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Diagnosis and Treatment of Gout Arthritis

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ABSTRACT

Gout is a metabolic disease that is heterogeneous, often familial, metabolic disease associated with abnormal uric acid deposits in tissues and is initially characterized by recurrent acute arthritis, usually monoarticular, and later by chronic deforming arthritis. Urate deposition occurs when serum uric acid is saturated (that is, at greater than 6.8 mg/dL [404.5 μmol/L]). Hyperuricemia is caused by excess or underexcretion of uric acid, sometimes both. The disease is especially common in the Pacific islands, for example, the Philippines and Samoa. Acute gouty arthritis is sudden in onset and often occurs at night. It may develop without a clear precipitating cause or may follow a rapid increase or decrease in serum urate levels. Common precipitants are excess alcohol (especially beer), changes in drugs that affect urate metabolism, and, in hospitalized patients, fasting before medical procedures. This literature review presents gout arthritis, symptoms, and signs in general to the prognosis of this disease.

1. Introduction

Gout is a metabolic disease that is heterogeneous, often familial, a metabolic disease associated with abnormal deposits of uric acid in tissues and is characterized initially by recurrent acute arthritis, usually monoarticular, and later by chronic deforming arthritis. Urate deposition occurs when serum uric acid is saturated (that is, at greater than 6.8 mg/dL [404.5 μmol/L]). Hyperuricemia is caused by excess or underexcretion of uric acid, sometimes both.¹

Primary gouty arthritis has an inherited component, and genome surveys have linked gout risk to several genes whose products regulate renal handling of urate. Secondary gouty arthritis has an inherited component, associated with acquired causes of hyperuricemia, eg use of drugs (especially diuretics, low-dose aspirin, cyclosporine, and niacin), myeloproliferative disorders, plasma cell myeloma,

hemoglobinopathies, chronic kidney disease, hypothyroidism, psoriasis, sarcoidosis, and lead poisoning. Alcohol consumption increases the incidence of hyperuricemia by increasing uric acid production and decreasing renal excretion of uric acid. Finally, hospitalized patients often suffer from gout attacks because of changes in diet, fluid intake, or medications that cause a rapid decrease or increase in serum gout levels.

Approximately 90% of patients with primary gout are male, usually over 30 years of age. In women, onset is usually postmenopausal. The typical lesion is tophus, a nodular deposit of monosodium urate monohydrate crystals with an associated foreign body reaction. Tophi are found in cartilage, subcutaneous and periarticular tissues, tendons, bones, kidneys, and elsewhere. Veins have been demonstrated in

synovial tissue (and fluid) during acute arthritis; indeed, acute inflammation of gout is believed to be initiated by ingestion of urate crystals uncoated by monocytes and synoviocytes.²

The relationship of hyperuricemia with gouty arthritis is still unclear because hyperuricemia is found in people who have never had gout or gout stones. Rapid fluctuations in serum uric acid levels, either increased or decreased, are important factors in the initiation of acute gout. It is characterized pathologically by the tophaceous invasion of the articular and periarticular tissues, by structural derangement and secondary degeneration (osteoarthritis).

Goat kidney stones occur in 5-10% of patients with gouty arthritis. Hyperuricemia is highly correlated with the likelihood of stone development, with the risk of stone formation reaching 50% in patients with serum uric acid levels greater than 13 mg/dL. Chronic urate nephropathy is caused by the deposition of monosodium urate crystals in the renal medulla and pyramids. Although progressive chronic kidney disease occurs in the majority of patients with chronic gout, the role of hyperuricemia in causing this outcome is controversial, because many patients with gout have multiple risk factors for chronic kidney disease (eg, hypertension, NSAID use, alcohol use, lead exposure, and other risk factors for vascular

disease).³

Clinical manifestations

Symptoms and signs

Acute gouty arthritis is sudden in onset and often occurs at night. It may develop without a clear precipitating cause or may follow a rapid increase or decrease in serum urate levels. Common precipitants are excess alcohol (especially beer), changes in drugs that affect urate metabolism, and, in hospitalized patients, fasting before medical procedures. The MTP joint of the big toe is the most vulnerable (the "podagra"), although others, particularly the foot, ankle, and knee, are commonly affected (Figure 1). Gout attacks can develop in periarticular soft tissues such as the arch of the foot. The hips and shoulders are rarely affected. More than one joint can sometimes be affected during the same attack; in such cases, the distribution of the arthritis is usually asymmetric. As the attack progresses, the pain becomes intense. The joint involved is swollen and very tender and the overlying skin is tense, warm, and dark red. Fever is common and can reach 39°C. Localized desquamation and pruritus during recovery from acute arthritis are characteristic of gout but are not always present. Tophi can be found on the pinna of the ear, feet, olecranon and prepatellar bursae, and hands. They usually develop years after the initial attack of gout.^{3,4}



Figure 1. Typical changes of inflammatory gout in the MTP-1 joint (podagra).

