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Childhood Asthma and its Comorbidities

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SUMMARY

Numerous comorbidities are frequently associated with asthma and may influence the clinical expression and severity of asthma. The aim of our study was to determine the presence and prevalence of other diseases in children with asthma, both of allergic and non-allergic origin. The study included 974 non - hospital patients, of whom 669 had asthma, while 305 children had wheezing bronchitis. Allergic rhinitis was diagnosed in 196 (29.30%) patients, eczema in 31 (4.63%) patients, and rhinitis and eczema, at the same time, in 13 children (1.94%). Non - allergic diseases diagnosed in children with asthma were: obesity in 31 (4.63%) patients, IgA deficiency in 8 (1.2%) patients, autoimmune diseases in 7 (1.05%) patients and infectious diseases in 6 (0.90%) patients. Atopic disease of childhood and their comorbidities comprise a large component of general pediatric practice and their incidence in developed countries has been increasing over the past few decades. Developing a sensible approach to the diagnosis and treatment of these disorders in an outpatient setting is essential.

Key words: **asthma, childhood, comorbidity**

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INTRODUCTION

Bronchial asthma is currently defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early in the morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment" (1, 2). Although epidemiological studies of childhood asthma are particularly difficult, there is evidence that the mortality and morbidity from asthma have been increasing, especially over the last 20 years (3).

Asthma is most frequently mild to moderate, but significant proportion of patients has severe asthma (3, 4). The prevalence of comorbidities seems to be particularly high in severe asthma, and may be particularly detrimental to asthma control in such individuals (1). Various comorbid conditions are increasingly recognized as frequent contributors to uncontrolled asthma, although their role in the clinical expression of asthma has not been fully elucidated (1, 3, 4). The most frequently encountered comorbid conditions associated with asthma are rhinosinusitis, gastro-esophageal reflux disease (GERD), psychological disturbances, chronic infections and obstructive sleep apnea (OSA). The conditions described above may modulate asthma severity in various ways. They may: 1) be responsible for the development, or an evolution towards, a different asthma phenotype (as is probably the case with obesity, smoking, aspirin intolerance and allergic bronchopulmonary aspergillosis); 2) be a part of the same pathophysiological process (*e.g.* rhinitis and asthma, as per the united airways hypothesis); 3) act as confounding factors in the diagnosis or control assessment (*e.g.* obesity and OSA); and/or 4) be associated with a specific exposure or condition that can modulate the clinical expression of asthma or affect the efficacy of or compliance to treatment (*e.g.* GERD, respiratory infections, smoking and psychological disturbances) (1).

AIM

The aim of the study was to determine the presence and prevalence of other diseases in children with asthma, of both allergic and non-allergic origin.

PATIENTS AND METHODS

In the period from January 1, 2005 to June 31, 2008, 974 outpatients (children) were analyzed, total number of visits - 3.376. Diagnosis and classification of asthma according to severity of disease was established on the basis of the guidelines provided by the Global Initiative for Asthma (GINA) in collaboration with The National Heart, Lung and Blood Institute and The World Health Organization (2). Allergic sensitization was determined in all subjects by using skin prick tests (SPTs) to standard (Institute of Virology, Vaccines and serums - "Torlak") aeroallergens (grass pollen mix, tree pollen mix, wedd pollen mix, dust mite mix, house dust mite, cat and dog epithelia, mold mix, feathering) and, in addition, histamine and physiological saline acted as the positive and negative controls, respectively. Sensitization was defined as present when there was a wheal greater than 3 mm and greater than a wheal produced by the saline negative control. Pulmonary function was tested by spirometer Schiller SP1. A child was considered to have asthma if it had asthma and a positive SPT response to at least one aeroallergen.

Diagnosis of wheezing bronchitis was based on an attack of wheezing in anamnestic data and one verified attack by a doctor with a negative family history of the presence of allergic diseases.

