HORIZONS

Crystal Arthritis - Past, Present and Future

Binoy J. Paul

The crystal related arthropathies represent a heterogenous group of disorders in which minerals are deposited in musculoskeletal tissue resulting in pathological alterations. Intra articular crystals can cause acute and chronic inflammation and joint damage via biomechanical and biochemical pathways.The most common crystal related arthopathies are Gout, Calcium pyrophosphate dihydrate disease (pseudogout) and calcific periarthritis/ tendonitis (Basic calcium phosphate crystal deposition disease). Of these gout is the most common but easily misdiagnosed problem in day to day practice. *" Screw up the vice as tightly as possible - you have rheumatism, give it another turn and that is gout" - Anonymous*

The word Gout is derived from the latin word *'gutta'* means drop. It is based on the ancient belief that the arthritis is due to deposition of malevolent humor by evil spirits into the joint, drop by drop (1). Way back in the 4th century BC, Hippocrates made astute observations about gout which is popularly known as "aphorisms of gout" He said that "*Eunuchs do not take gout, nor become bald. A women does not take gout unless her menses be stopped,An young man does not take gout unless he indulges in coitus. In gouty affection, inflammation subsides in 40 days".* In 3rd century BC, Galen described the tophi. Crystals in gouty tophi was first demonstrated by Antony Van Leeuwenhoek in 1679 (2). It is in 1848 Sir Alfred Garrod demonstrated hyperuricemia as the basic cause of gout (3). In 1961 McCarty and Hollander established the association between gouty arthritis and articular crystal deposition

Gout is a clinical syndrome occurs as a result of deposition of monosodium urate monohydrate crystals from hyper uricemic body fluids. The crystals may be deposited in a joint leading to an acute inflammatory response or in soft tissues such as cartilage causing no inflammation. Most cases of gout are characterised by the sudden onset of severe acute mono arthritis in a peripheral joint in the lower limb. The arthritis remits completely and then recurs with increasing frequency. After approximately 10 years of recurrent gouty arthritis, tophi develop in cartilage, tendons and bursae in some patients.

There is a marked increase in incidence of gout in certain parts of India like Kerala in the recent years. Rapid urbanisation with change in lifestyle leading to obesity, lack of physical exercise, high protein diet, alcoholism and increasing use of drugs like thiazides are some of the causes for this rise in the incidence.

Gout was extremely rare in menstruating females due to the uricosuric effect of estrogen. However the incidence of female gout is also rising in India due to increased longevity after menopause ,change in life style, increasing number of hysterectomies and use of various hyperuricemic drugs

The gold standard for diagnosis of gout is joint aspiration and identification of characteristic needle shaped negatively birefringent mono sodium nitrate crystals under compensated polarized light microscopy (4). Gram stain and culture of the aspirated fluid are often performed concomitantly to exclude septic arthritis and cellulites both of which may mimic acute gout. When crystals are not identified and culture is negative a presumptive diagnosis of gout is often made on the basis of other factors including a classic clinical presentation (eg. Podagra) positive family history, hyper uricemia and rapid resolution of symptoms with colchicine.

Although hyper uricemia is not a requirement for the diagnosis of gout and its presence in a patient with arthritis does not necessarily establish the diagnosis, the risk of gout increases with degree and duration of hyper uricemia.It is found that about one third of patients are normouricemic during the acute attacks of gouty arthritis. Even though a period of sustained hyperuricemia is required before accretions of uric acid to accumulate on the cartilage or synovial surfaces, the blood levels may normalize before crystals are liberated into the joint cavity. It is a fall in the serum uric acid, which so often

From the Division of Rheumatology, Department of Medicine, Medical College, Calicut, Kerala.
Correspondence to : Dr. Binoy J.Paul, Asso. Prof. In charge, Division of Rheumatology, Deptt. of Medicine, Medical College, Calicut, Kerala

precipitates acute episodes by encouraging tophus dissolution.The diagnosis of normouricemic gout can be conficidently made by demonstrating urate crystals by arthrocentesis. In cases where demonstration of crystals is difficult a positive family history, typical clinical presentation of acute mono/oligo arthritis and good response to colchicine often establishes the diagnosis.

