Oxford Journals Medicine Rheumatology Volume 38, Issue 10 Pp. 912-916.

Rheumatology
rheumatology.oxfordjournals.org

Rheumatology (1999) 38 (10): 912-916. doi: 10.1093/rheumatology/38.10.912

Management of crystal arthritis

The joint inflammation which characterizes gout and calcium pyrophosphate dihydrate (CPPD) crystal arthropathy requires the presence of either monosodium urate (MSU) or CPPD crystals in the joint cavity. Crystals were associated with arthritis after their identification in the synovial fluid (SF) of inflamed joints; subsequently, it was noted that crystal injection into healthy joints reproduced the attacks of inflammation. From these observations, it was concluded that the arthritis was triggered by shedding or injection of crystals from synovial or cartilage deposits into the joint cavity, followed by their phagocytosis by cells which resulted in intense inflammation. However, it is now evident that both in gout and CPPD arthropathy, after the crystals form in the joints, they stay in them indefinitely (in the case of gout, if the patients have not received hypouricaemic treatment): the crystals are regularly found in the SF of previously inflamed but currently asymptomatic joints, where finding intracellular crystals is also habitual; the modestly raised cellularity of these SF indicates that, in spite of the absence of symptoms, there is some modest inflammation in the joints [1–3], on top of which the bursts of intense inflammation which characterize the attacks take place. The factors which modulate the intensity of the inflammation in these joints—subclinical during intercritical periods or intense during the attacks—remain speculative, but may include a balance between pro- and anti-inflammatory mediators [4], or changes in the protein coating of the crystals [5]. Since either MSU or CPPD crystals are regularly found in SF samples during the intercritical periods, to reach a precise diagnosis by analysing SF of gout or CPPD arthropathy is feasible at any time [2, 20].

The attacks of arthritis are characteristic clinical manifestations of crystal arthritis. Hippocrates already noted that, in the absence of treatment, the attacks of gout subside spontaneously, and this also happens in the acute attacks of CPPD arthropathy. The attacks indicate a rupture in the equilibrium attained during the intercritical periods in the joint cavity, where the interaction between crystals and cells results in subclinical inflammation; the resolution of the attacks indicates that this equilibrium has been regained. The goal of the treatment of episodes of arthritis is to hasten the return to the intercritical equilibrium. This can be achieved by different drugs with anti-inflammatory potential: non-steroidal anti-inflammatory drugs (NSAIDs), corticoids and, in the case of gout, colchicine. The three approaches are effective and their choice depends on the side-effects of the different drugs, and on the presence of co-morbid conditions, but also the selection is often based on habit and custom. The treatment should be started as early as possible since the response tends to be better. Most NSAIDs are effective in this setting. The choice of NSAID is largely a matter of personal preference; among others, indomethacin, naproxen, ketoprofen, piroxicam or diclofenac are all effective. They should always be used in the high recommended doses for better efficacy; oral administration is usual, but either i.m. or rectal administration can be used if this is the physician's or the patient's preference. Corticoids offer an effective alternative, and should be seriously considered for those patients in whom the use of NSAID is undesirable because of associated morbid conditions, such as active ulcers, hypertension or renal insufficiency. Adrenocorticotrophic hormone (ACTH), which generally needs repeated doses [6–8], and different systemic corticoid preparations have been found to be very useful to stop attacks of gout [9, 10]. Intra-articular injection is also an effective

alternative, and very small doses, such as triamcinolone acetonide 10 mg in knee joints or 8 mg in smaller joints [11, 12], are effective and are unlikely to have significant systemic effects. Intra-articular injection requires precise diagnosis and should not be used if there is a suspicion of joint infection. The acute episodes of CPPD-related arthritis also respond to systemic steroids [13], and in our hands the intra-articular injection of small doses of triamcinolone also works well. Colchicine is a classical treatment for inflammation in gout. Its gastrointestinal side-effects represent a major inconvenience since they frequently precede the clinical improvement of the joint symptoms, with evident discomfort for the patient [14]; i.v. colchicine is available in some countries, but may produce severe systemic and local (in the case of extravasation) side-effects, mostly in the elderly. Since safer and effective alternatives to colchicine are available for the treatment of gouty attacks, it appears to be a less good choice [15] and, despite its historical importance, it probably should be substituted by the other more convenient agents.

The rupture of the equilibrium reached between cells and crystals in the joints during intercritical periods results in new attacks of arthritis. In gout, daily administration of 0.5–1 mg of colchicine in most cases greatly reduces or avoids further attacks of inflammation [16]. Administration of daily colchicine lowers the cellularity of the SF in asymptomatic gouty joints [17] and appears to work, at least in part, by setting the intercritical subclinical inflammation of the gouty joints to a lower, more stable, level. For those intolerant to daily colchicine, an every-other-day schedule can be tried. As an alternative, a small dose of an NSAID, such as 25 mg of indomethacin or 250–500 mg of naproxen, can be used. Probably, such prophylaxis should be maintained whilst MSU crystals persist in the joints —probably several months to well over 1 yr after reducing the uricaemia. Prophylaxis appears to be particularly important when initiating a patient on hypouricaemic drugs, since it is said that reduction of uricaemia may trigger attacks of gout. Gouty patients receiving colchicine prophylaxis should be kept on it if possible when affected by severe acute illnesses or undergoing surgical procedures because they are then prone to suffer attacks of gout. To prevent recurrences of CPPD arthropathy, colchicine may be tried in similar doses to those used in gout, but may be less effective. A number of these patients, mostly those with associated osteoarthritis, have persistent symptoms and may do better with a daily small dose of an NSAID.

