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Popular Article

Gout: A primitive disease in a new perspective

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Abstract

Gout is a chronic illness characterised by the deposition of monosodium urate (MSU) crystals. Gout often manifests like an acute, self-limiting inflammatory monoarthritis of the lower limb joints. This is the most well-known and well-described kind of arthritis. The main risk factor for MSU crystal deposition and the development of gout is an elevated serum urate level (hyperuricaemia). Although generally thought to be a purine metabolism problem, abnormal urate transport, in both stomach and the kidneys, plays an important role in the pathophysiology of hyperuricaemia. Important discoveries into to the pathophysiology of hyperuricemia and gouty arthritis, both acute and chronic, provide a deeper knowledge of the condition. Gout is classified into four clinical stages: asymptomatic hyperuricemia, acute gouty arthritis, the intercritical period, and chronic tophaceous gout. Gout is far more common in males than in women. Chronic conditions such as hypertension, diabetes, and renal impairment are more common in female gout patients.

Introduction

Gout has played an important role in the evolution of Homo sapiens from ancient times. It first featured in medical records throughout the early days of medical writing. More recently, we have a better knowledge of the illness and a more powerful arsenal owing the quantum leaps in molecular biology, diagnostic modalities, and pharmacology. Gout is a systemic illness caused by the buildup of monosodium urate crystals (MSU) in tissues. The development of uric acid crystals requires an increase in serum uric acid (SUA) over a certain threshold. Gout is biochemically defined by extracellular fluid urate saturation, which manifests as hyperuricemia in the blood, with plasma or serum urate concentrations surpassing 6.8 mg/dL (about 400 micromol/L); this level represents the approximate limit of urate solubility. Gout is mostly diagnosed by identifying pathognomonic MSU crystals in joint fluid or in tophi aspirate. Gout begins as an acute joint inflammation that is readily cured by NSAIDs and colchicine. Tophi and renal stones are late manifestations.

Epidemiology

Gout illness has a significant disease burden and is expanding in Developed nations and sections of the worldwide that are becoming Westernized, implying the possibility of a modern gout epidemic similar to the obesity pandemic. Both disorders are symptoms of the metabolic syndrome, the frequency of which has risen in tandem with the rise in hyperuricemia. Gout affects about 1-4 percent of the total population. In certain countries, prevalence might reach up to 10%. Men over the age of 80 have a 10% prevalence, while women over the age of 80 have a 6% prevalence. Gout has a yearly incidence of 2.68 per 1000 people. It affects males 2-6 times more than women. Gout is becoming more common across the world as a result of bad eating habits such as fast food, a lack of exercise, an increase in obesity, and metabolic syndrome.

Etiology

As hyperuricemia is widespread in humans, homo sapiens have been the only known animals can acquire spontaneous gout. The greatest risk factor for the development gout is a sustained increase in serum urate levels. Different variables that cause hyperuricemia, such as medical diseases, obesity, lifestyle factors, and drugs, are therefore linked to an increased chance of developing gout. Hyperuricemia is not really the main risk factor of gout, and only a small percentage of these people acquire the disease. The lower physiological uric acid ranges can be used to evaluate the effect of food on uric acid levels in non-uricase-producing animals. Consumption of animal foods such as shellfish and red meat is one dietary source that can lead to hyperuricemia and gout. Some beverages, such as alcoholic beverages, sugar drinks, soda, and high-fructose corn syrup, may also contribute to this condition. Gout is infrequent in women before menopause, and hormone replacement treatment reduces the incidence of incident gout in postmenopausal women. Women with gout have a later age of onset than males and are much more likely to be have comorbidities, including CKD, hypertension, and diseases needing diuretic therapy. Several genes have been linked to gout by genome-wide association studies (GWAS). SLC2A9, ABCG2, SLC22A12, GCKR, and PDZK1 are examples.

