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GOUT- A PAINFUL DISEASE

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ABSTRACT

The occurrence of gout in the population is steadily increasing. In research has found several variants of DNA sequences that predispose patients to irregular uric acid metabolism. Risk factor linked to gout include obesity and cardiovascular disease. Though the formal diagnosis is made with arthrocentesis and subsequent analysis, CT and ultrasound findings supplement the diagnosis and monitor disease management. Genetic mutations may be associated with overproduction or more often underexcretion of uric acid because of defects in the renal urate transporter system. Oral corticosteroids, intravenous corticosteroids, NSAIDs and colchicine are equally effective in treating acute flares of gout. They should be monitored periodically to assess preventive therapy in patients with recurrent gout and a history of elevated urate levels. Urate-lowering therapy should be continued for three to six months after a flare if there are no ongoing symptoms.

KEYWORDS: Gout, Monosodium urate crystals, Metabolic syndrome, Hyperuricemia, NSAIDs.

INTRODUCTION

Gout is a systemic disease that results from the deposition of monosodium urate crystals (MSU) in tissues. Increased serum uric acid (SUA) above a specific threshold is a requirement for the formation of uric acid crystals. Despite the fact that hyperuricemia is the main pathogenic defect in gout, many people with hyperuriceamia do not develop gout or even form uric acid crystals. In fact, only 5% of people with hyperuriceamia above 9 mg/dL develop gout. Accordingly, it is thought that other factors such as genetic predisposition share in the incidence of gout.[1,2]

Gout affects about 1 to 2% of the Western population at some point in their lives. It has become more common in recent decades. This is believed to be due to increasing risk factors in the population, such as metabolic syndrome longer life expectancy and changes in diet. Older males are most commonly affected. Gout was historically known as "the disease of kings" or "rich man's disease". It has been recognized at least since the time of ancient Egyptians.[3,4]

MSU crystals can be deposited in all tissues mainly in and around the joints forming tophi. Gout is mainly diagnosed by identification of the pathognomonic MSU crystals by joint fluid aspiration or in tophi aspirate. Early presentation of gout is an acute joint inflammation that is quickly relieved by NSAIDs or colchicine. Renal stones and tophi are late presentations. Lowering SUA levels below deposition threshold either by dietary modification and using serum uric acid lowering drugs is the main goal in management of gout. This results in dissolution of MSU crystals preventing further attacks.[2,3]

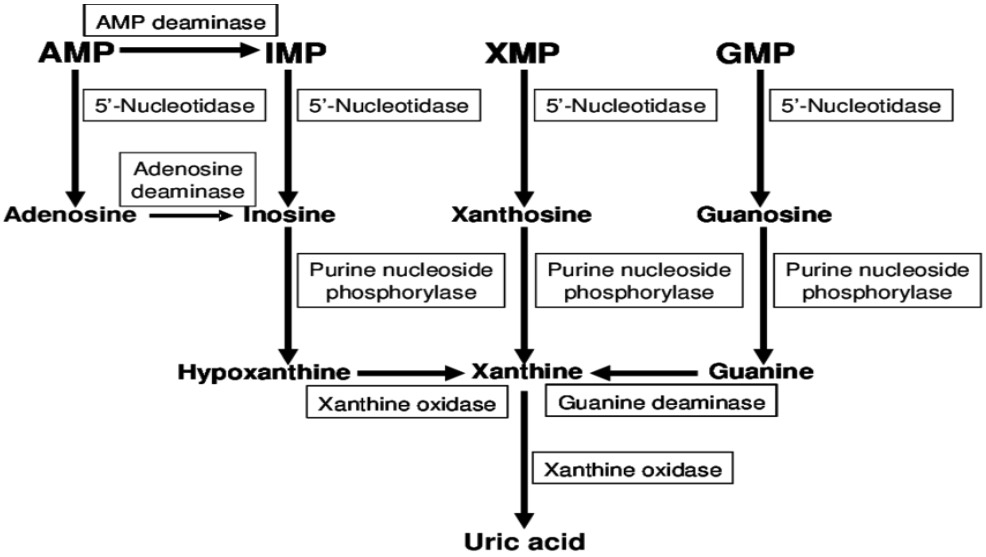

Fig. 1: Represent flow chart production of uric acid.

