - (allopurinol, febuxostat)

- Don’t **stop** chronic uric acid lowering therapy during acute attack
Gout – Prophylaxis

- **Colchicine** - low dose 0.6 mg once daily
  - Modulate nephrophil endothelial adhesion
  - Suppress crystal-induced activation of the inflammasome

- Clinical scenarios:
  - 1st 6 months of anti-hyperuricemic therapy
  - Tophacous gout

- Expensive; only available as brand name “Colcrys”
Gout – Prophylaxis

Colchicine Toxicities

- Hepatic metabolism: CYP450, 3A4
- Renally cleared, not dialyzable
- GI, diarrhea
- Neuromyopathy
- Bone marrow suppression
- Monitor CBC, CMP, CPK at least every 3 months
Gout Treatment – Urate Lowering Therapy

- Goal serum UA < 6 mg/dl
- Diet, lifestyle modifications
  - Weight loss
  - Low purine diet, EtOH avoidance, maintain good hydration
- Pharmacologic therapy
Urate Lowering Therapy

Pharmacologic therapy

- Xanthine Oxidase Inhibitors
  - Allopurinol
  - Febuxostat

- Uricosuric agents
  - Probenecid

- Other
  - Pegloticase, rasburicase
Uric Acid Lowering Therapy

Indications:
- 3 or more attacks per year
- Tophacous gout
- Erosions
- Recurrent nephrolithiasis
Allopurinol

- Inhibits xanthine oxidase, interfering with conversion of hypoxanthine & xanthine → uric acid
- Dose: start 100 mg/day, titrate up every 2-3 weeks based on uric acid level
  - Adjust for renal function
- Max dose 300-800 mg/day
- Hepatic metabolism, renal excretion
- Adverse Reactions
  - Gout flare
  - Minor dermatitis, itching
  - GI upset
  - Elevated LFTs
Allopurinol Hypersensitivity Syndrome

- Rare, but potentially fatal side effect
  - HLA-B*5801 (Han Chinese, Thai, or Korean)
- Dose-dependent
- Renal insufficiency
  - Eosinophilia
  - Severe dermatitis / Stevens-johnson Syndrome
  - Vasculitis
  - Hepatic necrosis and failure
  - Renal failure
Febuxostat (Uloric)

- Newer XO inhibitor safer for use in patients with CKD
- Dose: 40-80 mg PO QD
- Different mechanism than allopurinol
- Hepatic metabolism
- Adverse Reactions
  - CVA, MI
  - Transaminitis
- 30 pills (40 mg) = $160 [vs allopurinol ~$4]
Probenecid

- Use for “under-excreters” <600 mg/24hr
- Inhibits renal tubular urate resorption
- Dose: 250-500 mg bid, titrate up to 2 g/day
- Hepatic metabolism, renal excretion
- Ineffective if have moderate renal impairment
  - CrCl <50 mL/min
- Incr risk of urolithiasis

Adverse Reactions
- Hemolytic, aplastic anemia
- Hepatic necrosis
- Anaphylaxis
- GI upset
- Dermatitis
Other Uricosuric Agents

- Losartan
- Fenofibrate
- Atorvastatin
- Guaifenesin
Other Uric Acid Lowering Therapies

- **Pegloticase** (Krystexxa) – refractory tophaceous gout
  - Rasburicase (Elitek) – tumor lysis syndrome hyperuricemia
- Recombinant uricase
  - Converts uric acid to allantoin, which is an inactive, soluble metabolite, readily excreted by kidneys
- Pegloticase - IV infusion, every 2 weeks
- Screen for G6PD deficiency
- High risk of anaphylactic reactions
- Rapid reduction in UA levels, watch for gout flares
Thank you!

Questions?