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Characteristics of clinical manifestations of gout in the elderly people

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ABSTRACT

Introduction. Gout in elderly patients is characterized by a pronounced comorbid background, which causes difficulties in their management.

Objectives of the study. Analysis of the comorbid background for gout in different age groups. Identification of risk factors characteristics, the onset and evolution of gout in elderly people compared to middle-aged patients.

Material and methods. To achieve the goal of the cross-sectional study, 237 patients with gout (average age for the men 60 ± 8.0 years and for the women 63 ± 9.0 years) were examined.

Results. The patients were separated into two groups, depending on the age of onset of gout: the age of onset up to and including 59 years (group I, 146 people) and the age of onset after 60 years inclusive (group II, 91 people). The average age in group I was 58.1 ± 11.7 years, in group II - 72.8±4.1 years (p <0,1).

Conclusions. The average number of concomitant diseases is 2 times higher in the group of gout patients aged 60 years and older (4.0 [3.0; 5.0]) than in the group of patients with gout under the age of 59 years inclusive (2.0 [2.0;3.0], p <0,1), in patients with the onset of gout at the age of 59 years inclusive, the development of coronary artery disease, chronic heart failure and nephrolithiasis occurs significantly earlier than in patients with the onset of gout at the age of 60 years and older (48.4 ± 6.9 years and 59.1 ± 5.0 years; 53.6 ± 3.4 years and 65.6 ± 9.0 years; 37.3 ± 8.9 years and, respectively, 54.9 ± 14.6 years, p <0,05 in all cases).

Keywords: gout, elderly, comorbidities

INTRODUCTION

Gout is a disease characterized by the deposition of sodium monourate crystals in various tissues and organs and with the onset of inflammation that develops due to this, in people with hyperuricemia (HU) caused by environmental and/or genetic factors [1,2].

The predominant lesion of gout in middle-aged men who consume in excess foods rich in purines and alcoholic beverages was first observed by Hippocrates in the sixth century BC [1,3]. The pathogenetic role of increased uric acid (UA) levels in the development of gout was determined only in the middle of the XIX century by the English therapist A.B. Garrod [4]. For centuries, gout has been described as a characteristic disease for middle-aged men, but nowadays its frequency is rapidly increasing in the older age group [5]. At the same time, in most developed countries of the world, the demographic situation is characterized by an increase in

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the relative number of elderly and senile people, the frequency of occurrence of gout among which is maximum [6,7]. Comorbid diseases, which are associated with gout (dyslipidemia, obesity, insulin resistance (IR), type 2 diabetes mellitus (DM 2), arterial hypertension, coronary artery disease (CAD), chronic heart failure (CHF), chronic kidney disease (CKD)) are the main factors that worsen the quality of life [9-12] and, in some cases, the prognosis of people suffering from gout [11].

There is also insufficient knowledge of the features of its diagnosis, prevention and treatment [13].

Gout leads to additional economic costs both due to the treatment of the disease itself and concomitant pathogenetically associated pathological conditions [3,4,12]. However, despite the recently increased interest in the problem of gout in the elderly, the number of studies aimed at a comparative analysis of the disease in different age groups is limited and is reduced to the description of individual clinical cases [12].

It remains an unclear question – what contributes to the increase in the frequency of gout in the elderly and the elderly, the characteristics of its onset in these patients are not determined in a clear way. Also, in recent studies, the clinical and economic aspect of the gout problem has not been revealed [13]. Researchers have observed an increase in the incidence of the disease in postmenopausal women, which significantly levels the sex differences in the incidence of gout in the elderly [14].

In the 80s-90s, reports appeared showing the association of gout with osteoarthritis (OA), namely the localization of gouty tophi in the region of Heberden nodules (with inflammatory lesions of the distal interphalangeal joints of the hands) [15-17].

