GOUTY NEPHROPATHY: DIAGNOSIS, TREATMENT APPROACHES

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ABSTRACT

Clinical variants of kidney damage in patients with gout, including asymptomatic disorders of uric acid metabolism, are considered and discussed. The risk factor of hyperuricemia and associated kidney damage, target pH values of urine and uric acid levels in the blood, principles of nutrition and drug therapy of patients with gouty nephropathy are presented. Maintaining uric acid at the target level allows not only to control this disease, but also to prevent or slow down the formation of a number of complications, including gouty (urate) nephropathy.

Keywords: *nephrology, gout, nephropathy*

АННОТАЦИЯ

Рассмотрены и обсуждены клинические варианты поражения почек у больных подагрой, в том числе бессимптомные нарушения обмена мочевой кислоты. Представлены фактор риска гиперурикемии и связанного с ней поражения почек, целевые значения pH мочи и уровни мочевой кислоты в крови, принципы питания и лекарственной терапии пациентов с подагрической нефропатией. Поддержание мочевой кислоты на целевом уровне позволяет не только контролировать это заболевание, но и предотвращать или замедлять формирование ряда осложнений, в том числе подагрической (уратной) нефропатии.

Ключевые слова: *нефрология, подагра, нефропатия.*

INTRODUCTION

Gout is a systemic tophaceous disease that develops due to inflammation at the site of sodium monourate (SMU) crystal deposition in people with hyperuricemia (≥360 mmol/L) due to environmental and/or genetic factors [1-4].

Primary and secondary gout, metabolic (10-25%) and renal (75-90%) types are distinguished [5, 6].

The diagnosis of gout is made according to the WHO criteria (2002) - detection of SMU crystals in synovial fluid or tophus by polarization microscopy or arthritis of the first metatarsophalangeal joint + tophus + rapid response to colchicine, or magnetic resonance imaging (MRI)/USG data, as well as according to national or international (EULAR, ACR, etc.) recommendations [1, 2].

The main clinical manifestations of gout: recurrent arthropathy (including gout status); gouty tofus; nephrolithiasis; gouty nephropathy [1, 2, 7, 8]. Several forms of urate nephropathy are distinguished, often in combination: acute urolithiasis, urate nephrolithiasis, and chronic tubulointerstitial nephritis (CTIN) [5-9].

DISCUSSION AND RESULTS

Acute urate nephropathy (urinary tract obstruction by uric acid crystals - UAC - characteristic of tumour lysis syndrome) is acute and can manifest as acute renal damage (10). Patients report a relatively short period of decreased diuresis with a change in the colour of the urine to brown ("the colour of crushed bricks"). Oliguria may be followed by anuria. Subsequently, compensatory polyuria is observed, after which the amount of urine normalizes. Such episodes of partial urate obstruction of the renal tubules are usually reversible over a long period and may appear long before the first attack of joint gout [5]. It has been shown that even a short-term, 72-hour urinary obstruction leads to a residual functional defect of the kidney due to partial loss of nephrons.

At Increased levels of creatinine and potassium in the blood are diagnosed with increasing deterioration of renal function. A rise in BP is characteristic [10].

The clinical picture of urate nephrolithiasis does not differ from other variants of this kidney disease. Prolonged, virtually asymptomatic presence of urate concrements in the kidneys may be followed by episodes of renal colic, often recurrent. It can be combined with CTIN [5,7,8,10].

Cystic fibrosis is the most common form of urate nephropathy and is asymptomatic for a long time, which does not reduce its danger - it often becomes the cause of chronic kidney disease (CKD) [5]. In 18-25% of patients with gouty nephropathy the cause of death is the terminal stage of CKD. The development of CTIN can precede the first attack of joint gout, and in some patients gouty arthritis is not observed at all. In CTIN, proteinuria is more often "trace" or absent. Decreased activity of the tubular enzyme N- acetyl-β-D-glucosaminidase is found in the urine and is one of the early signs of CTIN. Reduced urinary UA excretion combined with marked hyperuricemia indicates the severity of renal tubulointerstitial damage. The

depression of relative urine density is accompanied by nocturia, and blood creatinine levels may increase [5].

Among the mechanisms of renal tissue damage in hyperuricemia, urate crystallization in tubulointerstitium and pelvis; reduced activity of fibrinolytic factors (urinary urokinase); endothelial dysfunction; renin excretion by juxtaglomerular cells accompanied by activation of the local-renal renin-angiotensin-aldosterone system have been described [2, 5, 7].

