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Atopic and Nonatopic Asthma in Children: Two Different Diseases?

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Abstract

The majority of the studies in the field of childhood asthma lie within the scope of allergy/atopic asthma; however, airway hyperresponsiveness is considered a marker of asthma, independent of the atopic status and should be regarded as a parallel pathological process that can lead to subsequent symptoms and clinical evidence of asthma in children, without the evidence of atopy. The aim of this study is to estimate the possible differences in clinical and lung functions, and the immunological status of children with atopic and nonatopic asthma phenotypes. In a prospective study design, 54 children (age 3-18 years) in Germany were monitored via active surveillance, by twice-a-week phone calls. All the children were divided into two groups, based on their atopic status, clinical date and lung function tests. The first 27 patients had atopic asthma (AA), whereas the second set of 27 patients had nonatopic asthma (NA). All patients underwent IgE and RAST tests for the most common inhalant allergens, and a quantitative measurement of Eosinophil Cationic Protein (ECP) by CAP-radioallergosorbent test-fluorescence enzyme immunoassay (UniCAP, Pharmacia Diagnostics, Germany). Further, the IgA, IgM, IgG subclasses, IL-6 and CRP levels in the serum were tested. The resultant data showed significant differences in the prevailing IgE level 317.5±58 g/l in AA versus 83±21 in NA. However, there was no significant distinction either in the ECP serum level in children with atopic and nonatopic asthma or in the IL-6 serum level. An unexpected result was the significant drop in the level of serum CRP in group NA – 0.68±0.37 g/l; while in group AA this result was 1.5±0.38 g/l. No significant differences were noted between the mean values of the IgM and IgG levels in patients of all groups; however, the IgG levels increased only in the children with nonatopic asthma. Our study did not reveal any type of immunoglobulin deficiency. The IgA level was relatively decreased in children with nonatopic asthma compared with those with the atopic form. Patients from group NA had significantly higher IgG4 subclass levels than patients from group AA. The results of our study show that both atopic and nonatopic asthma are diseases, with similar inflammatory changes, however having probably different pathogenetic immunological mechanisms. IJBM 2012; 2(3):214-221.

Key words: *asthma, allergy, pulmonary function, eosinophyl cation protein.*

Introduction

Asthma and other allergic diseases have generally been accepted as inheritable, and the contribution of the genetic factors is estimated to lie between 35 and 70% [1]. However, the genetics of asthma and allergy have been subjected to intensive investigation, although, no single gene has yet been identified as a risk factor, with any degree of certainty [2]. Not all asthma is atopic and most atopics do not develop asthma. The airway hyperresponsiveness is considered a marker of asthma, independent of an atopic status and should be regarded as a parallel pathological process that may lead to subsequent symptoms and clinical evidence of asthma [3].

Several epidemiologic studies have suggested that there are several different asthma phenotypes. Atopic asthma

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is defined as asthma that begins before age 6, associated with atopy, a genetic predisposition for sensitization to allergens, and an increased severity of bronchial hyperresponsiveness, which persists into adulthood. Nonatopic asthma is defined as a recurrent airway obstruction that begins during the first two to three years of life, following a lower respiratory tract illness caused by the spread of the spectrum of the infecting organism. RSV-associated wheezing resolves in most children by 13 years of age [4].

Prediction factors of the outcome after wheezing in infancy and the development of asthma are discussed, such as atopy, siblings, day-care attendance [5], respiratory illness, eosinophil count [6] and increased urban pollutants [7].

The aim of this study was to estimate the possible differences in clinical and lung functions and immunological status in children with atopic and nonatopic asthma phenotypes.

Material and Methods

This was a prospective study conducted between 1 October, 2002 and 1 October, 2003 at the University Child Hospital in Bonn, Germany. The study was approved by the university's Ethics Committee. The patients were recruited via active surveillance by twice-a-week phone calls if there was a reported coughing illness of more 10 days' duration and the exacerbation was not combined with a change in the basic therapy plan. Participants in the study were assessed through a repeat visit after 6 and 9 months from the first examination. Parents gave informed consent for their children's participation. Patients with a history of other chronic lung or heart disease were excluded.

