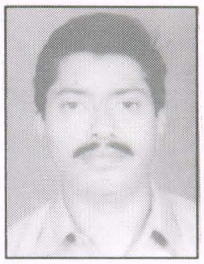
REVIEW ARTICLE



Gouty Arthritis

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The term gout, represents a group of heterogeneous metabolic dysfunctions characterized by deposition of monosodium urate crystals in the tissue from hyperuricemic body fluids. It can present as acute monoarthritis, chronic tophaceous arthritis, urate nephropathy and urolithiasis (1). The classical presentation is in form of acute monoarthritis usually involving first metatarso-phalangeal joint, however, untreated patients may acquire polyarticular course and may develop tophi. The ACR Criteria (2) for diagnosis of acute gouty arthritis are meant for epidemiological studies and not for diagnosis of an individual patient.

Epidemiology

Gout is the single most common cause of inflammatory arthritis in males above the age of 40 years (3). Though hyperuricemia is the single most important risk factor for the causation of gout, the epidemiology of gout and hyperuricemia are different (4). Hyperuricemia is arbitarily defined as serum or plasma urate concentration >7 mg/dl in males and >6 mg/dl in females (5). At this concentration of urate, the limit of solubility of MSU in plasma at 37°C is exceeded (6). The risk of gouty arthritis and renal stones increases in proportion to serum urate concentrations. The five year cumulative incidence rates of gouty arthritis for serum urate level of 8 mg/dl has been reported to be 2% as compared to 19.8% for urate levels 9-10 mg/dl and 30% for >10 mg/dl (7). Serum urate level increases sharply at puberty in males and at menopause in females (5). Therefore, gout is very uncommon in premenopausal females and males below 30 years of age (1,5,6). The precise incidence and prevalence rate of gout is difficult to determine because of remitting and relapsing nature of the disease, propensity to misdiagnosis (over diagnosis by patients), changing life styles, eating habits and longevity of life in different population worldwide (8). Male to female ratio has been reported to vary from 2-7:1 in different series (3,9). Data on the epidemiological profile of Indian patients is scantily reported in literature. In a recent population based study from South Korea, the prevalence of hyperuricemia has been reported to be 25.8% in males and 15% in females whereas 11.5% of males and 3% of females with hyperuricemia had gout (10). Western figures for the prevalence of hyperuricemia and gout varies 2-13% and 1.3-3.7% respectively, in the general population (11). Various risk factors which predisposes to gout are obesity, alcohol intake, hypertension, renal insufficiency, diuretics use, family history of gout and environmental or occupational exposure to lead.

Clinical Presentations of Gout

The natural history of gout is comprised of 4 phases (a) asymptomatic hyperuricemia, (b) acute gouty arthritis, (c) intercritical gout and (d) chronic gout. Asymptomatic

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hyperuricemia remains so in most of the patients and in remainder it ends with the first attack of acute arthritis. Usually it takes 20 years of sustained hyperuricemia to present as acute gouty arthritis and 10-40% patients will have renal colic before first articular event (6). Diagnosis of gout should be reserved for increased uric acid and arthritis but not for increased uric acid and renal stones or arthralgias (6). Acute gouty arthritis typically presents as monoarthritis in 85-90% cases with first metatarso-phalangeal (MTP) involvement at presentation in more than 50% cases (5). Around 30% of cases present with first attack at other sites such as other parts of foot, ankle, knee, hand and shoulder. Acute attacks are precipitated by trauma, surgery, acute illness, alcohol and drugs (diuretics, cyclosporine, IV heparin). Joints invloved in decreasing frequency are : ankle, heel, knee, wrist, elbow, fingers. Shoulder, hip, spine, sacroiliac and temporomandibular joints are seldom involved (6). First MTP joint involvement occurs in around 90% of patients with gout at some time during the course of illness. The classical description of Sydenham's describing the explosive onset of arthritis at night with features of inflammation and severe pain lasting few hours of days is valid till date. Usually, there are no sequelae of an acute attack. Occasionally, it can present as soft tissue involvement mimicking cellulitis in form of bursitis and tenosynovitis. Polyarticular presentation at the onset may occur in around 10% of patients with gout (12) and may occur in upto 40% of patients during long term follow-up (13). The polyarticular involvement is usually symmetrical and ascending type with involvement of hand joints. It is usually seen in eldery males and postmenopausal females, particularly those taking diuretics (1).

