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GENETIC FEATURES OF RESISTANCE TO ANTITHROMBOCYTIC DRUGS IN PATIENTS WITH ISCHEMIC HEART DISEASE AFTER CONDUCTED PERCUTANEOUS CORONARY INTERVENTION

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Abstract

The aim of the study: To study and evaluate platelets aggregation activity as primary phase of haemostasis and anti-platelet therapy in IHD patients after PCI, depending on the polymorphism of the gene ITGA 2 – C 807T.

Materials and methods: 54 patients who were on a treatment at the clinical hospital "Feofaniya" (Kyiv) and at the Kyiv Clinical Hospital on railway transport No. 2 were examined: 20 women and 34 men (mean age – 67.8±7.46 years). The study involved patients with stable forms of coronary artery disease (stable angina pectoris II–III) and acute coronary syndrome, with a history of percutaneous coronary intervention (PCI). All patients received antiplatelet therapy: acetylsalicylic acid (3.7 %), clopidogrel (9.3 %) or a combination of them (87 %).

Functional activity of the platelets was studied on a Biola Aggregation Analyzer laser agrometer. The response to antiplatelet therapy was confirmed by the Aggredyne test. The polymorphism of the C807T of the ITGA2 gene was determined by polymerase chain reaction (PCR).

Based on the results of the aggregation ability, antiplatelet therapy sensitivity, the patients were divided into two groups: group I – individuals with varying degrees of insensitivity to antiplatelet drugs (35 patients), group II – susceptible to treatment (19 patients). In each group was analyzed the polymorphism of the gene ITGA2 and features of the functional activity of the platelets, depending on the genotype.

Results: In 50 % of patients receiving ASA there was a different degree of non-sensitivity, with respect to thienopyridines – this figure was 20 %. Among patients who received dual antiplatelet therapy did not match at least one of the drugs – 83.3%. Among the "non responders" 78.9 % had a mutated T-allele, and a homozygous variant for the T allele was recorded in 53.15 % of patients, while "respondents" – 15.8 %. Most in the group of "respondents" was the group of the native genotype – C/C. The most pronounced tendency to influence the genotype on spontaneous aggregation was observed in relation to the T-allele, in particular in the homozygote (genotype T/T). The significant difference between the groups was obtained from the platelet response to ADP. Thus, the reaction of carriers in the T-allele, as homo- and heterozygotes, was significantly different.

Conclusions: In 64.8 % of patients with coronary heart disease after PCI was observed a decrease in antiplatelet sensitivity, which has a clear link with the polymorphism of the gene ITGA 2. The presence of the T-allele in the genotype of patients with IHD is associated with a less adequate platelet response in patients receiving dual antiplatelet therapy for ASA and thienopyridines on ADP, which may have an effect on the sensitivity to thienopyridines.

Keywords: ischemic heart disease, platelets aggregation, percutaneous coronary intervention, antiplatelet treatment.

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1. Introduction

The myocardial revascularization has for almost half a century always remained as the main strategy in the treatment of coronary heart disease (CHD). In most cases, restoration of blood flow in the coronary arteries in patients with stable forms of coronary artery disease leads to objective improvement of the somatic status, and in patients with acute coronary syndrome, timely revascularization of the myocardium saves lives. However, initiation of primary coronary intervention – PCI (urgent or planned) does not mean eliminating the main problem that caused the need for these procedures – systemic atherosclerosis. Progression of cardiovascular disease is a risk factor for recurrent ischemic incidents. To avoid them, the patient should receive optimal therapy aimed at reducing thrombocyte activity and preventing the formation of blood clots [1].

In recent years, with the increase in the frequency of percutaneous coronary interventions (PCI) with stenting, more and more attention is focused on solving the problems associated with thrombosis and restenosis within the stents. Restenosis inside the stent (in-stent restenosis-ISR) – the process of healing a damaged vessel after stenting, is found in approximately 10–40 % of patients [2]. Thrombosis inside the stent is observed in about 0.87–2.2 % of cases and develops, as a rule, during the first year after stent placement [3, 4]. It is well known that vascular wall injury during an intervention results in the development of a local inflammatory reaction, adhesion, activation and aggregation of platelets with the formation of a posterior thrombus, migration and proliferation of smooth muscle cells and re-endothelialization, as well as the synthesis of components of the extracellular matrix (hyaluronic acid, fibronectin, osteopontin, ivibronectin) [5].

The modern treatment of patients with acute myocardial infarction (AMI) with elevation of the ST segment includes a full list of antiplatelet drugs, including dual oral antiplatelet therapy (acetylsalicylic acid and thienopyridines) and anticoagulants. [6] Unfortunately, to date, there is not enough research that adequately evaluates the final results and the role of intravenous administration of IIb/IIIa glycoprotein receptor inhibitors in treating AMI patients with ST elevation [7].

