

## Importance of genetic factors in the development of allergic asthma

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### ABSTRACT

**Aim** To examine the importance and frequency of genetic factors in the development of allergic asthma.

**Methods** From March 2010 to June 2011, 96 patients with established diagnosis of asthma were analyzed retrospectively at the Institute for Pulmonary Diseases, Sremska Kamenica. According to the questionnaire, data related to gender, birth year, types of asthma, disease onset, association with other allergic diseases, types of allergens and the presence or absence of genetic predisposition based on first- or second-degree relatives, were collected and processed. The obtained data were statistically processed using standard statistical methods. Values of  $p < 0.05$  were considered as statistically significant.

**Results** Of the total number of 96 patients suffering from asthma, allergic and non-allergic asthma was diagnosed in 66 (68.75%) and 30 (31.25%) patients, respectively. Both allergic and non-allergic asthma patients were predominantly female, 64 (66.7%). Most of the patients were between 20 – 29 years of age, often followed by allergic disease (68.75%). There was a genetic predisposition to the disease in 57 (59.37%) patients. Positive atopy by mother and father was registered in 24 (66.67%) and eight (22.22%) patients, respectively. A hereditary predisposition to the disease both by mother and father was found in four (11.11%) patients ( $p < 0.0001$ ).

**Conclusion** Positive atopy by mother was verified in most of the respondents, which indicated that heritage can have an important role in the development of asthma.

**Key words:** hypersensitivity, atopy, dust mites.

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## INTRODUCTION

The number of people suffering from allergic diseases is constantly increasing. The incidence is especially high in highly developed countries, which can be associated with a higher level of industrialization, urbanization and lifestyle (1). Allergic rhinitis and allergic asthma are the most common diagnosed allergic diseases (1).

Allergic diseases mostly begin in early childhood, but they can also manifest in the later stages of life (1). Environmental factors are mentioned as the most important risk factors, primarily air pollution (1). However, there is growing evidence that the genetic factor plays an important role, mainly because it has been observed that allergic diseases occur more frequently in some families (1). Atopy is a predisposition of an organism to produce larger quantities of immunoglobulin E (IgE) as a response to diverse substances from the external environment (1). Allergic diseases have been increasing especially in the last 20 years, being particularly evident in children, teenagers and young adults in developing countries (2). In 2004, the World Health Organization (WHO) reported about 300 million people suffering from asthma all over the world (2). It has been estimated that additional 100 million people will be affected until 2025, because of the accelerated social development and the increasing industrialization (2).

From 2002 to 2007, both direct and indirect costs for the treatment of patients with asthma in the United States of America only, were \$56.0 billion per year. Otherwise, in 2009, there were more than 24 million patients in the United States suffering from asthma (3). Every year affected children lost 14.4 million of school days and affected adults lost 14.2 million of work days, which classified asthma in the group of leading diseases that limit daily activities (3).

Atopic asthma is the most common form of the disease, and is mostly seen in Western countries (4). It affects one out of seven children in some societies, and almost 15 million individuals all over the world (4). However, there are differences in prevalence within Europe, but the reasons for this is unknown, although it is almost certain that various genetic and environmental factors in different regions contribute to this (4).

Asthma is more common in young boys than in young girls, but there is a higher prevalence among young girls during the period of adolescence, so that the prevalence of the disease is similar in middle life. Also, it has been noted that asthma occurs more often in people with higher level of education (4).

Hereditary component in asthma ranges even up to 80% (5). The genes which are examined separately are atopy genes, genes in eosinophils, immune-tolerance genes, genes related to bronchial reactivity and asthma syndrome genes (5,6). Atopy and allergen exposure are not sufficient to provoke asthma, but there must be a tendency to inflammatory response and bronchial hyperresponsiveness (7,8).

For more than 100 genes there is evidence that they are associated with the development of asthma, but for most of them there are few functional data (9). Most attention goes to the chromosomes 2, 5, 6, 11, 12 and 13, because they have a large number of genes which connect them with asthma and allergy (9,10). The aim of this study was to define the frequency and type of sensitization to some inhalant allergens, the presence of other allergic disorders, gender structure and type of asthma, the age - related distribution over the examined period, as well as the presence or absence of hereditary predisposition based on first or second degree relatives.