Joint inflammation in crystal arthritis requires the presence of the associated crystals in the joint cavity. In their absence, inflammation appears impossible: by removing the crystals, we should cure the disease. At the present time, we have yet to find the means to remove the CPPD crystals from the joints; subsequently, the therapy of the related arthropathy is limited to controlling the consequences of their presence in the joints—either joint inflammation or osteoarthritic changes. On the other hand, the formation of MSU crystals in gouty joints is a direct consequence of hyperuricaemia (other local factors are still being defined [18]), and although the definitive evidence has not been produced yet, the available data indicate that reduction of uricaemia to normal levels results in disappearance of the crystals from the joints [1], similarly to what occurs in tophi [19]. In a recent series in which previously inflamed asymptomatic gouty joints were sampled for diagnostic MSU crystal identification, we found that all 43 joints from patients not receiving hypouricaemics, and all with hyperuricaemia, contained MSU crystals, whilst 14/48 obtained from patients being treated with hypouricaemics did not; interestingly, the absence of crystals correlated with lower uricaemia and a longer time elapsed since the initiation of therapy [20]. These data are consistent with the idea that normalizing the uricaemia and waiting long enough leads to the disappearance of MSU crystals from gouty joints. In addition, if the levels of serum uric acid are kept low, MSU crystals are very unlikely to form again. Of interest, after the introduction of probenecid to reduce uricaemia, it was noted that the attacks of gout, after an initial increase in frequency, became more infrequent and eventually ceased in most cases [21]. On the other hand, the reappearance of tophi and gout after discontinuing successful hypouricaemic treatment, or making it intermittent [22], has been noted [23]. All these data appear to indicate that we can cure gout (MSU deposition and the associated

inflammation) by dissolving MSU crystals deposited in the joints and tissues, but uricaemia has to be kept within normal limits indefinitely to avoid the formation of new crystals and, with them, the renewed possibility of gout. Some questions are now to be answered: (a) whether proper hypouricaemic treatment will result in the disappearance of the crystals in all/a subset of patients; (b) how much should uricaemia be reduced and for how long to dissolve all the crystals; (c) in which subsets of patients should the treatment be aimed to dissolve the crystals and be curative; (d) is there any role for sampling asymptomatic joints for crystals outside research? Physicians aware of the possibility of curing gout and informed patients will no doubt lead to a more careful planning of the treatment, and better compliance with the medications.

There are two effective alternative pharmacological approaches for reducing serum uric acid: allopurinol, which reduces the amount of serum uric acid produced and excreted, or the use of drugs that increase the renal clearance of uric acid, known as uricosuric agents. Interestingly, a low clearance of uric acid is the origin of hyperuricaemia and gout in a majority of the patients, and also occurs in patients with urate overexcretion [24]. The xanthine oxidase inhibitor allopurinol is an alternative substrate for this enzyme, and competes with hypoxanthine and xanthine to be metabolized. This results in a decreased amount of uric acid being formed, and results in lower uricaemia and a lower amount of uric acid excreted by the kidneys. The usual dose of allopurinol is 300 mg/day [25], but some patients may need less or occasionally more. The dose needs to be corrected in patients suffering from renal insufficiency [26]. Allopurinol is the drug of choice for patients whose uricaemia has to be reduced whilst at the same time reducing the urinary excretion; this may be the case in patients with hyperuricaemia secondary to overproduction and overexcretion of uric acid (generally considered as >700 mg/dl) and no doubt for those with a history of uric acid renal calculi, and probably with calculi of any type. The main inconvenience of allopurinol is its potentially serious side-effects [27], particularly frequent in elderly patients [28]. Desensitization schemes have been used successfully in patients with allopurinol-related skin reactions [29].

