The Evolution of Gout

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- Financial: None
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Educational Objectives:
- Evolutionary pressures favoring hyperuricemia
- Adverse effects of hyperuricemia
- Management of hyperuricemia
**Elevated Uric Acid**
- Higher Primates
- Giraffes
- Dalmatian Dogs

What are the evolutionary pressures leading to hyperuricemia?

**Benefits of higher Uric Acid levels**
- Adjuvant Effect on Immune System
  - Humeral
  - Cell Mediated
- Up regulation of Blood Pressure
- ?Antioxidant benefits
- ?Improved cognitive function
Benefits of higher Uric Acid levels

- Loss of Uricase Gene occurred independently on multiple occasions
- Higher Uric Acid levels in primates is NOT an accident
- On a “Primitive” diet-Levels still lower than seen in modern society, ~3 mg/dl

Early History

- Skeletal evidence of gout has been found in Egyptian mummies from 4000 years ago.
- Written evidence of the disease begins with the Hippocratic writings from about 400 BC.
- Colchicine, a natural plant alkaloid, has been used to treat gout for over 2000 years.

- Explosion of gout in literature and art after the middle ages.
- It became the “in” disease to have
Increased Prevalence or Increased Popularity in Literature and Art?

- Rich Food
- Increased alcohol intake
- Wine stored in lead lined jars

Alcohol – Not Just for Parties

- Water was not fit for human consumption, especially in heavily populated cities
- Alcohol based drinks were often only safe oral hydration
Alcohol – Not Just for Parties

- Alcohol, especially beer, increases risk of gout
  - Purine rich content
  - Alcohol inhibits excretion of Uric Acid
- 1 beer/day
  - Increases Uric Acid by 0.4mg/dl
  - Increases risk of gout by 50%
- Wine and hard liquor have less effect

20TH Century

- Got the lead out, then put it back in
  - Saturnine gout from moonshine
- Alcohol consumption was curtailed with prohibition and safer water sources
- Along came high fructose corn syrup, diuretics and other drugs.

Drugs causing Hyperuricemia

- Diuretics
- Ethanol
- Cyclosporine A
- Lead nephropathy
- Low-dose aspirin

Fructose raises uric acid levels

**Fructose**
- Raises uric acid 0.4 mg/dl with higher intake
  - 50% increase in gout risk (= 1 beer/day)
- Independent of age, alcohol, diuretics, HTN, BMI, renal function
- Fructose increases ATP degradation to AMP to Uric Acid
- IV infusion of fructose quickly raises Uric Acid levels
- Glucose does not have this effect
- Fructose increases insulin resistance

**Choi et al: A & R, 59, 309, 2008**

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**Gout Associated Diseases**
- Hypertension
- Peripheral, Carotid, Coronary Vasc. Ds.
- Metabolic Syndrome
- Stoke and Vascular Dementia
- Preeclampsia
- Renal Insufficiency
- Increased CRP
Evidence Linking Uric Acid and Hypertension

- An elevated uric acid level consistently predicts the development of hypertension.

- An elevated uric acid level is observed in 25–60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.

NEJM 2008; 359: 1811-1821

Gout Associated Diseases

- Cause and Effect or Guilt by Association?

- Will treating hyperuricemia prevent associated diseases?

Evidence Linking Uric Acid and Hypertension

- In adolescents, reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure, with hypertension of recent onset

- Withdrawal of xanthine oxidase inhibitors is followed by return of hypertension

JAMA. 2009 Jan 21;301(3):270

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Evidence Linking Uric Acid and Hypertension

- Raising the uric acid level in rodents by inhibiting uricase results in hypertension with the clinical, hemodynamic, and histological characteristics of hypertension.
- Allopurinol reverses all these changes.
- Renal changes of HTN prevented by allopurinol and losartan, but not by HCTZ even though HTN controlled.
- Appears to work through stimulation of renin-angiotensin system.

ESRD and Hyperuricemia

- Allopurinol reduces risk of ESRD.

VA mortality and allopurinol study

- VA retrospective study
  - 9,924 with gout and Uric Acid > 7.0
  - Those treated with allopurinol had more CV risk factors than those not treated.
  - Despite increased risk factors, there was a 23% reduction in mortality in patients treated with allopurinol vs. those not treated.

Possible Mechanisms of Action

- Stimulation of Cholesterol rafts in blood vessel walls
- Arterial Stiffness
- Elevated CRP/Inflammation
- Hypertension
- Activation of Renin-Angiotensin system
Unanswered Questions

- Do we screen for asymptomatic hyperuricemia?
- Do we treat asymptomatic hyperuricemia?

Treatment of Gout in 2010

In all of Rheumatology, nothing is easier to treat, yet so often screwed up

Why is it so screwed up?

