Acta Clin Croat 2018; 57:96-102 Original Scientific Paper

doi: 10.20471/acc.2018.57.01.11

THE ROLE OF PAI-1 GENE 4G/5G POLYMORPHISM AND DIAGNOSTIC VALUE OF BIOMARKERS IN ALLERGIC AND NON-ALLERGIC ASTHMA PHENOTYPE

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SUMMARY – Asthma is a chronic inflammatory disease that is characterized by reversible obstruction of airways, bronchial hyper-reactivity and airway remodeling. The etiology of asthma is multifactorial, with inheritance playing an important role. The aim of our study was to investigate the importance of biomarkers of asthma and the role of plasminogen activator inhibitor-1 (PAI-1) gene as a genetic factor that could be involved in the pathogenesis of asthma. The research was conducted at Jordanovac University Department for Lung Diseases and Croatian Institute of Transfusion Medicine. The research included 149 patients with asthma and 89 healthy individuals. We collected demographic data of both study groups, determined asthma severity using GINA guidelines, and the values of biomarkers and PAI-1 by using laboratory techniques. Based on the results, we concluded that patients with allergic phenotype of asthma were younger, had better lung function and higher levels of IgE. By observing FeNO values, we were not able to distinguish asthmatic patients that had been diagnosed with obstruction of airways from asthmatic patients with normal lung function because FeNO indicates the inflammatory component of disease. The 4G/5G polymorphism of PAI-1 gene did not show any statistically significant difference in the distribution of 4G/4G, 4G/5G and 5G/5G between the group of asthmatic patients and control group.

Key words: *Asthma; Hypersensitivity; Biomarkers; Plasminogen activator inhibitor 1; Polymorphism, genetic*

Introduction

Asthma is an inflammatory disease of bronchial tubes characterized by bronchial hyper-reactivity and recurring episodes of airway obstruction. It is one of the most common chronic diseases worldwide, especially in children, and its incidence is increasing in developed countries[1,2]. According to the 100-year-old inflammation theory, after analyzing the airways and lung parenchyma during autopsies of patients who died of asthma, a major cause of pathologic changes in asthma is chronic, non-infectious inflammation of the airways[3,4]. Asthma is a serious and common disease caused by complex interaction of multiple genetic and environmental factors. The prevalence of asthma in the world is between 1% and 18%, depending on geographic area[5]. Asthma affects around 300 million people worldwide and according to the growing prevalence, it is expected to affect 400 million people until

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Received November 21, 2016, accepted August 23, 2017

2020[6]. Asthma affects people of all ages, but it most often starts during childhood (around 90% of all cases), affecting more boys than girls. The incidence in female patients rises until adolescence and early adulthood, when it equalizes with the prevalence in men. By the age of 40, asthma affects more women than men. Asthma is more common in patients with other atopic diseases such as atopic dermatitis and allergic rhinitis[7].

It is believed that asthma is the most common chronic disease in children in most developed countries, with a particularly high prevalence of up to 32% in the UK, New Zealand and Australia[8]. Croatia has determined the prevalence of asthma in children and adolescents of 6.02%-6.90% (depending on the age of children and the county)[9,10], while the global prevalence of asthma in general population is 4.5%[11]. It is estimated that the global prevalence of asthma has a growing trend with the rate of 20% to 50% every ten years[12]. Recently, we observed a flat-rate increase in asthma worldwide, at least in countries with high prevalence[13], and it seems that further increase has been stopped[14]. Like most other chronic diseases, asthma causes not only great financial loss in health care systems, but also the general social one, due to the loss of many working hours (work or school absenteeism) with significant impact on the quality of life[15].

Atopy or inherited tendency to develop classic allergic reaction is the most important known factor for the development of asthma. If both parents are atopic, the risk of the child to develop an allergic disease is 40%-60%. If both parents and siblings are atopic, the risk is 80%. Despite the great progress in molecular biology, and considering multifactorial etiology, it may be difficult to determine all the genes involved in the pathogenesis of asthma and atopy. To date, several studies have identified many genes associated with asthma development, but localization of the IgE receptor (FcεRI) gene on chromosome 11q, cytokine gene on chromosome 5q and ADAM33 gene on chromosome 20p13 drew biggest attention[16-18]. Patients with allergic asthma have elevated levels of IgE antibodies directed against various environmental allergens, and in such patients other atopic diseases such as allergic rhinitis, conjunctivitis, dermatitis, urticaria, food allergy and insect stings are frequently encountered. The most important inhaled allergens in severe asthma are dust mites, feathers, animal dander and mold, while in seasonal asthma the most important ones are pollen of trees, grass and weeds[8].

Non-allergic asthma usually occurs after the age of thirty in patients without atopic tendency and with normal IgE concentration. The first attack of adult onset asthma is often associated with viral infection of the upper respiratory tract.

