GOUT, HYPERURICAEMIA, AND CRYSTAL ARTHRITIS

Michael L Snaith

Classic podagra: acute gouty arthritis of first metatarsophalangeal joint.

Chronic, relatively painless, tophaceous gouty arthritis of fingers, probably due to patient's long term treatment with diuretics.

Acute gouty olecranon bursa. This, the patient's first attack of gout for many years, occurred after major bowel surgery.

The term gout is sometimes loosely used to describe an acutely painful foot, but it is best reserved for those cases where deposition of crystals of uric acid (urate) is thought to be the cause of pain. The big toe (first metatarsophalangeal) joint is the classic site for urate gout, and an overweight, overindulgent man is the traditional sufferer. However, a substantial minority of patients (perhaps 30%) first get their gout at another site (such as other parts of the foot, the knee, the hand, or the shoulder), and, with more older women in the population and the widespread use of diuretics (which raise blood urate concentrations), this traditional view needs revising.

Gout is a condition of occasional attacks and long periods of remission. The prevalence of people at risk is therefore quite different from the incidence of actual attacks: a general practice with a list of 2000 patients might have 15 men and 3 women with a tendency to gout. Although most such patients are managed in primary care, acute gout may be precipitated by diuretics or by stresses such as acute infection, ketosis, or surgery, and cases therefore also crop up in hospital.

Chronic gouty arthritis is not common but can still be found, even though in most cases it can be treated and prevented. The *x* ray appearance is characteristic and should not be confused with other forms of arthritis. Tophi develop mainly in the ear but also occur elsewhere.

Hands of patient with chronic gouty arthritis (top) and his radiographs (bottom). Note lack of periarticular osteopenia and that the punched out erosions, especially at the right little finger proximal interphalangeal joint, are a little further away from joint margin than would be found with rheumatoid arthritis.

Chronic gouty arthritis may come to resemble other forms of inflammatory synovitis, such as here, with dorsal swelling of the wrist (left) and bilateral large knee effusions (right), from which urate crystals were identified. The arthritis resolved on appropriate treatment.

Acute gout

The most important differential diagnosis for acute gout is infection

Urate crystals from synovial fluid viewed with compensated polarised light: about the same length as the diameter of a polymorphonuclear leucocyte and negatively birefringent (coloured yellow when aligned parallel to axis of slow vibration of the red compensator inserted between polariser and analyser, and coloured blue when not so aligned).

Treatment of acute gout

Non-steroidal anti-inflammatory drugs or Colchicine
Avoid aspirin
Do not treat with allopurinol or uricosuric drugs

Diagnosis

Few things are as painful as a severe attack of gout: it often develops overnight and reaches a peak within hours so that, with an affected foot, it is impossible to bear weight or even the touch of bedclothes. The skin is red and may peel; nothing else except infection causes this, so infection is the most important differential diagnosis. Left to itself (which it rarely is) acute gout will start to improve in a week or two but will not settle completely for about a month.

A slight fever, leucocytosis, raised erythrocyte sedimentation rate and plasma viscosity, and increased C-reactive protein concentration are all non-specific indicators of inflammation and will be variably abnormal depending on the severity of gout. Blood urate concentration cannot be relied on to confirm or exclude gout: in a small proportion of cases it is normal during an attack but raised at other times. If it is feasible, fresh synovial fluid or tissue should be examined under polarised light for the presence of urate crystals, which can usually be clearly distinguished from pyrophosphate crystals of pseudogout.

Management

Non-steroidal anti-inflammatory drugs are much more effective for acute gout than any analgesic. A history of peptic ulcer is a relative contraindication, but appropriate H_2 blockade should permit treatment with non-steroidal anti-inflammatory drugs in most cases. There is no clear advantage in any one preparation, but a large dose of naproxen (1.5 g) or indomethacin (150 mg) on the first day, being reduced thereafter, is known to be effective. When non-steroidal anti-inflammatory drugs are clearly contraindicated colchicine is useful; 0.5 mg taken orally every three hours for 12 hours, with the dose being reduced thereafter. Diarrhoea is a probable side effect, but this soon settles after withdrawal of the drug. If all else fails, an intramuscular injection of a corticosteroid, such as 40 mg of methylprednisolone, is effective treatment for acute gout.

