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AGE AND GENDER ASPECTS OF COMORBIDITY AND CONCOMITANT PATHOLOGY FORMATION IN PATIENTS WITH GOUT

(PROSPECTIVE EXAMINATION)

The article presents the results of a prospective examination of gout course in 124 patients during the period from 2 to 3 years. At early stages in men before 50, gout is found to develop prevailingly in the form of episodes of acute gout arthritis against moderate degrees of arterial hypertension, obesity and acquired earlier pathology of the digestive system: gastritis, gastroduodenitis, ulcerous disease, cholecystitis,. At the age over 50 the signs of gout are changed into chronic gout arthritis with accurate symptoms of nephropathy, nephrolithiasis, tophus lesions of joints, the degree of comorbidity increases complemented with progressing forms of ischemic heart disease, type II diabetes, steatohepatosis, pancreatitis, and after the age of 60 — primary osteoarthrosis. With progressing comorbid diseases morbidity of patients with gout acquires new directions: visiting cardiologists, endocrinologists, urologists, angiosurgeon, and family doctor. It is the treatment prescribed by these professionals frequently causing medical provocation of gout exacerbations. In women gout develops mostly after the age of 55–60 against high multimorbid and comorbid grounds, and it is often found during treatment of cardiac, endocrine or other pathology. The authors suggest to single out the comorbid diseases having similar with gout pathogenetic links and causing high cardio-vascular risk, and those limiting realization of anti-gout therapy and provoking increased gastrointestinal risk, and those diseases which do not influence upon the course and treatment of gout.

INTRODUCTION

Gout as one of the topical problems becomes more and more general medical value. In recent decades the disease has become twice as spread in the world (Doherty M., 2009; Roddy E., Doherty M., 2010). In the USA gout is found in 3.9% of the examined people including 5.9% of men and 2.0% of women (Zhu Y. et al., 2010). In Ukraine gout cases constitute 5–28 per 1000 of men and 1–6 — in women, and the spread of hyperuricosuria is 15–20% (Коваленко В.М., Шуба Н.М. (ред.), 2013). Although, now the questions of treatment of gout at different stages of its course need to be improved (Richette P., Bardin I., 2010; Свінціцький А.С., 2013; Шуба Н.М., 2013), a new problem emerges in this respect connected with age increase of a multimorbid ground in this group of patients.

In this scope, examinations of peculiarities of the course and treatment of any disease under conditions of multimorbidity constitute a new scientific direction (Campbell-Scherer D., 2010; Marengoni A. et al., 2011; Meraer S.W. et al., 2011). However, among the spectrum of diseases constituting polymorbid ground the most important are those with similar pathogenetic links with the main disease or other dependence between them, so called comorbid diseases (Daves M., 2010; Белялов Ф.И., 2012; Коломоєць М.Ю., Вашеняк О.О., 2012; Фадєєнко Г.Д. та співавт., 2013). Attention should be paid to the complexity of treatment of a multimorbid patient with the signs of comorbidity and the need of a new vector of such research (Safford M.M. et al., 2007). As to gout and hyperuricosuria peculiar for it, Ukrainian scientists accentuate their attention on multipathogenic importance of hyperuricosuria, especially concerning cardio-vascular risk (Бильченко А.В., 2009; Ильина А.Е. и соавт., 2009; Шуба Н.М., 2013; Яременко О.Б., Микитенко А.М., 2013). The scientists pay special attention to gout comorbidity with arterial hypertension (Inokuchi T., 2010; Беловол А.Н., Князькова И.И., 2013). There were attempts to analyze comorbidity and multimorbidity in case of gout from retrospective view (Волошин О.І. et al., 2012). All the authors mention that the increase of cardio-vascular risk in patients with gout due to comorbid diseases is the main cause of mortality in 60% of patients with gout, and they require working out preventive methods. It should be noted that this direction concerning gout is not well studied.

The study of peculiarities of gout development under conditions of formation and growth of multimorbidity and comorbidity may improve the treatment of gout itself, and comorbid processes, prevent possible complications and side-effects of conducted therapy.

Objective: to study age and gender aspects of comorbidity and concomitant pathology in patients with gout.

