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Relationship between hyperferritinemia and clinical manifestations of gout

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim. To study the parameters of ferritin, uric acid in the serum and urine, high-sensitivity C-reactive protein (hsCRP) in patients with hypertension in combination with gout and the relationship between these data and clinical manifestations of gout.

Materials and methods. 61 patients with hypertension, middle age of whom amounted to 54.25 (10.29) years, had been surveyed, 39 (64 %) men and 22 (36 %) women. All patients were divided into two groups: the main group – 36 patients with hypertension in combination with gout and the comparison group – 25 patients with hypertension without gout. Determination of ferritin level in serum was carried out by using an immunochemical method with electrochemiluminescence detection (Cobas 6000 analyzer, Roche Diagnostics test system, Switzerland). Colorimetric analysis was used to determine the concentration of serum uric acid, the spectrophotometric method – of uric acid in urine, the immunoassay method – of hsCRP.

Results. The average serum uric acid level significantly differed (P = 5.4 E-5) in the main group and the comparison group and was 443.44 (129.66) μmol/L and 317.16 (77.60) μmol/L, respectively. The level of ferritin in the main group was significantly higher (237 (237; 247), P = 4.3 E-5 ng/mL) than in the comparison group (137 (83,23; 137) ng/mL), as well as the level of hsCRP (P = 4.4 E-6) 11.78 (3.70; 12.66) mg/L and 1.07 (0; 3.82) mg/L, respectively. The level of uric acid in urine was not significantly different (P = 0.23) in both groups and amounted to 2470.92 (836.89) μmol/L in the main group and 2198.00 (881.73) μmol/L in the comparison group. A significant correlation (r = 0.30; P < 0.05) was found between the levels of serum uric acid and ferritin in the main group patients, as well as a significant correlation between the levels of serum uric acid and the duration of gout (r = 0.41; P < 0.05), the total number of affected joints (r = 0.51; P < 0.05), gout severity (r = 0.36; P < 0.05), the level of ferritin and the number of gout exacerbation (r = 0.31; P < 0.05).

Conclusions. Elevated serum ferritin concentration increases the risk of gouty arthritis exacerbation. Establishing the relationship between the concentration of ferritin and serum levels of uric acid and the number of gout exacerbations in the main group suggests that iron plays an important role in the disease pathogenesis.

Key words: iron metabolism, inflammation, comorbidity, gout.

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Взаємозв'язок між гіперферитинемією та клінічними проявами подагри

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Мета роботи – вивчення показників феритину, сечової кислоти крові та сечі, високочутливого С-реактивного протеїну (hsСРП) у пацієнтів з артеріальною гіпертензією (АГ) у поєднанні з подагрою та встановлення взаємозв'язків між цими показниками та клінічними проявами подагри.

Матеріали та методи. Обстежили 61 пацієнта з АГ, середній вік (SD) становив 54,25 (10,29) року, серед них – 39 (64 %) чоловіків і 22 (36 %) жінки. Усіх пацієнтів поділили на дві групи: основна – 36 хворих на АГ у поєднанні з подагрою; група порівняння – 25 пацієнтів, які хворі на АГ без супутньої подагри. Визначення рівня феритину крові здійснювали імунохімічним методом з електрохемілюмінесцентною детекцією (аналізатор Cobas 6000, тест-системи Roche Diagnostics, Швейцарія). Колориметричним методом визначали концентрацію сечової кислоти у крові, спектрофотометричним – сечової кислоти в сечі, імуноферментним методом – hsСРП.

Результати. Середній показник рівня сечової кислоти крові вірогідно відрізнявся (p = 5,4 E-5) в основній групі та групі порівняння та становив 443,44 (129,66) мкмоль/л і 317,16 (77,60) мкмоль/л відповідно. Значення феритину в основній групі вірогідно більше (237 (237; 247), p = 4,3 E-5 нг/мл), ніж у групі порівняння (137 (83,23; 137) нг/мл), як і значення hsСРП (p = 4,4 E-6) – 11,78 (3,70; 12,66) мг/л та 1,07 (0; 3,82) мг/л відповідно. Значення сечової кислоти в сечі вірогідно не відрізнялося (p = 0,23) в обох групах і становило в основній групі 2470,92 (836,89) мкмоль/л, у групі порівняння – 2198,00 (881,73) мкмоль/л. Між рівнем сечової кислоти крові та феритину в пацієнтів основної групи встановили вірогідний кореляційний зв'язок (r = 0,30; p < 0,05). Крім того, вірогідний кореляційний зв'язок виявили між рівнем сечової кислоти у крові та тривалістю подагри (r = 0,41; p < 0,05), загальною кількістю уражених суглобів (r = 0,51; p < 0,05), ступенем тяжкості подагри (r = 0,36; p < 0,05), а також між рівнем феритину та кількістю спалахів подагри (r = 0,31; p < 0,05).