Study population

We included 69 children between 3 and 16 years with active atopic asthma (Group A) and nonatopic asthma (Group B). As a control, we included 15 children, suffering from recurrent bronchitis (Group C) (Table 1).

Patients in group A (n=27) had documented diagnosis of asthma based on the WHO criteria, with increased responsiveness to inhaled methaholine, defined as the provocative concentration of methaholine causing a ≥20% reduction in FEV1 (PC20 ≤32 mg) or reversible bronchial obstruction, defined as a ≥10% increase in FEV1 following β_2-agonist (Erich Eager, Germany). Atopy was defined as the production of a skin prick test weal greater than 2 mm in diameter to at least one of the most common inhalant allergens (house dust mite, animals, grass and mold). As additional serum samples were obtained, the total IgE and specific IgEs were detected against a broad panel of inhalant and dietary antigens by CASP-radioallergosorbent test-fluorescence enzyme immunoassay (Pharmacia, Germany). An elevated blood IgE level was defined as a concentration of ≥0.9 $kU \cdot l^{-1}$. An elevated specific IgE level was defined as a concentration of ≥0.35 $kU \cdot l^{-1}$ (≥ CAP class 1). Patients in group B (n=27) had current asthma, negative skin prick test and blood IgE levels <0.35 $kU \cdot l^{-1}$. Recurrent obstructive bronchitis, Group C (n=15), included children with two episodes of wheezing during the first three years of life but not asthma at enrollment period.

Parental questionnaire

At first visit, the parents participated in structured interviews with the doctors in the study focusing on the child's asthmatic and atopic symptoms, including a history of wheezing and the number of exacerbations. Further, several questions covered the earlier and recent infections, environmental exposures such as contact with animals, house dust mite collectors, the type of heating, number of siblings, day-care attendance, and exposure to air pollutants. Parental history of atopy was also considered, if they reported at least one of the following atopic disorders or relevant symptoms: atopic eczema, allergic rhinitis or asthma and sensitization to food, pollen, house dust mites, pets or mold. In this study, at baseline and last follow-up visit, patients completed the Juniper Asthma Quality of Life Questionnaire (AQLQ) [8].

Table 1
Comparative characteristics of atopic, nonatopic asthma, and recurrent bronchitis groups

Parameters	AA (n=27)	NA (n=27)	RB (n=15)	p value*		
				AA vs NA	AA vs RB	NA vs RB
Age, years	8.89±3.27	7.7±3.29	6.6±3.9	0.14	0.32	0.34
Sex, (M/F)	19/8	18/9	8/7	0.23	0.34	0.36
Weight, kg	36.74±14.5	31.3±15.8	26.74±14.5	0.12	0.21	0.24
Height, cm	135.6±16.4	127.7±21.2	119.8±21.2	0.09	0.05	0.64
IgE, $kU \cdot l^{-1}$	317.5±58	83.1±58	173.6±77.8	0.02	0.43	0.91

Notes: *AA - atopic asthma, NA - nonatopic asthma, and RB - recurrent bronchitis;*
** - p-value derived from chi-square tests (Fisher's Exact test for small expected numbers, ANOVA for normally distributed continuous variables, or Wilcoxon rank sum test for not normally distributed continuous variables (Kruskal-Wallis test for comparison in three groups).*

Laboratory Procedures

Serum samples were obtained from all the children. As described earlier, the total serum IgE and specific serum IgEs detected against the broad panel of inhalant and dietary antigens were determined by CAP-radioallergosorbent test-fluorescence enzyme immunoassay (Pharmacia, Freiburg, Germany).

Serum samples from 24 children were available for the quantitative measurement of Eosinophil Cationic Protein (ECP) by CAP-radioallergosorbent test-fluorescence enzyme immunoassay (UniCAP, Pharmacia Diagnostics, Germany). Furthermore the level of the Ig subclasses, IL-6 were tested in serum.