MATERIALS AND METHODS

The research has been conducted on 124 patients with gout being treated in rheumatologic departments of Chernivtsi Regional Clinical Hospital and Municipal Clinical Hospital No 3 since 2010, including 79 of them according to the data of repeated admissions from 2 to 4 times, as well as by the results of dynamic outpatient and polyclinic examinations, learning primary medical documents, including consultations with other specialists. The diagnosis of gout was made on the basis of EULAR Recommendations on gout diagnostics (2006). The diagnoses of cardiologic group of diseases were made according to the Order of the Ministry of Public Health of Ukraine No 621/60 dated 24.07.2013 «On Giving Medical Aid to Patients with Cardio-Vascular Diseases». Other diseases were verified at hospitals or during consultations by endocrinologists, urologists, gastroenterologists etc., as a rule, according to certain protocols and modern methods of diagnostics. The period of research was from 2 to 3 years. Among the examined people men constituted 97 (78.22%), women — 27 (21.78%). The age of men with gout was between 41 and 78 years (57.6±3.54), and women — 52–77 (65.3±1.32); the time of the disease in men was 9–23 years (18.2±1.16), and in women — 2–11 (7.1±0.82). Inherited susceptibility to gout was found in 36 people (29.03%).

RESULTS AND DISCUSSION

Anamnestic examination of age and time peculiarities of gout formation in men found that initial period of gout in men was characterized by 3–7-day episodes of a moderate acute gout arthritis in case of nutritive violations with alcohol excess. The first 1–3 episodes were arrested out-patiently by means of various non-steroid anti-inflammatory means, often by the «advice» of non-professionals. Almost all the patients were first hospitalized during 3–4th episode of acute gout arthritis into a specialized department where the diagnosis of gout was made for the first time. The frequency of episodes of acute gout arthritis was 1–2 a year and once during 2–3 years depending on keeping to the diet, medical treatment and avoiding other risk factors. Between attacks patients with gout, as a rule, seldom used any medicines and kept to the diet only in case of need. Exactly these main constituents defined the rates of gout progressing, transition into chronic gout arthritis, tophus formation of various locations, gout lesions of the inner organs. The first favourable period in patients lasted from 5 to 12 years.

Multimorbid and comorbid ground was moderate, the degree of severity — mild (table). Among comorbid diseases were: excessive body weight or obesity of I–II degree, arterial hypertension of the 1st degree, urine acid diathesis and digestive diseases acquired before gout (gastritis, gastroduodenitis, ulcerous disease, and chronic cholecystitis). Such manifestations of the disease were characteristic for the age of 50, rarely for 55. Concerning gastroenterologic pathology, patients were not very much disciplined in their diets and treatment. The patients were mostly observed by rheumatologist, less and out-patiently — by gastroenterologist or cardiologist. From 3 to 6 such diseases were found in an average in every patient.

Table

Age aspects of frequency of comorbid and concomitant pathologic processes in patients with gout (n, %)

Name of disease	Age before 50 (n=32)	Age after 50 (n=65(
Arterial hypertension I degree	10 (31,25)	2 (3,07)
Arterial hypertension II degree	1 (3,12)	49 (75,38)
Ischemic heart disease (IHD):		
moderate signs	8 (25,0)	42 (64,61)
pronounced signs	–	5 (7,69)
Excessive body weight	4 (12,5)	2 (3,07)
Obesity I–II degree	16 (50)	32 (49,23)
Obesity II–III degree	10 (31,25)	31 (47,69)
Diabetis mellitus	1 (3,12)	16 (24,61)
Steatohepatosis (hepatitis)	22 (68,65)	59 (90,76)
Chronic cholecystitis	12 (37,5)	33 (50,76)
Calculous among them	–	14 (21,54)
Chronic pancreatitis	6 (18,75)	22 (33,83)
Urine acid diathesis	27 (84,37)	40 (61,54)
Urolithiasis	1 (3,12)	25 (38,46)
Chronic pyelonephritis	1 (3,12)	21 (32,31)
Chronic gastritis, gastroduodenitis	17 (53,12)	41 (63,07)
Ulcerous disease	2 (6,24)	8 (12,31)
Irritated intestine syndrome	1 (3,12)	18 (27,69)
Primary osteoarthrosis	–	21 (32,31)
Chronic bronchitis	3 (9,37)	8 (12,31)
Chronic obstructive pulmonary disease (COPD)	1 (3,12)	5 (7,69)
Prostatitis, prostate adenoma	4 (12,5)	33 (50,76)
Skin diseases (fungal, dermatitis, chronic eczema)	3 (9,37)	9 (13,85)

On the stage of chronic gout arthritis there were found lesions of the joints of the feet, knees, elbows, wrists, and 2–3 years later — stratification of multiple tophus of various localizations, logical signs of gout nephropathy, and urolithiasis (table). The frequency of gout attacks increased to 4–5 long episodes a year, between the attacks remission was unstable, movements were limited in the afflicted joints, functional insufficiency was progressing, frequency of temporary inability to work increased, X-ray changes in the joints were progressing, the signs of secondary osteoarthrosis joined. Such peculiarities of gout lesions were found in men after 50–55 to 60–65 years.