Epidemiology

The general prevalence of gout is 1–4% of the general population. In western countries, it occurs in 3–6% in men and 1–2% in women. In some countries, prevalence may increase up to 10%. Prevalence rises up to 10% in men and 6% in women more than 80 years old. Annual incidence of gout is 2.68 per 1000 persons. It occurs in men 2–6 folds more than women. Worldwide incidence of gout increases gradually due to poor dietary habits such as fast foods, lack of exercises, increased incidence of obesity and metabolic syndrome.[5]

Overproduction of uric acid

Deficiency of enzymes involved in purine metabolism leads to overproduction of uric acid. For example, Lesch-Nyhan syndrome is an inborn error of metabolism resulting from deficiency of an enzyme involved in UA metabolism named hypoxanthine–guanine phosphoribosyltransferase. It is a genetic X-linked recessive disorder with varying degrees of severity according to the type.[1,2]

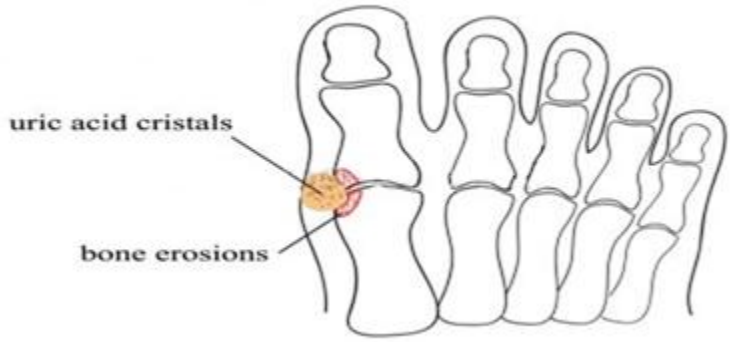

Fig. 2: Systematic diagram of gout.

The characteristic symptoms and signs of gout are

- Sudden onset of joint pain
- Joint swelling
- Heat in the affected area, and
- Joint redness.

These symptoms and signs usually affect a single joint. The pain is typically severe, reflecting the severity of inflammation in the joint. The affected joint is often very sensitive to touch to the point that some people with gout attacks experience pain from something as simple as pulling the bed sheets over the inflamed joint. The affected joint becomes swollen. The medical term for excessive fluid in a joint is a "joint effusion."

Gout frequently involves joints in the lower extremities. The classic location for gout to occur is the big toe. Podagra is the medical term for inflammation at the base of the big toe. Gout can also affect the foot, knee, ankle, elbow, wrist, hands, or nearly any joint in the body. When gout is more severe or longstanding, multiple joints may be affected at the same time. This causes pain and joint stiffness in multiple joints.[6,7]

Another sign of gout is the presence of tophi. A tophus is a hard nodule of uric acid that deposits under the skin. Tophi can be found in various locations in the body, commonly on the elbows, upper ear cartilage, and on the surface of other joints. When a tophus is present, it indicates that the body is substantially overloaded with uric acid.[8,9]

Pathogenesis of hyperuricemia

Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/dL.[1,6]

Some factors may affect the solubility of uric acid in the joint. These include synovial fluid pH, water concentration, electrolytes level, and other synovial components such as proteoglycans and collagen. SUA level in the body is determined by the balance between its production either from purine intake in diet or endogenous production by cellular turnover and its excretion by the kidneys and GIT. Increased production of uric acid is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under-excretion.[7]

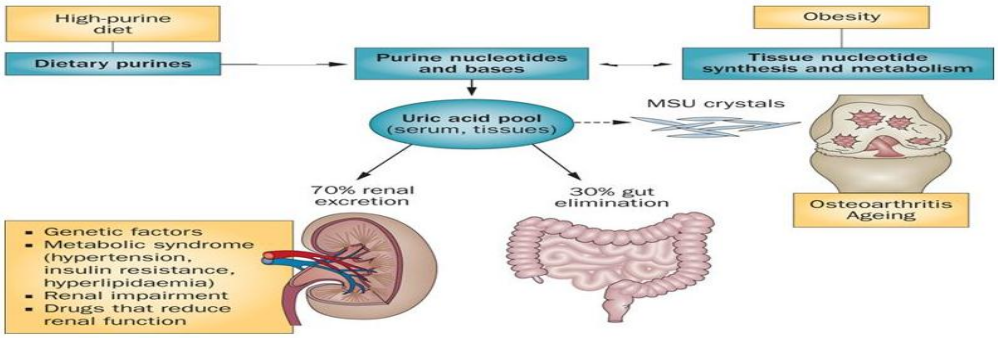

Fig. 3: Pathogenesis of hyperurecimia.

