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Allergic asthma and rhinitis comorbidity

Komorbiditet alergijske astme i rinitisa

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Introduction

Allergic respiratory diseases, asthma and rhinitis, are rightly called the 21st century epidemic and modern age diseases. Although modern medicine offers a variety of preventive and therapeutic strategies, the prevalence of these diseases has been dramatically increasing in both developed and undeveloped countries across the world, especially in children and young adults. The World Health Organization (WHO) estimates there are 300 million asthmatics in the world, and 500 million people with the symptoms of rhinitis. Very often, asthma and rhinitis coexist in one patient. Numerous contemporary studies, guided by the concept „one airway – one disease", have revealed the epidemiological, pathophysiological and clinical correlation of asthma and rhinitis. A greater scientific interest in these diseases is due to a constantly growing number of the affected in the world, accounting for describing the last three decades as „the age of respiratory allergy". The coexistence of the upper and lower airway disorders is not a new discovery, as it had been recognized over two thousand years ago. It is therefore amazing that it took centuries to establish the concept of concurrence of asthma and rhinitis, and realize the importance of their diagnosis and adequate treatment [1].

Definition of asthma and allergic rhinitis

The Global Initiative for Asthma (GINA) was promoted in 1995, proposing a new definition of asthma, which has been used and quoted in modern literature ever since. According to this definition „Asthma is a chronic inflammation of the airways, with a variety of cells playing an important role in it, including mastocytes, eosinophils, T-lymphocytes, and epithelial cells. In hypersensitive subjects, this inflammation induces recurrent episodes of wheezing, suffocation, chest tightness and cough, particularly during the night and/or early in the morning. These symptoms are related to a widely spread and changing, either spontaneously or by medicaments, at least partially reversible obstruction of the air flow through the airways. The inflammation also induces hyperreactivity of the airways to diverse stimuli, existing even when neither the disease symptoms, nor bronchial obstruction are manifested". The fundamental feature of asthma is a long-term, chronic inflammation which induces hyperreactivity and obstruction of the airways [2].

In 2001, the WHO published the guide „Allergic Rhinitis and its Impact on Asthma" (ARIA), representing a directive for prevention, diagnosis and treatment of rhinitis. Allergic rhinitis is defined as an inflammation of the nasal mucosa, mediated by the IgE mechanism, which is clinically manifested by the symptoms of sneezing, nasal secretion, blocked and itching nose, often accompanied with eye symptoms [3, 4].

Epidemiology of asthma and allergic rhinitis

In 2004, it was reported that about 300 million people of all ages suffered from asthma. This number has been increasing from year to year, becoming doubled or tripled in many countries. The disease severity is unevenly distributed, being mild in most cases, while severe asthma forms are registered in the minority of the patients (around 15%). It is assessed that another 100 million people will be affected by the disease until 2025 [5, 6].

Allergic rhinitis is the most common disorder of respiratory organs, owing its importance to its significantly in-

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creasing frequency, effects on the life quality and working ability of the affected, and high diagnostic and treatment costs. This disease is therefore recognized as a global health issue. It has been estimated that about 20–35% of the total world population suffer from allergic rhinitis, taking the fifth position on the morbidity list. The ARIA directive reports that about 500 million people all over the world have allergic rhinitis, which is four to six times as many as asthma cases, particularly in children [4].

Many studies have reported a coexistence of these two allergic disorders of the respiratory tract–asthma and rhinitis, in the same patient. The prevalence of allergic respiratory diseases has been doubling every ten years since the 80s of the 20th century. The reported prevalence varies from study to study, depending on the applied diagnostic criteria, the environment and age of the tested population. The ratio of "three rhinitis cases: one asthma case" has been registered in all countries, in both children and adults. The 1st International Study of Asthma and Allergies in Childhood (ISAAC) study revealed the presence of asthma in 25–35% subjects with rhinitis, and rhinitis symptoms in 75–90% of asthmatics. Rhinitis was found in 62.61% of atopic, and in 45.4% of non-atopic asthmatics, confirming that the concomitance of rhinitis and asthma was not limited exclusively to allergy [7–9]. In their study, Zvezdin et al. [10] reported that in 733 patients with diagnosed allergic asthma, the frequency of concomitant rhinitis was 64%, while in those with nonallergic asthma, it was 28%.