RESULTS

The study included 974 children, of which 669 (68.69%) were diagnosed with asthma, while 305 (31.31%) children were diagnosed with wheezing bronchitis. The study included children with asthma aged 1-18 years, mean aged 8.71±3.75 years. The onset of asthma in the 1st year of life was recorded in 156 (23.32%) patients, up to 3rd year in 263 (39.3%) and after the 3rd year in 250 (37.37%) patients. Average duration of disease in patients with asthma was 5.01 years, while in patients with wheezing bronchitis 0.53 years. The prevalence of asthma was higher in boys (56.80%) than in girls (43.20%), in ratio 1.31:1. Five hundred and four (75.33%) patients had atopic, while 165 (24.67%) patients had nonatopic asthma. Intermittent asthma was diagnosed in 289 children (43.20%), mild persistent in 288 (43.05%) and moderate persistent asthma in 92 patients (13.75%).

Preventive therapy was prescribed to some patients, depending on severity and frequency of attacks. The most frequently prescribed drugs: fluticasone propionate was prescribed to 304 (45.44%) patients, budesonide to 83 (12.41%) patients, beclomethasone dipropionate to 42 (6.28%) patients, montelukast to 166 (24.81%) patients, the combination fluticasone/salmeterol to 64 (9.57%) patients or the combination *budesonide/formoterol fumarate* dihydrate to 26 (3.89%) patients (Figure 1).

The length of the therapy (up to 6 months, 6 to 12 months and more than 12 months) was determined for each patient individually. Our results show that the majority of patients (44.66%) used a preventive medication lasting up to 6 months, 13.68% of patients were treated from 6 months to 12 months and 14.59% were treated more than 12 months.

Allergic diseases diagnosed in our patients were allergic rhinitis and eczema. Allergic rhinitis was diagnosed in 196 (29.30%) patients, eczema in 31 (4.63%), while rhinitis and eczema in 13 patients (1.94%).
Non-allergic diseases associated with asthma in our patients were overweightness and obesity - 31 (4.63%) patients, IgA deficiency - 8 (1.2%) patients, autoimmune diseases - 7 (2 RA, 2 Hashimoto's thyroiditis, 2 IDDM and 1 celiac disease) patients, infectious diseases (kala-azar disease, EBV infection) and heart defects. Other diseases, including hypercholesterolemia, hemophillia A, nephrotic syndrome, gastroesophageal reflux, telangiectasia, facial nerve paresis and focal gliosis of the central nervous system were present in 10 patients (Figure 2).

