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CORRELATION BETWEEN FIBRINOGEN BETA-CHAIN GENE POLYMORPHISM, PLASMA FIBRINOGEN AND THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH ATRIAL FIBRILLATION

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ВЗАИМОСВЯЗЬ ПОЛИМОРФИЗМА ГЕНА БЕТА-ЦЕПИ ФИБРИНОГЕНА И УРОВНЯ ФИБРИНОГЕНА ПЛАЗМЫ С РАЗВИТИЕМ ТРОМБОЭМБОЛИЧЕСКИХ ОСЛОЖНЕНИЙ У БОЛЬНЫХ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

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In a prospective cohort study the effect of the fibrinogen β -chain gene polymorphism -455G-A and fibrinogen plasma levels on the risk of stroke and systemic thromboembolism in 102 patients (83.3 % men, mean age 52.9±8.4 yrs) with non-valvular atrial fibrillation. Identification of fibrinogen B gene 455G-A polymorphism can be useful to customize the anticoagulation strategy in patients with atrial fibrillation.

Key words: atrial fibrillation, fibrinogen, thromboembolic complications, genetic polymorphism, fibrinogen β -chain gene

В проспективном когортном исследовании изучено влияние полиморфизма -455G-A гена фибриногена В и уровня фибриногена плазмы крови на риск развития инсульта и системных тромбоемболий у 102 пациентов с неклапанной формой ФП (83,3 % мужчин, средний возраст 52,9±8,4 года) в течение 24 месяцев. Определение полиморфизма -455G-A гена фибриногена В может быть рекомендовано с целью индивидуализации тактики антикоагулянтной терапии у больных с фибрилляцией предсердий.

Ключевые слова: фибрилляция предсердий, тромбоемболические осложнения, генетический полиморфизм, ген β -цепи фибриногена

The key focus in treating patients with atrial fibrillation (AF) is prevention of thromboembolic complications (TEC) [5]. Currently, assessment of TEC risk in patients with AF is done employing the *CHA₂DS₂-VASc* clinical scale, which leaves the doctor with no precise recommendation regarding tactics for antithrombotic therapy in case the number

of points scored on the scale belongs to the 0-to-1 range [2]. The issue of identifying certain additional TEC risk factors in this group of patients yet remains unresolved. Gene polymorphism of coagulation factors has a significant impact on the hemostatic system. Proper attention paid to the genetic parameters may facilitate developing individual

forecast and respective tactics for antithrombotic therapy in patients with AF who reveal low and moderate TEC risk subject to the data obtained through the CHA_2DS_2-VASc scale.

Fibrinogen is known to be involved in platelet adhesion and aggregation, and factor XIII activation [4]. Of all the fibrinogen β -chain gene (FGB) polymorphisms described until now, the -455G-A type stands out as the most studied one. We performed a prospective cohort study in order to examine the effect that the FGB gene -455G-A polymorphism and levels of fibrinogen in blood plasma have on the risk of TEC development in patients with AF.

Material and Methods. The study included 102 patients with non-valvular type of AF (83.3 % men, mean age 52.9±8.4 yrs). The inclusion criteria embraced non-valvular AF, lack of recently suffered traumas, surgeries, inflammatory diseases; voluntary consent to join the study; ability to maintain contact after discharge from hospital.

The patients were subject to follow up for 24 months. The endpoints implied the development of acute cerebrovascular accident (CVA) and/or systemic embolic events. The plasma fibrinogen level was identified through the Clauss method on an automatic coagulometer *Sysmex CA-500*. FGB gene 455G-A polymorphism was identified with polymerase chain reaction using a set of agents (SNP-Express).

The statistical processing of the data was performed using IBM SPSS Statistics 20 for Windows. The distribution normality was evaluated using the Kolmogorov – Smirnov test. In case of normal distribution the signs were presented as the arithmetic mean and standard deviation ($M\pm\sigma$), while the intergroup differences were assessed via Student's t-test in view of Levene's test for dispersions equality. In the event of abnormal distribution, the data were expressed as median and interquartile range ($Me(Q1-Q3)$); the differences between groups were analyzed using the Mann – Whitney U test. The χ^2 test and Fisher's exact test were employed to compare fractions. The evaluation of the prognostic role played by a particular feature was carried out through the odds ratio (OR) with a 95 % confidence interval (CI). Differences were considered statistically significant at $p<0.05$.

Results and Discussion. In the group, 72 (70.6 %) patients were homozygous carriers of the wild type allele of FGB gene G-455, with another 6 (5.9 %) patients

being identified as carriers of the mutant allele -455A. The heterozygous genotype was detected in 24 (23.5 %) patients. The distribution of genotypes was consistent with the Hardy – Weinberg equilibrium.

The average concentration of fibrinogen in the cohort was 2.6 ± 0.39 g/l. In the group of patients who were homozygous in terms of the G-455 allele, the fibrinogen level in blood plasma was significantly lower compared to the combined group of homo- and heterozygous mutant allele carriers (2.51 ± 0.26 g/l vs 2.83 ± 0.55 g/l respectively, $p<0.05$).

Within the follow-up period, the endpoints as transient ischemic attack and stroke were observed in 14 (13.7 %) patients. The group of patients with TEC revealed no statistically significant difference in view of demographic, clinical and laboratory features.

Among the patients with TEC, there were significantly more homo- or heterozygous carriers of the -455A allele (64.3 % vs. 23.9 %; OR 5.74; (CI 1.73; 19.03), $p=0.006$), while the average level of plasma fibrinogen was higher than in the group where the patients reached no endpoints; this trend, however, failed to reach any statistically significant levels (2.87 ± 0.69 g/l vs 2.56 ± 0.31 g/l respectively, $p=0.121$).

Our study, just like the case with the investigation carried out by V.A. Shulman and N.V. Aksyutina in central Russian population of patients, confirmed a relationship between the homo- or heterozygous carrier status of the mutant -455A FGB allele and the development of TEC in patients with AF in South Russian population [1,3]. Lack of accurate association of fibrinogen level with endpoints may be due to a high variability of plasma fibrinogen concentration subject to impact from numerous factors (from inflammatory diseases to the vitamin B12 and C levels), which are not always easy to detect and take into consideration.

Conclusions. The carriage of the fibrinogen B gene mutant -455A allele is associated with an increased risk of stroke and systemic thromboembolism in patients with atrial fibrillation. No significant relationship between the plasma level of fibrinogen and the TEC was found. Evaluation of fibrinogen B gene 455G-A polymorphism may be recommended in order to customize the anticoagulation strategy in patients with atrial fibrillation, especially in cases of low risk based on the CHA_2DS_2-VASc scale assessment.

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