ALLERGIC RHINITIS, PART OF THE ALLERGIC RESPIRATORY SYNDROME

ALERGIJSKI RINITIS, DEO RESPIRATORNOG ALERGIJSKOG SINDROMA

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Summary

Introduction. Diseases associated with immunoglobulin E hypersensitivity, such as allergic rhinitis, may have different clinical expressions. Patients with allergic rhinitis often have associated diseases, comorbidities, which supports the concept of allergy as a systemic disease. The aim of this study was to evaluate the incidence and types of comorbidities in allergic rhinitis. We also evaluated the possible effects of certain clinical and demographic parameters on the onset of comorbidities. Material and Methods. This retrospective, observational, and cross-sectional study included patients with a clinical diagnosis of allergic rhinitis treated at the Department of Ear, Nose and Throat in the period from October 2011 to April 2013. The collected data were analyzed using the Statistical Analysis System (Institute Inc. NC, USA) program, version 9.1.3. Results. The study included 319 patients with allergic rhinitis. Allergic rhinitis was intermittent in 30.7% of cases, persistent in 37.9%, and persistent with seasonal exacerbation in 31.3% of patients. We found that 86.8% of patients had some form of comorbidity. The most common were conjunctivitis (50.2%), almost equal percentage of asthma (29.8%) and chronic rhinosinusitis (28.8%), followed by otitis media with effusion (8.8%), atopic dermatitis (5.2%), urticaria (4.1%), and laryngitis (3.8%). Persistent allergic rhinitis, with persistent nasal obstruction as the dominant symptom, was significantly associated with chronic rhinosinusitis. Positive family history was significantly associated with the occurrence of asthma and allergic rhinitis. Conclusion. The results of our study showed that allergic rhinitis is rarely an isolated condition and it should always be observed in the context of the allergic respiratory syndrome. Key words: Rhinitis, Allergic; Respiratory Hypersensitivity; Comorbidity; Signs and Symptoms; Sinusitis; Asthma

Sažetak

Uvod. Oboljenja udržana sa imunoglobulin E preosetljivošću kao što je alergijski rinitis mogu imati različitu kliničku ekspresiju. Pacijenti sa alergijskim rinotisom često imaju i udružena oboljenja, komorbiditete, što ukazuje na to da je alergija sistemsko oboljenje. Postavili smo cilj da proceniemo učestalost i tipove komorbiditeta. Material i metode. To je retrospektivno, observacionalno i prospektivno studije preseka uključenih u prospektivnu, opservacionu studiju preseka na Odjelu za bolesti uha, grla i nosa Univerzitetskog kliničkog centra Republike Srpske u Banjaluci, tokom perioda od oktobra 2011. godine do aprila 2013. godine. Prikupljeni podaci analizirani su statističkim sistemom analize (Institute Inc. NC, USA), verzija 9.1.3. Rezultati. U studiju je uključeno 319 pacijenata sa alergijskim rinotisom. Alergijski rinotis je bio intermittentni kod 30,7% slučajeva, persistentni kod 37,9% slučajeva i persistentni sa sezonskim egzacerbacijama kod 31,3% pacijenata. Utvrdili smo da 86,8% pacijenata ima neki oblik komorbiditeta. Najčešći je bio konjunktivitis (50,2%), gotovu je bio jednak procenat astme (29,8%) i hroničnog rinoinzitusita (28,8%); slede sekretorni otitis medij (8,8%), atopijski dermatitis (5,2%), urticarija (4,1%) i laringitis (3,8%). Persistentni alergijski rinitis, sa persistentnom nasalnom oboljenjem kao dominantnom simptom, bio je značajno povezan sa hroničnim rinoinzitusitom. Pozitivna porodična anamneza je bila značajno povezana sa pojavnim astmom i alergijskom rinotistem. Zaključak. Prema rezultatima naše studije, alergijski rinotis je retko izolovano oboljenje i treba ga uvek posmatrati u kontekstu respiratornog alergijskog sindroma.

