Abstract.

Background

Diseases of the cardiovascular system, especially ischemic heart disease, are the most common cause of death in the world and in Poland. There are many documented, classical risk factors for cardiovascular diseases. Additionally, there are numerous potential risk modifiers, including genetic factors. Genetic factors can be decisive especially in young patients. The link between thrombophilia and thromboembolism in the venous system has been proven. Its association with arterial thrombosis is also becoming increasingly relevant. Among the genetic factors, those considered important are the carriage of mutations in genes associated with thrombophilia: *F2* (prothrombin factor II), *F5* (Factor V Leiden) and polymorphic variants C677T and A1298C of the *MTHFR* gene. The effect of these mutations on venous embolism is fairly well understood. The impact of congenital thrombophilia on arterial thrombosis remains controversial. Many papers suggest that congenital thrombophilia is important in the case of myocardial infarction, especially in the group of younger patients.

Objectives

The aim of the presented work was:

1. Assessment of the incidence of pathogenic variants c.*97G>A in *F2* (factor II prothrombin), c.1601G>A in *F5* (Factor V Leiden) gene and polymorphic variants C677T and A1298C in *MTHFR* gene (methylenetetrahydrophylocate reductase gene) in the study and control groups.
2. Assessment of the genotype-phenotype correlation between individual mutations/polymorphic variants and past cardiovascular events with the assessment of the dependence of individual mutations on classical risk factors for coronary artery disease.
3. Assessment of the importance of family history on stratification of the risk of cardiovascular disease in the group of carriers of individual mutations and in the group of people without mutations.

Methods

The study involved 118 patients (21 women and 97 men) with myocardial infarction aged ≤ 50 years. The control group consisted of 118 unrelated, healthy individuals from the Podlaskie

Voivodeship, aged ≤50, selected in terms of sex. The study was retrospective. Anamnesis was collected and the available medical records were analyzed. Patients' characteristics included: age, sex, BMI, concomitant diseases (diabetes, kidney disease, hypertension) and other potential causes of myocardial infarction. Selected laboratory parameters and the results of available imaging tests were taken into account. The subjects completed a questionnaire on family history of myocardial infarction, cancer, thrombosis, and stroke in first- and second-degree relatives. All subjects included in the study had blood collecte for genetic testing. The presence of pathogenic variants in the factor II (*F2*) and coagulation factor V (*F5*) genes and the polymorphic variant in the *MTHFR* gene were determined.

Results

In the presented work, the following classical risk factors for cardiovascular diseases were found in the study subjects: excessive body weight (72%), diabetes (14%), hypertension (45%), nicotinism (78%). High lipid values were observed: total cholesterol >200 mg/dl (35%), LDL-C >115 mg/dl (45%), HDL-C < 40 mg/dl (39%). A family history of myocardial infarction was present in 49 subjects (41.5%), thrombosis and stroke in 24 people (20.3%), cancer in the family in 17 (14.4%) patients. In the study group, men were more likely to be obese, more likely to smoke cigarettes, and had higher creatinine levels. In women, the left ventricular ejection fraction and HDL-C values were higher. Women were more likely to have a family history of cancer.

Mutation c.*97G>A in the *F2* gene of prothrombin occurred in 3 patients (2.45%) in the study group and 4 (3.3%) in the control group. There were no differences between either the study and control groups or between the sexes. The pathogenic variant c.1601G>A in the *F5* gene was found in 7 cases (5.93%) of the study group comparing to 12 cases (10.2%) of the control group. There were no differences between the study and control group nor between the sexes. The presence of an abnormal polymorphic variant of C677T in the *MTHFR* gene was found with a similar frequency in the study and control group (52.5% vs 50.8%). In the study group differences between women and men were observed at the level of statistical tendency ($p<0.1$), in men a polymorphic variant of the heterozygote type was more common, women were more likely to have a normal result. Polymorphism A1298C *MTHFR* was confirmed in 70 patients (59.3%) in the study group and 64 (54.2%) in the control group, there were no significant differences between groups and differences between women and men. In the study group, there were no differences between the age of myocardial infarction and the presence of *F2* mutations and *MTHFR* polymorphisms examined. In the presence of *F5* mutations in the subjects, the

heart attack occurred at a younger age (*Me* = 37) than in patients without this mutation (*Me* = 45). There was no association between any of the mutations studied and sex, BMI, total cholesterol, LDL-C, smoking, hypertension. There was no relationship between the occurrence of pathogenic variants of *F2*, *F5* genes and both polymorphic variants of the *MTHFR* gene and the occurrence of a family history of infarction. In the case of a family history of cancer and a stable relationship, the *MTHFR* gene in the C667T variant was revealed, these patients were more likely to have the normal variant (70.6% vs. 43.8%), and less often heterozygous abnormality (17.6% vs. 49.0%). A significant association occurred between *the F5* mutation and the presence of thrombosis/stroke in the family, the heterozygous pathogenic variant was more common in patients with a family history (43.4% vs 16.7%).

The co-occurrence of several risk factors (hypertension, lipid disorders, smoking, obesity, diabetes) additionally increases the chance of another infarction by 7.96 times, with the significance of this effect being at the level of the statistical trend.

A high incidence thrombophilia genes carriers was found. Analyzing all subjects in both groups, only in 11% of cases no mutation was observed. The most numerous group were people with one mutation (60.6%), the least numerous patients with three mutations (2.1%). Among the subjects of the study group, two mutations (32.2% vs 20.3%) were more common, less often one (53.4% vs 67.8%) compared to the control group.

Conclusions

1. There was no significant relationship between the presence of pathogenic variants in factor II (*F2*), coagulation factor V (*F5*) genes and both polymorphic variants in the methylenetetrahydrofolate reductase gene *MTHFR* and the occurrence of myocardial infarction before 50 years of age in relation to the reference group of healthy people.
2. There were no differences in the distribution of pathogenic variants of the factor II (*F2*), coagulation factor V (*F5*) gene, both polymorphic variants in the methylenetetrahydrofolate reductase-MTHFR gene between the sexes in the study and control groups and between women and men in the study group. In the case of an abnormal heterozygous variant of C677T in the *MTHFR* gene, its occurrence was more frequent in men in the study group (at the level of statistical tendency $p<0.10$).
3. There was no correlation between the individual classical risk factors for coronary artery disease and the presence of individual pathogenic and polymorphic variants in patients with a history of heart attack at a young age.

4. There was no association between any of the pathogenic and polymorphic variants studied and the occurrence of a family history of myocardial infarction. In the case of a family history of thrombosis, there was a higher incidence of c.1601G>A mutations in the *F5* gene in heterozygous form. In contrast, patients with a family history of cancer were more likely to have a normal result for C677T *MTHFR* polymorphism, less often a heterozygous abnormality.
5. The problem of premature myocardial infarctions is closely related to the occurrence of classical risk factors, and their modification is a decisive factor in the prevention of the first and subsequent coronary events.