Comorbid ground increased parallel to the mentioned above: the frequency and degree of obesity, moderately progressing various forms of IHD, hypertension, insulin resistance or type II diabetes, fatty liver degeneration as the main signs of metabolic syndrome increased, and after the age of 60–65 — other atherosclerotic lesions, age primary osteoarthrosis of the joints not afflicted by gout (table). It is these diseases that intensify the level of cardio-vascular risk to high and very high. As a result — myocardial infarction

occurred in 2 patients, and one patient suffered from ischemic stroke.

Lesions of the digestive system were progressing slowly and manifested less, but increased frequency and progress of chronic pancreatitis, hepatitis, calculous forms of cholecystitis, irritated intestine syndrome, dysbiosis etc., connected with them clinically and pathogenetically should be noted here. Relapses of these pathologic conditions were often provoked by the use of gastro- or entero-, hepatoprotectors, and they were limiting factors in proper realization of anti-gout therapy (reverse cause-effect comorbidity). Increase of gastrointestinal risk from anti-gout means should be considered in this respect.

A number of comorbid diseases constituting a multimorbid ground should be noted, but they did not have visible pathogenetic or other links with gout, and did not affect upon the course and treatment of the disease: chronic bronchitis, COPD, prostatitis, ENT diseases, fungal skin diseases (table). From 5 to 8 diseases were found in every patient.

However, exactly on this stage and age period of patients with gout due to increased spectrum of comorbid processes rheumatologic aspect becomes accompanied by new directions: cardiologic, endocrinologic, vascular, urologic, gastroenterologic, and the frequency of hospitalization because of these problems prevailed over rheumatologic. Intensity and period of pharmaceutical treatment even out-patiently deteriorate anti-gout therapy provoking gout progressing. On this stage of treatment of comorbid diseases, especially those causing high cardio-vascular risk, medicine-induced relapses of gout were found after the use of pentoxyphyllin, riboxin, ATP, diuretics, and low doses of aspirin. It should be noted that these medicines are included into the standards of treatment of appropriate comorbid pathology. Activation of gout was also registered in 2 out of 7 patients who were treated with heptral for chronic hepatitis administered by gastroenterologist during a long time. In these cases inherited susceptibility to gout was found. There was no answer found why some patients underwent the treatment with heptral well. But most often the use of anti-gout medicines was prescribed by the doctors of primary medical service.

Thus, multivector morbidity on this stage contains the danger of medicine-induced relapses of gout because of the ignorance of other doctors in existence of this danger in the treatment of patients with gout with high comorbid ground.

Certain peculiarities of gout development and multicomorbid and comorbid ground in men afflicted with gout are found after the age of 65. Besides further progressing of multi- and comorbidity, social-economic status changes, a free time appears for the retired persons for self-education, proper implementation of doctor's recommendations, especially concerning diet and treatment, control over health, reduction of psychophysical loading, economical causes. Cardiovascular or endocrine pathology become determinative ways of treatment; gout and primary osteoarthrosis become a common problem in treatment, gastroenterologic pathology gets ischemic component, and cardio-vascular means are one of the constituents of their treatment in addition to supplemental and symptomatic therapy.