Pathophysiology

In humans and higher primates, uric acid is the end result of purine metabolism because the gene encoding the enzymes uricase is silenced by mutation. Urate is an ionised form of uric acid that is found in the body. Uric with a pH of 5.8, weak acid. When serum uric acid levels above the usual threshold, urea crystals begin to form in tissues. The pathologic threshold of

hyperuricemia has been established as 6.8 mg/dL. Uric acid is the most prevalent naturally occurring antioxidant in the body, and its traditional job was thought to be the removal of reactive oxygen species. Because of the high sodium content, it exists in the ionized form at pH 7.4 and operates as monosodium urate (which is less soluble). Uric acid occurs in non-ionized form in acidic fluids such as urine, that is less soluble even in physiological range. In contrast to MSU, this explains the existence of uric acid crystals and stones within urinary system.

The overproduction of UA is caused by a lack of enzymes involved in purine metabolism. Purines are composed of nine carbon purine nuclei formed by fused pyrimidine and imidazole rings. Purines play critical roles in all living cells via the purine-based nucleic acids adenine, guanine, and hypoxanthine. The endogenous purine synthesis route, known as de-novo purine synthesis, includes the conversion of ribose-5-phosphate into PRPP (5-phosphoribosyl 1-pyrophosphate) to nucleotide inosine monophosphate in ten stages. Hypoxanthine and guanine are the urate precursors of purine breakdown. The majority of them are rescued, and any remaining guanine is deaminated to xanthine. Xanthine oxidoreductase converts hypoxanthine to xanthine. Xanthine oxidoreductase is a flavoprotein that contains a molybdenum-pterin and iron sulphide cluster. It exists in two forms: oxidase, which utilizes large amounts of oxygen hypoxanthine to xanthine and xanthine to urate, and dehydrogenase, which uses NAD+. The most common goal of urate-lowering in gout patients is inhibition of xanthine oxidoreductase. Lesch-Nyhan syndrome, for example, is an inborn metabolic mistake caused by a lack of hypoxanthine-guanine phosphoribosyl transferase, an enzyme involved in UA metabolism. It is an X-linked recessive genetic disease. In addition to renal stones, the symptoms of this condition include dystonia, chorea, cognitive impairment, obsessive harmful behavior, self-mutilation, and articular manifestations. If untreated, it can result in tophi formation and renal failure.

Gout has historically been thought to be a purine metabolism problem. However, urate overproduction is just a minor reason of hyperuricemia in a minute percentage of gout patients. When renal urate excretion is reduced, intestinal uricolytic increases to account for half of overall urate elimination, and the transporter ABCG2 plays an important role. Serum urate concentrations over 6.8mg/dl are saturating, increasing the likelihood of deposition. The SLC22A12 gene encodes URAT1, which is highly selective for uric acid. It influences renal uric acid transportation by regulating anion exchange. SLC22A12 mutations cause hypouricemia, hyperuricosuria, and exercise-induced renal functional impairment. Probenecid, benzbromarone, and leisured are uricosuric medications that inhibit URAT1 and promote uric acid excretion. The ABCG2 transporter in the gut is responsible for extrarenal urea excretion. Urate overproduction

hyperuricemia is a type of renal overload that includes subtypes of "extrarenal underexcretion" and "real urate overproduction."

Diagnosis

1. **Laboratory diagnosis** -non-rheumatologists frequently incorrectly diagnose gout based on hyperuricemia. Hyperuricemia is typically asymptomatic and does not require a gout diagnosis. Only 0.09 percent of people with SUA values between 7 and 7.9 mg/dL will develop gout each year. Gout may occur in 0.4 percent of people with SUA between 8 and 8.9 mg/dl. Only 0.5 percent of people with hyperuricemia above 9 mg/dl may develop gout. The detection of MSU crystals in synovial fluid aspirate using polarized light microscopy is the gold standard of diagnosis. When utilizing a compensator, diagnostic findings can be improved.