## EXAMINEES AND METHODS

From March 2010 to June 2011, 96 patients with established diagnosis of asthma were analyzed retrospectively at the Institute for Pulmonary Diseases, Sremska Kamenica, Serbia. Data were collected from medical records at the Allergology Unit, where patients with asthma were diagnosed and/or controlled.

Patients diagnosed with chronic bronchitis, emphysema and peripheral airway diseases were not included in this study. According to the questionnaire, data related to gender, birth year, types of asthma, disease onset, association with other allergic diseases (allergic rhinitis, atopic dermatitis and allergies on drugs, food allergy, insect venom allergy), types of allergens and the presence or absence of genetic predisposition based on first- or second-degree relatives, were collected and processed. Groups of patients were formed according to the age (20-29, 30-39, 40-49, 50-59 and older than 60). Respondents under the age of 18 were not

included in this study.

The obtained data were statistically processed using standard statistical methods - average value, minimum and maximum values, percentage,  $\chi^2$  test. Values of  $p < 0.05$  were considered as statistically significant.

## RESULTS

Of the total of 96 patients suffering from asthma, allergic and non-allergic asthma was diagnosed in 66 (68.75%) and 30 (31.25%) patients, respectively. A statistically significant difference was registered between the number of affected male and female patients ( $p < 0.0011$ ) (Table 1).

Average age of the patients was 37.66 (minimum 18, and maximum 75 years (Table 2). The age group from 20 – 29 was most frequently affected, in 27 (28.13%) (Figure 1).

In most patients the disease began to manifest itself in the period after puberty, that is after the age of 18 ( $p < 0.0001$ ) (Table 1).

**Table 1. Parameters examined in patients suffering from asthma**

Parameters	No of patients
<b>Etiology – related type of asthma</b>	
Allergic asthma	66 (68.75)
Nonallergic asthma	30 (31.25)
<b>Distribution of patients by gender</b>	
Male	32 (33.3)
Female	64 (66.7)
<b>Onset of asthma by age</b>	
<10	14 (14.58)
10 – 18	11 (11.46)
>18	71 (73.96)
<b>Frequency of concomitant allergic diseases</b>	
Presence	66 (68.75)
Absence	30 (31.25)
<b>Concomitant allergic diseases (n=66)</b>	
Allergic rhinitis	66 (68.75)
Atopic dermatitis	5 (5.21)
Allergies on drugs	7 (7.29)
Food allergy	0
Insect venom allergy	0
<b>Incidence of sensitization to allergens</b>	
Internal allergens	22 (33.33)
External allergens	7 (10.61)
Combined (internal and external)	37 (56.06)
<b>Genetic predisposition</b>	
Positive atopy	57 (59.37)
Negative atopy	39 (40.63)
<b>Presence of atopy by mother and father</b>	
Mother	24 (66.67)
Father	8 (22.22)
Mother and father	4 (11.11)

**Table 2. The average, minimum and maximum age of patients expressed by years**

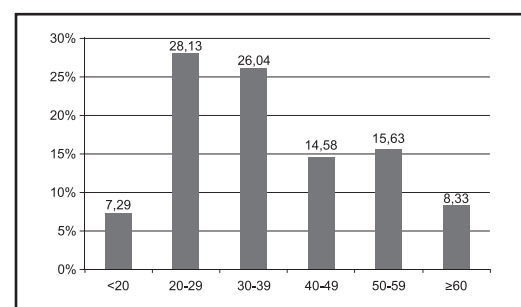
Age of respondents	Minimum	Maximum	Average age
Patients with allergic asthma	18	75	33.82
Patients with nonallergic asthma	19	70	46.1
Total number of patients	18	75	37.66

At least one concomitant allergic disease (allergic rhinitis, atopic dermatitis, allergies on drugs, food allergy, insect venom allergy) was registered in most patients. From the total of 96 respondents, 66 (68.75%) patients also had allergic rhinitis, but the number of patients suffering from atopic dermatitis and drug allergies was significantly lower (Table 1). It should be noted that not every patient had one concomitant disease. Some of them had a combination of these three illnesses.