Висновки. Надмірна концентрація феритину в сироватці крові підвищує ризик розвитку загострення подагричного артриту. Встановлення зв'язків між концентрацією феритину й сироватковим рівнем сечової кислоти у крові та кількістю загострень подагри свідчить, що залізо відіграє важливу роль у патогенезі захворювання.

Ключові слова: обмін заліза, запалення, коморбідна патологія, подагра.

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Взаимосвязь между гиперферритинемией и клиническими проявлениями подагры

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Цель работы – изучение показателей ферритина, мочевой кислоты крови и мочи, высокочувствительного С-реактивного протеина (hsСРП) у пациентов с артериальной гипертензией (АГ) в сочетании с подагрой и установление взаимосвязей между данными показателями и клиническими проявлениями подагры.

Ключевые слова: обмен железа, воспаление, коморбидная патология, подагра.

Запорожский медицинский журнал. 2020. Т. 22, № 1(118). С. 31–34

Материалы и методы. Обследовали 61 пациента с АГ, средний возраст (SD) которых составил 54,25 (10,29) года, среди которых 39 (64 %) мужчин и 22 (36 %) женщины. Всех пациентов поделили на две группы: основная – 36 больных с АГ в сочетании с подагрой; сравнения – 25 пациентов с АГ без сопутствующей подагры. Определение уровня ферритина крови осуществлялось иммунохимическим методом с электрохемилюминесцентной детекцией (анализатор Cobas 6000, тест-системы Roche Diagnostics, Швейцария). Колориметрическим методом определяли концентрацию мочевой кислоты крови, спектрофотометрическим – мочевой кислоты крови, иммуноферментным методом – hsСРП.

Результаты. Средний показатель уровня мочевой кислоты крови достоверно отличался (p = 5,4 E-5) в основной группе и группе сравнения и составил 443,44 (129,66) мкмоль/л и 317,16 (77,60) мкмоль/л соответственно. Значение ферритина в основной группе достоверно выше (237 (237; 247), p = 4,3 E-5) нг/мл), чем в группе сравнения (137 (83,23; 137) нг/мл), как и значение hsСРП (p = 4,4 E-6) – 11,78 (3,70; 12,66) мг/л и 1,07 (0; 3,82) мг/л соответственно. Значение мочевой кислоты в моче достоверно не отличалось (p = 0,23) в обеих группах и составило в основной группе 2470,92 (836,89) мкмоль/л, в группе сравнения – 2198,00 (881,73) мкмоль/л. Между уровнем мочевой кислоты крови и ферритина у пациентов основной группы установлена достоверная корреляционная связь (r = 0,30; p < 0,05). Кроме того, достоверная корреляционная связь отмечена между уровнем мочевой кислоты в крови и продолжительностью подагры (r = 0,41; p < 0,05), общим количеством пораженных суставов (r = 0,51; p < 0,05), степенью тяжести подагры (r = 0,36; p < 0,05), а также между уровнем ферритина и количеством обострений подагры (r = 0,31; p < 0,05).

Выводы. Чрезмерная концентрация ферритина в сыворотке крови повышает риск развития обострения подагрического артрита. Установление связи между концентрацией ферритина и сывороточным уровнем мочевой кислоты в крови, а также количеством обострений подагры свидетельствует, что железо играет важную роль в патогенезе заболевания.

Gouty arthritis is the most common type of inflammatory arthritis among the working-age population. In patients with gout, the following comorbidities are often recorded: hypertension, diabetes mellitus, and heart failure. The presence of hypertension in patients with gout increases the risk of complications, exacerbations, hospitalization and its duration [1]. The World Health Organization predicts a significant increase in the prevalence of hypertension to 60 % of cases by 2025 [2].

In the publications of recent years, it is assumed that iron could be a trigger of gouty arthritis exacerbation as a result of oxidative stress that is accompanied by an increased risk of cardiovascular disease [3].

The latest public health research in the United States revealed positive links between the level of ferritin as the main indicator of iron exchange and the level of uric acid [4]. In addition, T. Fatima et al. [5] report about a positive correlation between the number of gout flares and the ferritin level [3].

The issue of the relationship between ferritin and uric acid levels in patients with comorbid pathology remains relevant, as well as establishing the nature of this relationship.

Aim

To study the parameters of ferritin, uric acid in serum and urine, hsCRP in patients with hypertension in combination with gout and the relationship between these data and clinical manifestations of gout.

Materials and methods

The study was conducted at the clinical basis of the Department of Therapy, Cardiology and Family Medicine of Postgraduate Education Faculty of the State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine" – Municipal Institution "Kryvyi Rih City Clinical Hospital No 2 of Dnipropetrovsk Regional Council" from 2016 to 2018. In total, 61 patients with hypertension, middle age of whom amounted to 54.25 (10.29) years, had been surveyed, 39 (64 %) men and 22 (36 %) women.