Pulmonary function test

Baseline lung function tests, including the expiratory maneuvers and whole body plethysmography were performed according to the criteria of the European Respiratory Society [9] using Master-Lab (Erich Jaeger, Würzburg, Germany). The parameters, vital capacity (VC), forced expiratory volume in one second (FEV1), forced vital capacity (FVC), expiratory flow when 75, 50, and 25% of the VC remains to be exhaled (MEF 75%, MEF 50% and 25%) and effective airway resistance (RAW), intrathoracic gas volume (ITGV) were measured, and the FEV1/FVC ratio calculated. Results are expressed as a percentage of the predicted value according to the internal reference values.

Methacholine Challenge

The methacholine challenge technique was used in two follow-up visits. After baseline spirometry was recorded, the methacholine 0.025 mg/ml in saline was nebulized through a Hadson updraft nebulizer (output, 0.20±0.02 ml/min at airflow 6 l/min). The β_2-agonists were withdrawn within 12h, anti-leukotriene agents after 48h and inhaled steroids in 7 days prior to testing. If the FEV1 did not fall more than 20% below the initial baseline, a further five inhalations of a higher concentration of methacholine were given sequentially, in 10-fold increasing concentrations of 0.25, 2.5 and 25.0 mg/ml, with spirometry after each dose. The test was terminated when FEV1 declined by more than 20% of the baseline value or the final concentration was reached. The concentration of methacholine provoking exactly a 20% fall in FEV1 (PC20) was determined by interpolation on a log-linear plot of concentration vs FEV1. A PC20 ≤8 mg/ml was used to identify airway hyperresponsiveness [10].

Statistical analysis

The statistical significance of comparisons of the characteristics across the three groups with different wheezing patterns (Atopic, Nonatopic, and Recurrent obstructive bronchitis) as determined from the p-values derived from either chi-square tests (for categorical variables), Fisher's exact test (for categorical variables with small expected numbers: race, family history of atopic diseases, and food allergy), analysis of variance (for normally-distributed continuous variables), or Kruskal-Wallis test (for variables that were not normally distributed). p-values were also calculated to compare the enrollment characteristics for the following pairs: atopic vs. nonatopic; atopic vs. recurrent bronchitis; and nonatopic vs. recurrent bronchitis using the same methods mentioned as above, except that the Wilcoxon rank sum test was used for variables that were not normally distributed. Statistical calculation was performed by using the statistical package for the social sciences (SPSS for Windows, Version 5.0). On analysis, the mean and standard deviation were deduced.

Results

The results from studying the patient family history show that mean family size does not differ in the asthmatic groups and control. The number of parental and sibling history of asthma and allergic disease, such as hay fever, eczema and allergic rhinitis, was similar in patients with asthma, although in the first group brothers showed more significant frequency of having asthma 8 (29.6%) vs 2 (7.4%) in the second. By contrast, the nonatopic group was dominated by paternal atopy, but not allergic disorders in the siblings (Table 2). The prevalence of mother with asthma symptoms was higher in the nonatopics. Family size did not differ in all groups and accounted for 4.3±0.2 in group A, 4.1±0.2 in group B, 4.3±0.23 in group C.

Significantly, more children from the asthma groups were often found living in the city: 11 patients with atopic

Table 2

History of asthma/atopy in family of children with atopic, nonatopic asthma, and recurrent bronchitis

History of asthma/atopy	AA	NA	RB	p-value		
				AA vs NA	AA vs RB	NA vs RB
Father, (N/n, %)	19/27 (61%)	12/27 (38%)	6/15 (40%)	0.049	0.36	0.26
Mother, (N/n, %)	15/27 (63%)	9/27 (37%)	6/15 (40%)	0.080	0.52	0.08
Brother, (N/n, %)	8/19 (43%)	2/25 (7%)	3/12 (20%)	0.040	0.38	0.23
Sister, (N/n, %)	6/21 (22%)	3/24 (11%)	1/14 (14%)	0.230	0.19	0.54

Notes: *See Table 1;*
N – asthma+other atopic diseases (allergic rhinitis, pollinosis, atopic dermatitis), n - total number, % in group.

asthma (40.7%) and 13 (48.1%) while only 4 (26.7%) children from Group B (p=0.04). Patients with nonatopic asthma frequently inhabit in houses older than 10 years when compared with atopic individuals, 19/27 vs 14/27 (p=0.06), and near a road with high volume of traffic when compared with the control group (8/27 vs 1/15; p=0.03).