Since atherothrombosis is the basis of vascular catastrophes, stabilization of haemostasis processes plays a key role in the treatment and prevention of coronary artery disease [8, 9]. But the constant use of antiplatelet agents is not able to completely protect the patient from acute cardiovascular attacks. It turned out that despite the use of antiplatelet drugs, some people had no antiplatelet activity due to laboratory tests, the final cause of which has not yet been named.

According to various authors, aspirin resistance is a very common problem: the incidence of insensitivity to ASA in various studies varied from 6 to 47 %. Moreover, it has been proved that the emergence of acute cardiovascular situations in the treatment of ASA is a prognostic adverse factor and is accompanied by a higher risk of complications [10, 11]. Over time, this phenomenon has been confirmed with other antiplatelet drugs, especially the second most commonly used drug – clopidogrel.

But despite the enormous amount of clinical and experimental studies on this issue over the past decade, there is currently no consensus on mechanisms, resistance, and ways to overcome resistance to antiplatelet agents [12]. It is believed that resistance to antiplatelet may have multifactorial nature. One of the most important and frequent causes is the high activity of immune-inflammatory and prooxidant processes.

Over the past 30 years, PCI has become widespread in the primary strategy for treating patients with stable coronary heart disease in all countries in Europe and America, even though the treatment recommendations give preference to in-patient intensive care, risk reduction and lifestyle interventions [13].

Recently, despite the use of antiplatelet therapy, more frequent restenosis of stents and repeated acute cardiovascular attacks became occured. Therefore, many modern studies addressed to the issue of studying this question and discuss the possible involvement of genetic factors in the development of these incidents [14, 15].

3. Aim of the study

To study and evaluate the aggregation activity of platelets as primary phase of haemostasis and antiplatelet therapy, in patients with IHD and PCI, depending on the polymorphism of the gene ITGA 2 – C 807T.

4. Materials and methods

During the study were observed 54 patients that were on a treatment at the Department of acute coronary pathology, chronic ischemic heart disease of the clinical hospital "Feofaniya", at the Department of intensive care and cardiology of the Kyiv Clinical Hospital on railway transport No. 2: 20 women (37 %) and 34 men (63 %) at the age from 43 to 85 years (average age – 67.8±7.46 years). The study involved patients with stable forms of coronary artery disease (stable angina pectoris II–III) and acute coronary syndrome, with a history of percutaneous coronary intervention (PCI). The treatment protocol was determined on the basis of European and Ukrainian recommendations for the management of patients with stable forms of IHD and acute coronary syndrome. PCI of not damaged blood vessel was considered in some patients with STEMI and multi-vessel lesions that are hemodynamically stable either during primary PCI or as a planned stage-by-stage procedure. [13] Patients with stable coronary heart disease before revascularization should receive optimal drug therapy in accordance with the recommendations of the respective clinical protocol, as it has been proven to have a positive effect on the prognosis of the disease and the symptoms relief [16]. Dual antiplatelet therapy was prescribed to patients with stable forms of coronary heart disease after percutaneous coronary intervention [17]. The patient was given a primary PCI in a heart attack-dependent artery in the first hours of AMI with multi-vessel lesions with subsequent revascularization of the heart attack-independent arteries after 4 weeks of conservative treatment [18]. All patients received antiplatelet therapy: acetylsalicylic acid (3.7 %), clopidogrel (9.3 %) or a combination of them (87 %). During the examination of patients, an algorithmic standardized thematic outpatient's card was used, which included sections of anamnesis, general clinical, instrumental and laboratory research.

The study of haemostatic parameters in venous blood was carried out immediately when the patient arrived at the department. The study of functional activity of platelets was performed on a Biola Aggregation Analyzer laser agrometer with a computerized analysis of light transmission curves and platelet aggregate features. In this case, the presence of spontaneous platelet aggregation and stimulated aggregation with inductors were studied: arachidonic acid (AA), adenosine diphosphate (ADP), collagen. Concentrations of inductors were selected according to the recommended standards, while the lowest effective concentrations that caused aggregation were used which increased the sensitivity of this method in determining the functional activity of the platelets.

The features of changes in platelet activity were confirmed using the Aggredyne test, a modern laser light scattering technique that detects the level of platelet aggregation induced by the arachidonic acid agonist and adenosine diphosphate when adding whole blood to the test cartridge-AA/ADP. The result is recorded by the platelet activity index (PAI).