Ključne reči: alergijski rinitis; respiratorna hiperosetljivost; komorbiditet; znaci i simptomi; sinusitis; astma

Introduction

Respiratory allergies, including allergic rhinitis (AR), are complex disorders due to the heterogeneity of symptoms that vary in terms of localization, time of onset, co-occurrence of other conditions, response to treatment and prognosis [1]. They are associated with complex interrelationships with different expres-
The unity of the respiratory tract is confirmed both from a morphological and from a functional point of view. Knowledge that AR, rhinosinusitis, and asthma are manifestations of an inflammatory process within a continuous airway, has led to the introduction of a new concept of “united airway disease”. This concept is widely appreciated and is supported by findings from numerous studies [2, 3]. The AR is a common inflammatory chronic disease induced by an immunoglobulin E (IgE)-mediated reaction after allergen exposure in the nasal mucosa. Current estimates suggest that up to 30% of Europeans may be suffering from allergic rhinoconjunctivitis [4–6]. It is rarely isolated, so it should be considered in the context of upper and lower airway disease.

Clinical expression of AR may be viewed through the severity or presence of comorbidities. Moreover, in our daily practice, we can recognize different clinical entities of AR, from patients with mild symptoms to severe forms of the disease. In some patients AR is an isolated disease, while others have one or more comorbidities. To date, we have not been able to recognize the factors that contribute to the severity of symptoms or the onset of comorbid disorders in AR patients. However, AR needs to be considered in the context of systemic allergic disease associated with numerous comorbid disorders, including asthma, chronic middle ear effusions, sinusitis, and lymphoid hypertrophy with obstructive sleep apnea, sleep disorders, and consequent behavioral and educational effects [4].

The aim of this study was to evaluate the incidence and types of AR comorbidities in our clinical practice. We also evaluated the possible impacts of some clinical and demographic parameters on the onset of comorbidities.

**Material and Methods**

A retrospective, cross-sectional observational study included 319 adults and children with AR, diagnosed and treated as outpatients at our Rhinology Department during a study period of 19 months. All children were under the age of 18. Demographic data and place of residence were collected and AR was identified if patients were exposed to aeroallergens and showed a positive allergen skin prick test (SPT). Detailed medical history data, complete physical examination, and SPT were performed. A standard SPT was performed using a panel of standardized allergen extracts [7]. The recommended method of prick testing included appropriate use of specific allergen extracts, positive and negative controls, interpretation of the tests after 15–20 minutes of application, with a positive result defined as a wheal ≥ 3 mm diameter.

Sensitization to two or more allergens indicated polysensitization. Duration of AR was classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines with some modifications. Intermittent AR was defined by symptoms that occur for 4 or less days per week or not more than 4 consecutive weeks. Persistent AR was defined by symptoms occurring for more than 4 days/week and more than 4 consecutive weeks. We also took into consideration a group of subjects with persistent symptoms with seasonal exacerbation. The classification of AR severity was based on symptom intensity according to the ARIA guidelines as mild or moderate/severe [8].

The presence of comorbidities was also evaluated. The presence of asthma was obtained from the medical records. Evidence of otitis media with effusion (OME) was collected from medical visits to Audiology Department during the previous 3 months. Patients were considered to suffer from allergic conjunctivitis if they complained of ocular symptoms accompanying rhinitis. The criteria for diagnosis of rhinosinusitis were a history of > 2 nasal symptoms and either positive nasal endoscopy and/or positive sinus radiography based on the definition from the European position paper on rhinosinusitis and nasal polyps 2012 [9].

Formal ethical approval to conduct the study was obtained from the Ethics Committee before the commencement of the study. Informed consent was sought from each patient before being enrolled into the study.

A descriptive analysis of the study population was performed. The analysis was carried out using the Statistical Analysis System (Institute Inc. NC, USA) program, version 9.1.3. All variables were described for the total sample. The number of valid cases was used in all tables and graphs, and when calculating percentages or any other statistical data. Continuous variables were summarized based on the number of valid cases, mean, standard deviation, median, and extreme values; categorical variables were described by means of number of valid cases and percentages in every category, while variables with an asymmetric frequency distribution were described using the medians and their 25th to 75th percentiles. Other appropriate tests (chi-squared, Mann–Whitney, or Kruskal–Wallis) were used in each case for other comparisons. Statistical significance was set at a p value of < 0.05.