Factors affecting serum uric acid levels include age and gender. Serum uric acid is low in children. After puberty, Serum uric acid levels start to increase to reach their normal levels. In men, levels are higher than in women. However, Serum uric acid levels in postmenopausal women increase to reach men's levels. This explains why gout is usually a disease of middle aged and older men, and postmenopausal women. Rarely, it may happen in children and young adults in some rare inborn errors of purine metabolism. These enzymatic defects result in increased SUA with consequent production of uric acid crystals in kidneys and joints.[10,11]

Clinical diagnosis

Gout undergoes 4 stages during its course starting with asymptomatic hyperuriceamia. In this stage, patients have no symptoms or signs and are usually accidentally discovered when measuring SUA (serum level greater than 7 mg/dL). However, some patients with hyperuriceamia may develop an acute gouty attack. Acute gouty attack is usually monoarthritic that peaks within hours to severely inflamed joint with cardinal signs of inflammation including redness, hotness, tenderness, swelling and loss of function. In large joints such as knees and ankles, skin signs are infrequent, but swelling and pain can be intense.[12,13]

Gout has a predilection for lower extremities such as the first MTP, which is the commonest site for acute gout known as podagra. Other joints that can be affected are the tarsal and metatarsal joints, ankles, knees, wrists, MCPs as well as interphalangeal joints of the hands. Rarely, hip and shoulder joints can be involved. Vertebral column involvement is extremely rare. Soft tissue inflammation may also occur including olecranon bursitis and Achilles tendonitis. In such case, the joint has to be managed as septic arthritis until proven otherwise. Extreme caution should be taken when dealing with such cases, as septic arthritis may happen in a gouty joint with the presence of MSU crystals. On the other hand, gouty attack can be mild with low-grade inflammation.[13-15]

Synovial fluid

A definitive diagnosis of gout is based upon the identification of monosodium urate crystals in synovial fluid or a tophus. All synovial fluid samples obtained from undiagnosed inflamed joints by arthrocentesis should be examined for these crystals. Under polarized light microscopy, they have a needle-like morphology and strong negative birefringence. This test is difficult to perform and requires a trained observer. The fluid must be examined relatively soon after aspiration, as temperature and pH affect solubility.[16]

Blood tests

Hyperuricemiais a classic feature of gout, but nearly half of the time gout occurs without hyperuricemia and most people with raised uric acid levels never develop gout. Thus, the diagnostic utility of measuring uric acid levels is limited. Hyperuricemia is defined as a plasma urate level greater than 420 μmol/l (7.0 mg/dl) in males and

360 μmol/l (6.0 mg/dl) in females.Other blood tests commonly performed are white blood cell count, electrolytes, kidney function and erythrocyte sedimentation rate (ESR). However, both the white blood cells and ESR may be elevated due to gout in the absence of infection. A white blood cell count as high as 40.0×10^9/l (40,000/mm^3) has been documented.[16,17]

Differential diagnosis

The most important differential diagnosis in gout is septic arthritis. This should be considered in those with signs of infection or those who do not improve with treatment. To help with diagnosis, a synovial fluid Gram stain and culture may be performed other conditions that can look similar include pseudo gout, rheumatoid arthritis, psoriatic arthritis, and reactive arthritis. Gouty tophi, in particular when not located in a joint, can be mistaken for basal cell carcinoma or other neoplasm.[18]

Complication of Gout

Stages of Gout

Asymptomatic hyperuricemia is a preliminary stage of gout and many hyperuricemic patients never develop clinical manifestations of gout.

Acute gout commonly presents as an abrupt onset of an erythematous, warm, swollen, and exquisitely sensitive joint, classically the first metatarsophalangeal joint. Suspect gout if the patient has acute onset of monoarticular joint pain with the maximum intensity occurring within 12 hours. In some cases, acute gout may be self-limiting.