Many studies report the highest incidence of asthma in children and young adults at 20–29 years of age (7–11%). The highest incidence of rhinitis was also registered in children, adolescents, and young adults. In our population, the mean age of the patients with asthma and rhinitis, examined in two studies, was 29.71 years, and the majority of the affected patients belonged to the age group of 18–30 years (52%) [10, 11].

Causes of allergic respiratory diseases

The real cause of the increasing number of allergic subjects is unknown. Allergic diseases are complex and develop through interaction of internal factors of an organism, and external environmental factors. There are a lot of factors contributing to the development of asthma and rhinitis, which most commonly act in synergy. Generally, they are classified into predisposing, causing and contributing ones, representing a combination of internal and external factors [2].

Atopy is the major predisposing factor. It is defined as a disposition of an organism to produce increased quantities of IgE antibodies in response to different substances from the external environment. The atopic constitution has been confirmed to occur more frequently in some families, so the children with this constitution have a greater susceptibility to develop an allergic disease, even 16–20 times as high as non-atopic subjects. If a parent has allergy to an inhalant allergen, the probability that a child will also develop it amounts to 30–50%, increasing to even 60–80% if both parents suffer from allergy. Over 90% of asthmatic children have atopy. Asthma is usually associated with other atopic diseases, allergic rhinitis and atopic dermatitis. Atopic infants, hypersensitive to eggs, house dust and house dust mites are more at risk of developing asthma later in life [12, 13]. Of 733 subjects with diagnosed asthma in our country, 34.9% had a positive family history, more frequently on the mother's side [10].

Sex is considered a predisposing factor. Until the age of five, boys are more frequently affected than girls, explained by the fact they have narrower airways and an elevated tonus of the bronchial musculature, reacting more intensely to diverse stimuli, as well as a huger level of IgE antibodies. After puberty, the frequency is higher in females, which is explained by hormone effects associated with the reproductive and menopausal period, administration of oral contraceptives, greater exposure to internal allergens and indoor irritants, and a higher susceptibility to smoking effects 13. Zvezdin et al. [10] more frequently confirmed the comorbid disease of the airways in females (64.3%), in the ratio of 1.8:1 in favour of females.

Causing factors are inhalant allergens, which induce sensitisation of the airways, and stimulate production of specific T-lymphocyte clones and specific IgE antibodies. At a repeated contact with the allergen to which a subject has already been sensitised, the disease exacerbates, the inflammatory process is initiated, and characteristic symptoms of the disease emerge. Inhalant allergens are generally classified as internal, external, and professional. An exposure to inhalant allergens contributes to both an exacerbation of the symptoms, and the genesis of the disease itself. Hypersensitivity to at least one of the standard inhalant allergens has been registered in 79.5% of the patients diagnosed in the Institute for Pulmonary Diseases of Vojvodina, most of them hypersensitive to internal allergens (77.5%), predominantly house dust mites (76.1%) [14].

Contributing factors are those which increase the risk of the disease when they come in contact with a causing factor. Contributing factors are smoking, outdoor respiratory irritants (air pollution), indoor irritants, early allergic sensitisation, obesity, infections, nutritional factors, socio-economic status, life style, risk factors related to pregnancy, delivery, and early neonatal period of life, and many others. The role of smoking as a factor contributing to asthma exacerbation, recurrent hospitalisations, bad treatment response and disease control has been unquestionably confirmed for both the active and passive smoking, although some studies failed to establish a positive correlation. A higher risk of the disease is registered in children whose mothers smoked in pregnancy and early childhood. Smokers have higher IgE levels than nonsmokers. Smoking cessation has been established by the WHO as a sole reliable primary prevention measure to prevent the development of allergic diseases [15]. Among the subjects of the study carried out in our country, there were 73.9% nonsmokers, 12.2% *ex* smokers, and 13.9 % active smokers [11].