Possible causes include mechanical damage [18], a change in the structure of the proteoglycans of the articular tissues [19], the formation of sodium monourat crystals on the surface of the damaged cartilage [2,5,9,11], as well as an increase in the crystallization of the urates with a change in the acid-base gradient due to the local outflow of the joint fluid into the area of joint tissue damage [8,11,15].

Comorbid pathology is a condition that often occurs in old age [20]. Currently, the concept of comorbidity is considered as the presence of concomitant pathogenetically related diseases that have a reciprocal effect on the evolution of the other, complicating the management of the patient and aggravating his prognosis [1,4-9]. Even Paracelsus said that in an organism weakened by gout, "embryos of other diseases" can develop [20]. The association of gout with cardiovascular pathology, chronic kidney and metabolic diseases is generally recognized [7,12]. The relationship between HU and arterial hypertension was revealed most completely: a meta-analysis of 11 studies showed a significant increase in the risk of developing hypertension among patients with HU (1.41 (95% CI 1.23-1.58)) after adjusting for traditional risk factors (age, body mass index (BMI), smoking and alcohol). Several studies have reported an increase of 1.13 in the relative risk of arterial hypertension (95% CI 1.06 to 1.20) for each mg/dl increase in UA [4-9].

A meta-analysis of 25 studies conducted between 1972-2013 involving a total of 97,824 people also showed an increase in the relative risk of arterial hypertension (1.15; 95% CI 1.06-1.20) for each mg/dl increase in UA [18-20].

Following a study of 123,224 people aged 65 years and over, it was proved that in the group of those with multimorbid status (3 or more chronic diseases out of 46 detectable), the combination of arterial hypertension, lipid metabolism disorders and disorders of purine metabolism was the 4th most common "comorbid triad" in men (9.7%), and the 21st most common among women (5.9%) [17,18]. In 7 of the most common 16 "multimorbid triads" appeared gout and impaired metabolism of purines and pyrimidines [11-16].

A number of studies also demonstrate a nefarious prognosis for gout patients: a 12-year prospective study determined the association between a gouty history and the risk of death in 51,297 men: compared to non-gout and cardiovascular disease at the beginning of the study, the relative risk for total gout mortality was 1.28 (95% CI 1.15-1.41), for mortality from cardiovascular disease (CVD) 1.38 (95% CI 1.15-1.66), and 1.55 (95% CI 1.24-1.93) for fatal coronary artery disease. The relative risk of developing nonfatal acute myocardial infarction (IMA) was also higher in those with gout than in those without (1.59; 95% CI, 1.04-2.41) [3,7,11].

MATERIAL AND METHODS

In order to achieve the objective of the descriptive stadium, 237 patients with gout were analyzed (average age for the men 60 ± 8.0 years and for the women 63 ± 9.0 years). The study was carried out in accordance with the requirements of the Ministry of Health for "Clinical and financial-economic research" within the postdoctoral scientific program at the Rheumatology and Nephrology Discipline of the State University of Medicine and Pharmacy "Nicolae Testemitanu". The raw data was processed in SPSS version 26.0.

From the database of the Departments of Arthrology, Rheumatology and Nephrology of the Republican Clinical Hospital "Timofei Mosneaga" were extracted the clincio-paraclinical data and the performed treatment of patients with gout, including 658 patients with gout observed in the period 2015 – 2022, out of which 237 patients who meet the criteria of the study were selected. The diagnosis of

gout in the database was carried out according to the classification criteria for gout according to ACR and EULAR 2015 [5,6].

The duration of gout at the time of examination was 11.2 years (from 8.02 to 16.3). The number of inflamed joints in the anamnesis 10 [6; 20]. The number of exacerbations per year averaged 3 (from 2 to 6). The chronic arthritis 61 (30.5). The tophaceous shape 86 (42.5). The number of tophi 3.4 [0; 3]. At the time of the examination, 132 patients (66%) were taking allopurinol. The daily dose of the drug ranged from 100 to 600 mg, on average – 300 mg.

