

Hyperuricemia and Gout: A Review Article

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Abstract

Uric acid is a chemical, created in the body by the breaking down of purines. It is excreted out of the body by the kidneys, through urine, after it dissolves in the blood. If it is not excreted out of the body properly, high levels of uric acid gets accumulated which causes gout and kidney stones. Hyperuricemia is usually caused due to the regular intake of food having high content of purine and conditions such as hypoparathyroidism, lead poisoning, renal failure and side effects of chemotherapy. Hyperuricemia occurs when serum urate levels exceed urate solubility, ie, at approximately 6.8 mg/dL. At serum urate levels above this threshold, manifestations of gouty arthritis may occur, although asymptomatic hyperuricemia often persists for many years. Intercritical asymptomatic periods follow the resolution of acute gout flares, but crystals remain in the joint during these intervals and further deposition may continue silently. Ultimately this may lead to persistent attacks, chronic pain, and, in some patients, joint damage.

INTRODUCTION TO GOUT

Gout, or gouty arthritis, is a relatively common metabolic disorder. It is characterized by a painful, inflammatory response to deposits of sodium urate crystals in the synovial fluid of the joints and surrounding tissue. This condition may also present as deposits of urate crystals in cartilage (i.e., tophi), interstitial renal disease, or kidney stones. Gout is a recognized complication of hyperuricemia. In the acute phase it is characterized by a monoarticular arthritis that remits after one to two weeks and recurs periodically. Joints of the lower extremity are most commonly affected. The periods between flares of the disease may shorten over time and attacks may become polyarticular. Chronic tophaceous joints develop after many years of recurrent attacks and are characterized by deposits of urate in the skin or bursa, referred to as tophi. Common sites for tophi include the pinna of the ear, the olecranon bursa and adjacent to the small joints of the fingers.

GENETIC AND BIOCHEMICAL BASIS OF HYPERURICEMIA

There are three different inherited defects that lead to early development of severe hyperuricemia and gout: glucose-6-phosphatase (gene symbol = G6PT) deficiency; severe and partial hypoxanthine-guanine phosphoribosyltransferase (HGPRT, gene symbol = HPRT) deficiency; and elevated 5'-

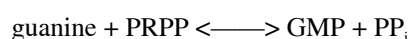
phosphoribosyl-1'-pyrophosphate synthetase (PRPP synthetase, gene symbol = PRPS) activity.

The familial association of gout was recognized hundreds of years ago but defining the exact genetic mechanisms was not possible until the advancement of modern genetic tools. Gout and Garrod have been linked in medical literature for more than a century. He identified uric acid as a normal constituent of the serum of healthy persons and devised a method for detecting its increased concentration in gouty subjects.

Overactivity of PRS is also an X-linked dominant disorder that can produce hyperuricemia. It is characterized by an overproduction of phosphoribosyl pyrophosphate (PRPP) and uric acid, which can cause hyperuricemia, nephrolithiasis, and gout at an early age. Overactivity of PRS is related to an accelerated transcription of the PRS-I gene, acting as a major determinant of synthesis of PRPP, purine nucleotides, and uric acid. At least three different isoforms of PRPP synthetase have been identified and are encoded by three distinct, yet highly homologous PRPS genes, identified as PRPS1, PRPS2, and PRPS3. The PRPS1 and PRPS2 genes are found on the X chromosome (Xq22-q24 and Xp22.2-p22.3, respectively) and the PRPS3 gene is found on chromosome 7. The PRPS3 gene appears to be expressed exclusively in the testes. All three PRPP

synthetase isoforms differ in kinetic and physical characteristics such as isoelectric points (pI), pH optima, activators and inhibitors. Phosphoribosylpyrophosphate synthetase (PRS) superactivity is characterized by hyperuricemia and hyperuricosuria and is divided into a severe phenotype with infantile or early-childhood onset and a milder phenotype with late-juvenile or early-adult onset. Variable combinations of sensorineural hearing loss, hypotonia, and ataxia observed in the severe type are not usually present in the mild type. In the mild type, uric acid crystalluria or a urinary stone is commonly the first clinical finding, followed later by gouty arthritis if serum urate concentration is not controlled.

Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is an enzyme involved in the salvage of purine nucleotides. HGPRT catalyzes the following two interconversions:



A complete or virtually complete loss of HGPRT activity results in the severe disorder, Lesch-Nyhan syndrome. Lesch-Nyhan syndrome is inherited as an x linked trait. Persons with this syndrome are missing or are severely lacking an enzyme called hypoxanthine guanine phosphoribosyltransferase 1 (HGP). The body needs this enzyme to recycle purines. Without it, abnormally high levels of uric acid build up in the body.

Hyperuricemia results from a combination of increased generation and decreased excretion of uric acid which is generated when increased amounts of G6P are metabolized via the pentose phosphate pathway. It is also a byproduct of purine degradation. Uric acid competes with lactic acid and other organic acids for renal excretion in the urine. In GSD I increased availability of G6P for the pentose phosphate pathway, increased rates of catabolism, and diminished urinary excretion due to high levels of lactic acid all combine to produce uric acid levels several times normal. Although hyperuricemia is asymptomatic for years, kidney and joint damage gradually accrue.