To diagnose gouty nephropathy, blood levels of MC and renal excretion (in some patients) of UA (normal, >800 mg/day in men and >750 mg/day in women) are determined; renal and urinary tract ultrasound and renal CT/MRI are performed [4, 5, 7]. Renal MC excretion (in daily urine) is investigated in individuals with a family history of gout, onset of gout before the age of 25 years and the presence of urolithiasis [1-3, 7, 8].

Treatment. Patients are trained to determine their urine pH using test strips in outpatient settings (target level is 6.1-7.1). There is an ongoing discussion about how many hours a day the urine pH should be in the target range: once a day (a few hours) or for a longer period. To achieve the target values of urine pH, it is recommended to take alkaline citrate mixtures in prophylactic or litholytic doses: blemarin - 6-18 g granulate per day (1 effervescent tablet = 3 g granulate) dissolved in a glass of mineral water or tea or fruit juice; uralite; magurlite (2 mg 4 times a day); soluran (9-10 g/day) or sodium bicarbonate – 1,5 g 3 times a day [4, 7, 8].

Diet. Previously, patients with gout were prescribed a numbered diet - №6 or №6е [6, 9], and with the development of urate nephropathy - №7р [9]. At present, according to Order No. 330 of the Ministry of Health of Russia of 05.08.03 "On Measures to Improve Therapeutic Nutrition in Medical and Preventive Treatment Institutions The Russian Federation", such patients are prescribed a basic variant of the standard diet, and in case of decreased glomerular filtration rate (GFR) - a variant of diet with reduced amount of protein (low, low-protein diet - LPD).

It is recommended to avoid alcohol (beer, port, spirits - whiskey, vodka, cognac, etc.) and sugar-sweetened beverages (Coca-Cola, etc.), reducing excess body weight. Dyslipidemia and hyperglycemia are corrected [1-3, 5, 6, 9].

A special antipodagric diet, poor in purines, proteins and fats is prescribed. It is necessary to limit products rich in purines - seafood; offal (kidneys, liver, lungs, brains); meat soups and extracts, jellies, cold cuts; crayfish, fatty fish (smoked, cisco, caviar); fried meat [1, 3, 9]. Meat or fish is consumed only in boiled form 2-3 times a week.

Of the meat products, chicken is recommended as it is relatively poor in purines. The amount of protein is 1.0-1.5 g/kg/day. The ratio of proteins of animal and plant origin in the diet of a patient with hyperuricemia is 1:1.5 (75% of proteins of plant origin in the development of urate nephropathy) [6, 9].

Excessive dietary fat prevents MK excretion by the kidneys and can provoke a gout attack. It is necessary to exclude/limit foods rich in fats - eggs, sausages, canned meat, fatty dairy products. The patient's food should not contain more than 1 g of fats per 1 kg of body weight. Low-fat dairy products are useful because casein and lactalbumin increase UA excretion with urine.

Salty sauces, sour cream sauces, mayonnaise, processed cheese, fatty dairy products, muffins, pastries, high quality bread, butter cream, cakes, cakes should be excluded/restricted [9].

Mushrooms, asparagus, cauliflower, spinach, lentils, soybeans, peas, beans, and green peas are also rich in purines, but according to studies, the consumption of plant purines does not cause an increase in blood MC and does not lead to gout [3].

Foods high in vitamin C are introduced into the diet, which reduces the level of MC in blood due to its increased excretion with urine [3, 6, 9].

Individuals who ate ≥5 apples at a time may have a 35% increase in blood MC levels due to fructose. A direct association between fructose intake and the development of gout in men has been demonstrated [3].

Recommended in quantities that ensure excretion of ≥2 l of urine per day: alkaline mineral water (without gases, up to 0.5-1.0 l/day), bottled, bicarbonate or bicarbonate- sulfate - Naftusya, Smirnovskaya, Slavyanskaya, Borjomi, Berezovskaya, etc. [6]; skimmed milk; citrus and berry juices/juices (cranberry, lingonberry, cherry); kissels; rosehip decoction; tea (especially green) and coffee (ground) - ≥5 cups per day [3, 5, 6, 9].

When GFR decreases to the level <90 ml/min, low protein diet (LPD) is prescribed, taking into account absolute or relative contraindications to it - 0.8-0.6-0.3 g/kg/day of protein with table salt restriction to 1.5-3.0 g/day [11]. At FFR <45 ml/min, protein preparations (ketosterol - 1 tablet per 5 kg/day in 3 intakes; soy isolate - 0.1-0.3 g/kg/day; amines, polyprotein nephro, peptoprotein nephro, nutrien nephro) are prescribed in addition to LPD [11]. If patients are reluctant to comply with LPD, highly selective adsorbents, enterosorbents (povidone, lignin hydrolysis, activated charcoal,etc.) may be recommended. In patients with CKD stage 5 and renal replacement therapy (haemodialysis, peritoneal dialysis,kidney transplantation), nutrition is organised in accordance with current recommendations [12]: fluid - 500-

750 ml/day over residual diuresis; calories - 30-35 kg/day; protein - 1.2-1.5 g/kg/day; sodium chloride - 5-6 g/day; calcium - up to 2 g/day; potassium - up to 2-3 g/day; phosphorus - 0.8-1.0 g/day.