At the time of inclusion in the study, the predominant majority of patients with gout suffered from hypertension (182 (91%) of patients). The average value of systolic blood pressure level was 136 (90; 180) mm Hg, diastolic – 82 (50; 120) mm Hg.

Patients with gout had a pronounced comorbid background. Most of them had 2-4 comorbidities. The average number of concomitant gout diseases was 3.3 ± 1.38. Only 2 patients did not have concomitant diseases, and 9 people had all the pathologies of comorbid gout. With a high frequency, those included in the study had urolithiasis (147 (73.5%) patients), coronary artery disease (123 (61.5%) patients), type 2 diabetes mellitus (DM type 2) was present in 79 (39.5%) patients, chronic heart failure (CHF) in 80 (40%) patients, chronic kidney disease (CKD) in 65 (32.5%) of the study participants.

RESULTS

The patients were separated into two groups, depending on the age of onset of gout: the age of onset up to and including 59 years (group I, 146 people) and the age of onset after 60 years inclusive (group II, 91 people). The ratio of men to women in group I (124 men (83%) and 26 women (17%)) and 37 men (74%) and 13 women (26%) in group II had no significant differences (p = 0.18). The average age of the patients at the time of examination in group I was 58.1 ± 11.7 years, in group II - 72.8 ± 4.1 years (p <0,1).

The chronic course of arthritis (persistent signs of inflammation in the joints) was observed in 61 (30.5%) of the patients included in the study, recurrent development - in 139 (69.5%). The average number of joints affected during the disease was 10 [6; 20]. The median number of joints showing signs of inflammation at the time of examination was [0; 3]. The frequency of attacks of arthritis with recurrent gout was 3 [2; 6] per year.

As a "onset course", most often reacted metatarsophalangeal joints (138 people, 69%), which is characteristic of the classical course of the disease. In 12% of cases, the development of the disease began with inflammation of the ankle joint, in 7.5% of cases - knees. Rarely, the disease began in the joints of the upper extremities (in the interphalangeal joints of the hands in 4 (2%) patients, in the radiocarpal joints in 3 (1.5%) patients).

The average age of onset of gout in group I was 43.1 ± 9.3 years, in group II - 64.9 ± 4.1 years (p <0.1). The duration of the disease in group I was 2 times longer than in group II: 15.0 years [9.4-18.8 years] compared to 7.8 years [5.3-10.0 years] (p <0.1). The age of onset of gout among male and female study participants had no significant differences (48.1 ± 12.9 years and 50.3 ± 14.3 years, p = 0.3 years, respectively. There were no significant differences in the age of onset of gout between men and women in groups: in group I 42.9 ± 9.7 years and 42.7 ± 10.6 years, respectively (p <0.94). In group II, the average age of onset in men and women also had no differences (65.5 ± 4.2 years and 65.5 ± 6.1 years, respectively (p <0.98)).

The following risk factors of gout were analyzed:

- the presence of a hereditary predisposition (diagnosis of gout in first or second degree relatives);
- pre-onset to gout taking diuretics;
- before the onset of gout, taking acetylsalicylic acid preparations;
- alcohol consumption noted by study participants in the survey (more than 20 conventional units per week);
- consumption of foods rich in purines;
- the presence of hypertension, which developed before the onset of gout;
- the presence of obesity, which developed before the onset of gout;
- the presence of chronic kidney disease (CKD) (pronounced decrease in kidney function – glomerular filtration rate (GFR) <60 ml/min/1.73 m^2), which developed before the onset of gout.

Age of onset of comorbidities

The frequency of concomitant diseases (hypertension, coronary artery disease, CHF, CKD) in the patients included in the study naturally increases with age, which generally shows a significantly higher comorbid background at older ages.