Classification of asthma

Many attempts have been made to classify asthma in regard to its etiology. The most common classification of asthma to extrinsic and intrinsic has been in use since the

first half of the 20th century. Atopy is defined as a genetic hypersensitivity and hyper production of IgE antibodies. The term is used to describe both the clinical condition and predisposition. Recently, more suitable terms "allergic" and "nonallergic" have replaced the former terminology, and they are included in the official nomenclature of the European Academy of Allergy and Clinical Immunology [16]. In time, it has become quite clear that asthma has heterogeneous manifestations, explained by the phenotype, defined as the interaction of the genotype and the environment. Some phenotypes have been described: aspirin-induced asthma, inflammatory-eosinophil and non-eosinophil (neutrophil) asthma, which respond to the applied corticosteroid treatment differently from exacerbations, and are confirmed by the induced sputum method and detection of inflammatory markers, which are predictive of the risk, and particularly of sensitising environmental substances [2]. According to its immunological mechanism and inducing agent, asthma is classified as allergic or nonallergic. Allergic asthma usually starts earlier in life and is characterised with an elevated specific IgE antibody level, positive "prick" test, positive family history, and other recurrent allergic diseases (atopic dermatitis, food allergy, allergic rhinitis). According to the Global Initiative for Asthma, 70–90% of the patients have allergic asthma [2]. The investigation carried out in the Institute for Pulmonary Diseases of Vojvodina has established that of 733 asthmatics, 79.5% had allergic, and 20.5% nonallergic asthma [10]. Nonallergic asthma usually develops later in life, after the forth life decade, more frequently in females, and is characterised with a negative skin test finding, no clinical or family history of allergy, normal serum IgE level, more commonly registered aspirin idiosyncrasyand nasal polyps, and usually a more dramatic clinical course. Intrinsic asthma is considered a form of auto-allergy (usually develops after a viral infection episode), i.e. the affected subjects are allergic to an unidentified allergen. Except a different etiological immune mechanism involved in two asthma types, they both have similar pathophysiological and pathoanatomical changes of the airways, and an identical therapeutic approach. The positive skin test finding to inhalant allergens does not necessarily mean the disease is allergic in type, or the disease or its exacerbation are caused by the allergen. The measurement of the total IgE antibody levels in the serum does not have a diagnostic value for atopy confirmation [2].

Specific entities of asthma include professional, seasonal (pollen), aspirin-, cough-, and effort-induced asthma [2, 17]. Professional asthma is defined as asthma induced by inhalant allergens present in the work environment. About 200 specific allergens have been identified so far, and this number has been constantly increasing. It has been estimated that professional asthma makes about 7% of the total adult asthma cases. The clinical, functional and pathological changes in professional asthma resemble those in nonprofessional asthma, and the therapeutic approach is also identical. An adequate and objective confirmation if the diagnosis is very important, and it is obtained by a specific challenge test, performed in high-specialised medical institutions, or by peak expiratory flow (PEF) monitoring measurement four times a day over two weeks, in the same time period at work and rest [2, 18]. Pollen, seasonal asthma is characterised by the onset of the symptoms during the pollination season, most frequently associated with allergic conjunctivitis and rhinitis [17]. Aspirin-sensitive asthma is a specific clinical syndrome in which asthmatic attacks are induced by aspirin and other non-steroid anti-inflammatory drugs. The mechanism is not allergological and is defined as a pseudo-allergic reaction (idiosyncrasy). Aspirin asthma is registered in 5–10% of adult asthmatics. These drugs inhibit cyclooxygenase, so the metabolism of the arachidic acid is mediated by lipoxygenase, inducing an increased production of cysteinyl leukotrienes and the development of bronchospasm. Having taken the incriminated drug, a severe asthma attack usually develops in an hour. Once developed, the drug intolerance persists during the lifetime. It is confirmed by the oral or inhalatory challenge test, if forced expiratory volume during the first second (FEV1) of a forced expiratory maneuver decreases for over 20%, or for 15% with the signs of bronchospasm, sneezing or conjunctivitis. These patients tolerate paracetamol, sodium salicylate, chloroquine, choline salicylate [19]. Cough-Variant asthma is one of the most common causes of chronic cough, persisting over two months. Cough is a sole symptom, often irritating in character, lasting day and night, provoked by effort or infection. It may develop in both children and adults. The bronchial challenge finding is usually negative, diurnal variability of the symptoms and lung function are absent. It is established by the positive bronchial challenge test finding, the presence of eosinophils in the induced sputum, but it is most often confirmed clinically, when cough disappears after the treatment with inhalant corticosteroids [2, 17, 20]. Exercise-induced asthma typically develops in younger adults, 5–10 minutes after exercise (rarely during exercise), with the symptoms of dyspnea and cough, lasting for about 30 to 45 minutes, and it most frequently disappears spontaneously. This type of asthma is considered to be induced by accelerated and increased ventilation, breathing through the mouth, cold air inhalation. A reduced hydro layer of the airways induces its hyper viscosity, which is a stimulus for mastocyte degranulation and a release of mediators. Cooling down on exercise induces vasoconstriction of peribronchial vascular plexuses; upon discontinuation of exercise, there develops heating, oedema, hyperemia of the mucosa and lumen constriction. Oscillations of the temperature and osmotic pressure stimulate both the local and central nerve reflexes. The accurate diagnosis is very difficult to establish. Some patients, most frequently children, develop the symptoms only at exercise. To confirm the diagnosis, they are submitted to exercise tests, including an easily performed 8-minute running protocol [17, 20].