An asymptomatic period of months or years usually follows the initial acute attack. After years of repeated bouts of severe lower extremity monoarthritis and untreated hyperuricemia, gout can progress to chronic polyarthritis, deforming the upper and lower extremities that mimic rheumatoid arthritis. Chronic lead poisoning can cause attacks of gouty arthritis (saturnine gout).⁴

Investigations for gout arthritis

Laboratory findings

Although serial measurements of serum uric acid detect hyperuricemia in 95% of patients, single uric acid determination during an acute gout attack is normal in 25% of cases. Therefore, a normal serum uric acid level does not rule out gout, especially in patients taking urate-lowering drugs. During an acute attack, the peripheral white blood cell count is often elevated. Identification of sodium urate crystals in joint fluid or material aspirated from tophus establishes the diagnosis. The crystals, which may be extracellular or found within neutrophils, are needle-like and birefringent negative when examined with a polarized light microscope.^{4,5}

Imaging

Early in the disease, radiographs show no changes. Later, perforated erosions with protruding edges of cortical bone ("rat-bite") develop. When these are adjacent to soft tissue tophus, they are diagnostic of gout. Ultrasound can be used to confirm the diagnosis of gout. Tophi that are too small to be seen on physical examination and smaller deposits of urate crystals can often be imaged by ultrasonography.⁴

Differential Diagnosis

Acute gout is often confused with cellulitis. Bacteriological studies usually rule out acute pyogenic arthritis but rarely, acute gout and pyogenic arthritis may coexist. Pseudogout is distinguished by the identification of calcium pyrophosphate crystals (positive birefringence) in the joint fluid, usually normal serum uric acid, and the radiographic

appearance of chondrocalcinosis. Chronic tophaceous arthritis may resemble chronic rheumatoid arthritis; Gout is suggested by a previous history of monoarthritis and confirmed by demonstration of urate crystals in a suspected tophus. Likewise, the hips and shoulders are generally spared from tophaceous gout. A biopsy may be needed to differentiate tophi from rheumatoid nodules.^{1,3}

Treatment

Asymptomatic hyperuricemia

As a general rule, uric acid-lowering drugs should not be given until acute gout, kidney stones, or tophi become apparent. Epidemiological studies show that treating asymptomatic hyperuricemia slows the progression of chronic kidney disease, but there are no definitive studies on this.

Acute attacks

Treatment of acute attacks focuses on reducing inflammation, not lowering serum uric acid. Indeed, a sudden drop in serum uric acid often results in further episodes of gouty arthritis.

NSAIDs

Oral NSAIDs in full doses (e.g naproxen 500 mg twice daily or indomethacin 25-50 mg every 8 hours) are effective treatments for acute gout and should be continued until symptoms subside (usually 5-10 days). Contraindications include active peptic ulcer disease, impaired renal function, and a history of allergic reactions to NSAIDs.⁶

Colchicine

Oral colchicine is an appropriate treatment option for acute gout, provided the duration of the attack is less than 36 hours. For acute gout, colchicine should be given orally as follows: an initial dose of 1.2 mg followed by a dose of 0.6 mg 1 hour later for a total dose of 1.8 mg on the first day; thereafter 0.6 mg twice daily was used until resolution. Patients already on prophylactic doses of colchicine and have an acute attack of gout may receive a full loading dose (1.2 mg)

followed by 0.6 mg 1 hour later (before continuing the usual 0.6 mg once or twice daily) provided they have not received this regimen within the previous 14 days (in which case, NSAIDs or corticosteroids should be used). The dose of colchicine should be reduced or avoided altogether if renal or hepatic impairment is present. The use of oral colchicine during the intercritical period to prevent gout attacks is discussed below.

Corticosteroids

Corticosteroids often provide dramatic symptom relief in acute episodes of gout and will control most attacks. They are the most useful in patients with contraindications to the use of NSAIDs. Corticosteroids can be given intravenously (eg, methylprednisolone, 40 mg/day) or orally (eg, prednisone, 40-60 mg/day). Corticosteroids can be given at the recommended dose for 5-10 days and then simply discontinued or given at the recommended starting dose for 2-5 days and then gradually tapered over 7-10 days. If the patient's gout is monoarticular or oligoarticular, intra-articular corticosteroid administration (eg, triamcinolone, 10-40 mg depending on joint size) is highly effective. Because gout and septic arthritis may coexist, although rarely, joint aspiration and Gram stain with synovial fluid culture should be performed. when intra-articular corticosteroids are administered.⁷

Interleukin-1 Inhibitor

Anakinra (interleukin-1 receptor antagonist) and canakinumab (monoclonal antibody to interleukin-1 beta) have efficacy for the management of acute gout, but they have not been approved by the FDA for this indication.

