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Gout: epitome of painful arthritis

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Abstract

Arthritic pain and disability are at or near the top of the list of reasons adult patients seek medical attention. At least 47.8 million US residents have arthritis. In Europe, the magnitude of the problem is similar, affecting 8 million in the United Kingdom and 108 million across the continent. Osteoarthritis is by far the most common form of arthritis. In a regional UK study, nearly half of adults 50 years or older reported some form of osteoarthritic knee pain over a 1-year period. Among the arthritides, gout is notable for the agonizing nature and unique pathogenesis of the pain it generates. Gout is the most common cause of inflammatory arthritis among men and postmenopausal women. Because of the atypical nature of some of its clinical manifestations, gout can present serious diagnostic challenges for practicing physicians. In recent years, knowledge about gout's pathogenesis, pathophysiology, and differential diagnosis has advanced on a broad front. Genetic variants within a newly identified transport gene, SLC2A9, have been associated with a low fractional excretion of uric acid and the presence of gout in several population samples. The SLC2A9 gene encodes glucose transporter 9—a unique hexose and high-capacity urate transporter. In addition, human ATP-binding cassette, subfamily G2 (ABCG2), encoded by the ABCG2 gene, has been found to mediate renal urate secretion. Introduction of a mutation encoded in a model system by a common single nucleotide polymorphism, rs2231142, resulted in a 53% reduction in urate transport rates compared with wild-type ABCG2. Based on a large population study, it has been estimated that at least 10% of all gout cases in white persons may be attributable to this single nucleotide polymorphism causal genetic variant. Of the various categories of arthritis, the crystal-induced arthropathies, gout and pseudogout, are manifested by acute inflammation and tissue damage arising from deposition in joints and periarticular tissues of monosodium urate (MSU), calcium pyrophosphate dehydrate, or basic calcium phosphate crystals. The innate immune system rapidly detects invading pathogenic microbes and nonmicrobial "danger signals" such as MSU crystals. When these crystals are deposited in synovial tissues, NLR proteins (NOD-like receptors) form multiprotein complexes known as *inflammasomes* that trigger secretion of inflammation-producing cytokines like interleukin-1β and interleukin-18. Usually, gout can be diagnosed by medical history, physical examination, and presence of hyperuricemia (urate >416 μmol/L). However, a urate concentration less than 416 does not by itself rule out gout. Confirmation of the diagnosis by identification of typical MSU crystals in aspirated synovial fluid is definitive. Analysis of joint fluid is mandatory to rule out septic arthritis, which can rapidly become lethal. Because of its special ability to identify and quantitate urate deposits in peripheral tissues, dual-energy computed tomography should prove valuable in the differential diagnosis of gout. Gout mimics a variety of illnesses; for example, spinal gout may masquerade as metastatic cancer, epidural abscess, and nerve compression syndrome.

1. Introduction

Arthritis is the most common cause of nociceptive pain and physical disability experienced by adults in developed countries and, probably, throughout most of the world [1]. Virtually all forms of arthritis involve joint pain, particularly upon movement. In 2005, 46.4 million US residents (21.6%) had arthritis. Of this number, 19 million (9%) had arthritic pain-attributable activity limitations. By 2030, arthritis is predicted to affect about 67 million US adults [2]. The magnitude of the problem in Europe is similar, with 8 million in the United Kingdom and 108 million across Europe suffering from pain-related restriction of activity caused by some type of arthritis [3].