DIET AND URIC ACID

Foods high in uric acid play a major role in the development of Gout. In association with a healthy lifestyle and changes in diet, it can actually be easier to manage than many people believe, as long as the sufferer is willing to make some significant changes in their eating habits. Diets that have

high contents of purine are extremely important. Restrictions of diet containing higher level of purine will help in reducing serum uric acid level. Normally, uric acid is eliminated from the body by the kidneys. However, some people are more sensitive to high levels of uric acid, and their bodies will form crystals that accumulate in the joints and cause painful gout symptoms. The main goals of treatment for acute gout are to get rid the pain that comes with this disease as well as prevention of future gout attacks. If untreated, it can also lead to joint disability and, ultimately, kidney damage. Diets to reduce uric acid also benefit gout sufferers by helping them lose weight, which has also been shown to help lower concentrations of uric acid in the blood. Foods containing purine and the compounds that metabolize into uric acid include most animal meats, such as beef, pork and seafood. White meat is better than red meat and can have some degree of purine content and should be eaten very sparingly, but they are not as detrimental as the red meats. Alcohol and foods that have high content purine should be kept out of the diet. Black cherry juice, is recommended as herbal therapy for treatment of gout. Celery seed extract and bromelain are some popular alternative medicine remedies that have been used as natural anti-inflammatories and have been well tolerated by those who suffer chronic inflammation. Adding eicosapentaenoic acid (EPA) and folic acid to the diet can also assist in relieving symptoms of gouty arthritis.

TREATMENT OF GOUT AND HYPERURICEMIA TREATMENT OF ACUTE GOUTY ARTHRITIS

Three treatments are available for patients with acute gouty arthritis. Colchicine is commonly used for treatment of acute gouty arthritis. Nonsteroidal antiinflammatory drugs, which are currently prescribed, are rapidly effective but may have serious side effects. Corticosteroids administered either intraarticularly or parenterally, are used increasingly in patients with monarticular gout, especially if oral drug therapy is not feasible. Urate lowering drugs should not be initiated or changed as long as any gouty joint inflammation persists, because such treatment may delay the recovery.

COLCHICINE

Colchicine is the most popular treatment for acute gout. The high dose of colchicine, up to 6 mg, usually advised for the treatment of gout may cause unnecessary toxicity; a lower dose of 0.5 mg every eight hours may be more appropriate. The toxicity of intravenous colchicine is too high to justify its use.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Most potent nonsteroidal antiinflammatory drugs are rapidly effective in relieving pain and reducing inflammation in patients with acute gout, particularly if the drugs are taken soon after the onset of the attack. Indomethacin, the first of these drugs to be used extensively, provides some pain relief within two to four hours. Depending on the severity of the attack and its duration, the appropriate dose ranges from 150 to 300 mg per day, given in divided doses, with a gradual reduction during a period of five to seven days as the attack subsides. Most other nonsteroidal antiinflammatory drugs are effective but no better than indomethacin, although few comparative data are available. The usefulness of nonsteroidal antiinflammatory drugs is limited by their side effects, but in general, the risks are greatest in elderly patients, particularly those with renal dysfunction.

CORTICOSTEROIDS

Corticosteroids such as prednisone can be used as a last resort for gout therapy, when neither NSAIDs nor colchicine can be used. As well, intra-articular steroids can be useful when medium to large joints are affected. Steroids are used to control pain and inflammation. Normally patients taking corticosteroids are given tapered doses when coming off of treatment. However, tapering is not usually necessary for gout patients because of the short duration of therapy.

TREATMENT OF CHRONIC GOUT

Gout can be prevented by identifying and correcting the cause of hyperuricemia or by administering drugs that inhibit the synthesis of urate or increase its excretion. Gout may be prevented by reducing serum urate concentrations to values less than 6.0 mg per deciliter (360 μ mol per liter). A reduction to less than 5.0 mg per deciliter (300 μ mol per liter) may be required for the resorption of tophi. Two classes of drugs are available: uricosuric drugs and xanthine oxidase inhibitors. Uricosuric drugs increase the urinary excretion of urate, thereby lowering the serum urate concentration. In contrast, xanthine oxidase inhibitors block the final step in urate synthesis, reducing the production of urate while increasing that of its precursors, xanthine and hypoxanthine (the oxypurines). In general, a xanthine oxidase inhibitor is indicated in patients with increased urate production, and a uricosuric drug in those with low urate clearance. A potential complication of these drugs is the precipitation of acute attacks of gout. The mechanism is poorly understood, but it is usually attributed to the sudden change in the serum urate concentration. The risk can be minimized by concurrently administering prophylactic drugs, delaying urate-lowering

therapy until several weeks after the last attack of gout, and commencing therapy with a low dose of the drug that is chosen.