Gout is associated with hypertension and heart disease, and a patient's visit to general practice after an attack provides a good opportunity to practise preventive medicine.

Hyperuricaemia

Causes of hyperuricaemia

Endogenous	Exogenous
Family history	Dietary purines
Body build	Alcohol
Cell breakdown	Drugs
Renal function	
Hypertension	

The risk of developing gout increases with increasing hyperuricaemia, but the rise is not proportional and there is no point at which gout is inevitable. Many factors are associated with a raised urate concentration. With normal renal function and an absence of drugs that affect renal handling of urate, its blood concentration depends mainly on the breakdown of nuclear proteins from internal catabolism and external purine load. Genetic factors are also important, but, apart from rare inborn errors of metabolism, the inheritance is polygenic.

The upper normal limit for serum or plasma urate concentration is about $420 \mu\text{mol/l}$ (7 mg/100 ml) in adult men and postmenopausal women and $360 \mu\text{mol/l}$ (6 mg/100 ml) in premenopausal women. The risk of gout rises appreciably with concentrations over $600 \mu\text{mol/l}$. There is a small diurnal variation in blood concentration. A low purine diet can reduce blood concentrations of urate by up to 15% and urinary excretion by rather more, so attention to diet in patients with habitually high intakes of purine can significantly reduce risk. Faecal urate is not an important consideration in diagnosis or management.

Outline of purine metabolism.

Management of hyperuricaemia and a tendency to gout

Tophus on foot of a man whose chronic gout had been treated with allopurinol 300 mg daily for many years. This diminished after adoption of a strict diet.

Uricosuric drugs

Action

Reduce blood urate concentration and increase urine concentration of urate

Side effects

Mainly gastrointestinal intolerance

Contraindications

Presence of kidney stones
Acute gout

Concurrent treatment

Low dose of non-steroidal anti-inflammatory drug or colchicine for at least four months

Allopurinol

Action

Reduces blood and urine concentrations of urate

Side effects

Occasionally rashes or hepatitis

Contraindications

Acute gout

Concurrent treatment

Low dose of non-steroidal anti-inflammatory drug or colchicine for at least four months

In an otherwise healthy person, the likeliest risk of a raised urate concentration is gout; formation of kidney stones and renal damage depend on other factors, so isolated hyperuricaemia should not normally be treated with allopurinol. The exceptions are the use of prophylactic allopurinol to prevent acute renal failure in patients given cytotoxic drugs or radiotherapy, and occasionally to treat a highly hyperuricaemic patient with an increased risk of stones who may become dehydrated.

There are various options for managing hyperuricaemia, and most patients usually have a preference once the risks have been explained.

Treating occasional acute attacks of gout

Some hyperuricaemic patients may suffer an acute attack as infrequently as once a year. They may be prepared to accept this risk and simply seek treatment for an attack as and when it occurs.

Reduction of risk by dieting

If dietary risk factors can be identified most patients prefer reducing these to a lifetime of taking pills. Crash diets for extremely obese patients are inappropriate: ketosis raises urate concentration and can cause an acute attack. A low purine diet consists of avoiding foods with high concentrations of metabolically active tissues. Examples are liver, kidneys, red meat, small muscular fish such as sardines, and vegetables such as pulses and whole grain cereals. Beer, lager, port, and some wines should be avoided: apart from their calorific value, they contain purines and the alcohol raises the blood lactate concentration.

Avoidance of drugs that affect urate excretion

Such drugs include aspirin in low doses and the second line antituberculous drug pyrazinamide, but thiazide diuretics are the likeliest to be encountered. There is no way of avoiding the risk if this group of drugs is necessary, and no thiazide is free of the effect.

Long term reduction in blood urate concentration

The two main choices of treatment are uricosuric agents and allopurinol. In addition, the non-steroidal anti-inflammatory drugs azapropazone and tiaprofenic acid have a uricosuric effect and so have a place in the long term management of gout as well as acute treatment.