All patients were divided into two groups: the main group – 36 patients with hypertension in combination with gout (the average age was 54.69 (10.22) years) and the comparison group – 25 patients with hypertension without concomitant gout (the average age was 53.6 (10.57) years).

The diagnosis of hypertension was established in accordance with the order of the Ministry of Health of Ukraine No 384 dated May 24, 2012, according to the recommendations of the Ukrainian Association of Cardiology and the Clinical Recommendations of the European Society of Hypertension and the European Society of Cardiology (2016). The diagnosis of gout was established according to the criteria of the American College of Rheumatology and the European League Against Rheumatism (2015). Clinical and anamnestic data were obtained from patient surveys, analysis of pre-medical documentation, general clinical, laboratory, and instrumental methods of examination.

The main inclusion criteria: patients with hypertension without gout who gave informed consent to participate in the study; patients with hypertension in combination with gout who gave informed consent to participate in the study; patients aged 30 to 80 years.

Exclusion criteria: patients who did not consent to participate in the study; patients abusing alcohol or narcotic drugs; oncological, psychiatric and rheumatologic diseases, other crystalline arthropathies; II B–III stage cardiac insufficiency, IV functional class; IV–V stage chronic kidney disease; viral hepatitis, tuberculosis; HIV-infected patients.

Determination of serum ferritin level was carried out by using an immunochemical method with electrochemiluminescence detection with the help of the Cobas 6000 analyzer and the Roche Diagnostics test system (Switzerland). Colorimetric analysis was used to determine the serum uric acid concentration, the spectrophotometric method was used to determine the concentration of uric acid in urine. The level of hsCRP was measured by the immunoassay method.

For statistical analysis of study materials we used: a Shapiro-Wilk test for verification of quantitative indicators normal distribution; a Student's t-test to assess the significance of difference in the mean for quantitative attributes with the normal distribution; a Mann-Whitney (U) test for abnormally distributed unrelated samples; a Pearson Chi-Square (χ^2) test to assess the significance of difference in relative indices including a Yates correction for values

of the index close to 0 or 100. A correlation analysis was carried out with a Spearman's Rank Correlation Coefficient (ρ) calculation.

Descriptive statistics were expressed as a mean (M) and a standard deviation (SD) for normally distributed values and as a median (Me) and an interquartile range (Q25; Q75) for non-normally distributed parameters.

P-values of <0.05 were determined to represent statistical significance. The statistical analysis was carried out using the Microsoft Excel 2010, data analysis program AtteStat 12.0.5 and Statistica 6.1 (StatSoft Inc.).

Results

The duration of hypertension in the main group was 4.5 (1; 10) years, in the comparison group – 4 (2; 8) years, no significant difference was found (P = 0.86). The number of exacerbations of hypertension per year in the main group – 4 (2; 6.25), in the comparison group – 3 (2; 5), no significant difference was found (P = 0.50).

In the main group, the duration of gout was 4.92 (3.23) years, the number of exacerbations of gouty arthritis was 7.08 (4.54) per year, the total number of affected joints – 5 (2; 10). Acute gouty arthritis was detected in 7 (19 %) patients with hypertension in combination with gout, chronic gouty arthritis – in 23 (64 %) patients, chronic tophaceous gout – in 6 (17 %) patients, while there were 10 (28 %) patients in a phase of exacerbation, a remission phase was in 26 (72 %) patients. A mild degree of gout was registered in 20 (56 %) patients, an average degree – in 14 (39 %), a severe degree – in 2 (6 %) patients. According to the radiological stage of the disease, the patients were divided as follows: there were no changes in 2 (5 %) patients, I stage – in 19 (53 %) patients, II stage – in 14 (39 %) patients, III stage – in 1 (3 %) patient. The general clinical characteristics of the groups are presented in *Table 1*.

In patients with hypertension in combination with gout compared with patients without concomitant gout, there were significant differences in the level of all studied parameters, except for uric acid in the urine (*Table 2*). The average serum uric acid level significantly differed (P = 5.4 E-5) in the main group and the comparison group and was 443.44 (129.66) μmol/L and 317.16 (77.60) μmol/L, respectively. The ferritin level was significantly higher (237 (237; 247), P = 4.3 E-5) ng/mL in the main group than in the comparison group (137 (83,23; 137)) ng/mL, as well as the concentration of hsCRP (P = 4.4 E-6) 11.78 (3.70; 12.66) mg/L and 1.07 (0; 3.82) mg/L, respectively, indicating the severity of inflammatory changes in patients with concomitant gout. The level of uric acid in the urine was not significantly different (P = 0.23) in both groups and amounted to 2470.92 (836.89) μmol/L in the main group and 2198.00 (881.73) μmol/L in the comparison group, that may indicate a kidney damage in patients of both groups.