Management between attacks

Treatment during the symptom-free period is intended to minimize urate deposition in tissues and to reduce the frequency and severity of relapses. Potentially reversible causes of hyperuricemia are a high-purine diet, obesity, alcohol consumption, and

the use of certain medications. Patients with one episode of gout who have normal kidney function and can lose weight and stop drinking are at low risk for another attack and may not need long-term medical therapy. In contrast, individuals with mild chronic kidney disease or with a history of multiple attacks of gout are likely to benefit from pharmacological treatment. In general, the higher the uric acid level and the more frequent the attacks, the more likely long-term medical therapy will be beneficial. All patients with tophaceous gout should receive urate-lowering therapy.^{6,7}

Diet modification

Excessive alcohol consumption can trigger attacks and should be avoided. Consumption of beer appears to confer a higher risk of gout than whiskey or wine. Although dietary purines usually contribute only 1 mg/dL to serum uric acid levels, moderation in consuming foods high in purines is advisable. Patients should avoid organ meats and drinks sweetened with high fructose corn syrup. A high fluid intake and, more importantly, a daily urine output of 2 L or more will promote urate excretion and minimize urate precipitation in the urinary tract.⁸

Avoidance of 'hyperuricemic' drugs

Thiazides and loop diuretics inhibit renal uric acid excretion and, if possible, should be avoided in patients with gout. Similarly, niacin can increase serum uric acid levels and should be discontinued if alternative therapies are available. Low-dose aspirin also worsens hyperuricemia.

Colchicine prophylaxis

Colchicine may be used when urate-lowering therapy is started to suppress attacks triggered by sudden changes in serum uric acid levels. The usual dose is 0.6 mg orally once or twice daily. Colchicine is cleared through the kidneys. Patients who have coexisting moderate chronic kidney disease should take colchicine only once daily or once daily to avoid peripheral neuropathy and other complications of

colchicine toxicity.³

Decreased serum gout

Indications for gout-lowering therapy in persons without gout include frequent acute arthritis (two or more episodes per year), tophaceous deposits, or chronic kidney disease (stage 2 or worse). The American College of Rheumatology guidelines recommends a treat-to-target approach to urate-lowering therapy. The minimal goal of uric acid-lowering therapy in serum uric acid at or below 6 mg/dL or 357 μmol/L (that is, below the level at which the serum is saturated with uric acid, thereby allowing urate crystals to dissolve); in some cases, control of gout may require reducing serum uric acid to less than 5 mg/dL or 297.4 μmol/L. Lowering serum uric acid levels is not beneficial for the treatment of acute gout attacks. Three classes of agents can be used to lower serum uric acid—xanthine oxidase inhibitors (allopurinol or febuxostat), uricosuric agents, and uricase (pegloticase).

Xanthine oxidase inhibitors

Allopurinol and febuxostat are the preferred first-line agents for lowering uric acid. They reduce plasma uric acid levels by blocking the final enzymatic step in uric acid production. Allopurinol and febuxostat should not be used together but maybe tried sequentially if initial agents fail to lower serum uric acid to target levels or otherwise tolerated. The most frequent side effect of both drugs is the precipitation of acute gout attacks; thus, patients should generally receive prophylactic doses of colchicine.^{3,4}

Hypersensitivity to allopurinol occurs in 2% of cases, usually within the first few months of therapy, and can be life-threatening. The most common early sign of hypersensitivity is a pruritic rash which may progress to toxic epidermal necrolysis, especially if allopurinol is continued; vasculitis and hepatitis are other manifestations. Patients should be instructed to discontinue allopurinol immediately if a rash develops. Chronic kidney disease and concomitant thiazide therapy are risk factors. There is a strong association

between allopurinol hypersensitivity and HLA-B*5801, which is a common allele in certain East Asian populations. The current recommendation is to screen for HLA-B*580 before starting allopurinol in all people of Han Chinese and Thai descent and Koreans with stage 3 chronic kidney disease or worse.