In group I, at the time of the examination, common pathologies were arterial hypertension (134 (89%) people) and urolithiasis (115 (76%) people). The frequency of urolithiasis at the time of examination in group I was reliably higher – 115 (76%) individuals than in group II - 33 (66%) individuals, despite the younger age of its representatives. DM 2 was determined 1.6 times more often in group I than in group II, although the differences were not significant. However, only 3% in the group we had the development of DM 2, which preceded gout. In group II, arterial hypertension (in 96%) and coronary heart disease (in 86%) frequently present themselves. The

development of naturally occurring concomitant diseases more often preceded gout in group II. Despite the previous average age of onset of gout in group I (42.9 ± 9.8 years and 65.5 ± 4.7 years in group II, respectively, p = <0.1), 44% of patients in group I already had arterial hypertension before the onset of gout, also 13% in group I before the development of gout suffered from coronary artery disease and 13% of urolithiasis (Table 1).

TABLE 1. Frequent diseases before and after the onset of gout (n (%))

Disease	Group I (n=146)		Group II (n=91)	
	Before the onset of gout	At the time of examination	Before the onset of gout	At the time of examination
Arterial hypertension	66 (44)	134 (89)	39 (78)	48 (96)
CAD	19 (13)	80 (53)	26 (52)*	43 (86)*
CHF	5 (3)	49 (32)	11 (22)*	30 (60)*
Urolithiasis	20 (13)	115 (76)	15 (30)*	33 (66)*
CKD	1 (0,7)	45 (30)	6 (12)*	20 (40)*
DM 2	5 (3)	65 (43)	6 (12)*	13 (26)*

*Note: * – statistical significance of the differences from patients in group I (p<0.05); CAD – coronary artery disease, CHF – chronic heart failure, CKD – chronic kidney disease, DM 2 – diabetes mellitus type 2.*

The average age of detection of DM 2 did not have significant differences between the groups. Significantly earlier, the occurrence of coronary heart disease in group I was observed: the average age of manifestation of coronary heart disease in 19 patients is 48.4 ± 6.9 years, and in 26 patients of group II – 59.1 ± 5.0 years, (p <0.1). The diagnosis of CHF was established before the development of gout in 5 patients in group I and 11 patients in group II; the age of development of CHF was significantly lower in group I (p <0.1). The average age of development of urolithiasis in group I was 37.3 ± 8.9 years and was 1.5 times lower than the average age of the onset of urolithiasis in group II (54.9 ± 14.6, p <0.1). The diagnosis of CKD was established before the development of gout in only 1 of group I and 2 of group II. The age of diagnosis was 47 years in group I and 55 and 66 years in group II. An analysis of kidney function was carried out at the time of the examination (Table 2). In group I, the median values of blood creatinine did not correspond to normal parameters in men and women and was higher than normal, the median value of the total protein in the urine was higher than optimal. In group II, the median values of serum creatinine in both men and women, the total protein in the urine was significantly higher than in group I, and at the same time higher than normal. Significantly lower than in group I, an average of GFR values was shown at the late onset of gout. In group I, the median GFR corresponded to a normal value, in group II showed a decrease in kidney function. A significantly higher number of patients in group II had stage 4 CKD (7 (14%)).

TABLE 2. Indicators of kidney function in patients with gout with early and late onset at the time of examination

Indicator	Group I (n = 146)	Group II (n = 91)
Creatinine in the blood, Norm 74.0-110.0 µmol/l, (m)	108.6 [94.6;127.0]	131.0 [113.0;157.0]*
Creatinine in the blood, Norm 44.0-80.0 µmol/l, (w)	89.0 [74.84;122.0]	156.0 [122.0;168.4]*
Proteinuria, (Norm <0.033 g/l)	0.07 [0.02;0.41]	0.05 [0.002;0.1]*
GFR (Norm ≥90ml/min/1.73 m^2))	98.2 [69.9;134.35]	88.4 [63.13;101.85]*
Stage 1 CKD (GFR≥90), n (%)	21 (14)	2 (4)
Stage 2 CKD (GFR 60–89), n (%)	72 (48)	16 (32)
Stage 3 CKD (GFR 30–59), n (%)	53 (35)	24 (48)
Stage 4 CKD (GFR 15–29), n (%)	4 (3)	7 (14)*
Stage 5 CKD (GFR <15), n (%)	0	1

