GOUT AND HYPERURICEMIA

1. **AIMS**

On completion of this chapter, you should be able to correctly diagnose and treat cases of acute or chronic gout.

2. **LEARNING OBJECTIVES**

   - How to diagnose gout
   - Pain control
   - Lowering of urate
   - Recognising Chronic Gout

3. **INTRODUCTION**

Gout is caused by an inflammatory response to the presence of sodium urate crystals in the tissues. These crystals form secondary to hyperuricemia, that is a serum urate concentration greater than 0.42 mmol/L. Hyperuricemia is due to a combination of environmental and genetic factors.

   GENETIC: Multigenetic
   ENVIRONMENTAL: Alcohol, drugs, obesity, diet

4. **THE CAUSES OF GOUT**

Serum urate starts rising in males at puberty while in women it only really rises after the menopause. In some people this rise is excessive. If the serum urate rises above 0.42 mmol/L, tissues become saturated with urate and then easily form crystals. This hyperuricemia is usually present for many years before the first attack, but not all people with hyperuricemia get acute gout. The reason for this is unknown.
Excessive amounts of urate in the serum result from overproduction of purines and/or the underexcretion of urate by the kidneys. Usually there is a bit of both.

Activity: Give a description of the type of person you think would develop gout. Motivate your answer.

4.1 Underexcretion of urate:

♦ Most patients with underexcretion have no demonstrable kidney abnormality. In some patients the kidneys are genetically limited in their ability to eliminate urate above a certain amount. If the diet intake is over this limit, hyperuricemia will follow.

♦ With kidney failure or reduced kidney function.

♦ Drugs that reduce the renal excretion of urate:
  - diuretics of the thiazide group
  - low dose aspirin
  - furosemide
Obesity

Hypertension as a result of:
- concurrent diuretic therapy that suppresses urate excretion
- hypertension reduces renal excretion of urate
- renal damage from interstitial microtophi may lead to secondary renal hypertension
- heavy alcohol consumption may cause both hyperuricemia and hypertension.

Dehydration. Urine flow rate of less than 1 ml/min decreases urate excretion.

Environmental toxins and in particular lead may cause hyperuricemia due to chronic lead nephropathy.

4.2 Overproduction of urate:

Diet. Some foods are high in purines (liver, kidney, heart, meat extracts, gravy, yeast extracts, peas, beans, spinach, lentils).

Alcohol reduces the excretion of urate by the kidney and increases the production of urate. Beer contains the purine guanosine and ingestion thus stimulates urate production.

Purine production is greatly increased in proliferative disorders of the bone marrow and by cytotoxic therapy.
♦ A deficiency of the enzyme HGPRT results in the overproduction of urate and is inherited as an X-linked trait.

♦ While moderate degrees of deficiency of HGPRT result only in overproduction of urate, severe deficiency results in the Lesch-Nyhan syndrome with mental retardation. The severe form is very rare.

♦ Some other rare enzyme defects, of little clinical importance.

5. **WHO GETS GOUT?**

Over the age of 40 years, gout is the most common inflammatory arthropathy of males. Gout is rare in children, premenopausal females and males under 30.

The peak age of onset is between 40 and 50 years in males, and later in females. In females it is often associated with identifiable causes of hyperuricemia, eg diuretic use.

Racial differences have been shown, but the relative importance of genetic versus environmental factors is unknown.

6. **WHAT TRIGGERS ACUTE GOUT IN THE HYPERURICAEMIC PERSON?**

Certain factors are known to precipitate gout:
- acute illness
- trauma
- surgery
- heavy binge drinking
- low temperatures can precipitate crystals, hence the big toe is often involved.
7. **PAIN MECHANISMS WITH ACUTE GOUT**

Once the crystals have been formed they become coated with IgG that promotes phagocytosis by polymorphs. The polymorph has no way of disposing of the crystal it has ingested, and ruptures. The entire contents of the polymorph, including various inflammatory cytokines and proteolytic enzymes, are then released into the tissues causing severe inflammation.