Intercritical* or *interval gout occurs after acute symptoms have resolved, and low-grade inflammation may remain within the joint, causing unnoticed damage. During this intercritical stage, persistent hyperuricemia drives monosodium urate crystal deposition and aggregation into tophi development, causing erosive changes to the bone, which may be seen radiographically in patients with chronic gout.

Chronic gout is persistent arthralgia or repeated episodes of acute gout, usually complicated by tophi formation. Although the time frame for tophi development has varied across studies, without urate-lowering therapy, about 30% of patients develop chronic gout within 5 years. Acute gout symptoms often are not well recognized in patients with chronic gout because of a lack of intensity or soft tissue swelling; in these cases, the patient presentation may simply mimic osteoarthritis.[19,20]

Genes responsible for uric acid regulation

SLC22A12 gene encodes for the transporter URAT1 present on the apical membrane of renal tubules. SLC2A9 is another gene involved in regulation of UA excretion. It encodes for a transporter protein in the membrane of renal tubules. Polymorphism of both genes results in decreased fractional excretion of UA leading to increased SUA levels. ABCG2 is a gene transporter for UA in the proximal tubular cells of the kidney as well as in the GIT. *SLC17A1, SLC17A3* genes are important determinants of SUA levels acting as membrane transporters in the kidenys. Other genes involved in determination of SUA levels include SLC22A11, the glucokinase regulatory protein (GCKR), Carmil (LRRC16A), and near PDZ domain containing 1 (PDZK1) genes.[19]

Complications

People with gout can develop more-severe conditions, such as:

- **Recurrent gout.** Some people may never experience gout signs and symptoms again. Others may experience gout several times each year. Medications may help prevent gout attacks in people with recurrent gout. If left untreated, gout can cause erosion and destruction of a joint.
- **Advanced gout.** Untreated gout may cause deposits of urate crystals to form under the skin in nodules called tophi (TOE-fie). Tophi can develop in several areas such as your fingers, hands, feet, elbows or Achilles tendons along the backs of your ankles. Tophi usually aren't painful, but they can become swollen and tender during gout attacks.
- **Kidney stones.** Urate crystals may collect in the urinary tract of people with gout, causing kidney stones. Medications can help reduce the risk of kidney stones.[19,20]

Prognosis

Without treatment, an acute attack of gout usually resolves in five to seven days; however, 60% of people have a second attack within one year. Those with gout are at increased risk of hypertension, diabetes mellitus, metabolic syndrome, and kidney and cardiovascular disease and thus are at increased risk of death. It is unclear whether medications that lower urate affect cardiovascular disease risks. This may be partly due to its association with insulin resistance and obesity, but some of the increased risk appears to be independent.

Without treatment, episodes of acute gout may develop into chronic gout with destruction of joint surfaces, joint deformity, and painless tophi. These tophi occur in 30% of those who are untreated for five years, often in the helix of the ear, over the olecranon processes, or on the Achilles tendons. With aggressive treatment, they may dissolve. Kidney stones also frequently complicate gout, affecting between 10 and 40% of people and occur due to low urine pH promoting the precipitation of uric acid. Other forms of chronic kidney dysfunction may occur.[21,22]

Pathophysiology and Risk Factors

Genetic mutations may be associated with overproduction—or more often under excretion—of uric acid because of defects in the renal urate transporter system. The occurrence of gout increases with age and

peaks at more than 12% in persons older than 80 years. Because female sex hormones increase urinary excretion of uric acid, pre-menopausal women have a substantially lower prevalence of gout compared with men.[23]

Risk Factors for Gout

Continues consuming alcoholic drinks (particularly beer), meat (especially red meat, wild game, and organ meat), some seafood (e.g., shellfish, some large saltwater fish), fruit juice, and beverages sweetened with high-fructose corn syrup higher the risk of gout. Purine-rich diet such as nuts, oat-meal, asparagus, legumes, and mushrooms also increase the risk. Milk higher the fractional excretion of uric acid but dairy products modulate the inflammatory response to monosodium urate crystal.[24,25]

Table I: Risk factor for Gout.

Factor	Consumption
Diuretic	Continues intake
Alcohol	≥ 50 g per day
Beer	≥ 2 drinks per day
Spirits	≥ 2 drinks per day
Wine	≥ 2 drinks per day
Sweetened beverage	≥ 2 drinks per day
Fructose	Continues intake
Sea food	Continues intake
Meat	Continues intake
Dairy products	Continues intake
Vitamin C	≥ 1,500 mg vs. < 250 mg per day
Coffee	≥ 6 cups per day vs. none.