URICOSURICS

Uricosurics like probenecid and sulfinpyrazone increase renal excretion of uric acid by inhibiting tubular reabsorption in the kidneys. It is important to start at low doses because large amounts of uric acid passing through the kidneys will increase the risk of forming uric acid stones. The anti-hypertensive drug losartan has been shown to have a uricosuric effect, but this effect decreases drastically once the drug has reach steady state. It can also worsen preexisting renal impairment. Uricosuric drugs are contraindicated for patients with kidney stones and renal insufficiency. Those patients should use a drug that will function independently of kidney function.

XANTHINE OXIDASE INHIBITORS

Allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed of these agents. The average dose is 300 mg per day, although dosing recommendations range from 100 to 800 mg per day, titrated to serum urate and creatinine clearance. The side effects of allopurinol, although uncommon, may be severe or life-threatening and occur more often in patients with renal insufficiency. Allopurinol has been considered the drug of choice for hyperuricemia because it can be conveniently administered once daily, and might prevent urolithiasis. Allopurinol and uricosuric drug may be used simultaneously in a few patients who can not be controlled with a single medication.

DISCUSSION

Hyperuricemia does not always lead to the typical clinical manifestations of gout. These symptoms usually only appear in a person suffering with hyperuricemia for 20 to 30 years. The normal course of untreated hyperuricemia, leading to progressive urate crystal deposition, begins with uric acid urolithiasis (urate kidney stones) and progresses to acute gouty arthritis and chronic tophaceous gout. Patients with gout tend to seek medical attention during gout attacks, at which point the standard diagnostic procedure is to search for monosodium urate crystals in synovial fluid. But patients are often seen during the intercritical periods, when, in the absence of tophi, the diagnosis is made on clinical grounds by applying the preliminary American College of heumatology classification criteria. However, classification criteria work best in the study of groups of patients, and they often fail in the evaluation of the individual patient. A

clinical approach for the diagnosis of gout may be problematic and may explain why other conditions are often incorrectly diagnosed and treated as gout. Monosodium urate crystals can be found in synovial fluid obtained from asymptomatic gouty joints. Other factors that can precipitate gouty attacks such as trauma, surgery, excessive alcohol consumption, administration of certain drugs and the ingestion of purine-rich foods.

Acute gouty arthritis consists of painful episodes of inflammatory arthritis and represents the most common manifestation of gout. Typical manifestations include a patient who goes to bed and awakens by severe pain in the big toe but may also be experienced in the heel, instep or ankle. The pain is described as that of a dislocated joint and is often accompanied or preceded by chills and a slight fever. The pain can become so severe even the simple act of cloth touching the area is unbearable. Gouty arthritis attacks usually dissipate within several hours but can also last for several weeks.

Long-standing persistence of MSU crystals may also cause chronic neutrophilic inflammation, osteoclast activation and chronic granulomatous infiltration of the synovium. Micro-aggregates of MSU crystals occur in all patients with gout, but in some, macroscopic aggregates occur, manifested as tophus formation. Tophi are usually considered to be a late manifestation of gout. The continued development of tophi results in destructive arthropathy (disease of a joint).

Aside from gouty arthritis and tophus formation, renal disease is the most frequent complication of hyperuricemia. Kidney disease in patients with gout is of numerous types. Uric acid stones, which represent 5-10% of all renal calculi in the United States, also result from uric acid precipitation in the collecting system. Uric acid stones are related to uric acid exceeding its solubility in the urine; thus, patients with hyperuricosuria have an increased risk of uric acid nephrolithiasis. Urine oversaturation with uric acid and subsequent crystal formation is determined largely by urinary pH. Individuals who form uric acid stones tend to excrete less ammonium, which contributes directly to low urinary pH. In addition, persons with gout and those who form stones, in particular, have a reduced postprandial alkaline tide (alkaline urinary pH).

Treatments aimed at lowering serum urate levels in hyperuricemic patients is usually only a consideration in the context of gout. Because acute gouty arthritis is an inflammatory event, treatment with anti-inflammatory drugs

is often successful in reducing the symptoms. Allopurinol is an inhibitor of xanthine oxidase and therefore prevents conversion of xanthine to uric acid. The usual dose of 300 mg/day should be adjusted for renal insufficiency. Patients with decreased renal function should begin taking allopurinol at a dose of 50-100 mg/day and then gradually increase the dose over a few months if it is tolerated well without fever, dermatitis or eosinophilia. The goal of urate lowering therapy is a serum uric acid level of 6 mg/dl or less. Once achieved, such therapy should be continued indefinitely. Care must be taken to avoid drug interactions of allopurinol in combination with ampicillin, cyclophosphamide, azathioprine, warfarin or theophylline.

CONCLUSION

Gout is an inflammatory arthritis caused by the deposition of monosodium urate crystals in a joint, characterized by acute attacks that, over time, can become a chronic arthritis. Untreated, progressive joint destruction occurs and tophaceous deposits develop. Common sites for tophi include the pinna of the ear, the olecranon bursa and adjacent to the small joints of the fingers. Gout must be diagnosed by arthrocentesis before initiating one of the many treatments that exist. Continuing drug therapy and lifestyle modifications can significantly improve patient outcome.

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