8. **CLINICAL FEATURES**

Two types of gout can be distinguished:

- Acute gout
- Chronic gout

**What are the main clinical features?**

- It is mainly a disease of middle aged males.
- It is very rare in women under 50 years but more common in the postmenopausal years.
- Acute gout is self-limiting but tends to reoccur.
- After repeated acute attacks a chronic form is seen. This is caused by deposits of urate crystals bone and joint destruction.
- The first metatarsophalangeal joints (the big toes) are the most common joints involved.

8.1 **Acute Gout**

Acute gout is characterised by the rapid onset of severe pain and swelling with associated redness of the affected joint.
50% of patients have their first attack in the big toe (the first metatarsophalangeal joint). Over 90% of patients will with time have attacks in the big toe.

Other joints involved in order of frequency are the midfoot, heel, ankle and knee, but any joint may be involved. Non-articular sites where gout may occur are the olecranon bursa and the Achilles tendon.

Gout is the only non-infected condition with marked redness over the involved joint.

Swelling can be very noticeable and in severe cases involve an entire region.

Mild attacks resolve within one to two days, with severe attacks taking days and occasionally weeks to completely subside.

Over 90% of first attacks are monoarticular and systemic features e.g. fever are mild or absent. Pauci- or polyarticular onset of gouty arthritis is more common in females than in males.

Later in the course of the disease polyarticular attacks become common, often with systemic features of fever and leucocytosis. These attacks also resolve completely with symptom free-intervals. The polyarticular form may easily be confused with other arthropathies. For some unknown reason, gout very seldom occurs together with rheumatoid arthritis, except if there is kidney failure. After years chronic gout, with almost continual pain of varying intensity, becomes established.

Gout in the elderly may be less painful and is often mistaken for osteoarthritis (OA). This is further complicated in some patients by the coexistence of both gout and OA at times in the same joints (particularly Heberden’s nodes).

The second attack usually occurs within one or two years. In a small minority of patients, many years may elapse between attacks.
8.2 Chronic Gout

Chronic gout develops after many years of hyperuricemia. Firm nodular or fusiform swellings called tophi develop with time. These are local deposits of urate. They can ulcerate with a white chalky material being exuded. Tophi may occur almost anywhere, the most common locations being the digits of the hands and feet, olecranon bursa, helix and antihelix of the ear. The pain of chronic gout is often mild except when acute attacks supervene.

8.3 Urate Nephropathy

The kidneys are the second most commonly involved organ after the musculoskeletal system. Accumulations of crystals (tophi) are seen in the kidney of patients who have suffered from uncontrolled severe hyperuricemia for years.

Interstitial kidney damage can occur after 10 years of hyperuricemia, with or without gout, with decreased kidney function and the possibility of kidney failure.

Approximately 1% per year will get urate based kidney stones which may cause an obstructive nephropathy.

9. INVESTIGATIONS:

9.1 Joint fluid

If in doubt about the diagnosis, the drop of synovial fluid at the top of the aspirating needle is sufficient fluid to find crystals.

Urate crystals are needle shaped with a length of 5 to 25um. The crystals must be phagocytosed to be of significance.
The cell count should also be determined. The synovial fluid in acute gout has a high leucocyte count, often exceeding 50,000/mm³, of which 70% are neutrophils. With any suspicion of septic arthritis, cultures must be done.

9.2 Biochemical and Haematologic Investigations

Baseline investigations of a newly diagnosed gout patient should include plasma urate, urea, creatinine, blood sugar, fasting lipids, as well as urinalysis for blood and protein. Liver function tests, especially y-glutamyl transferase, and a raised MCV on the full blood count, may indicate excessive alcohol intake.

9.3 Radiology

Radiological changes are only seen after repeated gouty attacks over many years. The typical radiological lesions are bone erosions due to crystal deposits (tophi) that form within the joint, in the subchondral bone or in para-articular bone some distance from the joint. The erosions are asymmetrical, unlike the erosions of rheumatoid arthritis that are symmetrical. The erosions classically show a “punched out” appearance. An overhanging rim of bone may be seen at both intra-or extra-articular locations. This feature, although highly suggestive, is not pathognomonic of gout and results from new bone formation at the edge of a gradually expanding tophus.