Intercritical gout is the asymptomatic period in between the attack of acute gouty arthritis. Most of the patients will have second attack within 6 months to 2 years (14). The frequency of attacks increases with time in untreated patients, however, the onset of attacks are less explosive. Though, recovery following an attack is complete, arthritis typically evolves into oligo-or polyarticular involvement with severe disease which lasts longer and abates more gradually (6).

Chronic gout is characterized by oligo-or polyarticular involvement with no pain free period. Much of the disability is due to tophi which may produce destructive deforming arthritis and non healing ulcers. The classic locations for tophi are joints of hands or feet, helix of ear, the olecranon bursa, and the achilles tendon. Before the advent of uric acid lowering drugs, 60% of the patients with untreated gout, used to develop tophi after 10 years (12). Rate of formation of tophi depends upon the degree and duration of hyperuricemia and severity of renal disease (1,14). Tophi at initial presentation is unusual in the primary gout but can occur in gout secondary to myleproliferative diseases, glycogen storage diseases, Lesch-Nyhan syndrome, allograft recipients on cyclosporine and patients on diuretics (5,6). Tophaceous gout is often associated with early age of onset, frequent acute attacks, high serum uric acid levels, polyarticular involvement at onset and renal dysfunction (1). However, with the use of uric acid lowering drugs and the ability to control hyperuricemia, incidence of tophi has decreased from 53% to 17% (15). Another series has reported the incidence of tophaceous gout to as low as 3% (3). However, the prevalence of tophaceous gout remain high in untreated patients.

Potential for Misdiagnosis of Gout

Idiopathic hyperuricemia is much more common than the clinical gout, and a flare of OA of Ist MTP in a patient with hyperuricemia can be misdiagnosed as gout. Acute hot joint in a patient receiving chemotherapy for maligancy or a transplant recipient on cyclosporine may be due to secondary gout (16) but may be labelled as septic arthritis. Similarly, an acute hot joint in a patient with chronic gout may be misdiagnosed to be due to acute flare whereas it may be due to septic arthritis due

to secondary infection of an ulcerated tophus. Occasional patient of gout who directly presents with chronic gout without history of recurrent acute attacks or symmetrical hand joints arthritis with tophaceous deposits over olecranon, wrists and deformities of fingers, metacarpo-phalangeal (MCP) and proximal interphalangeal (PIP) and erosions seen on X-ray hands may masquerade as erosive, deforming, nodular rheumatoid arthritis. Acute onset reactive arthritis (monoarticular or oligoarticular) with or without dactylitis of great toe or other toes may mimick acute gouty arthritis, especially in premenopausal females and males below 30 years of age.

Diagnosis

The definitive diagnosis of gout can only be made by demonstration of intracellular needle shaped negatively birefringent crystals in the synovial fluid, tophus or tissue under a polarizing microscope. Serum uric acid levels cannot be relied on to confirm or exclude gout (17). Acute gouty arthritis has been reported to occur in normouricemic patients (18).

Even if a polarizing microscope is not available, the characteristic needle shape of the monosodium urate crystals, especially when found within white blood cells, can be indentified with conventional light microscopy; in this case, they resemble a toothpick pierced through an olive (19). However, there is a chance of missing the MSU crystals in almost 20% of the patients (20).

Twenty-four hour urinary acid estimation is helpful in categorizing the patient into over producer (800 mg or more) vs underexcretor (less than 800 mg) of urate on normal purine diet and thus help in the choice of antihyperuricemic drugs.

Radiological features of gout during intercritical or chronic phase are : asymmetric joint invlovement, eccentrically placed soft tissue opacities due to periarticular tophi, bone erosions with sclerotic margins associated with soft tissue swelling, punched out appearance, preserved joint space, absent juxtaarticular osteopenia, calcified tophi appearing as radiodense mass and rarity of bony fusion.

Classification and Etiopathogenesis

Gout is classified into 2 main groups; over production or under secretion of uric acid (Table 1). Almost 90% patients with gout and 98% with primary hyperuricemia are undersecretors (6, 11). However, Kumar et al from North Inida had reported 57% patients with gouty arthritis as over producer as compared to western figure of 10% (21).