**Results**

There were 319 patients, both adults and children, with AR; 153 (48.0%) were male and 166 (52%) were female (Table 1). The median age was 17.0 years (min. 3.0 - max. 58.0). A particularly high proportion of patients (over 40%) were 8 - 19 years of age. According to the duration of AR, persistent allergic rhinitis was the most common type of AR (37.9%), followed by persistent AR with seasonal exacerbation (31.3%), and intermittent AR (30.7%). Almost all patients were in the moderate/severe group (92%) of AR due to the fact that data were collected from patients at a tertiary healthcare department. There were no
There were significantly more positive medical histories of allergies and poly-sensitized patients in the group of persistent AR with seasonal exacerbation. Distribution of allergen sensitization corre-

Table 1. Incidence of some demographic characteristics in patients with allergic rhinitis

|                         | n  | %  | p-value/p vrednost* |
|-------------------------|----|----|---------------------|
| **Gender/Pol**          |    |    |                     |
| Male/Muški              | 153| 48 |                     |
| Female/Ženski           | 166| 52 | .467                |
| **Age, years/Uzrast, godine/(median, min – max)/(prosek, min. – maks.)** | 17 | 3 - 58 |                     |
| **Place of residence/Mesto stanovanja** |           |                   |
| Rural/Selo              | 39 | 12.2|                     |
| Suburban/Predgrade      | 122| 38.2| < .001              |
| Urban/Grad              | 158| 49.5|                     |
| **Family history of allergies/Porodična istorija alergije** | 164| 51.4| .614                |
| **Polysensitization/Polisenzibilizacija** | 268| 84 | < .001              |
| **Type of allergic rhinitis/Tip alergijskog rinitisa** |           |                   |
| Intermittent/Intermitentni | 98 | 30.7|                     |
| Persistent/Perzistentni | 121| 37.9| .217                |
| Persistent with seasonal exacerbation/Perzistentni sa sezonskim pogoršanjima | 100 | 31.3|                     |

Legend/Legenda: *Based on chi-square test of equal distribution of categories/Bazirano na x^2 test jednake distribucije kategorija

Total N = 319/Ukupno n = 319; p value was set at 0.05/p < 0,05 vrednosti su imale statistički značaj

Table 2. The incidence of certain demographic characteristics related with the duration of allergic rhinitis

| AR type/Tip alergijskog rinitisa | Intermittent/Intermitentni | Persistent/Perzistentni | Persistent with seasonal exacerbation/Perzistentni sa sezonskim pogoršanjima | p-value/p vrednost |
|----------------------------------|-----------------------------|-------------------------|-----------------------------------------------------------------------------|--------------------|
| **Gender/Pol (%)**               | 42.9                        | 52.9                    | 47                                                                           | .325^1             |
| Male/Muški                       |                             |                         |                               |                    |
| Female/Ženski                     | 57.1                        | 47.1                    | 53                                                                           | .039^1             |
| **Age, median, years/Uzrast, prosek, godine** | 14 | 20 | 17 | .162^2 |
| **Place of residence/Mesto stanovanja (%)** |           |                   |
| Rural/Selo                       | 14.3                        | 10.7                    | 12                                                                           |                    |
| Suburban/Predgrade               | 36.7                        | 40.5                    | 37                                                                           | .682^1             |
| Urban/Grad                       | 49                          | 48.8                    | 51                                                                           |                    |
| **Family history of allergies/Porodična istorija alergije (%)** | 45.9| 47.1| 62| .091^1 |
| **Polysensitization/Polisenzibilizacija (%)** | 81.6| 76| 96| < .001^1 |
| **Allergens/Alergeni (%)**       |                             |                         |                               |                    |
| House dust/Kućna prašina         | 68.4                        | 93.4                    | 84                                                                           | < .001^1           |
| Grass pollen/Polen trava         | 72.4                        | 50.4                    | 76                                                                           | < .001^1           |
| Tree pollen/Polen drveća         | 29.6                        | 20.7                    | 46                                                                           | < .001^1           |
| Weed pollen/Polen korova         | 62.2                        | 53.7                    | 68                                                                           | .091^1             |
| Mould/Bud                        | 5.1                         | 7.4                     | 3                                                                            | .345^1             |
| Pet dander/Životinjski derivati   | 5.1                         | 6.6                     | 10                                                                           | .429^1             |