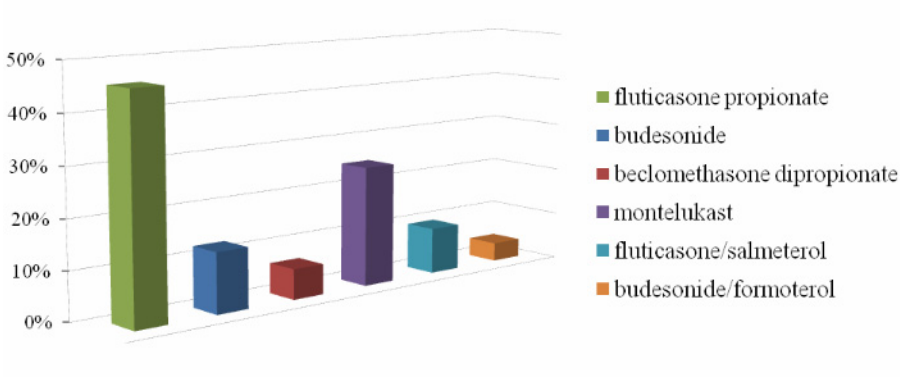

Figure 1. *The representation of drugs used to prevent asthmatic symptoms*

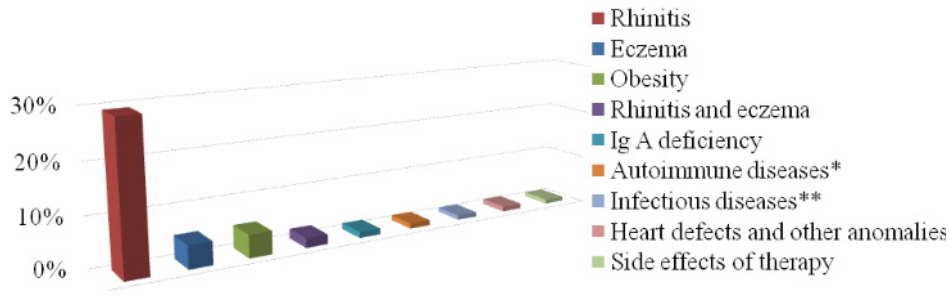

Figure 2. *Prevalence of comorbidities in children with asthma*

*Autoimmune diseases in our results included: rheumatoid arthritis, Insulin dependent diabetes mellitus, Hashimoto's thyroiditis and celiac disease
**Infectious disease that were found: kala-azar and Epstein- Barr Virus infection

DISCUSSION

Asthma is a chronic inflammatory disorder of the airways. This chronic inflammation is associated with increased airway responsiveness to a variety of stimuli and with recurrent symptoms and reversible airflow limitation, all typical of asthma. Childhood asthma is more prevalent in boys than in girls. Also, in our study a larger number of patients were male; the ratio of males and females was 1.31:1. Several studies suggest a role of sex hormones in the pathogenesis of asthma (5, 6). More females than males develop asthma during puberty and thereafter, so the prevalence of adult asthma becomes higher in females than in males (2).

Asthma is a disease caused by multiple environmental and genetic factors (7). There is a strong genetic predisposition towards atopic diseases. The term atopy has been used to define a variety of allergic disorders including allergic rhinitis, asthma, eczema, and other less well-defined allergic entities. The importance of atopy as the key factor for initiation and maintenance of clinical asthma is most widely accepted for childhood asthma. Overall, atopy is present in approximately 80% of asthmatic children (8, 9), and in our study in 75.33% of children.

Allergic rhinitis (AR) affects almost 94 million Europeans, 50 million Americans and 10 million Cana-

dians (10). In one study, 42% of children were diagnosed with AR by the age of 6. The prevalence of AR has dramatically increased in the past 30 years and continues to increase. Children with one component of atopy (AR, asthma, eczema) are thrice at risk of developing a second component (11). The overall prevalence of allergic rhinitis for the 13-14 years old children in Serbia and Montenegro is 15.9% (12).

Our results show that the greatest numbers of asthma - associated diseases are certainly rhinitis (29.30%) and eczema (4.63%), which is related to the influence of genetic factors (atopy) in the development of asthma and these comorbidities. Allergic rhinitis is associated with an increased risk of asthma. The upper airways conditions, such as allergic or nonallergic rhinitis and sinusitis, are commonly associated with asthma and influence asthma outcomes, although there is still controversy regarding the magnitude of this effect. There is epidemiological evidence that asthma and atopic dermatitis often overlap early in life, with the latter also being a risk factor for asthma and being associated with severe forms of this disease (1).

Obesity is associated with an increased prevalence of asthma, particularly among the morbidly obese and the females, and a causal relationship between obesity and asthma has been suggested by recent animal and human studies. Asthma in the obese patient appears to be a specific phenotype associated with pulmonary function changes caused by breathing at low lung volumes, a systemic inflammatory process that may possibly influence airways and a reduced response to asthma medications (13-15). During the five-year follow-up study, involving 9.828 children aged 6-14 years, there is evidence that obese children often suffer from asthma and that this trend is more expressed in girls (16, 17). The incidence of asthma is five to seven times higher in girls after 11 years, which are becoming obese, as opposed to those who stay slim, while this link does not exist in boys (17). One Finnish study (18) which included 4.719 children, showed higher risk of contracting asthma in adult age (31 years) in the subjects with obese phenotype at the age of 14 years. Recent examination of 4.393 children, without asthma symptoms until the second year of life, during the fourteen-year follow-up, shows that a group of children with elevated BMI has 2 to 4 times greater risk of developing asthma than children with normal BMI (19). In our study group of children with asthma, 31 (4,63%) children are obese or overweight.