According to the GINA, asthma is classified into four types, depending on the severity of clinical symptoms, applying no inhalant corticosteroids: occasional (intermittent), mild permanent (persistent), moderate persistent, and severe persistent. The severity of asthma is assessed in relation to the frequency and duration of the symptoms, intensity of the air flow limitation in the airways (FEV1), and variability of the bronchial obstruction (PEF variable). This staged classification has a clinical relevance, as the treatment approach,

although individual ("everyone has one's own asthma"), predominantly depends on the disease severity stage [2, 17]. In 2006, a new classification of asthma, related to the achieved disease control, was proposed. Depending on the exhibited clinical symptoms, this classification differentiates three asthma types: controlled, partially controlled and uncontrolled [2].

Classification of allergic rhinitis

Etiologically, rhinitis is classified as allergic and nonallergic [acute and chronic infectious, idiopathic, professional, drug- or food-induced, hormonal, irritant, emotional, atrophic and nonallergic rhinitis with eosinophil syndrome (NARES)] [1]. Since the mid 90s of the 20th century, several programmes and guidelines for the diagnosis and management of rhinitis have come out, supported by international allergology associations and the WHO. The first consensus, published in 1994 in Copenhagen (Rhinitis Management Group), proposed to classify the allergic rhinitis as seasonal and rhinitis persisting through the year [21]. The initiative of the WHO "Allergic Rhinitis and its Impact on Asthma", launched in 2001, was more widely supported and accepted [3]. The mission of this initiative was to promote the latest achievements in this field throughout the world, aiming to change the approach to these concomitant diseases and contribute to their better management. The initiative proposed a new classification of allergic rhinitis as intermittent and persistent, which were not synonymous with former classification classes. In intermittent rhinitis, the symptoms are manifested for less than four days a week, and less than four weeks a year, in persistent rhinitis more than four days a week, and more than four weeks a year. The new classification is therefore more appropriate, as most patients have a combined inhalant allergy [3, 4].

The severity assessment of allergic rhinitis does not depend on the applied treatment. The objective factors for the severity assessment of allergic rhinitis are the type and severity of symptoms, visual analogue scale (VAS), nasal obstruction measurement [(peak inspiratory flow, acoustic rhinometry and i rhinomanometry)], inflammation assessment (exhaled nitric oxide (NO) measuring, cells and mediators present in the nasal lavage fluid and nasal biopsy sample), nasal challenge test with histamine, metacholine, allergens, hypertonic solution, capsapicin or cold dry air, smell test. To assess the severity of rhinitis, VAS is applied in every-day clinical practice. A patient assesses the severity of each symptom scoring on the 0–10 scale, simply adding up the selected scores to provide the severity assessment score ("symptom score") of allergic rhinitis. The scores of 0–3, 4–7, and 8–10 characterise mild, moderate, and severe allergic rhinitis, respectively [4].

