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CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF GOUT, A DYSMETABOLIC DISABLING DISORDER

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CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF GOUT, A DYSMETABOLIC DISABLING DISORDER (Abstract): Gout is a disease caused by disturbances of uric acid metabolism and it manifests as rheumatic pain with various clinical and developmental issues, but without any major diagnosis problems; it might unfavorably interfere with other metabolisms, especially with carbohydrate and lipid metabolism that interact and erode each other.

Aims: To provide clinical and laboratory data and to follow the development of gout in patients treated in the clinic. Material and methods: The study included 28 patients (25 male and 3 female patients) diagnosed with gout, admitted to the First Clinic of Rheumatology of the Clinical Rehabilitation Hospital Iasi during 2012 - 2013. Results and discussion: A new diagnostic method, dual energy computed tomography, was effective in some selected cases of gout, as it may reveal uric acid crystals with specific densities in the damaged joints and periarticular soft tissues. Conclusions: Gout is a disorder that occurs when the uric acid produced by the body is stored in the form of crystals in joints and / or soft tissues. In joints, uric acid crystals precipitate and cause inflammatory arthritis that leads to swelling, redness, heat, pain and joint functional impotence. Keywords: GOUT, MONOSODIUM URATE CRYSTALS, METABOLIC SYNDROME, DISABLING DISORDER.

Although gout is a disease with a long history (it was described by ancient Egyptians and later by Hippocrates), the relationship between the disease and uric acid was shown in the nineteenth century by Sir Alfred Baring Garrod and it was seen as an acquired metabolic disorder only in 1909 (1,2).

Gout is a chronic disorder closely related to the metabolism of uric acid and to the release of monosodium urate crystals, identified by McCarthy and Hollander in the synovial fluid of inflamed joints (this became the gold standard in the diagnosis of gout). These crystals are deposited in the joints, causing episodic or persistent joint inflammation. They have a key role in understanding the disease. Consequently, local temperature rises, with pain and increased sensitivity of the joint (most often in the joint of the hallux), associated with very intense nocturnal pain (3, 4).

Gout is not merely a metabolic disease where uric acid is deposited in joints and
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tissues. It can also induce over time diabetes, atherosclerosis as well as major renal complications (5). Increased production of uric acid is usually caused by a purine-rich diet, by food containing a large amount of fructose or by excessive alcohol drinking, as well as by an increased production, by reduced renal excretion or a combination of these two mechanisms (6, 7). The occurrence of gout is influenced by factors such as gender (gout is more common in men than in women), age (the risk increases after the age of 65), race or diet.

There are some hematological lymphoproliferative and myeloproliferative disorders, hemolytic anemia, cutaneous psoriasis which are characterized by major cell damage associated with hyperuricemia and gout. Gene mutations in enzymes involved in purine metabolism (hypoxanthine-guanine-phosphoribosyltransferase deficiency or increased activity of phospho-ribosyl pyrophosphate synthetase) are known genetic causes of hyperuricemia and gout (7, 8).

Predisposing genetic factors were identified in order to evaluate gout in the general population, with possible therapeutic implications (polymorphism of genes involved in the synthesis of urate transporters in renal proximal tubules) (8). These transport proteins might be seen as pumps for urate, providing the renal excretion of uric acid (ABCG2 - ATP-binding cassette transporter isoform G2; Q141K variant, leading to a two-fold decrease of the urate efflux of and to its intracellular accumulation; URAT1 – one of the essential mechanisms of uric acid reabsorption; NPT1 - sodium phosphate transport protein 1, the protein involved in the tubular secretion of uric acid) (9, 10).

Gout has three stages: asymptomatic hyperuricemia - uric acid crystals deposit in tissues; acute attacks - crystals deposited in joints cause inflammation, usually in one single joint; chronic gout - persistent joint pain and swelling, uric acid deposits in soft tissues (called tophi) are usually located intra or periaricularly in the elbows, fingers and toes or ears. In addition to joint manifestations and tophi formation, renal impairment is one of the most common complications of hyperuricemia (11,12).

Gout is a common rheumatic disease with various clinical and developmental aspects, but it has a quite typical clinical picture, theoretically without major diagnosis problems.

MATERIAL AND METHODS
The study determined the clinical evolution of gout in 28 patients (25/89.28% men and 3/10.72% women) diagnosed with gout, (highly significant difference: $p < 0.005$), admitted to the First Clinic of Rheumatology of the Clinical Rehabilitation Hospital Iasi during 2012 – 2013. The aim was to provide clinical and laboratory data and to follow the development of gout.

The data was gathered using clinical and epidemiological survey forms that recorded age, sex, place of origin, eating and occupational behaviors, co morbidities and associated treatments, family history of gout in relatives of the last four generations, onset signs and development trends etc.

The processing and interpretation of collected data was performed using the Epid SPSS13.0 software and statistical and mathematical tests.