Owing to the improvements and latest findings in immunology and genetics, it will be easier to understand the pathophysiology of asthma, define biomarkers for its diagnosis and determine the potential treatment targets[19]. Recent molecular and genetic studies suggest that inappropriate gene activation is pivotal in the induction of allergic reaction, as confirmed by the gene expression changes upon specific imunotherapy[20].

Plasminogen activator inhibitor-1 (PAI-1) is a single chain glycoprotein of approximate molecular weight of 50 kD, which regulates fibrinolytic system, preferably inhibiting tissue (tPA) and urokinase (uPA) plasminogen activator. The main function of PAI-1 is fibrinolysis reduction resulting in the accumulation of fibrin, and consequently elevation of PAI-1 plasma level that affects the normal degradation mechanism of fibrin and promotes thrombosis. According to recent studies, rising concentration of PAI-1 leads not only to hypo-fibrinolysis, but decreases the activity of matrix metalloproteinases (MMP) and cell adhesion, playing a key role in tissue remodeling[21]. Due to its role in the coagulation cascade and inflammation, it is associated with the development of various diseases such as deep venous thrombosis, atherosclerosis, endometriosis, metabolic syndrome, breast cancer, etc. This finding prompted numerous studies on PAI-1 as a diagnostic marker for a number of diseases[22]. One of the characteristics of asthma is imbalance between MMP and their inhibitors, which contributes to remodeling of the airways and leads to the loss of lung function. PAI-1 contributes to the development of asthma by remodeling airways, bronchial hyper-reactivity and allergic inflammation. Activated mast cells are an important source of PAI-1 in tissue remodeling of the airways affected by inflammation[23].

In the promoter region of the PAI-1 gene, which is located on human chromosome 7q21.3-q22, the existence of a specific polymorphism 4G/5G affecting the expression of PAI-1 has been established. It is a polymorphism that includes deletion or insertion of guanine base at -675 bp of the PAI-1 promoter gene. Studies have shown that people with homozygous 4G/4G genotype have a significantly higher concen-

tration of PAI-1 than people with 5G/5G genotype, meaning that 5G allele is transcriptionally less active compared to 4G allele. In both 4G and 5G alleles, transcription activator can bind, but only the 5G allele can bind a transcription repressor[24].

The aim of this study was dual: to assess the impact of biomarkers on the obstructive disorders of ventilation and pathophysiology of allergic asthma; and to determine the frequency of 4G/5G polymorphism in the promoter region of the PAI-1 gene in patients with asthma and compare it with control group consisting of people with no asthma and allergy symptoms.

Patients and Methods

The study was conducted at the Jordanovac Department for Lung Diseases from February 2014 to April 2015. The study involved 149 adult patients with asthma. All patients were in a stable phase of the disease, without exacerbation, in good or partially good control of asthma on regular therapy adapted by Global Initiative for Asthma (GINA) guidelines.

Blood samples were collected along with the signed consent of the patient, which allows sampling for scientific research. Control group consisted of healthy voluntary blood donors (N=89) from the City of Zagreb and Zagreb County and employees of the Croatian Institute of Transfusion Medicine. Control group subjects were in good health and had normal spirometry values. The study was approved by ethics committees of the Jordanovac Department for Lung Diseases and Croatian Institute of Transfusion Medicine.

Patient parameters

Using medical records, we collected data on demographic characteristics of the patient group (gender, age, family history, data on smoking, comorbidities), need for urgent interventions, need for hospitalization, asthma phenotype (allergic *vs.* non-allergic) and nutritional status expressed as body mass index (BMI, kg/m^2). Furthermore, all our patients underwent spirometry and ventilatory dysfunction was diagnosed. Based on spirometry findings, we estimated asthma severity according to the GINA guidelines[25]. We also measured IgE levels in serum, partial pressure of oxygen in arterial blood (pO2) and eosinophil count in sputum and nasal swab.

PAI-1 4G/5G polymorphism analysis

Blood samples were collected in BD Vacutainer tube with EDTA. Genomic high purity DNA is extracted from whole blood using the QIAamp DNA Blood Mini Kit on QIAcube device (Qiagen, Germany). Genotyping of -675 4G/5G PAI-1 polymorphism (rs1799889) was performed using the TaqMan SNP Genotyping Assay Custom for Serpin-1 by allelic discrimination on the ABI 7500 real-time system device (Applied Biosystems, USA).

Statistical analysis

Asthma biomarker level of statistical significance was set at 5% ($p<0.05$) and all confidence intervals (CI) were calculated at the level of 95%. The normality of distribution of continuous variables (age, anthropometric characteristics) was tested using Kolmogorov-Smirnov test. Binary logistic regression was used for univariate and multivariate prediction of phenotype of allergic asthma and to predict obstruction (forced expiratory volume, FEV 1 ≥80%); odds ratios (OR) with 95% confidence intervals (95% CI) were calculated for each variable. The variables that were significantly associated in univariate analysis were included in the multivariate model. Statistical analysis was performed using the statistical package R, version 3.0.1 (R Development Core Team).