Legend: *p - values obtained through different procedures depending on predictor’s level of measurement: 1 = exact chi-square test; 2 = multinomial logistic regression; 3 = chi-square test for linear trend; p value was set at 0.05

Legenda: *p - vrednosti dobijene različitim postupcima, zavisno od nivoa merenja: 1 = x^2 test sa egzaktnim proračunima, 2 = multinominjalna logistička regresija; 3 = x^2 test za linearni trend; p < 0,05 vrednosti su imale statistički značaj
sponded to the type of AR. Approximately half the patients had positive parental history of allergies, (n = 164/319, 51.4%). Most of the patients lived in urban locations (49.5%, CI [44.1, 55.0]). One in eight patients were from rural (12.2%, CI [9.0, 16.3]) areas. Mites (82.8%) were the most common allergen, followed by grass pollen (65.2%), weed pollen (60.8%), tree pollen (31.3%), pet dander (7.2%) and molds (5.3%). Most of the patients were poly-sensitized (n = 68/319, 84%, CI [79.6, 87.6], p < .001) (Table 1).

The most frequent symptoms were nasal obstruction (97.5%) and rhinorrhea (98.4%) (Graph 1). We found that 86.8% of patients had some comorbidity (p < .001). The most frequent were conjunctivitis (50.2%), almost equal percentage of asthma (29.8%) and chronic rhinosinusitis, (28.8%), followed by otitis media with effusion (8.8%), atopic dermatitis (5.2%), urticaria (4.1%) and laryngitis (3.8%) (Graph 2).

Conjunctivitis was most common in patients with intermittent and persistent with seasonal exacerbation type of AR, while rhinosinusitis was most common in patients with persistent AR. There was a significant difference (p < .001) between presence of conjunctivitis and intermittent or seasonal occurrence of AR, as well as between sinusitis and persistent (43%) or persistent with seasonal exacerbation AR (35%). There were no significant differences between other comorbidities and type of AR (Table 3).

The Table 4 shows the incidence or influence of some clinical and demographic parameters on the onset of comorbidities. Asthma was significantly more frequent (p < .001) in patients with positive history of allergies. The probability of rhinosinusitis as a comorbidity significantly increases (p < .001) with age. Persistent nasal obstruction or persistent symptoms of AR rather than intermittent symptoms were significantly associated with rhinosinusitis (p < .001). Cough, deviated septum and polyps were significantly associated with rhinosinusitis (p < .001).

### Table 3. The incidence of different comorbidities in regard to the type of allergic rhinitis

| Comorbidity/Komorbiditeti | AR type/Tip alergijskog rinitisa | (%) | (%) | (%) | p-value* |
|---------------------------|----------------------------------|-----|-----|-----|----------|
|                           | Intermittent | Persistent | Persistent with seasonal exacerbation | Intermittentni | Perzistentni | Perzistentni sa sezonskim pogoršanjima | p vrednost |
| Conjuguntivitis/Konjunktivitis | 65.3 | 24.8 | 66 | <.001 |
| Asthma/Astma | 28.6 | 28.9 | 32 | .831 |
| Rhinosinusitis/Rinosinusitis | 5.1 | 43 | 35 | <.001 |
| Otitis media with effusion | 10.2 | 10.7 | 5 | .274 |
| Urticaria/Urtikarija | 5.1 | 1.7 | 6 | .280 |
| Laryngitis/Laringitis | 2 | 5 | 4 | .539 |

* Based on exact chi-square test of equal distribution of categories; Total = 319; p value was set at 0.05

* Bazirano na x² testu jednake distribucije kategorija. Ukupno = 319; p < 0.05 vrednosti su imale statistički značaj
outdoor pollution and urban lifestyle are a likely cause of the increase of allergies in developing countries, including ours. We are still unable to identify endophenotypes of AR which develop from complex genetic and epigenetic interactions. The concept of precision medicine in allergic diseases requires higher efficiency in conducting diagnostic procedures and personalized management.

Results of this study validate these trends, since almost all patients from the study were in the moderate/severe group (92%) of AR. This finding is clearly influenced by the fact that data were collected from patients at a tertiary department, although the evidence from a previous survey showed that the majority or approximately 75% of AR patients reported moderate/severe forms of rhinitis [10].