TABLE-I

UNDER SECRETION		OVER PRODUCTION	
Genetic	Acquired	Genetic	Acquired
Polycystic	Idiopathic	Enzyme defects	Idiopathic
Down syndrome	Renal insufficiency	HGPRT deficiency	Hemolytic processes
	Dehydration/starvation	PRPP overactivity	Lymphoproliferative
	Hypertension	Glycogen storage disorder	disorders
	Drugs (diuretics, alcohol, cyclosporine aspirin, pyrazinamide)		Psoriasis
			Purine rich diet
			Alcohol
	Toxemia of pregnancy		Obesity
	Lead intoxication		

The formation of MSU crystals depends upon the concentration of urate at the site, local temperature and substances maintaining urate in solution specially proteoglycans (6,22). Increased diffusion of water out of a joint has been postulated to increase urate concentration and promote crystallization (23). The concentration of other cations in synovial fluid such as sodium and calcium is also important (24). The predilection of gout to attack peripheral joints has been attributed to the lower temperature of these joints. Once the urate crystals are formed, they are coated with IgG. These crystals are now taken up by polymorphonuclear leukocytes via Fc receptors for IgG. Inside the phagolysosome crystals are stripped of IgG, thereby causing the exposure of the hydrogen bonds on the

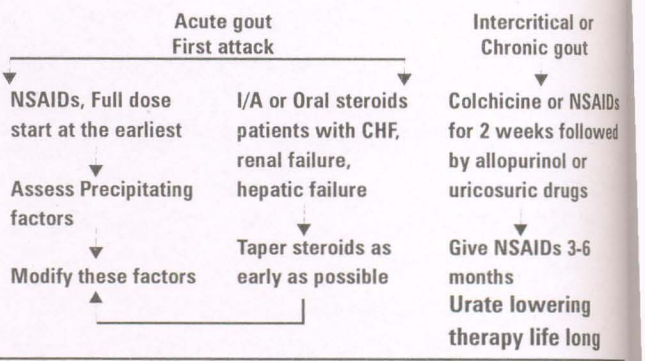
surface of the crystal. This causes membranolysis of the phagolysosome thereby liberating various potent enzymes causing activation of humoral and cellular arms of the immune system and marked inflammatory response (25-27).

Management

Despite awareness of the disease amongst patients and medical practioners, the over diagnosis and under as well as over treatment is far too common. The commonest error we observed is the sole reliability on serum uric acid to confirm the diagnosis. Asking for serum uric acid in a premenopausal female, young men (<30 years) and in a patient with symmetric polyarthritis or low back pain or cervical pain is too gross an error. Other lacunae we found were confusion regarding when and how to begin antihyperuricemic therapy, how to treat acute gout and how to monitor therapy. Identification and correction of various risk factors associated with gout like CAD is neglected in most of the cases. Serial x-rays of the involved areas and 24 hour urinary uric acid are also wanting in most cases.

Majority of the patients presenting with acute monoarticular gouty arthritis should be stratified and treated as per the protocol mentioned above (Table-2). However, 10% of the patients may present as polyarticular gouty arthritis and may pose a diagnostic problem and are very often treated as rheumatoid arthritis (RA). There are several case reports of polyarticular presentation of gout mimicking rheumatoid arthritis (28-30). The distinguishing features between the two are discussed at length in an earlier report (31). Over a span of last 6 months, we happen to see 6 such patients. Two patients had classical history of recurrent attacks of gout for almost 20 years and were correctly diagnosed as gout, even then improper management resulted in polyarticular chronic tophaceous gout with renal dysfunction, a stage which should have never reached.

TABLE-2



General Principles

1. Termination of acute attack as quickly as possible.
2. Prevent recurrence (identify precipitating factor and try to correct it).
3. Prevent or reverse complications of disease such as renal calculi and tophi.
4. Prevent or reverse associated features such as obesity, hypertriglyceridemia and hypertension.
5. Education of patient as per change in dietary habits, weight reduction and avoidance of alcohol.

Asymptomatic hyperuricemia should not be treated as most of the patients will never develop gout (12). However, in a setting of malignancy, xanthine oxidase inhibitors should be started along with good hydration (urine output >100 ml/hour) prior to start of chemotherapy so as to prevent acute uric acid nephropathy. Earlier, this entity was associated with mortality up to 59% however, nowadays with proper hydration and antihyperuricemic therapy mortality is almost nil.