Allergic respiratory diseases: the diagnosis

It has been generally assessed that allergic respiratory diseases are insufficiently diagnosed and inadequately treated all over the world. To diagnose both allergic rhinitis and asthma is a continuous process, which often requires numerous and recurrent examinations of patients. The diagnosis is established on the basis of a patient's history, physical and objective examination, and additional examinations. Asthma-suggesting symptoms include suffocation attacks, wheezing, tight chest and cough during the day or most often at night, preceded by provoking factors (exercise, cold, exposure to allergens or irritants, specific food or drug intake, positive or negative emotions, premenstrum, etc.). The symptoms are episodic in character, appearing after an exposure to allergens, and season-variable. Rhinitis-suggesting symptoms are sneezing, dripping nose, nasal teasing and itching, blocked nose. The information of the family, personal and professional history are also important [4].

The following diagnostic procedures are recommended to establish the diagnosis of asthma: clinical examination (symptoms and physical examination, complete history), lung function tests (spirometry, PEF, bronchodilatatory test, specific and nonspecific bronchial challenge), which establish the diagnosis of asthma, the severity of bronchial obstruction and their reversibility/irreversibility, allergological tests ("prick" skin test, specific IgE antibody measurements), which identify the risk factors for exacerbations, in some patients, radiological examinations [chest X-ray, sometimes computed tomography (CT) of the chest], measurements of inflammation markers (inflammatory cells and mediators in an induced sputum sample, bronchoalveolar lavage fluid and bronchial biopsy sample, measurement of mediators or their metabolites in the blood and urine, measurement of NO concentrations in the exhaled air) [2].

The diagnostic procedures for allergic rhinitis include: clinical examination (history taking and anterior and posterior rhinoscopy), allergy status tests ("prick" skin test, measurement of specific IgE antibody levels), nasal mucociliary clearance tests (saccharine test, measurement of the cilia frequency in the nasal mucosa, electronic microscopy) in some cases, rigid and flexible endoscopic examination of the nasal cavity, radiologic examinations, smell tests, nasal flow tests [peak nasal inspiratory flow (PNIF), anterior and posterior rhinomanometry], bacteriological diagnostics, cytological examination of scraped nasal mucosa and analyses of nasal secretions for inflammatory mediators (cytokines, chemokines…), measurements of mediators and enzymes in the peripheral blood (histamine, prostaglandine D2 (PGD2), leukotriene C4 (LTC4), LTD4, LTE4, tryptase, quinines, eosinophil cationic protein (basally or after allergen challenge), nasal challenge tests (risky in patients with asthma) [4].

Allergic respiratory disease: therapy procedures

Inflammatory lesions in allergic asthma and rhinitis are very complex, so it is not always sufficient to inhibit only one mechanism in the treatment of these diseases. Multiple therapeutic approaches are required to achieve a good control of both diseases. The treatment objectives in asthma, according to the GINA, are reduction or elimination of the symptoms, improvement of life quality, prevention of complications, improvement of the course and prognosis of the dis-

ease, long-term control of the disease using as few medicaments as possible in the lowest possible doses. The treatment includes education, prevention, pharmacological treatment, and immune treatment [2].

Preventive measures include the general preventive measures, avoiding the contact with allergens. The general measures mean evasion of all the factors which increase the nasal and bronchial hyperreactivity and the symptoms, such as: smoking, sudden external temperature changes, air conditioners, strong and irritating scents and light. The patients are advised how to avoid the contact with allergens and reduce their concentration (for some allergens or in cases of an established professional disease, these measures may be very efficient). It is also necessary and very important to educate the patients about their diseases' primary features, way of life, treatment mode, adequate application of inhalant substances, what to do in exacerbations, particularly of asthma. The patient-physician partnership is very important [2]. Medicamentous treatment includes a specific combination of drugs for each disease. A uniform approach is not possible due to different severity stages of the disease, predisposing factors, patients' age, length of the disease. An individual approach is applied for each patient. The therapy of asthma included several pharmacological groups of drugs (inhalant and oral corticosteroids, β2-agonists, anticholinergics, theophylline (xanthines), antileukotrienes and anti- IgE therapy (omalizumab)), as well as the treatment of rhinitis (oral and intranasal H-1 antihistaminics, intranasal and oral corticosteroids, antileukotrienes, intranasal chromones, oral and intranasal decongestives, anticholinergics). The choice of the pharmacological treatment depends on the severity and frequency of symptoms, patients' motivation and compliance, availability of the drugs and their possible undesirable side effects.