   A standard light microscope, on the other hand, may be used to identify crystals and distinguish MSU from other crystals such as calcium pyrophosphate dehydrate (CPPD) crystals. MSU crystals can be seen in synovial fluid at any stage of the illness, including attacks, the inter-critical phase, and chronic tophaceous gout.
2. **Radiological diagnosis -** It is critical in clinical practice for diagnosis and follow-up. Its utility as an outcome metric in clinical studies is also expanding. Recent technological advancements are changing the stage and even the kind of gout terminology.
3. **Ultrasound (US) -** Recently, advancements in US technology (machines, transducers, procedures) have prompted rheumatologists to adopt it for the diagnosis and therapy of gout. These include detecting joint effusion and synovitis, distinguishing between active and inactive synovitis, analyzing cartilage, characterizing bone shape for erosions and osteophytes, evaluating tendons, evaluating crystal deposition, carrying out US-guided operations monitoring disease evolution, and being useful in the differential diagnosis with other arthritis's. US characteristics in gout might be either general or particular. Nonspecific characteristics include:
   1. Synovial fluid
   2. Synovial proliferation and hypervascularization
   3. Bone erosions
4. **Conventional CT (CCT) -**Because CT has good resolution and contrast, it is the ideal tool for assessing and characterizing crystal arthropathies. CCT has a higher specificity for detecting tophi than US or MRI. CCT can assist monitor disease load and treatment response, but it has the downside of exposing patients to radiation.
5. **MRI -** Nonspecific inflammation, synovial thickening, effusion, erosion, and bone marrow edoema are MRI characteristics of arthritis. Depending on the degree of hydration and

categorization, tophi exhibit homogeneous T1 signal intensity (low to moderate) and heterogeneous T2 signal intensity (varying low to intermediate). The role of MRI is limited due to cost and availability.

Treatment and Management

Treatment of gout flares, urate-lowering medication, anti-inflammatory prophylaxis when initiating urate-lowering therapy, and screening and management of gout-related comorbidities are the four main concepts in gout care.

1. **Gout flares -**The therapy of gout flares is based on the rapid and successful management of the acute inflammatory reaction. Gout flare treatments include colchicine, NSAIDs, and steroids, which can be used combined in severe situations and are most effective when administered soon after the flare begins. The anti-inflammatory medicine used is determined on the individual's comorbidities and concurrent medications. An action plan and medicine supply should be accessible so that patients may begin treatment as soon as the flare begins.
2. **Urate-lowering therapy -** The long-term therapy of gout requires a sustained lowering in serum urate levels. Long-term urate-lowering medication reduces blood urate to sub-saturation levels (0.36 mmol/l, 6 mg/dl), resulting in MSU crystal breakdown, avoidance of increasing joint injury, suppression of gout flares, and better function. For such reasons, all main rheumatology organisation guidelines propose that serum urate levels be measured on a regular basis and that urate-lowering medicine be titrated to attain a specified serum urate goal.

   ULT may be divided into three categories (based on the mechanisms): -

   1. Xanthine oxidase inhibitors (XOI)
   2. Allopurinol
   3. Febuxostat
3. **Uricosurics -** Uricosuric medications are second-line urate-lowering treatments for gout. Uricosurics reduce uricemia by increasing urine uric acid production. As a result, they expose patients to the danger of uric acid stone, which is exacerbated at the start of treatment. Probenecid and lesinurad are examples of drugs in this class. They inhibit URAT1 in the apical membrane of the epithelial cell of the renal proximal tubule. Lesinurad was recently licenced in the United States and Europe at a dose of 200 mg/d as an add-on treatment to xanthine oxidase inhibitor when these failed to decrease uricemia to the appropriate goal.
4. **Non-Pharmacologic -** There are several lifestyle and dietary rules that may be followed to defend against flares or to prevent gout from arising in the first place. Reducing alcohol intake,

restricting purine-rich meals and replacing low-fat or non-fat dairy products with higher fat content equivalents are all diet suggestions. Weight loss and appropriate hydration also will help lessen the frequency of gout flare-ups.

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