Pain and disability caused by osteoarthritis (by far the most common form of arthritis) are principal reasons why adults throughout the world seek medical care [4]. In one regional study in the United Kingdom, nearly half of adults 50 years or older reported some form of osteoarthritic knee

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Table 1
Contribution of common forms of arthritis to burden of pain carried by U.S. adults

Diagnosis	Prevalence in US (approx)	Male-female ratio	Age range of peak incidence	Mechanism of pain
Gout	3 million (6.1 million lifetime prevalence)	4:1 until age 65 y 3:1 after age 65 y	Men: 40-60 y Women: after middle age	Urate crystal-induced inflammation of joints and other synovial tissues
Osteoarthritis	26.9 million	1:1.2-1.4	Incidence increases with age until ~80 y.	Focal and progressive loss of hyaline cartilage of joints
Rheumatoid arthritis	1.3 million	~1:2	Women and men 60-70 y	Autoimmune disease, chronic inflammatory polyarthritis
Systemic lupus erythematosus	<500 000	1:6-10	Primarily women aged 15-40 y	Autoimmune disease with many clinical manifestations

Source: http://www.cdc.gov/arthritis/resources/spotlights/dsArthritis.htm.

pain over a 1-year period [5]. According to the Centers for Disease Control and Prevention, the 4 most common forms of joint inflammation and pain among adults are gout, osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus [6]. Table 1 provides prevalence and incidence data about these conditions.

Gout is a particularly instructive example of painful arthritis. It is the most common cause of inflammatory arthritis among men and postmenopausal women [7]. Among the arthritides, acute gout is notable for the agonizing character and the unique pathogenesis of the pain it generates. The nociceptive pain experienced during an acute attack of gout results from the inflammation that occurs when masses of monosodium urate (MSU) crystals are deposited into the synovial tissues of a peripheral joint, most often the great toe. Because this process is readily reproducible in experimental models, MSU crystal–induced inflammation has provided valuable information about the sequence of events that characterize the phenomenon of innate immunity.

Gout's prevalence continues to increase rapidly, owing to the world's enlarging population of older individuals, many of whom take thiazide diuretics and prophylactic aspirin (drugs that promote hyperuricemia), and the proliferation of unhealthy lifestyles characterized by unsatisfactory diets that include excessive fructose and alcohol intake, physical underactivity, and abdominal fat accumulation (a hallmark of the metabolic syndrome)—all favoring hyperuricemia [8,9].

This review describes recent findings that throw new light on the role of genetic factors in gout's pathogenesis, the metabolic setting that predisposes to gout, and the mechanism of the florid inflammatory process responsible for gout's excruciating pain. Gout's mimicry of other serious illnesses is also scrutinized, with particular emphasis on the diagnostic confusion that can be created by deposits of tophi (masses of MSU crystals) in the spine. The differential diagnosis of gout is examined, with attention given to the improved diagnostic capability of dual-energy computed tomography and the often perplexing clinical picture presented by gout, particularly in the elderly. Finally, several promising areas of pharmacologic investigation are identified that may provide useful clues for development of new drugs for control of hyperuricemia and for prevention or treatment of gout's painful inflammation.

2. Genetic vulnerability to gout

Owing to their loss of hepatic uricase activity, humans and great apes have uniquely high serum uric acid concentrations (200-500 μmol/L)[1] compared with other mammals (3-120 μmol/L) [10]. Loss of uricase activity in these species has been attributed to missense mutations in the uricase gene [11]. Vitart et al [10] have reported the existence of genetic variants within a transport gene, SLC2A9, that explain 1.7% to 5.3% of the variance in serum uric acid concentrations in a Croatian population sample. SLC2A9 variants have also been associated with a low fractional excretion of uric acid and/or the presence of gout in several other European population samples [12]. The SLC2A9 gene, found on human chromosome 4, encodes the facilitative glucose transporter 9 (GLUT9), which is a unique hexose and high-capacity urate transporter. The gene's 2 splice variants, (b) and (a), are expressed in the apical and basolateral membranes, respectively, of the proximal convoluted tubule. Several studies have disclosed correlations between 2 different sets of single nucleotide polymorphisms (SNPs) and increases in plasma urate levels and gout incidence. Glut9 is also a fructose transporter—a fact that might help explain why a high intake of fructose (associated with frequent consumption of soft drinks sweetened with sucrose or high-fructose corn syrup) has been reported to elevate plasma urate concentrations and increase the risk of developing gout [13].