Modern pharmacotherapy of allergic respiratory diseases provides a better quality of life of the affected patients, and normal personal, social, professional and physiological functioning. As asthma is a chronic inflammatory disease, it is considered it should be continuously and permanently treated. The staged treatment approach means that the medicaments are applied depending on the achieved effects and response to the treatment applied so far. The kinds and doses of the applied drugs are increased with the increasing severity of the disease, and the next, higher treatment level is indicated when a satisfactory control of the disease is not achieved by the former one. The major treatment objective is the best disease control with fewest drugs [2, 4].

Asthma and rhinitis: correlation mechanisms

The interpretation of respiratory allergy has been significantly changed due to the recognized correlation between rhinitis and asthma, including their epidemiology, anatomy, physiology, immunopathogenesis, and particularly therapy.

The relationship between the upper and lower part of the respiratory system was recognized 2000 years ago. In the 2nd century, Galen recommended frequent elimination of the nasal content to free the lungs, and in the 19th century Bostock emphasized that the respiratory system is a united entity. After these historical observations had been made, there succeeded a long period of silence until three decades ago, when „the age of respiratory allergy“ started, marked with a great interest of scientists and clinicians in this field, and a great number of published papers on allergic diseases of the respiratory system. Respiratory allergy is nowadays considered the disease of the entire respiratory tract, which is clinically manifested as asthma and/or rhinitis. Many terms have been proposed in the literature to describe this phenomenon: combined allergic rhinitis-asthma syndrome, allergic rhinobronchitis/allergic asthma-rhinitis association, allergic rhinitis/asthma syndrome, allergic rhinitis and asthma comorbidity, allergic rhinitis and asthma – the same disease, chronic allergic inflammatory respiratory syndrome, united airway disease, generalised respiratory inflammation, total respiratory inflammation, and other terms. In 2011, the WHO promoted the ARIA initiative, and the World Allergology Organization formulated the Combined Allergic Rhinitis and Asthma Syndrome (CARAS) initiative. These two organizations and their initiatives enabled a uniform approach in the diagnosis, classification and treatment of these, until recently separated diseases [1].

The relationship between rhinitis and asthma has first been recognized empirically, in the clinical practice, and then confirmed epidemiologically, as well. In the 80s of the 20th century, it was for the first time reported that 28–60% of asthmatics had nasal symptoms (compared to 20% of the general population), and 19–38% of the patients with allergic rhinitis might have asthma (compared to 3–5% in the general population) [21]. In 1999, it was reported that about 80% patients with asthma had rhinitis, while asthma was registered in 38% of the patients with allergic rhinitis, and similar findings were also reported by the ISAAC study [3, 22]. It has been estimated that about 5% of the general world population concurrently have both allergic respiratory diseases. In our region, the frequency of comorbid rhinitis in asthmatics amounts to 63.9% [10].

The symptoms of allergic rhinitis usually precede those of asthma. The longitudinal study by Settipane et al. [23] followed the patients with a positive allergy test finding and rhinitis symptoms, reporting that in ten years, 50% of the examined patients had identical symptoms, while 20% (those with perennial rhinitis) developed asthma. The study carried out in our country reports the symptoms of allergic rhinitis preceded asthma in three fifths (60%) of the examined population over the period ranging from 1–27 years, while a concurrent (within the same year) onset of both diseases was observed in two fifths (40%) of the examined [10]. Similar results were also obtained in a former study including fewer patients. A concurrent onset of both diseases occurred in 37%, and rhinitis preceded in 63% of the cases, over the period ranging from 1–11 years. All patients had confirmed allergy to internal allergens and characteristics of persisting allergic rhinitis [11]. The history of pollen fever in childhood increases the risk of asthma three times, or even six times in females, and other factors which also increase this risk are atopy status, patients' age at the moment of the onset of atopy (the younger the patients are, the higher the risk), and severity of rhinitis symptoms [22, 24].

According to Linneberg et al. [25], the relationship between rhinitis and asthma is less evident in pollen hypersensitivity than in hypersensitivity to internal allergens, which is explained by greater dimensions of the pollen seed (10–20 μm) compared to house dust particles (≤ 3 μm). All the patients in our study with concomitant asthma and rhinitis also had allergy to house dust mites [11].