The key to the therapy of acute gout is to start NSAIDs in full dose as early as possible, after infection has been ruled out. Choice of NSAID varies with the physician's preference and experience. Colchicine, at the dose required to control acute gout, leads to significant side effects in more that 80% patients and so is not preferred

for management of acute gout. In patients with peptic ulcer disease, renal failure, congestive heart failure, liver dysfunction and patient on anticoagulation, choice of therapy is intraarticular corticosteroids or oral prednisolone; or intramuscular ACTH or triamcinolone with rapid tapering over 7-10 days. Once the first attack is managed, identification and treatment of the precipitating factor like alcohol and drugs should be done so as to decrease the risk of next attack. Dietary restriction of purine rich foods like chicken, pork, beef, liver, kidney, asparagus, shrimp and spinach may help in an individual case.

Most of the rheumatologists believe that antihyperuricemic therapy should not be started until after 2nd attack. Before start of antihyperuricemic therapy, 24 hour urinary uric acid levels (over producer vs under excretor) and status of kidney function, liver function and drug intake due to associated conditions like low dose aspirin for coronary artery disease (CAD) and cyclosporine for organ transplant should be known. Uricosuric drugs, sulfinpyrazone, probenecid and benzbromarone, should be used in underexcretors whereas xanthine oxidase inhibitors, allopurinol and oxypurinol, in over producers. However, in patients with underexcretor status, with nephrolithiasis or renal failure and on low dose aspirin for CAD or cyclosporine for organ transplant, uricosuric drugs are not recommended. These patients and 'overproducers' should be treated with xanthine oxidase inhibtor, allopurinol. Recently, Wortman has proposed the use of allopurinol as the urate lowering drug in all the patients of gout without measuring the 24 hour urinary uric acid levels (32). The main advantages of such a practice are single daily dose of drug, lesser side effects, fewer drug interactions and being effective in patients with renal insufficiency and nephrolithiasis (32). One great caution to be observed is not to start antihyperuricemic therapy within 4 weeks of an acute attact and to begin prophylactic low dose colchicine (0.5-1 mg/day) or NSAID, 2 weeks prior to start of antihyperuricemic therapy. This prophylactic therapy with colchicine or NSAID should be continued for a period of at least 6 months after the target serum uric acid levels are maintained below 5 mg/dl. Discontinuation of prophylactic therapy earlier than this period may lead to precipitation of acute attacks. In an earlier study, intermittent therapy with antihyperuricemic drugs was found to be associated with increased frequency of acute attacks and continued deposition of urate crystals in the tissue (33). Thus antihyperuricemic therapy is recommended for life long period.

References

1. Becker MA, Levinson DJ. Clinical gout and the pathogenesis of hyperuricemic arthritis and allied conditions. In : Koopman WJ (ed), text book of rheumatology, 13 edition. Vol 2, Williams and Wilkins, United State of America 1997 : 2041-67.
2. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977 ; 20 : 895-900.
3. Roubenoff R. Gout and Hyperuricemia. *Rheum Dis Clin North Am* 1990 ; 16 : 539-550.
4. Hall AP, Barry PE, Dawber TR, McNamara PM. Epidemiology of gout and hyperuricemia. A long-term population study. *Am J Med* 1967 ; 42 : 27-37.
5. Cohen MG, Emmerson BT. Crystal arthropathies. In : Klipel JH, Dieppe PA (eds). Rheumatology, Mosby, United States of America 1995 ; 7.12.1-12.16.
6. Kelley WN, Wortmann RL. Gout and hyperuricemia. In : Kelley WN, Harris ED, Sledge CB (eds). Text book of Rheumatology. W.B. Saunders company, USA 1997 ; 1313-15.
7. Campion EW, Gylnn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med* 1987 ; 82 : 421-26.
8. Lawrence RC, Hochberg MC, Kelsey JL, *et. al.* Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. *J Rheumatol* 1989 ; 16 : 427-41.

9. Yu TF. Some unusal features of gouty arthrits in females. *Semin Arthritis Rheum* 1977 ; 6 : 247-55.

10. Lin KC, Lin HY, Chou P. Community based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. *J Rheumatol* 2000 ; 27 : 1045-50.