Medications for Treatment of Gout

Treatment is based on the particular clinical phase of gout that the patient is experiencing. Treatment for acute gout is aimed at reducing the pain and inflammation that accompany acute gout attacks, whereas treatment for the intercritical period of gout aims to maintain low levels of serum uric acid in order to prevent the formation of tophi. Chronic tophaceous gout is treated by initiating long-term hypouricaemic therapy. There currently is no evidence for the efficacy of treatment of asymptomatic hyperuricaemia.[26]

Management of Acute Gout

To achieve rapid and complete resolution of symptoms of acute gout by corticosteroids, NSAIDs and colchicine. NSAIDs are the first-line drug for treatment. Indomethacin has historically been the preferred choice. Naproxen, indomethacin and sulindac; similar pharmacokinetics of other NSAIDs suggest comparable efficacy. Intramuscular ketorolac appears to have similar effectiveness. Colchicine is another treatment option for acute gout. Generic colchicines, which has been used for decades. In clinical practice this drug appears as much less efficient when given long after the flare onset. Corticosteroids are an appropriate alternative for patients who cannot tolerate NSAIDs or colchicine. Patients with diabetes mellitus can be given corticosteroids for short-term use with appropriate monitoring for hyperglycemia. When gout is limited to single joint, intra-articular corticosteroid injections may be preferable to systemic corticosteroids because of their lower adverse effect profile.[26]

Management of chronic gout

Any patients with frequent attack of gout possibly two or more a year, patients who have tophi, uric acid over-presentation, have urolithiasis, have severe or difficult to treat attacks or with chronic persistent of gouty arthritis, should routinely be treated with urate lowering therapy.

Uricostatic agents

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is a first-line agent to prevent recurrent gout. In patients with gout and chronic kidney disease or congestive heart failure, allopurinol has the added benefit of preventing chronic disease progression. It is the most well-established and cheap urate lowering agent available and it should be our first line option. Allopurinol dose should be titrated from a starting dose of 100 mg daily and increase by 100 mg monthly until the target serum urate level is achieved with up to a maximum of 800 mg daily.

Febuxostat

Febuxostat (Uloric) is a xanthine oxidase inhibitor that was approved by the FDA in 2009. Although febuxostat is superior to 300 mg allopurinol at lowering serum uric acid levels, it is not more effective at reducing the frequency of gout flares.35,36 Febuxostat is considered a first-line agent to prevent recurrent gout,9 but it is considerably more expensive than allopurinol. In patients with chronic kidney disease stage 2 and 3, febuxostat at a dose of 40-80 mg is superior to allopurinol at a dose of 200-300 mg daily in achieving the target serum urate level. Febuxostat may be used without dose adjustment in patients with mild to moderate renal impairment.[27,28]

Uricosuric therapy

Other urate lowering medication which could be used is the uricosuric agents such as sulfinpyrazone, probenecid and benzbromarone. These agents enhance renal uric acid excretion primarily by decreasing the urate

reabsorption in the renal tubules. In patients with adequate renal function, uricosuric agent can be effective. Uricosuric therapy can also provide extra benefit in combination with xanthine oxidase inhibitor in patients who fail to achieve the target serum urate level. Probenecid increases urinary excretion of uric acid and is typically used as a second-line treatment because of numerous drug interactions.[26-28]

Dietary Modifications

Increase in weight is a important risk feature for gout in men, whereas weight loss lower the risk. Intake of high-fructose corn syrup should be controlled because the fructose contributes to increased uric acid production as a byproduct of adenosine triphosphate catabolism. Patients with gout should limit their intake of purine-rich animal protein (e.g., organ meats, beef, lamb, pork, shellfish and avoid alcohol (especially beer). Purine-rich vegetables do not increase the risk of hyoperuricemia.[29]

Conclusions and Future Perspectives

To recognize gout and consequently to control it, has been a challenge to the expertise of physicians along the medical history. Advances in this field that took the shape of continuous progress, have recently witnessed quantum leaps. We enjoy a deeper insight into the disease pathogenesis. We can rely on more sophisticated diagnostic techniques and most importantly, we have at our disposal a wider spectrum of pharmacological agents to deal with it.

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