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ROLE OF GOUT IN ATRIAL FIBRILLATION

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Abstract: Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice. Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice. There is increasing evidence for the role of inflammation in the development and maintenance of AF and gout is associated with inflammation and oxidative stress. In the last years several studies were published to assess the role of gout as a risk factor for occurrence of atrial fibrillation (AF). There are not enough data on the importance of gout in patients, who already have AF. The aim of the study is to assess the impact of gout on the clinical course of AF. Overall 101 patients – 51 females and 50 males at mean age 68,02 ± 7,001, with AF after sinus rhythm restoration were included in a clinical trial of one-year placebo-controlled treatment with spironolactone. Gout was reported in 6,8% of them. They were analyzed for AF recurrence, hospitalization for AF, all-cause admissions, composite endpoint (recurrence episodes of AF, all-cause hospitalization and death) and value of biomarker Galectin-3 (Gal-3). Results: Patients with gout had double risk of recurrence of AF, even though not significant, HR=1.97, 95%CI=0,78-4.98, p=0,15. In our study presence of gout was significant predictor for hospitalization for AF in unifactor analysis (HR 4,46, 95% CI=1.51 – 13.19, p=0,007) and the only significant in multifactor analysis – model, including gender, age categories, hypertension, diabetes and use of spironolactone (HR=4,23, 95%CI=1,28–14,1, p=0,018). Gout influenced significant also the all-cause hospitalizations, HR =3.17, 95%CI 1.10-9.14, p=0.033. There was a significant difference between the value of Gal-3 in patients with gout as opposed to patients without (28,52±15 vs 16,02±5,49, p=0,002). Conclusion: We found that gout significantly influences the course of AF. Presence of gout in patients with atrial fibrillation is a risk factor for recurrence and hospitalization – cause-specific for AF and all-cause. The value of Gal-3 as a marker of fibrosis and inflammation is higher in patients with AF and gout.
Keywords: atrial fibrillation, gout, Galectin-3

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice. It affects 2% of the general population and is associated with increased morbidity and all-cause mortality (1). Gout is the most common reason for inflammatory arthritis in adults (2). It is associated with deposition of urate crystals in joints. Both conditions are frequently seen in elderly. There is increasing evidence for the role of inflammation in the development and maintenance of AF (3) and gout is associated with inflammation and oxidative stress (4). Urate crystals activate nucleotide oligomerization domain (NOD)-like receptor protein 3 inflammasome and induce release of TNF-α, IL-1, IL-6 and IL-8 (5). The up-regulation of xanthine oxidase leads to endothelial and vascular dysfunction, mechano-energetical decuplation and reduced myocardial function. The uric acid decreases the levels of NO-synthase. This causes accumulation of oxidized products and inhibition of vasodilatation (6-8). Patients with gout are more often diagnosed with metabolic syndrome and associated comorbidities, such as hypertension, hyperlipidaemia and diabetes, which are also risk factors for AF (9). In the last years several studies were published to assess the role of gout as a risk factor for occurrence of AF (10-13). There are not enough data on the importance of gout in patients, who already have AF. The aim of the study is to assess the impact of gout on the clinical course of AF - AF recurrence, hospitalization for AF, all-cause admissions, composite endpoint (recurrence episodes of AF, all-cause hospitalization and death) and value of biomarker Galectin-3 (Gal-3).

Materials and methods: This is a substudy of a randomized single-center clinical observation of the effect of mineralcorticoid receptror antagonist (MRA) Spironolactone on top of standard treatment in patients with atrial fibrillation after sinus rhythm restoration on the recurrence of the arrhythmia and on value of biomarker Gal-3. All 101 participants - 51 females and 50 males at mean age 68,02 ± 7,001were followed up for 1 year and had 6 follow-up visits – at 14 days, 1 month, 3 months, 6 months, 9 months, and, finally, at 12 months. Inclusion criteria were as follows: age more than 55 years, restored sinus rhythm after an episode of paroxysmal/persistent AF, signed inform consent. Exclusion criteria included: history of, clinical and echocardiographic evidence of chronic heart failure NYHA class III-IV; open heart surgery during the last 3 months for any indication; survivors of acute myocardial infarction and left ventricular dysfunction within 3 months of randomization; pregnancy; drug and alcohol abuse; presence of severe progressive concomitant disease with life expectancy less than 1 year; chronic kidney disease defined as serum creatinine more than 200 mmol/l or eGFR less than 40 ml/min/1.73 m2; liver cirrhosis Child C; treatment with powerful CYP3A4 inhibitors or inductors; serum potassium levels >5 mmol/l at screening;