Phytotherapy. Urisan is an herbal complex with antihyperuricemic and anti-inflammatory effects - 2 capsules or 5 pills 2 times a day for 1-3 months, 3 times a year for 2 months as prevention [3, 13]. For patients with urolithiasis the administration of Prolit 2 capsules or 5 pills 2 times a day in combination with urisanum 2 capsules or 5 pills 2 times a day in for 2 months, for prophylactic purposes twice a year for 2 months [8].

Pharmacotherapy. In patients with hyperuricemia (gout) in the presence of comorbid pathology, the pharmacotherapy given is reviewed. One should keep in mind the drugs (fructose, warfarin, nicotinic acid, vitamin B12, etc.) that increase MC formation, as well as pharmacotherapies (acetylsalicylic acid, diuretics, nicotinic acid, levodopa, cyclosporine, etc.) that slow its elimination [5].

In acute gouty arthritis, colchicine 0.5-1.0 mg (up to 2 mg/day) or nonsteroidal anti- inflammatory drugs (oral or injected); glucocorticosteroids (oral, intraarticular, intramuscular, intravenous - pulsterapia: 250-500 mg/day) [1-4], interleukin-1 inhibitors (anakinra, rilonacept, canakinumab) [1, 2].

Drug therapy is indicated in patients with persistent blood levels of MC

>360 μmol/L, in urinary UA excretion >1100 mg/day, in cytolytic tumor therapy [1, 2]. Principles of antihyperuricemic therapy: not earlier than 2-4 weeks after complete relief of arthritis attack; start with minimum doses, increase doses until target UA levels (≤360

- 300 μmol/L) are achieved. Criteria of therapy effectiveness: absence of arthritis attacks (frequency), resorption/reduction of tophuses (size). During therapy, it is necessary to monitor UAnd creatinine levels, calculate FFR, monitor urine pH, identify adverse reactions [2].

A variety of drugs are used to treat gout - uricoinhibitors (allopurinol, febuxostat, hepatocatalase), uricoeliminators (benzbromaron, probenecid, etamide, sulfinpyrazone), combined drugs (allomaron) [1-5, 7, 8], uricolytics (pegloticase - recombinant uricase), uricase preparations (uratoxidase, rasburicase, peguricase) [2]. Drug of 1st line - allopurinol uricoinhibitor (50-100 mg - 10 days, then +50 mg every week until target MC level is achieved). Maximum daily dose of allopurinol is determined taking into account GFR [2, 4, 5] (see table). Uricoeliminators should not be prescribed in moderate to severe CKD and in patients with IBC [2, 3, 5].

Febuxostat is a selective xanthine oxidase inhibitor and is the drug of choice for patients with moderate to severe CKD (40-80 or 120 mg/day). Unlike allopurinol, no dose titration is required [2].

Uricolytics are prescribed for severe gout, patients with ineffectiveness of other drugs (uricoinhibitors, uricoeliminators) or in the presence of contraindications; persons with leukemia, lymphoma, solid malignancies [2].

In the presence of arterial hypertension (AH) in patients with gouty nephropathy, hypotensive drugs(angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist; calcium antagonist or β-blocker) are given, often in combination. In patients with gout and AH, losartan is the drug of choice to achieve target BP [1, 5]. It has been found that losartan blocks 2 major transport systems of distal tubule epithelial cells involved in urate reabsorption (urate/lactate and urate/chloride). Therefore, the structures of the renal tubulointerstitium are protected from the damaging effects of urate [3-5].

Successful treatment of urate nephropathy is determined by its timely diagnosis. It is one of the few chronic progressive diseases that can be prevented with early and adequate primary and secondary prevention of urate dysmetabolism. Normalization of UA levels is aimed at preventing attacks of joint gout, urate kidney damage, as well as reducing the risk of cardiovascular complications.

CONCLUSION

In conclusion, it should be noted that systematic rational treatment allows achieving good results in more than 2/3 of patients with gout. The prognosis of gouty nephropathy is largely determined by the quality of medical measures with constant dispensary supervision.

Thus, gout belongs to those "grateful diseases", the early recognition of which and the correct therapeutic tactics help to preserve the health and ability to work of patients for many years.

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