Numerous studies have confirmed the presence of nonspecific bronchial hyperreactivity in patients with allergic rhinitis but no symptoms of asthma, as compared to the patients without rhinitis. The oldest study dating back to 1965 showed that even 73% of the patients with rhinitis had in increased bronchial reactivity to metacholine or histamine. Diverse studies have reported an elevated bronchial reactivity, with no respiratory symptoms, in 24–60% of the patients with rhinitis, who also developed asthma more frequently. Bronchial hyperreactivity (BHR) is higher in subjects with perennial rhinitis and hypersensitive to internal allergens, and in those with a longer history of rhinitis symptoms. Many authors opine the presence of bronchial hyperreactivity in patients with rhinitis may be helpful in identifying those with an increased risk of asthma. Bronchial hyperreactivity may be characteristic of the stage between rhinitis and manifested asthma [24, 26, 27].

Probably, there is a junction between the lower and upper part of the respiratory tree, which may be due to a reduced protective function of the nose, neural interrelation, or inflammatory propagation from the upper into the lower respiratory tree area [28]. Montefort et al. [29] performed bronchial biopsy in atopic asthmatics, atopic non-asthmatics and healthy subjects, and registered histological lesions specific for the asthmatic inflammation in non-asthmatics, which were less intense than in asthmatics.

Although it is out of question that allergic rhinitis may affect the onset and clinical course of asthma, the mechanism of this relationship and mutual influence has not been completely enlightened yet. These mechanisms are generally classified as indirect and direct. Indirect mechanisms are a nasal obstruction and oral breathing, with the important preparation function of the nose impaired. Direct mechanisms include: aspiration of the postnasal secretion with mediators and/or cells into the lungs (post nasal «drip»), resorption of inflammatory cells and/or mediators into the systemic circulation, and the nasobronchial reflex. Oral breathing due to a nasal obstruction induces bronchospasm, while nasal breathing with the preserved nasal function reduces asthma symptoms on exercise. This mechanism is explained by inspiration of the air which has not been formerly hydrated, heated, and purified from allergens and pollutants, which is the major function of the nose [30–32].

The concept that inflammatory cells and mediators descend by gravitation into the lower respiratory tree sounds logical. Investigations on animal models (downward head positioning and intubation-prevented secretion flow) have revealed an inhibited bronchial hyperreactivity, thus proving that the upper respiratory tree inflammation affects nonspecific bronchial hyperreactivity [31]. Littel et al. [33] have pointed out the possibility of a systemic propagation path of spasmogenic substances, instilling higher metacholine doses into the asthmatics' nose, thus increasing the bronchial resistance. They blocked this effect by a vasoconstrictor, showing that the vascular transit of mediators induced a constriction of the lower airways. Another possible mechanism is the presence of inflammatory cells and mediators in the systemic circulation and respiratory system, which are produced by the bone marrow in response to the nasal stimulus. Reversely, Braunstahl at al. [32] have in their study confirmed an inflammatory reaction in the nasal mucosa 24 hours after a segmented bronchial challenge test.

The causes of a significantly increased frequency of allergic respiratory diseases have not been definitely established yet. Numerous factors have been reported as possible agents which affect the expression of these diseases, varying greatly, depending on the geographical region and population features and age. The factors considered important or possible inducing agents of allergic respiratory diseases include: family history (genetic factor), type of allergic sensitisation, active and mothers' smoking in pregnancy and postpartum, living conditions (dirty and humid apartments), climate and life style.

The genetic factor is considered crucial for both diseases. A person whose family member suffers from asthma has three to four times greater risk to develop this disease, too; if a family member has rhinitis, the risk of this disease is five to six times higher. Atopy is inherited autosomally and dominantly (*via* the gene located on the 11th chromosome, but only if maternally). Some studies have revealed the maternal asthma, accompanied with rhinitis and smoking, may additionally increase the risk of asthma [10].

The exposure to tobacco smoke in childhood and active smoking are significant risk factors. Lundback [8] have confirmed that both smokers and ex-smokers with a positive family history of atopy have seven times increased risk to develop rhinitis and/or asthma. In our study, 80% of the patients never smoked, 12% were ex-smokers, and others (8%) were current smokers [5, 10, 11].