- Ineffective dosing of allopurinol
- Patient and doctor don’t appreciate that it takes 6-12 months with uric acid <6 before patient is free of gout attacks
Presentation of Gout

- Normally presents in middle aged males
  - Acute Podagra
  - Polyarticular Gout

- Presentation in older patients may be quite atypical

Subtle gout
Diagnosis of Gout

1. Positive Crystals from Joint, or
2. Positive Crystals from Tophus, or
3. 6 of 12 of following:
   - >1 attack of acute arthritis
   - Max. infl. <24hr of onset
   - Acute attack monoarticular arthritis
   - Joint redness
   - Podagra
   - Unilateral podagra
   - Acute Mid foot arthritis
   - Suspected tophus
   - Hyperuricemia
   - Radiographic swelling
   - Radiographic cysts
   - Negative joint culture

Arthritis & Rheum 1977; 20: 895-900

Treatment of Gout

- **Acute Attack**
  - NSAIDs
  - Colchicine
  - Corticosteroids
  - IL-1 Inhibition*

- **Chronic**
  - Allopurinol
  - Probenecid
  - Febuxostat
  - Pegloticase*
  - Colchicine

* Not FDA approved yet
Treatment of Hyperuricemia

- Asymptomatic Hyperuricemia
  - ? No Active Medical Management
  - Modify Life-Style
    - Wt. Loss, Avoid Purine rich foods
    - Decrease ETOH
    - Avoid Diuretics, ASA
    - Use Losartan if appropriate for HTN control

Treatment of Gout

- 1-3 Attacks per Year
  - Treat Acute attacks with full dose NSAIDS
  - Colchicine
  - Steroids
  - IL-1 Inhibitors (unapproved)

NSAID side effects

- GI bleeds
- Acute Renal Insufficiency
- Elevated Blood Pressure
- Worsening of CHF
- CNS effects, especially indomethacin
- Chronic Cardiac effects
- No long term benefit for gout

Colchicine for Acute Attack

- IV colchicine taken off market
- High dose: 0.6 mg q hour x 6-8
  - 33% effective at aborting attack
  - 100% toxicity
- Low dose: 1.2 mg stat, 0.6 mg 1 hour later
  - 38% effective at aborting attack
  - 10% toxicity
Corticosteroids

- Very effective
- PO, IV, IM, Intra-articular
- Inexpensive
- Use with care in diabetic patients
  - Minimal risk of GI problems with short term use
  - No Renal risk
  - Transient HTN and CHF risk
  - May have CNS effects in sensitive patients

IL-1 Inhibition

- Anakinra (Kineret)
- Rilonacept (Arcalyst)
- Canakinumab (Ilaris)

  - Effective in aborting an acute attack
  - Effective in preventing attacks
  - Few contra-indications
  - Unapproved for gout (but available)
  - Ultra expensive at present
    - $2 – 20,000 / month

Treatment of Gout - Chronic

- >3 Attacks per Year
  - 24 hour Urine for Uric Acid (<750 mg/24 hr.)
    - Under excreter – Probenecid (1-2gm/day)
      - Increases risk of kidney stones
    - Over producer – Allopurinol (or Febuxostat)
      - Start low (100 mg) and gradually increase
      - Maximum dose **800 mg/day**
      - Lower dose if Renal Insufficiency
      - Treat to get Uric Acid under 6

Allopurinol

- 66% of gout patients do **NOT** achieve target goal with 300 mg Allopurinol per day
- Yet <3% of patients treated are treated with >300 mg Allopurinol per day
- Average dose of 4mg/kg required to achieve target goal = 400 mg/day average
Febuxostat (Uloric)–Approved 2009

- **Compared to Allopurinol**
  - Same mechanism of action
  - Both inhibit azathioprine/6-MP catabolism
  - May have more effective dosing with renal insufficiency
  - Can use in Allopurinol allergic patients
  - Dose: start with 40 mg/day, can increase to 80mg/day
  - Because of cost and “new drug” issues, allopurinol should still be standard initial therapy for most patients
  - Cost $160/month vs. $5/month for allopurinol

Pegloticase

- PEG-Porcine Uricase
  - IV q 2 weeks
  - Very effective at lowering Uric Acid levels to 1-2 mg/dl range
  - Very effective at rapidly reducing tophi
  - FDA approval pending

Colchicine for Prophylaxis

- 0.6 mg BID
  - Reduces flares by 75% during first 6 months of urate lowering therapy

The Colcrys Story

- Colchicine grand-fathered in with formation of FDA, hence not “FDA approved”
- Grand-fathered drugs can gain FDA approval with submission of limited safety data, most of which was done with generic “unapproved” colchicine
- Once approved they can be granted 3 years exclusivity and can sue to have non-approved versions taken off the market
- Most manufactures of generic Colchicine have stopped production under threat of suit
- Result: a $0.10 pill has become a $5.00 pill
Success
- Patient and Physician Education
- Prophylaxis for acute attacks
- Treat to Target
- Perseverance and Compliance

Evolution of Hyperuricemia
Too much of a good thing, isn’t such a good thing

The Evolution of Man and Gout