*Note: * – statistical significance of the differences from patients in group I (p<0.05); GFR – glomerular filtration rate, CKD – chronic kidney disease*

The previous development of chronic non-communicable diseases associated with gout (arterial hypertension, coronary artery disease, CHF, urolithiasis, CKD) is accompanied by its previous onset. In addition to pathogenetic associations, therapy with drugs that are usually considered risk factors for gout – acetylsalicylic acid, diuretics – can also play a role in their development. Also, CKD, urolithiasis and hypertension may be directly related to gouty nephropathy, preceding the onset of arthritis.

Features of the onset of gout depending on age:

A much longer time passed from the moment of manifestation of the disease to the diagnosis of gout in patients of group I: 4 [1.8; 7.2] years and 1 [0.4; 4.0] years in group II (p = 0,0003).

The first metatarsophalangeal joint was the onset in 107 (71%) in group I, which was not significantly more often than in patients of group II - and in 31 (62%). Damage to other joints of the lower extremities occurred with comparable frequency in both groups: the ankle joints in both groups I and II 12% each. Rarely, gouty inflammation began in the radiocarpal joint: in 2 in group I and in group I in group II. Significantly more often with gout were af-

fected interphalangeal joints of the hands of group II: 6% compared to 0.7% in group I (p = 0.02).

The chronic course of arthritis was initially appreciated in 4 (8%) patients of group II, while in group I, the initial chronicization of the gouty process was observed in only 2 patients (1.3%) (p = 0.0017).

A shorter period of time passed until the formation of the chronic course of the disease in group II: in 42%, chronic arthritis was formed 2-5 years after the onset of gout, and in group I this period lasted from 5 to 10 years. After 6 years, chronic arthritis was established in only 2 representatives of group II, in group I 10 years passed from the onset to the formation of chronic arthritis in 26 patients (17%), in group II there was not such a long period of formation of chronic arthritis.

Osteoarthritis (OA) was present in 21 (16.2%) in group II, 2 times more frequently than in group I (6 (8.4%)), p = <0.1. Among patients with the onset of gout in the interphalangeal joints of the hands, in 3 women of group II, gouty joint lesions were simultaneously associated with arthrosis lesions of the interphalangeal joints.

In elderly patients, chronicization of the gouty process occurred earlier. The clinical manifestation of the onset of gouty arthritis does not have significant age differences, which can help in the early diagnosis of gout in elderly patients. Attention should be paid to the more frequent localization of gouty arthritis in the area of the small joints of the hands in elderly patients, who require differential diagnosis with OA.

DISCUSSIONS

The development of gout in older patients participating in the study was most often manifested in the incidence of I metatarsophalangeal arthritis (MTPh), which could have contributed to a previous diagnosis of the disease. In the elderly, the interphalangeal joints of the hands were significantly more often affected primary, and the chronicity of the gouty process occurred earlier.

Previously noted in other works, the association of gout with OA was also observed among elderly patients. Since OA is an age-dependent disease, the increase in the frequency of its occurrence in old age, especially in women, is natural [4,9,11,20]. It should be noted that the onset of gout in old age in the interphalangeal joints of the hands was present in only 3 people, women, and in all cases was localized in the joints affected by OA. Since a total of 39 women participated in the study, it was not possible to objectively assess the characteristics of the course of gout, although earlier it was noted that gouty inflammation in the area of the Bouchard and Heberden nodes is a feature of the clinical picture of gout in women [11-15]. The course of gout in patients divided by age at the time of examination did not have significant differences in the comparable time of development of the disease.