On analyzing the results of PAI-1 genotyping we used statistical tests to compare independent categorical data, as follows: χ^2-test to determine the level of significance of differences between the groups; and OR with 95% CI to assess the strength of connection between variables, or to assess the impact of PAI-1 genotypes in the development of asthma.

The level of significance was set at 0.05 in all analyses and patient results were considered statistically significant when $p<0.05$ compared to control group. We used the MedCalc software for data analysis.

Results

The study involved 149 patients in a stable phase of the disease and their demographic data are presented in Table 1. There were 58 (38.9%) men and 91 (61.1%) women, average age 60. The mean BMI was 26.6 (range, 23.3-30.1); 54 (36.2%) patients had normal body weight, 56 (37.6%) were overweight, and 39

Table 1. Demographic characteristics of study subjects (sex, age and BMI)

Patient characteristic	N=149	%
Sex:		
male, n	58	38.9
female, n	91	61.1
Age (yrs)*	60	40-70
BMI (kg/m^2)* 26.6		23.3-30.1
normal (BMI <25.0) 54		36.2
overweight (BMI 25.0-29.9) 56		37.6
obesity (BMI ≥30.0) 39		26.2

*Median (interquartile range); BMI = body mass index

Table 2. Clinical parameters of study subjects

Clinical parameter	N=149 n	%
Asthma phenotype:		
non-allergic	68	45.6
allergic	81	54.4
Obstructive ventilation dysfunction:		
no obstruction (FEV1 ≥80%)	81	54.4
obstruction (FEV1 <80%)	68	45.6
GINA classification:		
I	16	10.7
II	27	18.1
III	45	30.2
IV	61	40.9
IgE*	165	(49.5-405)
FEV1 (%)*	76.2	(56.1-90.1)
FEV1 (L)*	1.9	(1.3-2.7)
FEV/FVC*	67.8	(58.9-76.3)
FeNO*	19.4	(9.6-38.6)
PEF*	73.1	(56.8-92.4)

*Median (interquartile range); GINA classification = Global Initiative for Asthma (GINA); FEV = forced expiratory volume; FVC = forced vital capacity; FeNO = fractional exhaled nitric oxide; PEF = peak expiratory flow

(26.2%) were obese. Clinical parameters of patients are shown in Table 2. Based on diagnostic parameters, 68 (45.6%) patients had non-allergic asthma, whereas 81 (54.4%) patients had allergic asthma. In 81 (54.4%) patients, we did not find airway obstruction (FEV1 ≥80%), whereas airflow limitation (FEV1 <80%) was recorded in 68 (45.6%) patients.

Based on spirometry results, we categorized asthma severity according to GINA guidelines. There were 16 (10.7%) patients with occasional asthma (GINA I), 27 (18.1%) with mild continuous asthma (GINA II), 45 (30.2%) with moderately severe persistent asthma (GINA III) and 61 (40.9%) with severe persistent asthma (GINA IV). The mean laboratory value of IgE was 165 kU/L, while the mean value of fractional exhaled nitric oxide level (FeNO) was 19.4 ppb. Out of 89 control subjects, 41 were male and 48 were female, average age 41 (23-65). The frequency of particular PAI-1-675 4G/5G genotypes in the group of patients with asthma and healthy control group is shown in Table 3. Analysis of genotyping results in the group of patients with asthma and control group using χ^2-test showed no statistically significant differences in the frequency of PAI-1 4G/5G genotypes between the two groups ($p>0.05$). OR and 95% CI for different PAI-1 genotypes were not statistically significant either (Table 3). The frequency of 4G and 5G alleles in both groups is shown in Table 4. The frequency of 4G allele was 51.3% in patient group and 51.1% in control group. The frequency of 5G allele was 48.7% in patient group and 48.9% in control group. Therefore, there was no statistically significant difference in the frequency of 4G and 5G alleles between the group of patients with asthma and control group ($p=0.9613$).

Discussion

Asthma is a serious respiratory system disease that occurs because of complex interaction of multiple genetic and environmental factors. Recent studies that investigated the influence of multiple genetic factors on asthma risk identified several genes that might be involved in the pathogenesis of asthma, and one of them is PAI-1 gene. In this study, we assessed the significance of asthma biomarker genes and the potential role of PAI-1 4G/5G polymorphism in the pathogenesis of asthma.