There is little loss of joint space, in contrast to the early joint space narrowing of rheumatoid arthritis. Late in the disease extensive erosive disease will result in loss of joint space and is then difficult to differentiate from that seen in rheumatoid arthritis.

10. DIFFERENTIAL DIAGNOSIS OF GOUT

Other conditions which must be considered are:

- Septic arthritis
- Cellulitis
- Trauma to the joint
- Pseudogout or acute CPPD arthritis (see later)
The tophi of chronic gout should not produce any diagnostic problems but may appear similar to rheumatoid nodules.

11. MANAGEMENT

11.1 Asymptomatic Hyperuricemia

Treating asymptomatic hyperuricemia is of little benefit except for severe hyperuricemia (>0.65mmol/1) or with acute urate overproduction as occurs during chemotherapy with massive breakdown of tumour cells.

11.2 The treatment of gout consists of:

♦ Controlling the pain
♦ Reducing the serum urate levels
♦ Preventing the complications of chronic gout
♦ Changing unhealthy life styles

Treatment should aim to reverse any of the complications of gout that may have arisen. Factors of an unhealthy lifestyle that contribute to gout, such as obesity, hypertension, excessive alcohol consumption and hyperlipidaemia, should be corrected.

It is important to distinguish between therapy for reducing inflammation and that for managing hyperuricemia. The inappropriate use of urate lowering drugs, while the acute pain and inflammation are still present, can lead to severe exacerbations of pain that can be very difficult to control.

♦ Controlling the pain of acute gout

The first aim of therapy is the relief of the severe pain. Medication for acute gout is divided into three groups:
- anti-inflammatories
- colchicine
- steroids

The anti-inflammatories (NSAID’s), either on their own or in combination with colchicines, are very effective in the treatment of acute gout. In addition, NSAIDs are superior to colchicine in terms of speed of onset of action.

Regardless of which NSAID is chosen in acute gout, the earlier the therapy is instituted, the quicker the resolution of the attack. Patients should always keep a supply of medication and use it at the first indication of an attack. If medication is taken early, gout attacks can be quickly controlled.

**DO NOT ATTEMPT TO REDUCE THE SERUM URATE LEVEL DURING AN ACUTE ATTACK OF GOUT. EITHER A SUDDEN INCREASE OR A DECREASE IN PLASMA URATE LEVELS MAY PRECIPITATE OR PROLONG AN ATTACK OF GOUT.**

The patient must be three to four weeks pain free before starting therapy to reduce the serum urate levels.

The NSAIDs must be used in high dosage to get the optimum benefit. The dosage can be reduced as the attack resolves. A suppository or injectable can be used in place of oral dosage.

**Colchicine**

Colchicine has anti-inflammatory effects in acute gout and a prophylactic effect against recurrent attacks. It has no effect on the serum urate concentration.

The mechanism of action of colchicine is principally on the neutrophil, with inhibition of crystal phagocytosis, altered cell motility and a reduction in the release of inflammatory cytokines by the cells.
Colchicine is metabolized in the liver and excreted in the bile, but 20% is excreted unchanged in the urine. Because of this patients with reduced renal function must be treated with reduced dosages to prevent serious toxicity. The therapeutic and the toxic doses of colchicine are very close. When used within the first few hours of an attack, there is usually a good response, with the attack subsiding within 24 hours. If colchicine therapy is not started very early, the clinical improvement can take as long as 24 hours.

Dose: 1mg followed by 0.5mg every 2 hours until improvement in the pain, or diarrhoea and vomiting occur. The maximum daily dose is 8mg.

Colchicine may also be used for the acute arthritis of sarcoidosis, psoriatic arthritis, the arthritis of acute Mediterranean fever and the arthritis of pyrophosphate and hydroxyapatite crystals.

Side effects:
♦ diarrhoea
♦ vomiting
♦ bone marrow suppression (very rare)
♦ myoneuropathy (very rare)
♦ proximal muscle weakness

Corticosteroids

Intra-articular administration of corticosteroids is a very effective means of terminating an attack of gout. Resolution is typically complete within 12-24 hours. Response to oral corticosteroids is variable and rebound attacks frequently occur on the withdrawal of this therapy.