In women (27 patients) gout was found as a rule at the age after 55–60 on the stage of chronic gout arthritis, against the ground of considerable multimorbidity and comorbidity both from the side of cardiovascular system (23 persons — 85.18%) mostly in the context of metabolic syndrome, and digestive system (20 persons — 74.1%), dominating lesions of hepatobilliary system and pancreas, often in combination with primary osteoarthrosis (17 patients — 62.96%). Often patients were treated in the therapeutic hospitals of the secondary link of medical aid for primary osteoarthrosis or cardiac pathology. Among medicines used for the previous 5 years before making the diagnosis of gout patients often used diuretics in the content of hypotensive means. Late diagnostics of gout can be suggested here, as from the moment of making the diagnosis 2–5 years later tophus, early affliction of the kidneys by the type of urolithiasis complicated by secondary pyelonephritis were found. Metabolic syndrome revealed by higher degrees of obesity, IHD with dominating cardiosclerosis with various conductive disorders, myocardial stimulation and heart failure of II–III functional classes, type II diabetes (7 persons — 25.4%), steatohepatosis, calculous cholecystitis (25.9%). Gout nephropathy was often accompanied by moderate anemic syndrome (8 persons — 29.63%). Multimorbid ground in women, especially afflictions of the cardio-vascular system, formed during 7–10 years before gout was found, and it was the main cause of coming to cardiologists, gastroenterologists, later — endocrinologists including hospital treatment. In primary medical documents during comprehensive examination in 19 out of 27 patients the concentration of uric acid was determined, and in all the cases its level was not higher than 320–360 mkmol/L.

Concerning the characteristic of hyperuricosuria it was found in the period of exacerbation in 86 (88.66%) men and 25 (92.6%) women, and the level of hyperuricosuria in women was 20–35 mkmol/L lower than in men, although clinical signs of gout in women were more systematic. Hypercholesterolemia was characteristic for 83 (85.6%) men and 23 (85.18%) women, hypertriglyceridemia — in 88 (90.72%) and 25 (92.6%) respectively.

In addition to the above mentioned multimorbid ground in women the following comorbid diseases were found: adnexitis, other gynecological diseases, skin lesions, having no influence upon the development, course and treatment of gout.

Thus, arterial hypertension, IHD, obesity, insulin resistance, type II diabetes, steatohepatosis in the sense of metabolic syndrome to the development of hyperuricosuria and gout lesions of joints and organs are not comorbid diseases with gout in general sense, but those when certain medicines can promote formation and progress of gout. It proves the well-known fact concerning the role of estrogens in women as to the

influence on the metabolism of purines in the reproductive and post-menopausal periods. That's why in the respect of early diagnostics of gout in menopausal women the appearance of hyperuricosuria should be examined in laboratory. From the moment of detection of hyperuricosuria against metabolic syndrome in women attention should be paid to an intensive influence of this combination upon the increase of cardio-vascular risk. These features of gout, comorbidity and multimorbidity, cause considerable difficulties in the planning of strategy of treatment of the main and comorbid diseases, realization of standards of treatment according to appropriate Protocols on the main disease. The possibility of certain contradictions in these situations and the necessity of further scientific search in this direction are indicated by Ukrainian and foreign scientists (van Weel C., Schellevis F.G., 2006; Dawes M., 2010; Caughey G.E., Roughead E.E., 2011; Белялов Ф.И., 2012; Фадєєнко Г.Д. та співавт., 2013; Шуба Н.М., 2013).

Thereby, according to the data of our research the following can be stated: with age, duration, and severity of gout multimorbidity increases. Among multimorbid conditions there should be differentiated comorbid pathologic processes and diseases having common with gout etiopathogenetic links of development as metabolic syndrome; those which are not connected by direct pathogenetic links but by their cause-effect interrelations limit the realization of anti-gout therapy and require additional therapeutic-preventive means — these are early acquired or medicine-induced lesions of the digestive system; age joining of primary osteoarthrosis as additional late with gout condition; and casual, independent and not limiting the treatment of gout diseases like bronchitis, prostatitis, adnexitis, skin diseases etc.

Treatment of gout in patients with multimorbid, especially comorbid ground, is not simply complicated: the action of some gout provoking medicines used for the treatment of comorbid pathology should be taken into consideration. Such an approach will promote the formation of a new pathogenetic thinking of a doctor, estimation of interrelations between diseases, improve the treatment of gout and comorbid processes, prevent possible complications and side effects caused by pharmaceutical agents.

CONCLUSIONS

The longer is duration and age of the patient and the more severe is gout, the more severe is multimorbidity of the patient; comorbid conditions should be differentiated in prognostic and therapeutic-preventive aspects which considerably increase cardio-vascular risk (they have common with gout etiopathogenetic roots — metabolic syndrome), reverse cause-effect relations (diseases of the digestive system) increasing gastrointestinal risks, and they limit realization of anti-gout therapy, and casual comorbid diseases which existence does not affect upon the development of gout and its treatment.

Gout in women is formed mostly during post-menopausal period and develops against a considerable multimorbid and comorbid ground with high cardio-vascular and gastrointestinal risks.