DNA molecules of patients isolated from venous blood by a sorbent method were used for molecular genetic analysis. The polymorphism of the C807T of the ITGA2 gene was determined by polymerase chain reaction (PCR) using a two-particle system.

Based on the results of aggregation ability, antiplatelet therapy sensitivity, genotyping and according to the purpose of the study, all patients were divided into two groups: I group with different degrees of not sensitivity to antiplatelet drugs (35 patients), II group – sensitive to treatment (19 persons) Each group was analyzed on the polymorphism of the gene ITGA2 and features of the functional activity of the platelets, depending on the genotype. The control group consisted of 15 practically healthy persons, matched by age and sex.

To solve the set tasks during the study were used a general clinical and instrumental examination of patients with a subsequent statistical treatment of the obtained results. Both parametric and nonparametric statistical methods were used: Kraskele Wallis and Mann-Whitney [19].

5. Results

The complex of conducted surveys allowed to find that the functional activity of platelets in the surveyed patients according to data such as spontaneous aggregation of platelets and all investigated inducers of platelet aggregation (ADP, AA, collagen) practically did not differ from the indicators of the control group, those who did not receive antiplatelet treatment (**Table 1**).

Table 1
Functional activity of platelets in the examined patients

Indicator	Control (1)	Patients after PCI (2)	P 1-2
Degree of spontaneous aggregation, %	0.88±0.31	1.87±1	>0.05
Degree of ADP induced aggregation, %	34.92±5.23	35.7±4.7	>0.05
Degree of AA induced aggregation, %	28.82±4.87	29.6±5.67	>0.05
Degree of collagen-induced aggregation, %	20.94±4.68	28.14±9.17	>0.05

Taking into account that all patients after treatment with PCI were treated with antiplatelet drugs, the vast majority of them received dual antiplatelet therapy, the findings revealed an inadequate efficacy of treatment. In this regard, the aggregation sensitivity of platelets to antiplatelet therapy was performed using the Aggredyne test. The appropriate test cartridge was selected taking into account the mechanism of action of the drug: in patients receiving ASA, sensitivity was assessed using AA cartridges (since the effect of ASA is realized through the influence on the metabolism of arachidonic acid), in patients treated with clopidogrel – using ADP cartridges (given the effect of the drug on the ADP receptors of the platelet membrane). The difference in the degree of resistance to treatment in the application of the method indicated the value of the platelet index above 5 (**Table 2**).

Table 2
Results of anti-platelet treatment sensitivity determination with Aggredyne-test

Anti-platelet treatment	Results of Aggredyne-test	
	1–5	>5
Patients receiving ASA (n=2)	50 %	50 %
Patients receiving clopidogrel (n=5)	80 %	20 %
Patients receiving dual therapy (n=47)	16.7 %	83.3 %

It was shown that among patients treated with ASA, a different degree of non-susceptibility to the drug was noted in 50 % of the subjects, with respect to thienopyridines – this figure was lower and was 20 %. Among patients receiving dual antiplatelet therapy, 83.3 % of patients did not respond to at least one of the drugs used. Thus, it was concluded that a sufficiently large percentage of patients with coronary heart disease who received antiplatelet therapy after the PCI failed to respond to the treatment. In this regard, based on the Aggredyne test, two groups were formed, 35 patients with varying degrees of non-susceptibility to treatment (non-responders) were included in group I, 19 patients in whom the test results were sufficient to respond to the drug, came in to the group II of respondents. Taking into account recent research on the role of the genetic factor in the development of resistance to antithrombotic treatment, it was decided to conduct a study on the effect of the polymorphism of the gene ITGA2 on the platelet response in patients with coronary artery disease after PCI. It was found that among patients who did not respond adequately to the treatment received, 78.9 % had a mutated T-allele, and a homozygous T-allele variant was recorded in 53.15 % of patients. Instead, among respondents this percentage was much lower and amounted to only 15.8 %. It should be noted that the overwhelming majority in the group of respondents was the group of the native genotype – C/C (**Table 3**).

Comparing the functional activity of platelets in both groups, depending on the genotype, it was found that spontaneous aggregation of platelets did not differ significantly between the groups, however, the most significant tendency to influence the genotype on spontaneous aggregation was observed in relation to the T-allele, in particular, in the homozygote (genotype T/T) The significant difference between the groups was obtained from the platelet response to ADP. Thus, the reaction

of carriers in the T-allele, both homo- and heterozygote (T\T and C\T genotype), is significantly different, so the presence of the T-allele in the patient's genotype has a significant effect on platelet aggregation in ADP.