♦ Reducing the serum urate levels
Obviously the best way to prevent future attacks is to attack the root cause of the disease, ie the high urate levels. A number of drugs are very effective for this purpose. Severe attacks of gout can be precipitated when introducing these drugs, as the serum urate level drops very quickly. **Prophylactic therapy** is always required when drugs are introduced to correct hyperuricemia and may still be required even when urate concentrations have been normalized.

Colchicine in a dose of 0.5 to 2.0mg/day, is highly effective in reducing the frequency of attacks.

Prophylaxis should be continued for 9 to 12 months after normouricemia has been achieved and the patient has remained free of attacks.

**Activity:**

A sixty year old woman presents with her first attack of acute gout. Describe your approach to the management of her problem.

Once all acute inflammatory activity has passed i.e. the patient is pain free for at least 3-4 weeks, the next aim of therapy is to reduce the serum urate levels to the midnormal range (about 0.3mmol/1).

Two groups of drugs are used to lower urate levels:

1. **Uricosuric agents** which promote the renal excretion of urate.
2. **Allopurinol** which decreases urate production by inhibiting the enzyme xanthine oxidase

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**Uricosuric agents**

The main drugs in this group are probenecid and benzbromarone. They are all weak organic acids and lower the serum urate by increasing the uric acid excretion in the urine through competitive inhibition of the tubular reabsorption of urate in the renal tubular system.

**Indications:**
Uricosuric drugs are indicated when there is decreased renal excretion of urate. They are contraindicated in the presence of renal calculi and in patients with a poor urine volume (<1ml/min).

Initial doses must be low and then gradually increased, as large amounts of urate are excreted with the risk of kidney stone formation. For the first 8 weeks the urine must be alkalised (sodium citrate or sodium tartrate twice or three times daily) to prevent urate stone formation. Urine volume must remain over 1500ml/day. The patient must drink at least 10 glasses of water per day. This is especially important on hot days.

**Dosage:**
- Probenecid 0.5g/day increasing to 3gm/day maximum
- Brenzbromarone as a single drug is not available in South Africa anymore.

Remember probenecid is a banned substance in athletes.

Probencid also reduces the renal excretion of many drugs and is itself blocked by aspirin. Side effects are few with gastric pain in 5% and hypersensitivity in 2%.

**Allopurinol**

Allopurinol inhibits the enzyme xanthine oxidase which converts hypoxanthine to xanthine and then to uric acid. Both hypoxanthine to xanthine can form crystals, but do not cause clinical problems.
Dose: Start with 50mg/day, increased monthly until the serum urate is reduced to 0.3-0.4mmol/L. It is seldom necessary to exceed 300mg/day, but the maximum dose is 900 mg per day.

Side effects:
Hypersensitivity can be mild to very severe. Ampicillin must never be used with allopurinol as the risk of hypersensitivity is increased 3 fold. Mild renal failure is also associated with an increased risk.

N.B. Should you not be able to reduce the urate to 0.3mmol/L, other factors must be sought. By far the most important is alcohol. If your patient continues drinking, you will almost certainly not be able to control his gout. Tell the patient in these cases that his drinking (even in moderation) is now a problem. He has the choice – stop drinking or have the gout!

Tophaceous Gout

Reducing the serum urate level to 0.3mmol/L and keeping it there, will result in the slow but steady reabsorption of the tophi. Large tophi can take up to two years to resolve. Surgery should be avoided due to poor wound healing, except in some cases where tophi exert pressure on important structures eg the median nerve.

Life style

As we have already seen, an unhealthy life style, resulting in obesity, hypertension and hyperlipidaemia, plays an important role in the pathogenesis of gout. Severe dietary restriction of purines rarely causes a significant enough fall in the urate concentration to be of therapeutic value. Patients also do not comply in the long term with such a restrictive diet. However, at least the more important dietary sources of
purines should be eliminated. In contrast, alcohol restriction has a much greater effect on the plasma urate concentration and should be strongly encouraged.
CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) ARTHRITIS ALSO CALLED CHONDROCALCINOSIS.

Definition

An arthritis associated with the deposition of calcium pyrophosphate dihydrate (CPPD) crystals in the cartilage of joints. The main joints involved are the knees, wrists, shoulders and hips.