Woodward and associates [14] have found that human ATP-binding cassette, subfamily G, member 2 (ABCG2), encoded by the ABCG2 gene, is located in the brush border membrane of kidney proximal tubule cells, where it mediates renal urate secretion. Introduction of a mutation encoded by a common SNP (rs2231142) in *Xenopus* oocytes resulted in a 53% reduction in urate transport rates compared with wild-type ABCG2 ($P < .001$). Data obtained in a population-based study of 14 783 individuals support rs2231142 as the causal variant in the region, exhibiting highly significant associations with urate concentration [14]. These findings suggest

[1] To convert micromoles per liter of urate to milligrams per deciliter, divide by 59.48.

that at least 10% of all gout cases in white persons may be attributable to this SNP causal genetic variant.

3. Hyperuricemia: necessary but not sufficient for occurrence of a gout attack

Risk of developing gout is directly related to degree of hyperuricemia. However, other factors also play an important role in determining whether an acute attack of gout will occur in a hyperuricemic individual. In the Normative Aging Study [15], the proportion of new gout cases was found to be 0.1% among men with serum MSU levels less than 420 μmol. In the same population, the proportion of new gout cases was 0.5% for MSU concentrations 420 to 529 μmol and 4.9% for concentrations greater than 535 μmol. In another population study [16], the 5-year prevalence of clinically manifest gout was 0.6% in patients with MSU levels less than 420 μmol, but 30% among those with concentrations greater than 595 μmol.

These studies clearly show that risk of developing clinically manifest gout rises rapidly after the MSU concentration exceeds 416 μmol/L (close to the 405-μmol level at which urate crystals precipitate out of the serum in vitro) [17]. Despite the evident relationship between MSU concentration and risk of having a gout attack, 78% of men in the Normative Aging Study with MSU levels greater than 535 μmol/L did not develop gout over a 5-year period of observation [15]. Factors other than simple MSU concentration obviously play an important role in determining which patients with hyperuricemia will develop clinically manifest gout.

4. Immunologic basis of MSU crystal–generated inflammation

The innate immune system is designed to rapidly detect invading pathogenic microbes as foreign and destroy them. Toll-like receptors are a class of membrane receptors that identify extracellular microbes and initiate antipathogen signaling cascades. Intracellular microbial sensors also have been identified, of which some are NLR proteins (formerly known as NOD-like receptors). Many NLR proteins are believed to serve as pattern recognition receptors [18]. Some of these receptors can also sense nonmicrobial danger signals (eg, signals arising from tissue deposition of MSU crystals). When that happens, NLRs form large cystoplasmic complexes known as *inflammasomes*. By activating caspase-1, inflammasomes link the sensing of such "danger signals" to the activation of the proinflammatory cytokines interleukin (IL)-1β and IL-18. The NALP3 inflammasome has been found in association with the inflammation and pain that occur during an acute attack of gout [19]. As a consequence of an enhanced understanding of the mechanism of the inflammatory response to the deposition of MSU crystals in synovial tissues, it has become widely accepted that the innate immune system plays an integral role in the triggering of crystal-induced pain and inflammation.

In the absence of treatment, spontaneous resolution of the inflammation that characterizes acute gout usually occurs within 7 to 10 days. The processes that underlie this predictable resolution are still not well understood; however, involvement of the nuclear hormone receptors peroxisome proliferator-activated receptor–γ and liver X receptor–α during the termination of acute gout has been demonstrated [20]. During the subsidence period, the affected area is cleared of leukocyte debris, whereas anti-inflammatory cytokines and transforming growth factor–β become active [21]. Furthermore, human fibroblast-like synoviocytes release monocyte chemoattractant protein–1 in vitro when exposed to urate crystals. High-density lipoproteins (HDLs) have been found to inhibit release of monocyte chemoattractant protein–1 in a dose-dependent fashion. These findings confirm the anti-inflammatory function of HDL in this system, suggesting that HDL may play a significant role in the termination of an acute gout attack [22].