11. Wortmann RL. Gout and other disorders of purine metabolism. In : Fauci AS, Braunwald E, Isselbacher KJ *et al.* (eds). Harrisons Principles of Internal medicine, McGraw-Hill, USA, 1998 ; 2158-65.

12. Nuki G, Crystal Arthropathies. In : Maddison PJ, Issenberg, Woo P, Glass DN (eds). Oxford text book of rheumatology. Oxford Unversity Press Hongkong 1993 ; 983-1005.

13. Lawry GV, Fan PT, Bluestone R. Polyarticular vs monoarticular gout. A prospective comparative analysis of clinical features. *Medicine* 1988 ; 67 : 335-43.

14. Gutman AB. The past four decades of progress in the knowledge of gout, with an assessment of the present status. *Arthritis Rheum* 1973 ; 16 : 431-45.

15. Yu T, Yu TF. Mile stones in treatment of gout. *Am J Med* 1974 ; 56 : 676.

16. Sturrock RD. Gout. Easy to misdiagnose. *Br Med J* 2000 ; 320 : 132-33.

17. Snaith ML. ABC of rheumatology. Gout, hyperuricemia, and crystal arthrits. *Br Med J* 1995 ; 25 : 521-24.

18. McCarty DJ. Gout without hyperuricemia. *JAMA* 1994 ; 271 : 302-303.

19. Mark D. Harris, Lori B. Siegel, Jeffery A. Alloway. Gout and Hyperuricemia. *Am Fam Phys* 1999; 59 : 925-36.

20. Pascual E, Gout update : from lab to the clinic and back. *Curr Opin Rheumatol* 2000 ; 12 : 213-18.

21. Kumar A, Singh YN, Malaviya AN, Chaudhary K, Tripathy S. Clinical profile, therapeutic approach and outcome of gouty arthritis in northern India. *JAPI* 1990 ; 38 : 400-402.

22. Loeb JN. The influence of temperature on the solubility of monosodium urate. *Arthritis Rheum* 1972 ; 15 :189-92.

23. Simkin PA, Pizzorno JE. Transynovial exchange of small molecules in normal human subjects. *J Appl Physiol* 1974 ; 36 : 581-87.

24. Wilcox WR, Khalaf AA. Nucleation of monosodium urate crystals. *Ann Rheum Dis* 1975 ; 34 : 332-39.

25. Terkeltaub RA, Ginsberg MH. The inflammatory reaction to crystals. *Rheum Dis Clin North Am* 1988 ; 14 : 353-64.

26. Nagase M, Baker DG, Schumacher HR Jr. Immunoglobulin G coating on crystals and ceramics enhances polymorphonouclear cell superoxide production : correlation with immunoglobulin G adsorbed. *J Rheumatol* 1989 ; 16 : 971-76.

27. Beutler A, Schumacher HR, Jr. Gout and 'pseudogout'. When are arthritic symptoms caused by crystal deposition ? *Postgrad Med* 1994 ; 95 : 103-06, 109 : 113-16 passim.

28. Yunus M, Plattner PF, Masi AT, Shah IK, Lindhal LS, Conner DE. Ulnar deviation of the fingers in gout simulating rheumatoid arthritis. *J Rheumatol* 1982 ; 9 : 619-23.

29. Uy JP, Nuwayhid Saadeh C. Unusual presentations of gout. Tips for accurate diagnosis. *Postgrad Med* 1996 ; 100 : 253-254, 257-60.

30. Sewell KL, Petrucci R, Keiser HD. Misdiagnosis of rheumatoid arthritis in an elderly woman with gout. *J Am Geriatr Soc* 1991 ; 39 : 403-06.

31. Agarwal V, Aggarwal A, Misra R. A case of nodular deforming polyarthritis. *JIRA* 2000 ; 8 : 146-48.

32. Wortmann RL. Effective Management of Gout. An Analogy. *Am J Med* 1998 ; 105 : 513-14.

33. Van Lieshout-Zuidema MF, Breedveld FC. Withdrawal of longterm antihyperuricemic therapy in tophaceous gout. *J Rheumatol* 1993 ; 20 : 1383-85.