Nonatopic asthmatics experienced no seasonal differences in the number of exacerbations, whereas atopics have a peak of exacerbation in spring. Group A children have pet cats 10 (37.7%) while only 4 children (14.0%) do so in group B. On the contrary, children with nonatopic asthma more frequently have dogs 5 (18.5%) vs atopic - 1 (3.7%) and a variety of diseases, but there was no difference between group B and C.

The first group of patients differed markedly from the second in the type of the treatment used to achieve control of the asthmatic symptoms (Table 3) as well as in the QL level; thus, inhalant corticosteroids are used by about half i.e. 14 (53.8%) the children with atopic asthma vs 9 (33.3%) p=0.002; nevertheless, they show a significant rise in the QL level (Fig 1).

Lung function

There was no significant difference in the determinants of pulmonary function within the asthma subgroups; however, the atopic patients revealed the greatest reduction in all the measured positions. Children with persistent wheeze showed evidence of emphysema, detected by the increase in total resistance compared with those with transient wheeze (R_{tot} 225.9±13.7% and 214.9±14.6% vs 165.0±24.5%, p=0.023). Atopic and nonatopic asthma, but not recurrent bronchitis, was associated with impaired MEF 50% (86.8±4.3% and 97.2±4.4% vs 106.0±6.3%; p=0.04). The bronchial hyperresponsiveness was estimated by using the conventional test with methacholine in all the children with asthma, compared with patients who suffered from transient wheeze (Table 4). The concentration of methacholine provoking an exactly 20% fall in the FEV1 (PC20) was similar in children with persistent wheeze 0.436±0.087 PD20MC, μg (atopic) and 0.44±0.08 PD20MC, μg (nonatopic asthma), but significant lower, than in patients with transient wheeze 0.880±0.13 (p A vs C =0.014; p B vs C=0.023).

Table 3

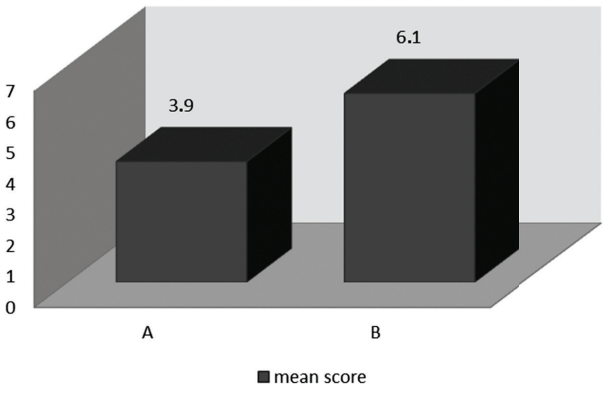
Variant of the therapy, that was used to achieved asthma control in children is atopic and nonatopic asthma

Variant of the therapy	AA (n=27)	NA (n=27)	Total (n-54)
Beta-blockers as needed	2 (7.4%)	3 (11.1%)	5 (9.3%)
Antileukotrienes	7 (25.9%)	9 (33.3%)	16 (29.6%)
Inhaled glucocorticosteroids	15 (55.6%)*	9 (33.3%)	23 (44.4%)
Inhaled glucocorticosteroids +antileukotrienes	3 (11.1%)	6 (22.2%)	9 (16.7%)
Total	27 (100%)	27 (100%)	54(100%)

Notes: *AA - atopic asthma, NA - nonatopic asthma, and RB - recurrent bronchitis;*
** - p=0.002.*

Figure 1

The quality of live in children with atopic (Group A, n=27) and nonatopic (Group B, n=27) asthma.