RESULTS AND DISCUSSION
Gout is a common disease in the general population and it is caused by hyperuricemia, which is a major risk factor in the
development of the disease and it is however easy to detect. If hyperuricemia levels are higher than 7 mg / dL, the risk of joint and kidney damage increases also. An attack of gout is caused by the precipitation of uric acid crystals in the synovial fluid. It is a slow process, resulting from persistent hyperuricemia.

The highest frequency of the disease was found in the age range of 51-60 years in men and above 60 years in women, with a sex distribution of 89.28 % male to 10.72 % female.

Differences in age and sex of patients with hyperuricemia are likely related to variations in renal clearance of uric acid that are influenced by estrogen and androgen levels (12) (fig. 1).

Hyperuricemia was positively correlated with male gender, obesity, body size, body mass index, dietary intake of proteins, social status. 6 of the 28 cases (21.42%) had a body mass index BMI of > 25 kg/m².

17 of the 28 patients (60.71%) were from urban areas and 11 patients (39.29%) were from rural areas (fig. 2).
The epidemiology of gout is closely related to that of hyperuricemia, which is defined as a serum urate concentration higher than two standard deviations above the normal maximum values related to sex, namely, over 7.0 mg / dL (0.42 mmol / l) in men and above 6.0 mg / dL (0.36 mmol / l) in women.

Epidemiological studies have shown a strong correlation between serum urate levels and chronic alcohol ingestion, due to increased production of urate and suppression of the renal excretion of uric acid caused by hyperlactatemia (8,12). In our study, 35.71% of gout patients were chronic consumers of ethanol.

The average duration of the disease at admission was: less than 1 month in 2 cases (10.71%); 1-2 months in 7 cases (25.00%); 2-5 years in 13 cases (46.42%); over 5 years in 6 cases 21.42%.

Our data have also shown that gout has four clinical pictures corresponding to four stages of the disease: asymptomatic hyperuricemia, acute attacks of gout, intercritical period and chronic tophaceous gout.

Rarely, the gout patients did not have a second acute attack. Usually, acute episodes reoccurred between six months and two years after the first attack.

In untreated patients, the acute attacks occurred more often and with more severe symptoms, for long periods, often associated with fever and having a polyarticular character.

Joints were damaged at the onset of gout, as follows: metatarsal phalangeal (MTP I) and proximal interphalangeal (PIP I), bilateral in 3 patients (10.71%); median region of tarsus in 2 patients (7.14%); knees in 9 patients (32.14%) and polyarticular damage in 14 patients (50.00%). The typical attack of gout with sudden onset of intense pain was found mainly in one joint, namely, the metatarsal phalangeal joint; the objective examination showed purple shiny skin, especially in the affected joint; local temperature was increased and cutaneous hyperesthesia was present, increased sensitivity to gentle palpation of the area as well as attempts to mobilize the damaged joint. Signs of lymphangitis were found in some cases (32.14%) and cellulite effusion was rare (7.14%).

In some cases the onset was polyarticular, with damage of knees (26 patients; 92.85%), ankles (23 patients; 82.14%), MTP hallux (14 patients; 50.00%), PIP (8 patients; 28.57%) elbow (12 patients; 42.85%), hand (11 patients; 39.28%), shoulder (3 patients; 10.71%), hip (3 patients; 10.71%).

Usually, the clinical onset of primary gout occurred in a state of full health, either as an attack of acute arthritis or due to a renal colic as the result of uric acid lithiasis. In some cases, the gout of the joints was acute, with extreme paroxysmal pain caused by inflammations. Chronic arthritis was preceded or not by an acute attack.

Recurrent episodes of acute arthritis in MTP are characteristic of gout, but there may be also other causes for this location of arthritis, such as infections, psoriasis and other crystal deposition arthropathies (7, 8).

Over 50% of patients may have arthritis in another location, which is less specific for the first attack of gout – temporomandibular, acromioclavicular, sternoclavicular, manubriosternal, sacroiliac, pubic symphysis, femoral hip; it may be accompanied by flexor tenosynovitis associated with carpal tunnel syndrome (9,10).

The less acute polyarticular manifesta-
tions are not rare. Therefore it is important to detect monosodium urate crystals in the synovial fluid of the affected joints in order to diagnose gouty arthritis when there is no clear cause of the disease.

Musculoskeletal ultrasound shows good results in the ability to detect crystal deposits and other characteristics of gouty arthropathy. Recently, specific elements of gouty arthropathy were described in the literature: hyperechoic image of the external surface of hyaline cartilage - the so-called sign of “double contour” (12), hyperechoic areas in the synovial fluid, with the appearance of “soft” or “hard” tophi (13).

A new diagnostic method, dual energy computed tomography, was effective in some cases of gout, as it may reveal uric acid crystals with specific densities in the damaged joints and periarticular soft tissues (3).

Extraarticular manifestations are present in structures rich in proteoglycans, as they have a high susceptibility to develop tophi, due to their high affinity for sodium urate. Thus, 6 patients of the study group (21.42%) had gouty tophi localized in the pinna, fingers and toes, knees, olecranon bursa, Achilles tendon. In 2 patients with chronic tophaceous gout (7.14%) - pseudorheumatoid form - the skin covering superficial tophi was pressed and ulcerated, leading to the drain of a white pasty substance composed of sodium urate crystals.