The initial daily dose of allopurinol is 100 mg/day orally (50 mg/day for those with stage 4 chronic kidney disease or worse); the dose of allopurinol should be titrated upwards every 2-5 weeks to achieve target serum uric acid levels. The typical dose of allopurinol is 300 mg, but most patients need more than 300 mg daily to reach target uric acid levels. The maximum daily dose is 800 mg.

Allopurinol interacts with other drugs. The combined use of allopurinol and ampicillin causes drug rash in 20% of patients. Allopurinol can increase the half-life of probenecid, whereas probenecid increases the excretion of allopurinol. Thus, patients taking both drugs may need to take a slightly higher than usual dose of allopurinol and a lower dose of probenecid.

Febuxostat also rarely causes hypersensitivity reactions, and those with previous hypersensitivity to allopurinol appear to have a slightly higher risk. May be administered without dose adjustment in patients with mild to moderate renal disease. However, abnormal liver tests may occur in 2-3% of patients taking febuxostat. In addition, febuxostat was associated with higher rates of fatal and nonfatal cardiovascular events than allopurinol. The FDA recommends that febuxostat be reserved for patients for whom allopurinol is ineffective or contraindicated, and there is an FDA warning box regarding febuxostat's higher risk of death. The initial dose of febuxostat is 40 mg/day orally. If target serum uric acid is not achieved within 4 weeks, the dose of febuxostat may be increased to 80 mg/day and then up to a maximum dose of 120 mg/day.⁹

Uricosuric drugs

Uricosuric drugs decrease serum uric acid levels by blocking tubular reabsorption of filtered urate, thereby

increasing renal excretion of uric acid. Probenecid (0.5 g/day orally) and lesinurad (200 mg/day orally) are the uricosurics of choice in the United States and are usually reserved for patients who cannot achieve a serum uric acid level of less than or equal to 6.0 mg/day. dL with allopurinol or febuxostat alone. Lesinurad carries an FDA black box warning that acute kidney injury can occur with treatment, especially when Lesinurad is used without a xanthine oxidase inhibitor; contraindicated in patients with a creatinine clearance of less than 45 mL/min. Probenecid can be added to a xanthine oxidase inhibitor or used as monotherapy. Probenecid should not be used in patients with a creatinine clearance of less than 50 mL/min because of limited efficacy; Contraindications include a history of nephrolithiasis (uric acid or calcium stones) and evidence of high uric acid excretion (ie, more than 800 mg of uric acid in a 24-hour urine collection). To reduce the development of uric acid stones (which occur up to 11%), patients should be advised to increase fluid intake and physicians should consider prescribing an alkalizing agent. (eg, potassium citrate, 30-80 mEq/day orally) to maintain urine pH > 6.0.

Uricase

Pegloticase, a recombinant uricase that must be administered intravenously (8 mg every 2 weeks), is indicated for rare patients with refractory chronic tophaceous gout. Pegloticase carries an FDA black box warning, which advises administration of the drug only in healthcare settings and by healthcare professionals who are prepared to manage anaphylaxis and other serious infusion reactions.^{9,10}

Chronic tophaceous arthritis

With strict medical compliance, allopurinol, febuxostat, or pegloticase shrink tophi and in time can cause tophi loss. Extensive tophi resorption requires maintenance of serum uric acid below 6 mg/dL. Surgical excision of large tophi offers mechanical repair of certain deformities.

Gout in transplant patients

Hyperuricemia and gout commonly develop in many transplant patients because they have decreased renal function and require drugs that inhibit uric acid excretion (especially cyclosporine and diuretics). Treating acute gout in these patients is a challenge. Often the best approach to monoarticular gout—after ruling out the infection—is to inject corticosteroids into the joint. For polyarticular gout, increasing the dose of systemic corticosteroids may be the only alternative. Because transplant patients often have recurrent attacks of gout, long-term treatment requires lowering serum uric acid with allopurinol or febuxostat. The renal dysfunction seen in many transplant patients renders uricosuric agents ineffective. Both allopurinol and febuxostat inhibit azathioprine metabolism and should be avoided in patients taking azathioprine.

Prognosis

Without treatment, acute attacks can last from a few days to several weeks. The interval between acute attacks varies to years, but the asymptomatic period often becomes shorter as the disease progresses. Chronic gouty arthritis occurs after repeated attacks of acute gout, but only after inadequate treatment. The younger the patient at the onset of the disease, the greater the tendency to progress. Destructive arthropathy is rarely seen in patients whose attacks are after age 50.

2. Conclusion

The management of gouty arthritis includes treatment of acute attacks, treatment in the phase between attacks, and medication to lower blood uric acid levels. Chronic gouty arthritis occurs after repeated attacks of acute gout, but only after inadequate treatment.

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