Differential diagnosis of acute gout include palindromic rheumatism, septic arthritis, cellulites, pseudogout and haemarthrosis. Even though septic arthritis and cellulitis can be easily excluded by joint aspiration and bacteriological work up, palindromic rheumatism often causes confusion.

Aims of therapy in gout are rapid resolution of acute attack and prevention of recurrence prevention of complications like renal involvement or tophus formation These are achieved with life style modifications with pharmacotherapy (5). Control of any underlying precipitating causes and associated problems like hypertension and hyperlipidemia are also equally important. The major life style modifications include cessation of alcohol consumption (6), weight reduction, adequate hydration and low purine diet and avoidance of drugs like diuretics. These measures may help to alleviate some of the symptoms and signs of gout when used in conjunction with pharmacotherapy.

The drugs used for acute gout are Non Steroidal Anti Inflammatory Agents (NSAIDs), Colchicine and Corticosteroids (7) Urate lowering drugs should not be commenced during an acute episode but can be continued throughout the acute phase if they have been started previously.

Non-salicylate NSAIDs are the drug of choice, if the diagnosis is certain as they are better tolerated than colchicine and have more predictable effects. High dose Indomethacin (150mg/day) is most effective but Piroxicam, Ibuprofen and Naproxen are also useful. Etoricoxib (120mg/day) can be used in patients who cannot tolerate conventional NSAIDs. The use of NSAIDs should be limited in patients with cardiovascular and/or renal diseases.

Colchicine is the other commonly used drug for acute attack. Though not well tolerated in many patients, high dose colchicine (0.5mg hourly up to 5gm till the joint symptoms ease or side effects develop) is tried if the diagnosis is not certain or NSAIDs are contraindicated (8) The drug must be stopped promptly at the first sign of gastro intestinal side effect. Intravenous colchicine is not available in India.

Corticosteroids (intraarticular /systemic) are also useful in acute gout. Intraarticular steroids are useful when the use of NSAIDs or colochicine is problematic as in heart failure, renal or hepatic impairment. They are very useful in acute gout limited to a single joint or bursa. High dose oral (prednisolone 30-40mg/day) or intramuscular steroids tapered over a 7-10 day period may also be useful in patients who cannot tolerate colchicines or NSAIDs or who have failed on this treatment. ACTH has been used effectively especially in attacks in patients following surgery.

Optimal treatment of chronic gout requires long term reduction of serum urate to the lower half of the normal uric acid range, in order to eliminate acute gouty attacks, reduce tophi and prevent ongoing joint or organ damage. Urate lowering therapy should not be commenced during acute attacks. Urate lowering drugs are indicated for : Patients who have more than two attacks of gout per year, chronic tophaceous gout, uric acid over production (primary and purine enzyme defects), chronic gout associated with renal impairment or urate renal calculi and adjunct to cytotoxic therapy for haematological malignancy.

At present there are three groups of drugs available for reduction of serum uric acid

1.Uricostatic drugs –Allopurinol, Oxpurinol, febuxostat

2.Uricosuric agents-Probenecid, Benzbromerone, Losartan

3.Uricolytic drugs -Uricase

The most commonly used urate lowering uricostatic drug is allopurinol. The risk of precipitatory acute episode of gout on initiation is reduced by starting with a small daily dose of 50 to 100mg and increasing slowly. Use of Colchicine at a dose of 0.5mg twice daily or low dose NSAIDs (Indomethacin 25mg twice daily) is highly useful to avoid acute episode. Normalisation of serum urate is usually seen within four weeks and acute attacks cease within 6 months of continuous therapy. Tophi reduction may take years. Most of the Indian patients need a dose of 100mg-300mg/day but occasionally doses upto 600mg may be needed.The most important side effect of allopurinol is the skin rashes and hypersensitivity reactions including Steven Johnson syndrome. These reactions are common in people who are allergic to sulphonamide and on concomitant use of thiazides or ampicillin.

Oxipurinol the active metabolite of allopurinol (available in compassionate grounds in UK), can be tried in allopurinol allergy but similar side effects are involved in 40% patients.Allopurinol desensitization is also found to be effective in many individuals (9).