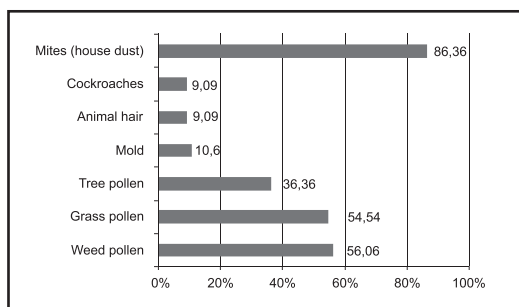
Between patients with allergic asthma, sensitization to external allergens was verified in seven (10.61%), and combined sensitization to both internal and external allergens in 37 (56.06%) patients (Table 1). A statistically significant difference has been proved in comparison to the type of allergy ( $p < 0.0001$ ). There were examined internal allergens such as mites (house dust), cockroaches, animal hair, mold, and external allergens such as tree pollen, grass and weed pollen (Figure 2).

According to the data obtained in this study, there was no statistically significant difference between positive and negative atopy ( $p > 0.05$ ) (Table 1).

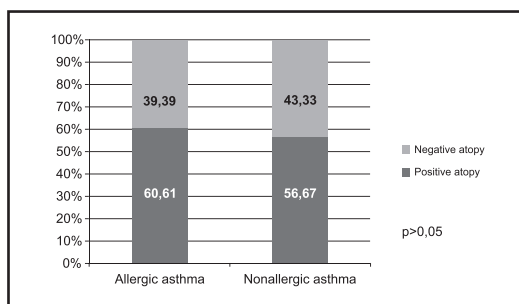
There were more patients with positive genetic predisposition in both groups of patients suffering from allergic and non-allergic asthma. Analyzing the data leads to the conclusion that there was no statistically significant difference in the presence of atopy, depending on



**Figure 1. Distribution of the patients with asthma by different group of age**



**Figure 2. Percentage of sensitization to different kind of allergens**



**Figure 3. Presence of atopy in comparison to the type of asthma**

the type of asthma ( $p > 0.05$ ) (Figure 3). Also, the presence of atopy (hereditary factors) in family members of the first and second degree was monitored. It was registered that there were more patients with presence of atopy by mother than father. Some of them had hereditary predisposition to the disease both by mother and father (Table 1). The difference between these parameters proved to be statistically significant ( $p < 0.0001$ ).

## DISCUSSION

A significantly higher number of patients had allergic asthma, in comparison to those who had non-allergic asthma, which is in line with previous research conducted in this field (2). In the first few years of life, asthma is more common in young boys than in young girls, because of the anatomy and physiology of the chest (4,6). Late in adolescence, the prevalence in young women rises, so that the prevalence of the disease is similar in middle life (4). The results obtained in this study match with the leading trend, because it was found that asthma is diagnosed more often in females than in males (4,6).

Asthma in children and young adults is more often associated with allergies (atopic asthma) (4). The results of this study have shown most asthmatic patients belonged to 20–29 year age

group, followed by 30–39 year age group. This results correspond to previously conducted researches in Serbia and in the world (2,11). The onset of the disease in more than half of the patients was in the period after the age of 18. Asthma may be associated with the presence of other diseases. It is well known that the symptoms of allergic rhinitis precede the symptoms of asthma (11). In 1999 it was reported that about 80% of patients with asthma also have symptoms of rhinitis, and that asthma occurs in 38% of patients with allergic rhinitis. Symptoms of allergic rhinitis usually precede the onset of asthma in about 1 – 11 year after the onset of allergic rhinitis (1). It is estimated that about 5% of the world population have both allergic diseases at the same time (1). Based on the collected data, most of the patients had allergic rhinitis, that is in line with literature data (2,12). It has been proved that treatment of rhinitis can relieve the intensity and course of asthma according to some research, and that application of immunotherapy may even prevent onset of asthma (1, 2, 12).

Causes of the increasing prevalence of allergic diseases of the respiratory tract have not been clearly defined yet. Numerous factors are referred to as causes, but some of them vary depending on a geographic area in which the study population lives (1,13). The most important allergens are internal, especially mites (1, 11). Majority of patients with asthma have sensitization to dust mites, as in most of the studies conducted in the world and in our country (1, 11). This research gives results that a half of patients have sensitization to one or more internal allergens, and smaller percentage of respondents to one or more external allergens. A slightly smaller percentage of patients with asthma has been hypersensitive to both internal and external allergens, at the same time, which is all correlated with other studies (1). In this study, among external allergens the most common was sensitization to weed pollen. This was confirmed by research studies about sensitization to external allergens conducted in Vojvodina and some parts of South Europe, but it differs from the similar studies conducted in other geographic areas (11). The reason for this is because of their distinctive climate and vegetation (1). Among internal allergens sensitization to mites was the most common in this study, and among external allergens grass pollen, according to the research conducted in 14 countries, mostly

West European (1,11,13). There are some studies that have shown that symptoms of asthma occur more often in people with proven sensitization to three or more allergens (1, 11).