Uricosuric drugs—Probenecid (500 mg rising to 1500 mg a day) and sulphinpyrazone (100 mg rising to 600 mg a day) increase urate excretion and so are relatively contraindicated for patients with renal failure and absolutely so in patients with urate stones. Gastric intolerance is a relatively common problem with both drugs.

Allopurinol inhibits xanthine oxidase, diverting purine breakdown to xanthines, which are more soluble than urate. A dose of 100 mg a day, rising progressively to 300 mg a day, controls most cases of gout and eventually eliminates tophi, but doses of 600 mg a day or more are occasionally required.

A new attack of acute gout should never be treated with allopurinol or a uricosuric drug as these will prolong the attack (presumably because of a gradient between blood and tissue stores). Likewise, when the attack has settled the start of treatment should be accompanied by either colchicine (0.5 mg twice or thrice daily) or by a maintenance dose of a non-steroidal anti-inflammatory drug for at least three months. Even then sporadic attacks may occur for the first year of treatment.

Kidney and gout

Chronic lead poisoning from vessels used to distil "moonshine" is still a cause of gout and renal disease in some parts of the world

Blood urate concentration does not rise until the glomerular filtration rate (creatinine clearance) falls to below about 20 ml a minute. People rarely get clinically important renal impairment from hyperuricaemia alone. Thus, although renal failure can occasionally present with gout and a patient may present with a first attack of gout and simultaneously be found to have renal impairment, a moderately raised concentration of urea or creatinine in the blood is unlikely to be the sole explanation of a raised blood urate concentration. Patients with chronic severe gout and tophi are more likely to have hyperuricosuria and stones, but they represent a small minority.

Patients who habitually form non-urate kidney stones may benefit from allopurinol, even if they have a normal urate concentration, as this drug seems to reduce urolithiasis in general. The association between hypertension and gout is obviously relevant to renal impairment.

Pseudogout and calcium pyrophosphate deposition disease

Crystals of calcium pyrophosphate viewed under compensated polarised light: crystals are usually short and stubby, often much smaller than urate crystals, and are weakly positively birefringent (blue when aligned with slow axis and yellow—as here—when perpendicular).

Pseudogout is an acute attack of inflammatory arthritis due to shedding of pyrophosphate crystals from articular cartilage. Chondrocalcinosis (radiological calcification of articular cartilage) is an essential prerequisite of the condition but is only strong circumstantial evidence in diagnosis. Confirmation requires the demonstration of crystals 1–10 μm long, rhomboidal, with weak positive birefringence (blue when aligned to the slow axis of the red compensator).

Radiographs showing examples of pyrophosphate arthritis: (left) calcified triangular ligament of wrist and (right) linear calcification at knee.

Radiograph showing calcification at insertion of rotator cuff.

It is of a broadly similar nature to urate gout, but the affected joints are more likely to be the knee, wrist, or shoulder. Attacks are rarely quite as acute or severe as with urate gout but may be more difficult to diagnose: the patient may present with systemic features of fever and malaise sufficient to suspect sepsis, and crystals are often difficult to find in the synovial fluid, which should be centrifuged before examination. With other types of calcium pyrophosphate deposition disease, the arthritis may be more chronic and resemble non-erosive inflammatory arthritis, or the clinical picture may be that of osteoarthritis with episodes of inflammation and somewhat atypical joint pattern (wrists and shoulders, more genu valgus than genu varus).

Other forms of crystal arthropathy include post-traumatic or heterotopic calcium phosphate, calcific bursitis or peri-arthritis due to hydroxyapatite, and a rare destructive arthritis (Milwaukee syndrome) due to mixed crystal deposition. These conditions emphasise the need for a high quality analysis of synovial fluid to be available. This service should be in the pathology laboratory of hospitals and therefore accessible to all clinical departments rather than confined to interested rheumatologists or orthopaedic surgeons.

Michael L Snaith is senior lecturer in rheumatology at Nether Edge Hospital, Sheffield.

The ABC of Rheumatology is edited by Michael L Snaith.