Gout is an independent risk factor for death from CHF and kidney disease, which was presented in a prospective study involving 52,322 Chinese in Singapore. After 8 years of observation, 6,660 people died during participation in the study. 2,117 (4.1%) developed gout during monitoring and had a higher risk of death (OR 1.18; 95% CI 1.06-1.32), death from coronary heart disease (OR 1.38; 95% CI, 1.10-1.73) and kidney disease (OR5.81, 95% CI, 3.61-9.37) [1-8,16].

The appearance of acute gouty inflammation in the joints affected by OA is indicated in the work of E. Roddy and the co-authors [16,17]: among the representatives of the database of patients of general practitioners (n = 4,249) who answered the questionnaire's questions, 164 cases of gout (average age of 63.4 years) were identified, while a reliable association was determined between the localization of acute gouty inflammation and the presence of arthrosis lesions of these joints (adjusted OR 7. 94; 95% CI 6.27-10.05). Individual joint research has led to a significant association between these parameters for MTPh I (corrected OR 2.06; 95% CI 1.28-3.30), ankle (corrected OR 2.85; 95% CI 1.34-6.03), knees (OR 3.07 corrected; 95% CI 1.05-8.96) and distal interphalangeal joints of the hands (corrected OR 12.67; 95% CI 1.46-109.91) [16,17].

In the group of those who received adequate treatment of gout for 3 years (53 patients), there was no significant increase in the incidence of concomitant diseases, while in the group that did not receive adequate therapy (147 patients) there was a more than double increase in the frequency of arterial hypertension (from 22% to 48%, p <0,001), a three-rate increase in DM 2 (from 6% to 18% (p <0,001)), as well as a significant increase in cardiovascular disease (from 5% to 12%, p = 0.004) and urolithiasis (from 3% to 11%, p = 0.001). And this happens despite the older age of the participants in the first group (54 ± 13 years and 44 ± 12 years, p = 0.001) and a high initial frequency of hypertension in it [5,6,9,19].

Less than half of the patients with gout received antihyperuricemic therapy (allopurinol), while the normalization of au levels against the background of allopurinol was observed only in 20% of cases. Perhaps this fact is associated with an insufficiently selected dose of the drug, which does not provide the necessary hypouricemic effect, since the average dose of allopurinol practically corresponds to the subtherapeutic dose in both young and elderly patients [20-22].

CONCLUSIONS

Gout is associated with a pronounced comorbid background, increasing significantly in old age and

developing earlier with the early onset of gout: the average number of concomitant diseases is 2 times higher in the group of gout patients aged 60 years and older (4.0 [3.0; 5.0]) than in the group of patients with gout under the age of 59 years inclusive (2.0 [2.0;3.0], p <0,1), in patients with the onset of gout at the age of 59 years inclusive, the development of coronary artery disease, CHF and nephrolithiasis occurs significantly earlier than in patients with the onset of gout at the age of 60 years and older (48.4 ± 6.9 years and 59.1 ± 5.0 years; 53.6 ± 3.4 years and 65.6 ± 9.0 years; 37.3 ± 8.9 years and, respectively, 54.9 ± 14.6 years, p <0.05 in all cases).

With age, the frequency of acquired risk factors for gout increases: taking low doses of acetylsalicylic acid increases from 6 to 40%, diuretics from 18 to 44%, alcohol consumption from 14 to 28%, arterial hypertension from 44 to 78%, consumption of foods saturated with purine from 51 to 68%, overweight and obesity from 58 to 76% in groups of patients with gout onset at the age of age 59 years old inclusive and 60 years old and older.

The young age of the onset of arterial hypertension is associated with the early development of gout: the average age of onset arterial hypertension in patients with the development of gout under the age of 59 years inclusive is significantly lower than the population (37.4 ± 9.6 years) and shows that young patients suffering from arterial hypertension belong to the risk group for gout.

In the elderly, the chronicization of gouty arthritis occurs in a shorter time: in 42% of elderly patients, chronic arthritis formed in 2-5 years from the onset of gout, while in middle-aged patients this period lasted 5-10 years.

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