5. Diagnosis of gout

In 1683, Thomas Sydenham (1624-1689) [23], a prominent English physician, described his own memorably painful experience with gout, as follows:

> The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like a dislocation.... Then follows chills and shivers and a little fever. The pain, which was at first moderate, becomes more intense. So exquisite and lively, meanwhile, is the feeling of the part affected that it cannot bear the weight of bedclothes nor the jar of a person walking in the room.

In addition to a history and physical findings suggestive of gout, demonstration of concomitant hyperuricemia (a serum uric acid level $\geq$416 μmol) is helpful in supporting the diagnosis. Not infrequently, patients have circulating uric acid levels in the reference range during an acute attack; hence, a urate concentration less than 416 μmol does not by itself rule out gout [24]. However, confirmation of the diagnosis by identification of birefringent, needle-shaped MSU crystals in the aspirated synovial fluid from a joint is definitive [25]. Before the availability of crystal detection techniques such as polarizing light microscopy, gout was mistakenly diagnosed in a significant proportion of nongout crystal arthropathies [25]. Nonurate microcrystals that may be responsible for arthritic and/or periarthritic symptoms include calcium pyrophosphate dehydrate, calcium apatite, and calcium oxalate.

Because the clinical presentations of the different crystal arthropathies are sometimes similar, it is essential to obtain synovial fluid, whenever that is possible, to identify the type of crystal involved. However, analysis of effusions is mandatory in any case to check for the presence of infectious arthritis, a condition that can be mistaken for gout, particularly in older individuals. In rare instances, septic arthritis can coexist with gout; hence, the presence of urate crystals in an inflamed joint does not exclude infection [26]. Septic arthritis, which can rapidly evolve into a lethal septicemia [27], should be ruled out by prompt performance of a joint fluid aspiration, with microscopic examination of the aspirate, crystal identification, cell morphology and cell count, and bacterial stains and cultures.

Dual-energy computed tomography has been found to be uniquely effective in the diagnosis of gout in the emergency setting, as well as under routine conditions [28]. Dual-energy computed tomography is more accurate than conventional x-ray procedures in assessing urate deposits in joints and soft tissues situated in hands, wrists, feet, ankles, and knees (Fig. 1). Dual-energy computed tomography–generated images in patients with gout have disclosed previously unsuspected urate deposits in tendons, cartilage, bursae, soft tissues, bone, cruciate ligaments, and menisci in various peripheral body locations [29].