Febuxostat is an oral non-purine, xanthine oxidase inhibitor currently being developed (10). Preliminary human studies at doses of 80 to 120mg /day has shown more potent and long lasting hypouricemic activity than allopurinol. After promising phase III trials, this agent now being considered for approval by the USFDA. The drug can be safely given in patients who are allergic to allopurinol and in patients with mild to moderate renal impairment as the drug is mainly metabolized in the liver. Its long term safety and efficacy in renal transplant patient needs further trials. The other group of drugs that lowers the uric acid levels are the uricosuric agents like Probenecid and Sulfinpyrazine. Unfortunately sulfinpyrazine is not available in India and probencid is currently in limited supply. These drugs are useful in patients with decreased uric acid excretion. They appear to be useful in diuretic induced hyperuricemia. They are better avoided in conditions where there is overproduction of uric acid or known nephrolithiasis.

Benzbromerone and benzidazone are potent uricosuric agents used successfully in patients with renal impairment, in patients who have no improvement with allopurinol and in renal transplant patients on cyclosporin A. Eventhough there is concern regarding the potential hepatotoxicity, doses of 25-100mg/day Benzbromerone is found to be safe.

Losartan, an angiotensin II converting enzyme inhibitor used for hypertension inhibit renal tubular reabsorption of urate and therefore has uricosuric effect (11). (This does not appear to be a class effect). It also reduce the hyper uricemia caused by thiazides and hence a useful adjunct in patients with hypertension and gouty arthritis. *Fenofebrate*, a lipid lowering agent has also been found to have uricosuric effect, again not a class effect. This may be useful in patients with hyperlipidemia and gout (12).

The third group of hypouricemic drugs are the uricolytics which metabolizes uric acid (13). The urate oxidase (uricozyme) is an enzyme present in lower animals but not in man which catalyses the conversion of uric acid into allantoin. The native uricozyme introduced in 1974 was producing hypersensitivity in human. The recombinant uricases (Rasburicase) is now available in US for the management of tumour lysine syndrome is under trials for hyperuricemia in renal transplant recipients (14).

Conclusions

Eventhough Hippocrates recognized gout as an affection of older men and a product of high living long back in 5th century BC, this painful condition promises to accompany humanity to the 21st century. The incidence is progressively rising and females are also affected in the modern era. But the recommended best therapy for the acute attacks and long term prophylaxis has remained unchanged for many years. However, patients are often treated inadequately and risk factors for their disease are not well explored. Although well designed long term comparitability studies of current and newer treatment are welcomed, educating doctors especially the primary care physicians who manage majority of gout cases in our country, in optimizing the currently available management options would improve the present care

References

1. Copeman WSC. A short history of gout and rheumatic diseases. Berkley Calif, University of California Press, 1964 pp. 1-20
2. Porter A, Rousseau GS. Gout, a patrician malady. New Havon, Conn. Yale University Press, 1998 pp. 64-79
3. Beam AG. Archibald Garrod and the individuality of man, New York, Oxford University Press, 1993 pp. 108-109.
4. Terkeltaub RA. Clinical practice- Gout. *N Engl J Med* 2003,349;1647-55.
5. Rott KT, Agudelo CA. Gout. *JAMA* 2003 , 289 : 2857 - 60.
6. Snaith M. Gout and alcohol. *Rheumatology* 2004 ; 43 : 1208 – 09.
7. Pascaul E, Pedraz T. Gout. *Curr Opin Rheumal* 2004 ; 16 : 282 – 86.
8. Morris I, Varughese G, Mattingly P. Colchicine in acute gout. BMJ 2003 ; 327 : 1275 – 76.
9. Fam AH, Dunne SM, Lazzitha J *et al.* Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001 ; 44 : 231 – 38.
10. WortmannRL. Recent advances in the management of gout and hyperuricemia. *Curr Opin Rheumal* 2005 ; 17: 319 – 24.
11. Sica DA, Schoolworth AC. Uric acid and losartan. *Curr Opin Nephrol Hypertens* 2002; 475- 82.
12. Yamanoto T, Moriwaki T, Takahashi S *et al.* Effect of fenofibrate in plasma concentration and urinary excretion of purine bases and oxypurinol. *J Rheumatol* 2001 ; 28 : 2294-97.
13. Jordan KM. Topical reviews, An update on gout. *ARC Reports* on the rheumatic diseases series 2004 ; 5 : 4.
14. Suresh E. Diagnosis and management of gout: a rational approach. *Post Graduate Med J* 2005 ; 81 : 572-79.