In allergic responses, exposure to environmental allergens leads to a predominance of T cells, termed Th2 cells, which produce IL-4, IL-5, and IL-13. Th2 cells and their cytokines stimulate allergen-specific IgE production to orchestrate aberrant immune responses and allergic inflammation ensues. The two pathways, Th1 and Th2, are thought to be mutually exclusive and the decision of helper T cells to differentiate into Th1 cells inhibits the production Th2 cells, and vice versa (20). The simplistic interpretation of the Th1/Th2 paradigm implies that Th1-dominant and Th2-dominanat diseases are mutually exclusive. However, recent studies have demonstrated that these diseases can coexist and some of the factors responsible for the increasing prevalence of atopic diseases (*eg*, reduced number of infections) may also play a role in the increase in autoimmune diseases in developed countries (21). An evaluation of 60 254 children during the first 7 years of life in the cohort of the Finnish Medical Birth Register revealed that asthma was associated with the presence of celiac disease, RA and IDDM (22).

In our study group, there were seven children with autoimmune diseases, two of them had RA, two children had Hashimoto's thyroiditis, and there were two children with IDDM and one with celiac disease.

Numerous comorbidities are frequently associated with asthma and may influence the clinical expression and severity of asthma. The presence of comorbidities has significant implications in terms of the evaluation and assessment of asthma control and medication needs. It has been shown that many of these conditions may worsen asthma severity or render asthma control more difficult to achieve, in addition to altering the response to current asthma medications (1).

CONCLUSIONS

Atopic disease of childhood and its comorbidities comprise a large component of general pediatric practice and their incidence in developed countries has been increasing over the past few decades. Pediatricians are in the position of being able to identify and treat these disorders at an early age. Early diagnosis and aggressive management of these disorders seem to offer the possibility of altering their natural history. As such, developing a sensible approach to the diagnosis and treatment of these disorders in an outpatient setting is essential.

APPENDICES

Abbreviations

SPT- skin prick test
RA - rheumatoid arthritis
IDDM - Insulin dependent diabetes mellitus
EBV - Epstein- Barr Virus
AR - Allergic rhinitis
BMI- Body mass index

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ASTMA U DETINJSTVU I NJENI KOMORBIDITETI

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Sažetak

Brojni komorbiditeti povezani sa astmom kod dece mogu da utiču na kliničku sliku i težinu astme. Cilj našeg istraživanja bio je da se utvrdi učestalost drugih bolesti, alergijskog i nealergijskog porekla, kod dece sa astmom. Istraživanjem je obuhvaćeno 974 vanbolničkih bolesnika od kojih je 669 imalo astmu,

dok je 305 dece imalo wheezing bronhitis. Alergijski komorbiditeti, rinitis i ekcem, dijagnostikovani su kod 196 (29.30%) i 31 (4.63%) bolesnika, dok istovremeno rinitis i ekcem kod 13 dece (1.94%). Nealergijske bolesti koje su dijagnostikovane kod dece sa astmom su: gojaznost 31 (4.63%), Ig A deficijencija 8 (1.2%), autoimune bolesti 7 (1.05%) i infektivne bolesti 6 (0.90%). Učestalost atopijskih bolesti i njihovih komorbiditeta u detinjstvu je u poslednjih nekoliko decenija u porastu u razvijenim zemljama i čine veliki deo opšte pedijatrijske prakse. Od suštinske je važnosti razvijanje razumnog pristupa dijagnozi i lečenju ovih poremećaja u ambulantnim uslovima.

Ključne reči: **astma, detinjstvo, pridružene bolesti**