Due to high frequency and progression of metabolic syndrome in patients with gout this group should be detected as a high risk group concerning the development of vascular diseases, and thus correct therapeutic process and improve the way of life.

PROSPECTS OF FURTHER RESEARCH

The problem arises concerning the search and choice of medicines with multi-target, multi-organic, systemic action influencing upon the available comorbid diseases in patients with gout, their testing and studying their efficacy.

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ВІКОВІ ТА ГЕНДЕРНІ АСПЕКТИ ФОРМУВАННЯ КОМОРБІДНОСТІ ТА СУПУТНЬОЇ ПАТОЛОГІЇ У ХВОРИХ НА ПОДАГРУ (ПРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ)

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Резюме. *У статті наведено результати проспективного дослідження перебігу подагри у 124 хворих впродовж 2–3 років. На ранніх стадіях подагри у чоловіків віком до 50 років перебіг останньої відбувається переважно у формі епізодів гострого подагричного артриту на тлі помірних артеріальної гіпертензії, ожиріння та набутої раніше патології системи травлення: гастриту, гастродуоденіту, виразки шлунково-кишкового тракту, холециститу. У осіб віком старше 50 років прояви подагри набувають ознак хронічного подагричного артриту з чіткими ознаками нефропатії, нефролітіазу, тофусних уражень суглобів, наростає ступінь коморбідності з доповненням прогресуючими формами ішемічної хвороби серця, цукрового діабету II типу, стеатогепатозу, панкреатиту, а після 60 років — первинного остеоартрозу. З прогресуванням коморбідних захворювань морбідний маршрут хворих на подагру набуває нових напрямків: до кардіолога, ендокринолога, уролога, судинного хірурга, сімейного лікаря. Лікування у цих спеціалістів нерідко зумовлює медикаментозну провокацію загострень подагри. У жінок подагра проявляється переважно після 55–60 років на тлі високого поліморбідного і коморбідного стану та нерідко виявляється при лікуванні з приводу кардіальної, ендокринної чи іншої патології. Автори пропонують виділяти коморбідні захворювання, що мають спільні з подагрою патогенетичні ланки та спричиняють високий кардіоваскулярний ризик, ті, які обмежують реалізацію протиподагричної терапії та зумовлюють підвищений гастроінтестинальний ризик, та супутні захворювання, що не впливають на перебіг і лікування подагри.*

Ключові слова: подагра, коморбідність, поліморбідність, діагностика.

ВОЗРАСТНЫЕ И ГЕНДЕРНЫЕ АСПЕКТЫ ФОРМИРОВАНИЯ КОМОРБИДНОСТИ И СОПУТСТВУЮЩЕЙ ПАТОЛОГИИ У БОЛЬНЫХ ПОДАГРОЙ (ПРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ)

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Резюме. *В статье приведены результаты проспективного исследования течения подагры у 124 больных в течение 2–3 лет. На ранних стадиях формирования подагры у мужчин в возрасте до 50 лет течение последней происходит преимущественно в форме эпизодов острого подагрического артрита на фоне умеренных артериальной гипертензии, ожирения и приобретенной ранее патологии системы пищеварения: гастрита, гастродуоденита, язвы желудочно-кишечного тракта, холецистита. У лиц в возрасте старше 50 лет проявления подагры приобретают признаков хронического подагрического артрита, нефропатии, нефролитиаза, тофусных поражений суставов, нарастает степень коморбидности с дополнением прогрессирующих форм ишемической болезни сердца, сахарного диабета II типа, стеатогепатоза, панкреатита, а после 60 лет — первичного остеоартроза. С прогрессированием коморбидных заболеваний морбидный маршрут больных подагрой приобретает новые направления: к кардиологу, эндокринологу, урологу, сосудистому хирургу, семейному врачу. Лечение у этих специалистов нередко обусловливает медикаментозную провокацию обострений подагры. У женщин подагра проявляется преимущественно после 55–60 лет на фоне высокого полиморбидного и коморбидного состояний и нередко выявляется при лечении по поводу кардиологической, эндокринной или иной патологии. Авторы предлагают выделять коморбидные заболевания, имеющие общие с подагрой патогенетические звенья и повышающие уровень кардиоваскулярного риска, которые ограничивают реализацию противоподагрической терапии и обусловливают повышенный гастроинтестинальный риск, и сопутствующие заболевания, не влияющие на течение и лечение подагры.*

Ключевые слова: подагра, коморбидность, полиморбидность, диагностика.

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