A positive, moderate, significant correlation was found (r = 0.30; P < 0.05) between the level of serum uric acid and ferritin in patients of the main group. Moreover, a significant correlation was found between the level of serum uric acid and the following clinical manifestations of gout, the disease duration (r = 0.41; P < 0.05), the total number of affected joints (r = 0.51; P < 0.05), gout severity (r = 0.36, P < 0.05), but there was no significant relationship between the level of ferritin and the above manifestations. Only positive correlation was found between the level of ferritin and the number of gout flares (r = 0.31; P < 0.05), indicating that a high level of uric acid worsens the clinical course of gout, and hyperferritinemia increases the risk of gouty arthritis exacerbation.

Table 1. General and clinical characteristics of the studied groups, M (SD), Me (Q25; Q75)

Indicator, units of measurement	Main group (n = 36)	Comparison group (n = 25)	P-values
Age, years	54.69 (10.22)	53.6 (10.57)	0.69*
Duration of hypertension, years	4.5 (1; 10)	4 (2; 8)	0.86*
Number of exacerbations of hypertension per year	4 (2; 6.25)	3 (2; 5)	0.50*
Stage of hypertension, n (%)			0.51*
I	2 (6)	4 (16)	
II	31 (86)	19 (76)	
III	3 (8)	2 (8)	
Degree of hypertension, n (%)			
1	21 (58)	15 (60)	0.93*
2	11 (31)	7 (28)	
3	4 (11)	3 (12)	
Body mass index, kg/m^2	32.39 (5.24)	31.6 (6.09)	0.59*

*: there is no significant difference between the groups (P > 0.05).

Table 2. Levels of ferritin, serum uric acid, uric acid in the urine, hsCRP in patients of the main group and the comparison group, M (SD), Me (Q25; Q75)

Indicator, units of measurement	Main group (n = 36)	Comparison group (n = 25)	P-values
Ferritin, ng/mL	237 (237; 247)	137 (83.23; 137)	4.3E-5
Serum uric acid, μmol/L	443.44 (129.66)	317.16 (77.60)	5.4E-5
Uric acid in the urine, μmol/L	2470.92 (836.89)	2198.00 (881.73)	0.23*
hsCRP, mg/L	11.78 (3.70; 12.66)	1.07 (0; 3.82)	4.4E-6

*: there is no significant difference between the groups (P > 0.05).

Discussion

According to the literature data, the association of serum ferritin and uric acid with gout does not depend on the level of hsCRP, that is, the association is not due to an increased ferritin level in inflammation, but plays an immediate role in the metabolism of iron in gout [4].

Cross studies have shown that elevated levels of ferritin are associated not only with the development of gout, but also with other conditions, such as hypertension, central obesity, dyslipidemia, increased blood insulin and glucose levels [3]. In a work of A. G. Mainous et al. [6], the data is given on the association between elevated serum uric acid levels and high ferritin levels in the absence of symptoms such as joint pain or mobility limitations. That is, it should be noted that the level of ferritin, as the main indicator of iron accumulation in gout, may be increased at a stage of clinical manifestations absence and act as a factor of gout exacerbation. This statement is confirmed by the detection of iron in tophi and synovial membrane of joints [4].

On the one hand, this indicator shows an increase in the degree of inflammation during gout, and on the other hand, it increases in response to oxidative stress development, which is not a negative link of pathogenesis. Some authors suggest determining the serum level of uric acid as

a risk factor for concomitant iron overload in patients due to significant association with ferritin. In addition, it has been reported that increased levels of uric acid and ferritin are associated with an alteration of liver and kidney function, indicating an additional mechanism for gouty nephropathy development, which may be resulted from the accumulation of iron and an increase in ferritin level in gout.

Conclusions

1. Serum ferritin level is significantly 1.73 times increased in patients with hypertension in combination with gout compared to patients without concomitant gout.

2. Elevated concentration of serum ferritin increases the risk of gouty arthritis exacerbation.

3. Establishing the relationship between the concentration of serum ferritin and uric acid levels and the number of gout exacerbations in the main group suggests that iron plays an important role in the disease pathogenesis.

4. Establishment of the links between the level of uric acid and the clinical manifestations of gout: the disease duration ($r = 0.41$; $P < 0.05$), the total number of affected joints ($r = 0.51$; $P < 0.05$), gout severity ($r = 0.36$; $P < 0.05$). All the above manifestations suggest that hyperuricemia worsens the clinical course of gout.

The perspective for further scientific research. It is planned to determine the predictive role of ferritin and hsCRP concentration in the model of gouty arthritis exacerbation as well as the described parameters comparison in the group of patients with hypertension in combination with gout after treatment with combinations of basic therapy drugs.

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