In this study, patients from urban and suburban areas came somewhat more frequently for examination, but there were no significant differences in terms of the prevalence of AR in patients from a particular area. This confirms the results of previous studies according to which people from rural areas, including ours, are increasingly adopting urbanized Western lifestyle, and so it is not possible to determine whether the place of residence is the factor that modifies the clinical manifestations of AR [11].

In regard to the age of patients, these results are in agreement with the previous ones which show that AR is most prevalent in the pediatric and adolescent population [5, 12]. A study performed in Spain reported that AR was the most frequently diagnosed allergic disease (44.9%) in patients under the age of 14 [13]. There were almost equal types of AR in our study, but the majority of patients suffered from persistent symptoms, taking into account the total number of patients with persistent and persistent with seasonal exacerbation AR. Similar findings were also reported in other studies. Results of a survey conducted in the United States show that the majority of patients with AR reported perennial symptoms [14]. Results of a survey conducted by
Canonica et al. found that 42.5% of the AR patients had persistent symptoms [15]. A study by Bachert et al. reported that approximately 40% of patients with AR compared with 23.5% of patients with non-allergic rhinitis had persistent symptoms [10].

According to our results, the incidence of patients with positive history of allergies was much higher in the group of patients with persistent AR with seasonal exacerbation and in the group of patients with asthma. Positive family history is mentioned as a predictive factor in the development of asthma and AR. Earlier results show that positive family history of asthma or rhinitis increases the risk of developing asthma and AR compared to persons with no family history [16].

Nasal congestion and rhinorrhea were identified as the most frequent symptoms and that is consistent with previous studies. Intermittent and persistent presence of symptoms reported by patients corresponded to the type of AR [15]. Moreover, most patients were likely to be sensitized to both pollen and house dust mites. Other perennial allergens, such as mould and pet dander, were less present. Distribution of allergen sensitization corresponded to the type of AR. Most of our patients were polysensitized, which is in agreement with earlier studies according to which polysensitization is highly prevalent in patients with AR. Different studies found different results in terms of the frequency of polysensitization [17, 18].

Immunoglobulin E associated diseases such as AR may have several clinical expressions. Respiratory allergy can be considered as a global disorder of the airways. Therefore, AR, asthma, and rhinosinusitis frequently coexist, and are considered as part of a common syndrome, for which different terms, including chronic respiratory allergy have been proposed [19–21].

We found that 86.8% of patients had some concomitant disease. This was in agreement with previous studies which found that patients with AR were at a higher risk of other comorbidities compared with a large number of adults without AR [22].

In a previous study, it was reported that sinusitis and conjunctivitis were frequent past or current comorbidities, and that coexistence of otitis media and nasal polyposis was less frequent. The same study estimated that asthma was present in 32.7% of cases [23].

We found that the most frequent was conjunctivitis (50.2%) in patients who were sensitized to outdoor allergens. A recent study found that about 75% of AR patients complained of the symptoms of allergic conjunctivitis [24].

We also found that 29.8% of patients had asthma. It was in agreement with previous studies which found that up to 40% of patients with AR suffered from asthma [20, 22].

Several studies have reported a strong association between asthma and AR, which is why these two diseases, which have been considered separate entities until recently, are now considered a single entity, for which different terms, including “chronic respiratory allergy”, “united airway disease” have been proposed [2, 25]. The AR is associated with asthma in 40% of patients, whereas 80% to 95% of patients with allergic asthma also have rhinitis [4].

There were no significant differences in terms of the presence of asthma in different types of AR, which is in disagreement with earlier studies which found that asthma was more prevalent among AR patients with more severe and persistent disease [26]. In this study, asthma was significantly more frequent (p < .001) in patients with positive history of allergies.

We found that 8.8% of patients had otitis media with effusion. Evidence suggests epidemiologic and pathophysiological links between allergy and OME. One of the contributing factors to the development of OME is allergic inflammatory response. The prevalence of AR in patients with OME ranges from 24% to 89%, usually around 23% [27]. According to a study by Kreiner-Møller et al., OME was closely associated with AR presumably caused by allergic inflammation, but not mechanical nasal mucosal swelling [28]. In a recent study, Passali et al. showed significant association between OME and persistent allergic rhinitis [29].