Note: *the mean score from completed the Juniper Asthma Quality of Life Questionnaire.*

Immunological status

The ECP serum level in children with different wheezing phenotypes was estimated as the following: 30.042±8.9 pg/ml in group A, 24.6±7.7 pg/ml in B and 10.65±14.7 pg/ml in group C. Thus, we found a significant distinction in the ECP serum level in children with asthma and bronchitis, although there was no difference between the atopic and nonatopic patients.

We found negative correlation between the ECP serum level and such parameters as the peripheral blood eosinophil count (p=-0.046), quality of life (r=-0.285; p=0.07) and bronchial hyperresponsiveness (r=-0.091). Positive correlation was found between serum ECP and IL-6 levels (r=0.199), but this interaction was not statistically significant.

We tested serum IL-6 and CRP levels as nonspecific biological markers of the systemic inflammation present to the estimated possible role of infection in the pathogenesis of nonatopic asthma in children (Table 5). The IL-6 serum level

was six times higher in the asthma groups, than in group C. On considering individual clinical cases these parameters appeared to vary markedly within each group; therefore, on the whole, the values found do not differ significantly. An unexpected result was the significant increase in the serum CRP level in group B, while in groups A and C this result was identical.

To determine the possible difference in the humoral immune status, we tested the serum IgG, IgA, IgM levels in all the children. No significant differences were found between the mean values of the IgM and IgG levels in the patients of all groups; however, the IgG level was increased in children with nonatopic asthma. The IgA level was decreased in children with nonatopic asthma (1.1±0.1 g/l) compared with the atopics (1.3±0.3 g/l; $p<0.05$). In our study, we found a partial immunoglobulin deficiency of IgA 3/27 in group A and 1/17 in group C; IgM 2/27 and in group A and 1/17 in group C.

The mean levels of the IgG subclass differed more markedly in children with atopic and nonatopic asthma than transient wheeze. We found a decrease in the levels of IgG 2 and IgG 3 subclasses in children with bronchitis. Patients from group B had significantly higher mean levels of the IgG 4 subclass, than patients from groups A and C. Seven children demonstrated partial deficiency of the IgG 4 subclass as 3/27 from group A, 1/27 from group B and 3/17 from group C.

Table 4
Lung function and methacholine test-parameters in children with different patterns of wheezing.

Parameters	AA (n=27)	NA (n=27)	RB (n=15)	p-value
R_{tot}	225.93±13.7	214.93±14.6	165.0±24.5	A vs C = 0.023
VC	92.07±5.2	84.77±5.32	82.77±7.53	NS
FEV1	103.93±2.83	101.85±2.89	100.38±4.09	NS
ITGV	104.11±10.8	111.41±11.4	125.78±16.83	NS
MEF75%	86.89±3.74	91.53±3.18	94.46±5.4	NS
MEF50%	86.85±4.37	97.26±4.45	106.0±6.3	A vs C =0.04
MEF25%	87.78±6.12	98.92±6.25	104.85±8.85	NS
PD20MC (μg)	0.436±0.087	0.44±0.08	0.880±0.13	A vs C = 0.014 B vs C = 0.023

Notes: *See Table 1.*

Table 5
IL-6, CRP, and serum Igs levels in patients with atopic, nonatopic asthma, and recurrent bronchitis.