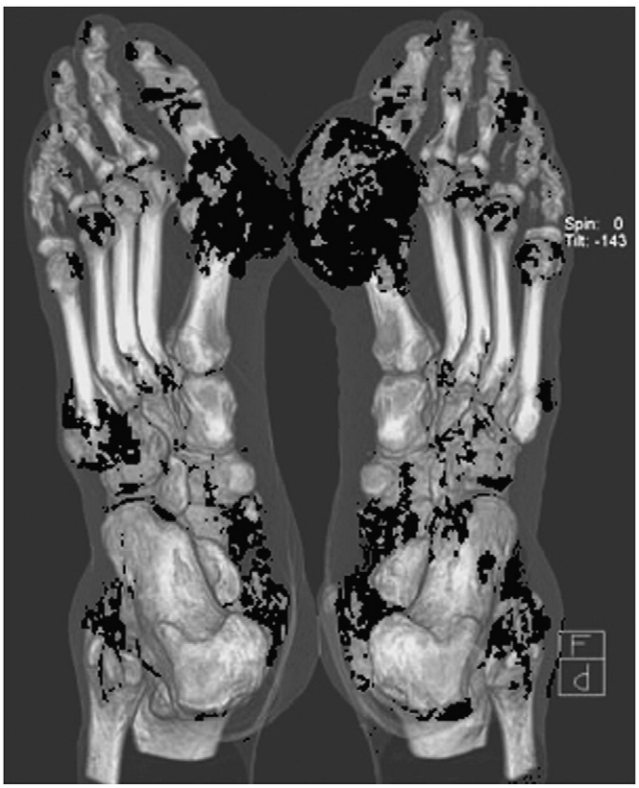

Fig. 1. A dual-energy computed tomogram of the feet of an individual with gout. When computed tomographic scans are performed at several different energies (ie, 80 and 140 kV), uric acid deposits are readily distinguishable from calcium (for example). By color coding the different attenuation values, it becomes possible to recognize and semiquantify uric acid deposits (coded, for example, in red), whereas other bone formations are displayed in contrasting colors. The black and white image shown herein was adapted from a color-coded (urate shown in red) tomogram generously provided by S Nicolaou, MD, of the Vancouver General Hospital [28]. In the image, deposits of MSU crystals are clearly visible as prominent black particles or aggregates of such particles.

6. Clinical manifestations in the elderly

Gout's incidence rises rapidly with advancing age. After menopause, women develop gout in increasing numbers—eventually at an incidence rate equal to that of men [2].

In elderly patients, an attack of gout is usually less dramatic than in middle age and often involves an upper extremity poly- or monoarticular presentation rather than the classic monoarticular lower extremity picture commonly exhibited by middle-aged men.

In older patients, gout can resemble the clinical picture of osteoarthritis or rheumatoid arthritis. The problem of diagnosis is further complicated by the fact that (especially in the elderly) masses of MSU crystals may be deposited in osteoarthritic nodes, causing them to become inflamed, tender, and further enlarged [30].

7. Atypical gout

Because certain manifestations of gout mimic a variety of illnesses, the causative role of atypically located gouty tophi in generating clinical findings suggestive of entirely different medical conditions may remain unrecognized for prolonged periods. As one important example, spinal (axial) gout is infrequently reported and may be identified only after completion of an exceptionally thorough and expensive diagnostic workup [31]. In many patients with spinal gout, its symptoms may be missed or misinterpreted. The result is inappropriate treatment and persisting pain. Spinal gout has been found to mimic such diverse conditions as metastatic cancer [32], epidural abscess [33], and nerve compression syndromes [34]. Gout can also masquerade as pancreatic cancer [35] and soft tissue tumors [36].

8. Molecular targets for pharmacologic intervention and disease prevention

At the present time, lifestyle changes and pharmacologic blockade of uric acid synthesis are the cornerstones of medicine's efforts to control serum MSU levels and prevent occurrence/recurrence of acute gout attacks. Recent advances in our understanding of the genetics and pathophysiology of gout have afforded additional, promising approaches to both the prevention and treatment of this protean illness.

The discovery in large population samples that variants of certain genes (SLC2A9/GLUT9 and ABCG2) are associated with an increased risk of hyperuricemia and gout may have application in the conduct of preventive medicine programs.

Furthermore, the finding that GLUT9 and ABCG2 play roles in the renal tubular excretion of uric acid could well lead to the new drugs designed to enhance renal excretion of MSU.

It has been reported that administration of an IL-1 inhibitor prevents and relieves MSU-induced pain and ankle joint inflammation in a mouse model of acute gouty arthritis [37]. Thus, agents that inhibit IL-1 signaling may prove useful in aborting or mitigating an acute attack of gout in man [38]. Further study of the processes involved in the "spontaneous" resolution of gouty attacks, including the actions of anti-inflammatory cytokines, HDLs, transforming growth factor, peroxisome proliferator-activated receptor−γ, and other agents that become active during gout subsidence [20,21] also may help scientists create drugs to prevent or reduce the marked collateral damage inflicted by gout's inflammatory process on articular structures.

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