Table 3

Distribution of ITGA 2 genotypes in the groups of patients "non responders" and "respondents" on antiplatelet treatment

Genotypes	Non responders (%)	Respondents (%)
C\C	17.14	63.15
C\T	25.71	21.05
T\T	53.15	15.80

Concerning the aggregation induced AA – no similar effect was found.

Collagen aggregation data indicate that there is no significant effect of the mutation of the ITGA2 gene on the platelet sensitivity to collagen.

Thus, the existence of the effect of the genotype on the peculiarities of the platelet reaction in patients with PCI who received antiplatelet therapy on inductors used was noted. Major changes were found on the side of ADP aggregation, which may not directly indicate the possible effect of T-allele on sensitivity to thienopyridines (taking into account the mechanism of action on the ADP receptors of the platelet membrane) (**Table 4**).

Table 4

Features of changes in the functional activity of platelets in patients of the studied groups depending on the polymorphism of the gene ITGA 2

Indicator of platelet aggregation	Group	C/C	C/T	T/T
Spontaneous, %	non responders responders	1.59±1.02 1.08±0.57	1.77±0.48 2.27±1.18	2.34±1.14 1.97±0.25
ADP-induced, %	non responders responders	37.3±3.17 34±6.6	35.68±2.8** 31.7±2.29	36.93±4.68* 36.7±2.8
AK-induced, %	non responders responders	29.64±3.23* 24.85±4.31	28±3.37 26.52±3.34	33.55±5.62 31.17±6.07
Collagen-induced, %	non responders responders	21.32±1.46 21.6±2.94	24.3±3.71 26.7±5.4	34.96±9.94 35.8±11

*Note: * – p <0.05 in comparison with the group of "respondents"; ** – p=0.003 in comparison with the group of "respondents"*

5. Discussion

Considering that the use of antiplatelet drugs is an integral part of the treatment of patients with coronary heart disease after PCI, the sensitivity question can be considered one of the main in determining the adequate prevention of thrombotic complications. The performed analysis of platelet activity in this category of patients allowed establishing the inadequate efficacy of the antiplatelet agents that they were treated with (ASA, thienopyridines, and a combination of them). With the help of the Aggredyne-test, it was found that a different degree of antiplatelet resistance was found in 64.8 % of patients, which is consistent with the current literature, as noted in the study "Special antiplatelet therapy can overcome resistance to aspirin and clopidogrel" with a total of 504 patients among which 30.8 % was found with a low response to clopidogrel and 19.4 % with a low response rate to aspirin [10]. Also, in the study of the effect of the CYP2C19 gene on antithrombotic resistance in patients with coronary heart disease, it was found that 53.8 % of patients had an accelerated ADP-induced aggregation [21].

Among the possible causes of thrombocyte insensitivity to therapy are increasingly called genetic aspects [14, 20]. It deals with a large number of candidate genes, the polymorphism of which is associated with a change in the function and structure of the platelets. One of them is ITGA 2, whose genetic mutations cause increased propensity to thrombotic and complications associated with it [20].

The results of genotyping of patients and comparing the obtained data with the definition of sensitivity to antiplatelet therapy showed that the effect of polymorphism of the gene ITGA 2 on the functional platelet reactivity. In the vast majority of cases (78.9 %) among patients who did not respond to treatment, the mutant alleles of the gene were found, and 53.15 % of the surveyed cohort of "non-responders" appeared to be homozygotes on the T-allele (T/T genotype).

For comparison, in the group of patients, who were sensitive to antiplatelet therapy, only 15.8 % had a T/T genotype. The obtained data suggest that the polymorphism of the gene ITGA 2, changing the adhesive ability of platelets by affecting their membrane receptors, creates the preconditions for the development of resistance to antiplatelet drugs, the target of which are certain components of the receptor apparatus. However, it is obviously impossible to consider platelet insensitivity to specific treatment only in the context of the genetic determinants. Confirmation of this fact should be considered the presence in the group of "respondents" of a certain number of patients with mutant T-allele, and vice versa. Taking into account that the data suggest a significantly lower sensitivity to ASA, which, however, was not associated with the ITGA 2 polymorphism. This problem needs further investigation.

6. Conclusions

1. Functional activity of platelets in patients with coronary heart disease and post-PCI receiving antiplatelet (predominantly dual) therapy is almost the same as that of the control group, which indicates an inadequate treatment efficacy in this category of patients.

2. Among patients with coronary heart disease and after PCI, in 64.8 % of cases, there is a decrease in antiplatelet susceptibility that has a clear association with the polymorphism of genome IDGA2.

3. The presence of T-alleles in the genotype of patients with CHD is associated with a less adequate response of platelets in patients receiving dual antiplatelet therapy of ASA and thienopyridines on ADP, which may have an effect on the sensitivity to thienopyridines.

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