A causal mechanism between allergic nasal inflammation and development of sinus disease is still unclear. Rhinosinusitis is a heterogeneous group of diseases with different underlying etiologies and the pathophysiological mechanism involved in its development is complex [30]. The survey also documents a strong relationship between nasal allergies and sinus conditions, with 66% of AR patients reporting that they also suffer from rhinosinusitis or sinus conditions. In contrast, only 20% of adults without nasal allergies suffer from rhinosinusitis or sinus problems [22].

Due to a very similar presentation, it is very difficult to distinguish AR and rhinosinusitis. In this study, sneezing, itchy nose and/or eyes, obstruction and rhinorrhea were symptoms related to AR, whereas adults and children with sinus disease complained of headache, facial pressure, cough, postnasal drip, and/or smell disorder. According to our results, rhinosinusitis was found in 28.8% of patients. Increasing number of studies have found a significant correlation between AR and rhinosinusitis and one of them revealed that 50% of adults and 43% of children with nasal allergies reported having chronic rhinosinusitis [31].

Several mechanisms could explain the link between allergic inflammation and sinus disease. Allergic inflammation of the nasal mucosa may give rise to mucosal congestion, leading to impaired mucociliary drainage at the ostiomeatal complex in predisposed patients. Allergy is considered to be a predisposing factor for developing rhinosinusitis, although the theory is still controversial. Many studies have suggested that allergic inflammation could affect acute or chronic rhinosinusitis. However, epidemiologic studies have suggested that the incidence of rhinosinusitis is not significantly higher in AR patients than in healthy subjects. The observation that asthma and rhinosinusitis coexist in patients at a higher frequency than would be expected from...
the prevalence of each in the general population provides a strong connection between the upper and lower airways [21, 32]. In this study, there was a significant difference between sinusitis and persistent (43%) or persistent with seasonal exacerbation AR (35%) as shown in Table 2. Cough, deviated septum and polyps were significantly associated with rhinosinusitis (p < .001) as shown in Table 4.

The previous studies confirmed that rhinosinusitis was more prevalent in cases with perennial AR [33] and that rhinosinusitis was associated with sinonasal anatomical variants [34, 35]. There is no strong evidence for a correlation between nasal anatomical variations in general and the incidence of chronic rhinosinusitis [9].

There is a well-established relationship between atopic dermatitis and airway allergic diseases and its progression over time is well known as atopic march. Patients with extrinsic atopic dermatitis with specific IgE antibodies to common environmental allergens, present in early childhood, are at a higher risk for progressing in the atopic march to allergic rhinitis and asthma [36]. The prevalence of atopic dermatitis in this study was 5.2% and there was no significant relationship between other comorbidities. In this study, another less common comorbidity associated with AR was laryngitis with prevalence of 3.8%. It is still controversial whether AR may be a causative mechanism of laryngeal inflammation and symptomatology [37].

The reasons for differences in the clinical presentation of comorbid diseases in patients with AR are still unknown. One of the possible explanations why there is no definite answer is the overlapping of hereditary, physiological and clinical characteristics of patients, which affects variety of conditions. In order to fully respond to these challenges, AR should be understood as a part of chronic allergic respiratory syndrome, not as an isolated allergic disease.

**Conclusion**

This study is in agreement with others in regard to the presence of comorbidities in patients with allergic rhinitis. Although these relationships are well established from a clinical and epidemiologic point of view, the mechanism of how allergic rhinitis predisposes comorbidities or affects their course, remains unclear. This continues to be a subject of investigation and debate.

Due to cross-sectional nature of this study, the results should be interpreted with caution, and the variability of results, regarding the incidence of some clinical and demographic parameters, may be related to regional differences, selection methodology and definition used. These results point to presence of comorbidities in many patients with allergic rhinitis, which corresponds to the fact that allergic rhinitis is part of a systemic disease. In spite of all the limitations, this study indicates that allergic rhinitis is a major health problem in the region. The aim of further studies will be to understand the complexity of the mechanisms underlying the varieties in the clinical phenotype of allergic rhinitis and predisposition to the onset of comorbidities.

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