Parameters	AA (n=27)	NA (n=27)	RB (n=15)	p value*		
				AA vs NA	AA vs RB	NA vs RB
IL-6 (pg/mL)	39.78±20.82	30.27±18.7	5±37.54	0.24	0.38	0.08
CRP (pg/mL)	1.5±0.38	0.68±0.37	1.2±0.52	0.02	0.54	0.66
IgA (g/L)	1.3±0.3	1.1±0.1	1.1±0.2	0.04	0.21	0.42
IgM (g/L)	0.86±0.1	1.0±0.1	0.89±0.1	0.29	0.15	0.26
IgG (g/L)	11.6±1.6	9.9±1.7	8.9±2.2	0.32	0.57	0.27
IgG1 (g/L)	6.8±0.4	6.3±0.3	6.2±0.5	0.34	0.12	0.33
IgG2 (g/L)	2.1±0.2	2.0±0.1	1.9±0.2	0.51	0.02	0.37
IgG3 (g/L)	0.62±0.1	0.6±0.04	0.54±0.1	0.12	0.08	0.09
IgG4 (g/L)	0.3±1.7	1.96±1.1	0.2±1.5	0.02	0.17	0.07

Notes: *See Table 1.*

The authentic distinctions in the parameters of red blood are revealed: in patients with obstructive bronchitis the erythrocyte count was much less (4.4±0.1/(μl) than in the group with atopic asthma (4.6±0.1/μl; p=0.001), although the given parameter did not fall outside the normative. Hematocrit, showed the highest white blood cell count in the group of patients with nonatopic asthma; the distinctions revealed are significant, both in the case of comparison with atopic asthma and bronchitis. The expected result was the difference seen in the eosinophil count, which was much higher in patients with asthma (4.2±0.7 vs 3.5±0.7 in nonatopics vs 1.5±0.9 in bronchitis; p=0.001), which also correlates with the results of research on the ECP levels.

In children suffering with obstructive bronchitis, the increases in the erythrocyte sedimentation rates were revealed in association with lymphocytosis, which testifies to the role of an infection in the pathogenesis of this condition.

Discussion

Our study indicates the conceptual distinction between atopic and non-atopic asthma and bronchitis in children, including the parental history of atopy, clinical picture, lung function and immunological status. The first remarkable difference as revealed by the present study is the significantly higher prevalence of fathers and lower prevalence of brothers with a history of asthma and allergic diseases in non-atopic asthmatics when compared with the atopics. Mothers' history of asthma and atopy dominate in children with atopic asthma, as the majority of studies revealed [11, 12].

Our data did not support the theory that children attending day care centers and those with older siblings have less atopy due to the increased risk for infections, which in turn may protect them against the development of allergic diseases, including asthma [13, 14]. The largest prevalence of children with any variant of day care was in the group of nonatopic asthma patients, while this number was significantly lower in patients with bronchitis. In addition, we did not find any distinction in family size, in both asthmatic groups and in the control. There are many explanations for these results: organization of day centers and family lifestyles, which remain in every country dependent on several factors, such as economical status, climate and ethnic traditions. Apparently, the number of families in West Germany maintaining a typical «Western» lifestyle, is not large, and kindergarten entry before 6 months of age is uncommon.

Exposure to allergens and viral infections are the main environmental factors causing exacerbations of asthma and/or the persistence of symptoms in children [15]. Analysis of the environmental factors of the children with different phenotypes of wheezing in West Germany confirm the specific manner of the development of asthma. Thus patients with nonatopic asthma frequently occupied houses older than 10 years, with near night volume of traffic, and with ownership of pet dogs, whereas atopics were collectors of house dust in the sleeping room as a marker of house dust mite exposure. Therefore, the different phenotypes are a result of the interaction of a genetic predisposition with different environmental factors which influence the development of asthma in predisposed individuals, precipitate asthma exacerbations and/or encourage persistence of the symptoms.

Asthma is a chronic inflammatory disorder of the airways that become hyperresponsive; it can become obstructive and lead to airflow limitation (by bronchoconstriction, mucus plugs, and increased inflammation) when the airways are exposed to various risk factors [16]. The main result of this study is having established significant distinctions in the degree of airway hyperresponsiveness in children with the major forms of asthma, which was measured using the methacholin bronchoprovocation test and supported by a volume of anti-inflammatory medication plan to achieve control over the asthmatic symptoms, as well as quality of life: atopic asthma in children is characterized by more severe symptoms and demands more active anti-inflammatory therapy; the quality of their life is authentically lower. There is no available data that compares the severity of atopic and nonatopic asthma in children.