Our study results showed that patients with allergic phenotype were of younger age, with better lung function, higher IgE level and higher FEV1 value, when compared to patients with non-allergic phenotype of asthma. The latter could be related to the fact that individuals with allergic phenotype respond better to inhaled corticosteroid treatment, or that those with non-allergic phenotype are basically elderly and have

Table 3. Results of PAI-1-675 4G/5G polymorphism genotyping in patient and control groups

PAI-1 genotype	Patients with asthma (N=149) n (%)	Control group (N= 89) n (%)	OR (95% CI)	p (χ^2-test)
4G/4G	35 (23.49)	26 (29.21)	1.58 (0.838-2.981)	0.2091
4G/5G	83 (55.70)	39 (43.82)	1.65 (0.856-3.171)	0.1832
5G/5G	31 (20.81)	24 (26.97)	1.04 (0.499-2.175)	0.9381

Table 4. Frequency of PAI-1 alleles

Frequency of alleles	Patients with asthma (N=149)	Control group (N=89)	p
Allele 4G	51.3	51.1	0.9613
Allele 5G	48.7	48.9	

bronchi remodeled to a greater extent. Furthermore, our study showed that FeNO biomarker could not distinguish patients with impaired airway obstruction from those with normal pulmonary function, as it is known that it is an inflammatory reaction marker, as well as a good indicator of asthma control.

A large number of patients with asthma are overweight, and adipose patients more often present with non-allergic asthma phenotype. These results indicate that increased BMI could be of predictive value for disease development (together with other genetic factors), but not an objective characteristic of asthma itself.

The predominant feature of asthma is chronic inflammation which leads to bronchial hyper-reactivity, mucous hypersecretion and airway remodeling. PAI-1, a key inhibitor of fibrinolysis, takes part in all three of these complications of chronic airway inflammation[25,26].

Statistical analysis of 4G/5G polymorphism frequency in the promoter region of the PAI-1 gene did not show any statistically significant difference in the frequency of 4G/4G, 4G/5G and 5G/5G genotypes between patients with asthma and control subjects. There was no statistically significant difference in the incidence of 4G and 5G alleles between these two groups either. In conclusion, we could not confirm connection between the 4G/5G polymorphism in the promoter region of the PAI-1 gene with the development of asthma in the study group. Results of our study coincide with previous studies in Caucasian populations, which did not confirm a statistically significant correlation between 4G/5G polymorphism and development of asthma, although it has been proven that PAI-1 has an important role in the pathogenesis of asthma and that its level is increased in people with 4G/4G genotype[27]. Further studies on a larger population group are required, involving other potential genetic risk factors for asthma development, apart from 4G/5G polymorphism, in order to determine whether there is a connection between genetic factors and development of asthma in the Croatian population.

Acknowledgment

The authors are thankful to all the colleagues having contributed to this study.

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Sažetak

ZNAČENJE POLIMORFIZMA 4G/5G PAI-1 GENA I DIJAGNOSTIČKA VRIJEDNOST BIOČIMBENIKA U BOLESNIKA S ALERGIJSKIM I NEALERGIJSKIM FENOTIPOVIMA ASTME

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Astma je kronična upalna bolest koju obilježava reverzibilna opstrukcija dišnih putova, bronhalna hiperreaktibilnost te remodelacija dišnih putova. Etiologija astme je multifaktorska, gdje nasljeđe ima važnu ulogu. Cilj našega rada bio je ispitati važnost biočimbenika astme i ulogu gena za inhibitor aktivatora plazminogena 1 (PAI-1) kao genetskog čimbenika koji bi mogao biti uključen u patogenezu astme. Istraživanje je provedeno u Klinici za plućne bolesti "Jordanovac" i Hrvatskom zavodu za transfuzijsku medicinu. U istraživanju je sudjelovalo 149 bolesnika sa stabilnom astmom i 89 zdravih davatelja krvi. Prikupili smo demografske podatke obiju skupina, odredili stupanj težine bolesti koristeći smjernice GINA te laboratorijskim tehnikama odredili vrijednosti biomarkera (FeNO, IgE) i PAI-1 4G/5G polimorfizma. Temeljem dobivenih rezultata zaključili smo da su osobe s alergijskim fenotipom astme mlađe dobi, imaju bolju plućnu funkciju i više vrijednosti ukupnog IgE. Prema vrijednostima FeNO nismo mogli razlučiti astmatičare koje imaju dokazanu opstrukciju dišnih putova u odnosu na astmatičare s urednom plućnom funkcijom, budući da je FeNO pokazatelj upalne komponente bolesti. Polimorfizam 4G/5G u promotorskoj regiji gena za PAI-1 kod bolesnika s astmom u usporedbi s ispitanicima kontrolne skupine pokazao je da ne postoji statistički značajna razlika u učestalosti genotipova 4G/4G, 4G/5G i 5G/5G između skupine oboljelih od astme i skupine zdravih ispitanika.

Ključne riječi: *Astma; Alergije; Biomarkeri; Aktivator plazminogena, inhibitor 1; Polimorfizam, genetski*