Renal lithiasis was identified by ultrasound in 9 patients (32.14%), who had hyperuricemia for long periods of time (> 9 mg %) and high levels of uricosuria.

In the 28 cases, laboratory examinations showed during the acute episode the following data: uric acid values between 6-7 mg % and 9 mg; uricosuria values < 0.4 g / 24 h (14.28%); 0.4-0.8 g / 24 h (17.85%); 0.8-1 g / 24 h (3.57%); > 1 g / 24 h (28.57%); these examinations were not carried out in 10 cases.

Dyslipidaemic syndrome was found in 7 cases with high cholesterol levels (25.00%); in 11 cases with high triglyceride levels (39.28%), in 7 cases with high levels of total lipids (25.00%) and in 3 cases with diabetes mellitus type II (10.71%).

Serum uric acid during the acute episode may be normal and measuring hyperuricemia levels is not a prerequisite for diagnosis. Hyperuricosuria was present in 32.14% of patients.

Radiological changes in the acute stage of the disease included the swelling of the periarticular soft tissue, juxtaarticular osteoporosis, joint space narrowing. In 9 patients (32.14%), radiological lesions indicated the development of secondary arthritis, as osteophytes, subchondral osteosclerosis or significant clearing of joint space were found.

Treatment is aimed at eliminating the monosodium urate crystals. Joint inflammation resolves after their removal and the disease can be considered cured. Serum uric acid levels should be maintained indefinitely within normal limits, in order to prevent the formation of new crystals and the relapse of gout attacks (9).

It is important to treat arthritis because it can occur at any time, even after the treatment started and it can persist for as long as the crystals in the joints remain undissolved. The prevention of episodes of arthritis may be achieved using anti-inflammatory drugs that reduce mild subclinical inflammation caused by the presence of monosodium urate crystals in joints.
The presence of gout may indicate also the presence of metabolic syndrome or of some of its components (hypertension, dyslipidemia, obesity, glucose intolerance), which should be also recognized and treated (14).

The treatment of evolving gout aims at stopping the acute attacks and preventing the relapses, reducing the levels of hyperuricemia and treating complications and comorbidities.

Patients in the study group received early treatment of acute gouty arthritis that solved the inflammatory phenomena as rapid as possible by delivering a non-steroidal anti-inflammatory drug for the remission of the inflammatory phenomena (0.5 mg, 1-3 times / day). The treatment of recurrent episodes of arthritis, gouty tophi or nephrolithiasis was made, in order to avoid lesions of the cartilage and bone and the development of tophi.

Uricase therapy is an option for the treatment of hyperuricemia in gout, but its use is limited due to side effects. In humans, the uricase may decrease the level of uric acid by 0.78 mg/dL after 4 hours of administration. Rasburicase, a recombinant uricase, was successfully used in severe cases of gout. It is delivered in a monthly single dose, due to the development of tolerance after multiple doses.

All non-steroidal anti-inflammatory drugs (NSAIDs) were effective for the treatment of gouty attacks. Studies show that naproxen (500 mg two times a day) has similar effects as prednisone 35 mg / day (32, 33). Gastrointestinal, cardiovascular and renal adverse effects are the main reasons for limiting the use of NSAIDs in the treatment of gouty arthritis. A short course of 30-40 mg prednisone for 2-4 days proved to be effective in the treatment of gouty arthritis (8).

The most common drug used to lower serum uric acid is allopurinol, an inhibitor of xanthine oxidase, which is an enzyme involved in the metabolism of purines into uric acid (11).

Febuxostat is used in patients intolerant to allopurinol and in gout patients with renal failure, as it is a selective inhibitor of xanthine oxidase, which is metabolized in the liver.

Pegloticase is a new drug approved in the USA in 2010 for the treatment of gout resistant to conventional therapies. It is a drug obtained from a porcine recombinant enzyme.

**CONCLUSIONS**

The study group showed multiple comorbidities, especially diabetes mellitus, hypertension, dyslipidemia, obesity.

Hyperuricemia was positively correlated with male gender, obesity, body size, body mass index, dietary intake of protein, social status.

Our data have also shown that gout has four clinical pictures corresponding to four stages of the disease: asymptomatic hypouricemia, acute attacks of gout, intercritical period and chronic tophaceous gout.

The risk of developing articular manifestations of gout or tophi is related to duration of hyperuricemia, sex and age of the patient. Both gouty arthritis and tophi are minor manifestations which are fully treatable and reversible; therapy should be initiated on onset; however, renal impairment is more severe and sometimes irreversible, so that early diagnosis and treatment is required.

A better evolution and prognosis of
gout may be achieved through close cooperation between patient and doctor, by providing early and effective treatment, in order to prevent osteoarticular and renal lesions.

All these correlations found in practice and also reported in the literature show that gout is a complex metabolic nosological entity, characterized mostly by rheumatic manifestations.

REFERENCES