Uricosuric agents increase the tubular secretion of urate and result in an increased renal clearance of uric acid; they represent a more pathogenic approach for this majority of hyperuricaemic gouty patients in whom hyperuricaemia is needed to maintain the urate excretion when its renal clearance is low. After their initiation, there is an increase in renal excretion of uric acid, but after reaching a new equilibrium, the increase in renal excretion is modest and the labelling of these agents as `uricosurics'—which may be interpreted as an indication of an important load on the renal excretory system—may be misleading. The more classical probenecid requires repeated daily dosing. Benzbromarone has received recent attention; a 100 mg daily dose results in lower serum uric acid levels than 300 mg of allopurinol [30], and 50 mg is often sufficient. Of interest, it has also been successfully used in patients with tophaceous gout intolerant to allopurinol [31], for whom it is a good alternative. It retains its efficacy despite moderate renal insufficiency, reducing uricaemia to normal levels in patients in whom allopurinol did not [32], and can be used to treat hyperuricaemia and gout due to the use of cyclosporin in transplanted patients [33]. Isolated cases of liver toxicity have been reported with this drug [34]. Sulphinpyrazone (200–400 mg/day) is another possible alternative in this group of uricosurics. These drugs should be avoided in patients with a history of nephrolithiasis, especially if calculi were made of uric acid, or in those known to have hyperuricaemia as a result of significant uric acid overproduction, which results in an increased excretion. High ingestion of liquids at the initiation of treatment, when the higher load of uric acid is excreted, or even alkalinization of the urine, may help to avoid nephrolithiasis when there is such a risk. When hyperuricaemia results from ingestion of diuretics, the possibility of switching to the diuretic bumetanide [35], which does not result in hyperuricaemia, may be an alternative. A lack of response to hypouricaemic treatment is unusual, and generally due to poor compliance; maintenance of heavy alcohol consumption may also result in a poor response to the drugs.

The influence of diet on hyperuricaemia is highlighted by its frequency in some native populations after they have switched to an occidental type of diet [36, 37]. Of interest, the fractional renal excretion of uric acid is diminished in those hyperuricaemic patients with associated hypertriglyceridaemia (and probably this low renal excretion is the cause of hyperuricaemia in this group) [38]; a low-calorie diet administered to hyperuricaemic-hypertriglyceridaemic patients resulted in a reduction in serum triglycerides and VLDL components along with increased renal excretion of urates, and a decrease in uricaemia, which did not occur in control normolipaemic- hyperuricaemic patients [39]. Hyperuricaemia is now considered to be a part of the syndrome of insulin resistance [40, 41], and may be an independent risk factor for hypertension-associated morbidity [42, 43]. These data indicate that an appropriate low-calorie diet is a very desirable measure at least in those patients with hypertriglyceridaemia, obesity or other associated risk factors, and that its benefits go beyond the effect on hyperuricaemia. In patients with a heavy ingestion of alcohol, especially in the case of beer [44], its restriction is a desirable measure.

Deposition of crystals in the joints may damage their structure. Tophi eroding the juxta-articular bone or soft tissues result in joint damage. Dissolution of tophi after reduction of uricaemia results in a peculiar arthropathy which should be considered as a sequel. CPPD crystal deposition damages the cartilage and may result in osteoarthritis [45]; since the cartilage is often eroded away in the process, and with it the crystal deposits which allow radiographic recognition of the disease, the diagnosis may easily pass unnoticed; in these patients, SF analysis is necessary to achieve the diagnosis [46]. These same patients with osteoarthritis and CPPD crystals may have small episodes of inflammation superimposed on the osteoarthritis symptoms; they may benefit from a very small daily dose of an NSAID, such as naproxen 250-500 mg or indomethacin 25 mg. If we could get rid of CPPD crystals, as we do with MSU, it remains speculative whether the associated osteoarthritis could be halted or even avoided with early treatment. Being a frequent and invaliding condition, research in this direction appears to be highly desirable.

E. Pascual

+ Author Affiliations

E. Pascual, Sección de Reumatología, Hospital General Universitario de Alicante, Maestro Alonso 109, 03010 Alicante, Spain.

© 1999 British Society for Rheumatology

References

1. Pascual E. Persistence of monosodium urate crystals, and low-grade inflammation, in the synovial fluid of untreated gout. Arthritis Rheum 1991;34:141-5.
Medline Web of Science

2. Martínez A, Pascual E. Intra and extracellular CPPD crystals are regularly found in the synovial fluid of uninflamed joints of CPPD related arthropathy. Arthritis Rheum 1995;38:S246.

3. Pascual E, Jovaní V. A quantitative study of the phagocytosis of urate crystals in the synovial fluid of asymptomatic joints of patients with gout. Br J Rheumatol 1995;34:724-6.
Abstract/FREE Full Text

4. Terkeltaub RA. Gout and mechanisms of crystal induced inflammation. Curr Opin Rheumatol 1993;5:510-6.
Medline

5. Ortiz-Bravo E, Sieck MS, Schumacher HR. Changes in the proteins coating monosodium urate crystals during active and subsiding inflammation. Immunogold studies of synovial fluid from patients with gout and of fluid obtained using the rat subcutaneous air pouch model. Arthritis Rheum 1993;36:1274-85.
Medline Web of Science

6. Ritter L, Kerr LD, Valeriano-Marcet J, Spiera H. ACTH revisited: Effective treatment for acute crystal-induced synovitis in patients with multiple medical problems. J Rheumatol 1994;21:696-9.
Medline Web of Science

7. Siegel LB, Alloway JA, Nashel DJ. Comparison of adrenocorticotropic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. J Rheumatol 1994;21:1325-7.
Medline Web of Science