Epidemiology

It is mainly a disease of the elderly and is more common in women. The incidence rises rapidly after the age of 60 years. Although many cases occur sporadically, a familial tendency is often seen.

CPPD may also be associated with some metabolic diseases:

- strong association - hyperparathyroidism
  - haemochromatosis
- weak association - hypophosphatasia
  - hypomagnesemia
  - Wilson’s disease

Clinical Features

Four clinical presentations are recognised:

♦ Acute synovitis
♦ Chronic arthritis
♦ Incidental finding on joint X-ray (asymptomatic)
♦ Unusual presentations

♦ Acute Synovitis (Pseudogout)
  This is the most common cause of acute monoarthritis in the elderly. It is easily mistaken for gout, hence it’s other name of ‘pseudogout’. The attacks may occur
without any warning or might be superimposed on a low grade chronic arthritis. Triggering factors include surgery, trauma to the joint, intercurrent medical illness and at the start of thyroid replacement therapy. The attack develops quickly with severe pain, swelling and erythema. On examination the joint is acutely tender, often with an effusion. Erythema of the overlying skin may be very prominent. Any joint may be involved, but the knee is by far the most common. This is followed by the wrist, shoulder, ankle and elbow. Low grade fever is common. The acute attacks are self limiting and resolve over a period 1-3 weeks.

Acute monoarthritis from CPPD crystals is the most common cause of an acute arthritis in a single joint in elderly women. It must not be mistaken for gout.

♦ Chronic Pyrophosphate Arthritis
A common condition seen mainly in elderly females. The knees are the most commonly affected, followed by wrists, shoulders, elbows, hips and midtarsal joints of the feet. In the hand the 2nd and 3rd metacarpo-phalangeal joints are often involved.

The patients complain of chronic pain, morning stiffness as well as inactivity stiffness and function problems with the joint.

Varying degrees of synovitis and effusions are encountered, from mild to severe. Synovial thickening can be marked, particularly in the knee, radiocarpal or glenohumeral joints. This can be confused with rheumatoid arthritis, but examination of joint movements usually shows the signs of osteoarthritis with bony swelling and crepitus. The knees show a predominance of patello-femoral joint involvement. CPPD disease often accompanies generalised osteoarthritis with Heberden’s nodes.

Chondrocalcinosis must be considered in osteoarthritis patients with acute attacks of pain or with a marked inflammatory element.
The natural history of chronic pyrophosphate disease is poorly understood, but a generally benign course is seen in the small and medium joints. Severe destruction can occur with large joints (knee, shoulder, hip).

Recurrent haemarthrosis of the knee and shoulder is well described.

- **Incidental Finding**
  
  CPPD is a frequent incidental finding seen on radiographs in elderly patients with no clinical symptoms.

- **Unusual sights**
  
  Tendonitis as a result of CPPD crystal deposition in the tendon or paratendon sheaths of the triceps, Achilles tendon and hand flexor and extensor tendons is well recognised.

  N.B. Otherwise unexplained tendonitis in an elderly person could be chondrocalcinosis.

**INVESTIGATIONS**

Plain radiographs and the identification of crystals in synovial fluid are the two most important investigations.

Radiography:

The characteristic feature of CPPD disease is calcification seen on X-ray in the fibrocartilage of knee menisci, triangular ligament of the wrist and symphysis pubis. Linear deposits parallel to, but separate from the subchondral bone, are seen in the hyaline cartilage of the knee, glenohumeral joint and the hip. Capsular and synovial calcification is also seen in the metacarpophalangeal joints. The calcification may decrease with time. Calcification of ligament to bone insertions occur particularly the patella tendon to the patella, Achilles tendon insertion to the calcaneus and the plantar fascia of the foot. The end stage of the disease is secondary osteoarthritis.
TREATMENT

Acute Synovitis.

Joint aspiration relieves much of the pain and is often all that is required. If the fluid reaccumulates, the joint must be reaspirated and an intra-articular corticosteroid injected.

If joint aspiration alone does not give adequate relief, simple analgesics, non-steroidal anti-inflammatories or colchicine will be of help.

Any possible triggering illnesses should be identified and treated.