Atopy and gender are the most important predisposing factors (1,4). A higher incidence of allergic asthma in some families indicates a hereditary propensity or an increased risk of developing of the disease, therefore research on genetic predisposition is increasing (4,5). However, for the development of clinical manifestation of asthma, interaction of genetic predisposition and environmental factors is necessary, actually, the occurrence and severity of allergic asthma must be determinate by hereditary and additional risk factors (4,5,9). In this study, the patients with allergic asthma had positive atopy more than those with non-allergic asthma, expressed as a percentage, but statistically significant difference was not confirmed. In a study conducted in the period 2004-2008 year in Serbia, results that a genetic factor was present in 34.9% of the respondents were obtained (2). Some studies have received more significant percentage results, for example 8.5% of adults and 1.5% of children did not have a positive atopy (5). According to the literature a person, who has a family member suffering from asthma, has a three to four times higher risk of developing asthma (1). It is estimated that importance of asthma ranges from 36 – 79% in terms of hereditary predisposition to the disease (9).

Atopy is inherited autosomal dominant by gene located on chromosom 11, only when it is inherited from the mother (1,14). Some studies have shown that the existence of maternal asthma, with a presence of rhinitis and smoking habits, increases the risk of developing asthma (1). According to the research conducted by Deichmann et al. no significant difference was obtained compared to the inheritance of asthma by mother. Data obtained in this study point out that there is a distinct difference when it comes to atopy by first and second – degree relatives by mother or father, or by both parents at the same time, respectively.

In the development of asthma, heritage can have a significant role, but existence of asthma in family does not mean that other family member will get it for sure. Although, identification of asthma genes is not complete, some discoveries change the current view of the pathogenesis of asthma. There is hope that discoveries in the genetics will lead to a better classification of such complex diseases and that environmental factors which act in a protective manner will be identified. Therefore, new therapies may be developed too.

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## TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

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## Značaj genetskog faktora u nastanku alergijske astme

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### SAŽETAK

**Cilj** Ispitati značaj i učestalost genetskog faktora u nastanku alergijske astme.

**Metode** Retrospektivno je analizirano 96 pacijenata, s utvrđenom dijagnozom astme u Institutu za plućne bolesti Vojvodine u Sremskoj Kamenici, u periodu od marta 2010. do juna 2011. godine. Prema korištenom upitniku, prikupljeni su i obrađeni sledeći podaci ispitanika: pol, godina rođenja, tip astme, početak bolesti, pridruženost drugih alergijskih bolesti, vrsta alergena i prisustvo ili odsustvo genetske predispozicije na osnovu prvog i drugog stepena srodstva. Prilikom obrade podataka korišćena je standardna statistička metoda. Za granični nivo značajnosti razlika smatrana je verovatnoća greške  $p < 0,05$ .

**Rezultati** Od ukupno 96 pacijenata obolelih od astme, kod 66 (68,75%) je dijagnostikovana alergijska astma, u odnosu na 30 (31,25%) pacijenata s nealergijskom astmom, i to pretežno ženskog pola, 64 (66,7%). Najveći broj obolelih bio je starosti od 20 do 29 godina (28,13%), a najčešće dijagnostikovana prateća bolest bio je alergijski rinitis (68,75%). Genetska predispozicija postojala je kod 57 (59,37%) ispitanika ( $p > 0,05$ ). Kod 24 (66,67%) pacijenta bilo je prisustva atopije u porodici preko majčine strane, u odnosu na osam (22,22%) preko očeve, a četiri (11,11%) pacijenta imala su pozitivnu atopiju i s očeve i s majčine strane ( $p < 0,0001$ ).

**Zaključak** Kod najvećeg broja ispitanika dokazano je postojanje atopije u porodici preko majčine strane što ukazuje da nasleđe može imati važnu ulogu u nastanku astme.

**Ključne reči:** preosetljivost, atopija, grinje.