The early (in the first years of life) contact with allergens is a significant risk factor, explained by the immunological vulnerability in this period, in which the internal allergens (house dust, house dust mites, animal hair, mold), are more important than the external (pollens) ones. Almost all in the studies world have reported similar results – most patients with allergic respiratory diseases are hypersensitive to house dust mites. The percentage of allergies to external (pollens) allergens varies from country to country, because it depends on geographical features, climate and vegetation. In European countries, hypersensitivity to grass pollens has been most frequently established, and then to tree and weed pollens (allergy to tree pollens is more common in northern, and to weed pollens in southern European countries). The results of the studies performed in our country show the patients with both diseases are mostly sensitive to house dust mites (76.1%), and less to pollens, and the symptoms of the diseases, particularly those of rhinitis, emerged earlier in life [10, 34].

It was long ago when clinicians had empirically observed that an effective treatment of rhinitis and improved nasal function resulted in improved symptoms and a better control of asthma. Since the mid 80s of the 20th century,

several trials have attempted to prove this effect, i.e. the anti inflammatory corticosteroid treatment of rhinitis improves the symptoms of asthma, lung function and bronchial hyperreactivity. The first study which confirmed the positive effects of nasal beclomethasone dipropionate and chromone on rhinitis symptoms, and those of nasal corticosteroids on asthma symptoms in the subjects with confirmed allergy to external allergens was published in 1987. (Welsh et al. [35]). It was followed by the study of Aubier et al. [36] in 1992, having confirmed that nasal corticosteroids reduced bronchial hyperreactivity, unlike orally inhaled ones. In the same year, Corren et al. [37] came to a similar conclusion in their study of seasonal rhinitis and asthma, finding a significantly increased hyperreactivity in the patients receiving a placebo, while in those treated by nasal corticosteroids it remained unchanged.

Numerous studies have been assessing the effect of rhinitis anti-inflammatory treatment on the course and control of asthma. Most studies have reported the positive results of anti-inflammatory corticosteroid treatment of allergic rhinitis on bronchial hyperreactivity and asthma symptoms, although some trials have not confirmed this positive effect [38]. The results of the trials carried out in our country have demonstrated that corticosteroid treatment of rhinitis significantly contributes to improved asthma and rhinitis symptoms, as well as lung function parameters, and is an integral part of the treatment of asthma [11, 39]. Three large-scale prospective studies in the United States have reported fewer hospital and emergency admissions of asthmatics treated for comorbid rhinitis, compared to asthmatics receiving no therapy for rhinitis. The diagnosis and treatment of rhinitis is obligatory and should be included in the treatment of asthma. Untreated rhinitis is one of the causes of frequent asthma exacerbations, its difficult control and treatment, as well as a bad prognosis of the disease [40, 41].

Conclusion

All the studies performed so far conclude rhinitis is a risk factor and predictor of asthma, which it usually precedes. Some authors consider rhinitis and asthma are different clinical manifestations of the same systemic disease. They may occur simultaneously, or the symptoms of rhinitis may follow those of asthma, although more rarely. The ARIA guidelines suggest the patients with asthma should be evaluated for the presence of rhinitis, and *vice versa*. The presence of one of these diseases increases the probability for the development of the other. About 50% of the patients with early developed, long-term rhinitis and allergy to internal inhalant allergens will develop asthma as well. It is therefore important to identify the subjects predisposed for asthma among those with rhinitis. All possible predictive factors known so far cannot confirm the risk with certainty. It is difficult to establish whether rhinitis is the first manifestation of respiratory allergy, or it has a direct role as an inducing agent of asthma. In addition, both asthma and allergic rhinitis are modern-age diseases, most common in well-developed countries, in younger-age, active population. The relationship between asthma and allergic rhinitis has not been explained only theoretically, but its practical relevance has been recognized, as well. The recommendations of the world guidelines (ARIA, GINA and others) for every day clinical practice have been discussed, recognizing the need of additional studies in the diagnostic and therapy management of asthma and comorbid allergic rhinitis. The ultimate imperative is better life quality of the affected patients and their families, and positive effects on the global factors, such as the health care system and financial expenses.

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