hypersensitivity towards MRA; metabolic acidosis; known thyroid pathology with lab results consistent with hyper- or hypothyroidism. At baseline all patients were asked for history of gout and the disease was reported in 6,8% of them. At each visit the patient was examined, ECG was done, any recurrent episodes of AF and hospitalizations were documented. Blood for galectin-3 determination was collected at baseline and one year after. Serum galectin-3 levels were determined using enzyme-linked immunosorbent assay kit for quantitative measurement Galectin-3 AssayTM, LOT G3P-014 (BG Medicine, Waltham, MA, USA) according to manufacturer's instructions and were measured on StatFax 3200 microplate reader (Awareness Technology, Inc., USA). Calculation of results was performed with MikroWin 2000 ver. 4.31 software (Mikrotek Laborsysteme GmbH, Germany) and expressed in ng/mL units. All continuous variables are presented as means ± standard deviation for relatively normally distributed and as median /interquartile range/ for these with deviation from normality. When approximately normal distribution is present, the independent variables are compared by Student's t-test or ANOVA test in repeated measures in one patient. For categorical variables, absolute values and percents are presented and the chi-square test or Kendall's τ-analysis are used to test the null hypothesis. P-value <0.05 is used for significance testing. All analyses are performed on SPSS® version 19 (SPSS, Texas, USA). The project was approved by the local Committee of Medical Ethics of the University Hospital "St. Marina" Varna and complied with the Declaration of Helsinki. Informed consent was obtained in all patients.

RESULTS

Patients with gout had double risk of recurrence of AF, even though not significant, HR=1.97, 95%CI=0,78-4.98, p=0,15. In our study presence of gout was significant predictor for hospitalization for AF in unifactor analysis (HR 4,46, 95% CI=1.51 – 13.19, p=0,007) (fig.1) and the only significant in multifactor analysis – model, including gender, age categories, hypertension, diabetes and use of spironolactone (HR=4,23, 95%CI=1,28–14,1, p=0,018).

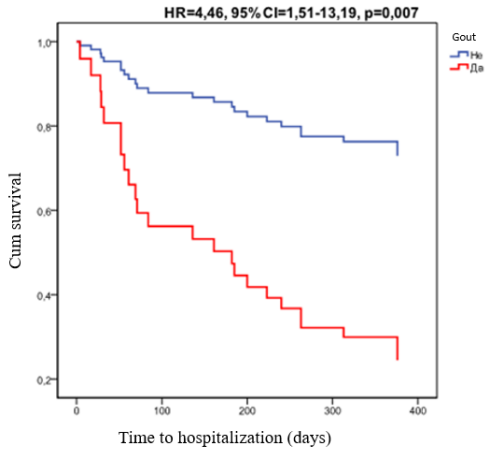

Fig. 1 Hospitalizations for AF according to presence of gout – unifactor analysis

Gout influenced significant also the all-cause hospitalizations, HR =3.17, 95%CI 1.10-9.14, p=0.033(fig.2).

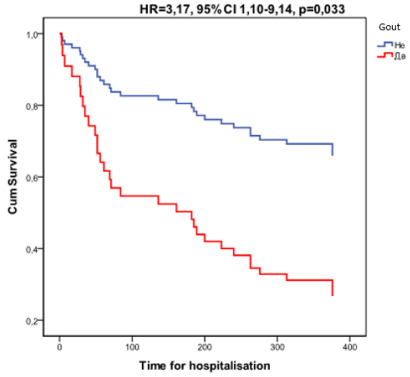

Fig. 2 All-cause hospitalizations according to presence of gout

We found no relationship between gout and composite endpoint.
There was a significant difference between the value of Gal-3 in patients with gout as opposed to patients without (28,52±15 vs 16,02±5,49, p=0,002).

DISCUSSION

One meta-analysis of seven cohort trials with 146 792 participants (13) found that hyperuricemia is a significant independent predictor of AF onset (RR 1,92 95% CI, 1,54, 2,40) and AF recurrences (RR 2,07; 95% CI, 1,61, 2,67). Our data are similar, although not significant, which confirms the hypothesis that gout is a possible etiological factor for ocurrence and perpetuation of AF. We found no data in the literature about the impact of gout as a risk factor for hospitalization in patients with AF. The levels of Gal-3 in gout are not examined till now. This association between them is not surprising, because Gal-3 is a marker of fibrosis and inflammation.
Limitation: The greatest limitation of our study is the small number of patients.

CONCLUSION

We found that gout significantly influences the course of AF. Presence of gout in patients with atrial fibrillation is a risk factor for recurrence and hospitalization – cause-specific for AF and all-cause. The value of Gal-3 as a marker of fibrosis and inflammation is higher in patients with AF and gout. Further studies are needed to confirm these results and to evaluate the role of hyperuricemia and gout in AF.

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