The results of our study, describing the lung function tests, has revealed the most significant deviations in the group of children with the atopic variant of asthma, which testifies to the maximal degree of chronic inflammation expressiveness and respiratory tract remodeling in this phenotype of asthma.

Our dates confirm the results of the MAS study [17] regarding asthma patients and children with transient symptoms of bronchial obstruction and with the result of studying lung functions in children with atopic and nonatopic asthma from Turkey [18].

Our study indicates the highest mean s-ECP level that was measured in children with atopic (30.0±8.9 pg/mL) vs nonatopic (24.6±7.7 pg/mL) asthma, but not in those with bronchitis (24.6±7.7 pg/mL, p=0.012). These results correlate with those of Joseph-Bowen J [19], which found higher serum ECP levels in atopic children (20.5±18.4), in those with asthma (22.4±19.6), and in those with asthma and atopy (26.6±22.4; all p<0.001) when compared with children with no asthma or atopy (16.1±15.9). The Korean research group [20], showed significantly elevated sputum eosinophil percentages and ECP levels in the cough variant asthma and classic variant asthma vs the control, and no significant differences were found between the two asthma groups. In this study, the ECP parameters did not correlate significantly with methacholine PC in the two asthma groups. Selnes A., suggested the highest mean s-ECP level, (7.1 μg/L; 95% CI: 4.0-10.3), was measured in children with clinically diagnosed asthma [21]. However, the serum eosinophil cationic protein (ECP) concentration to peripheral blood eosinophil count ratio, but not ECP alone, was found to be the best predictor of asthma severity in Polish children and correlates with airway hyperresponsiveness measured by histamine challenge [22].

Therefore, an increased serum level of ECP in a patient with diagnosed asthma indicates an ongoing eosinophilic inflammation. Such inflammation may have been induced not only by allergens, but also by infections, environment or intrinsic factors. The ongoing eosinophilic inflammation should, therefore, be assessed as an increased risk of evolving symptoms and acute asthma exacerbation in case of further

exposure to trigger factors.

However, the development of a chronic inflammation and bronchial hyperresponsiveness in patients with the absence of atopy and sensitizations, testifies to the presence of alternative Th-2 skewed mechanisms of the pathogenesis of bronchial asthma.

The majority of the earlier studies have showed the association of selective IgG subclass (IgG Sc) deficiency with increased susceptibility to upper respiratory tract infections. Since then, IgG Sc measurements have become an established tool in the differential diagnosis of immunologic deficiencies. The prevalence of the IgG subclass antibody deficiency in children is controversial, for example Caksen et al. [23], found a decreasing mean IgG 4 level in children with recurrent respiratory tract infection. Karaman showed a trend towards a higher concentration of the IgG 4 subclass in wheezing infants [24]. Kitz R., observed an increasing IgG 1 level in the bronchoalveolar lavage fluid in children with nonallergic asthma [25]. These changes were identical to the group with chronic bronchitis. Cleonir de Moraes et al., found IgA and IgG 3 subclass deficiency in asthmatics 7-15 years of age, although patients were not divided according to their atopy status [26]. The own dates of the studying of the status of Igs revealed significantly higher mean levels (1.96±1.1 g/L) of the IgG 4 subclass in nonatopics when compared with the atopics (0.3±1.7 g/L; p=0.016), which was associated with a decreased IgA level (1.1±0.1 g/L) when compared with the atopics (1.3±0.3 g/L; p<0.05). Earlier studies showed the different patterns of infection factors in the exacerbation of asthma in children with evidence of atopy. Related to these findings, we postulate, that exposure to viral and bacterial infections is the main environmental factor that influences the susceptibility to the development of asthma in nonatopic individuals with changes in the antimicrobial immune response.

Conclusion

The results of our study show that both atopic and nonatopic asthma are inheritable diseases, with similar inflammatory changes and BHR, but with probably different genetic mechanisms, including the genetic changes in susceptibility to infection.

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