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DIFFERENT PHENOTYPES OF INTERMITTENT AND PERSISTENT RESPIRATORY ALLERGY IN ZAGREB, CROATIA

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Abstract: Allergic rhinitis (AR) is a major chronic respiratory disease because of its prevalence, its impacts on the quality of life, economic burden and links with asthma. A significant relationship between the severity of rhinitis and prevalence of asthma in allergic patients was found both in patients suffering from seasonal rhinitis and in those suffering from perennial allergic rhinitis (PAR) and asthma. The aim of the study was to investigate allergy phenotypes in patients with intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PAR) in residents of Zagreb, and to determine if there were any other differences in the clinical (*in vivo*) and diagnostic (*in vitro*) presentations of the phenotype of subjects suffering from different types of rhinitis. 205 subjects were divided into 2 groups, 102 with IAR sensitized to ragweed pollen (*Ambrosia elatior*) and 103 with PAR sensitized to house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*). The diagnosis was based on a detailed medical history, examination and diagnostic tests (spirometry, reversibility after appliance of salbutamol, skin prick test, and total IgE). Rhinitis symptoms in subjects with IAR were significantly different than in those with PAR. Sneezing and a runny, itchy nose were frequently present in the IAR group, but not in the PAR group. Prevalence of the coexistence of asthma was higher in the PAR group (35:57%), as well as more severe clinical phenotype of asthma. The covariation of sensitization was similar (70:74%). The most frequent sensitization in the IAR group was found to house dust mite (38%), and in the PAR group to animal dander (40%). The clinical presentation of the IAR was different from that of the PAR. The prevalence of coexisting asthma was significantly higher in the PAR group. The covariation of sensitization was similar.

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INTRODUCTION

Allergic rhinitis (AR) is a major chronic respiratory disease because of its prevalence, its impacts on the quality of life, economic burden and links with asthma [8, 11]. Many patients with AR are unaware of their pathology and few seek help from health professionals [12]. AR is often associated with other respiratory disorders such as sinusitis, otitis, as well as with atopic dermatitis/eczema, urticaria, angioedema, oral allergy syndrome and sun or aspirin hypersensitivity but the most important co-morbidity is with asthma. AR was found to be a risk factor for developing asthma, a chronic inflammatory disorder of the airways, in which many cells and cellular elements play an important role [5]. The chronic inflammation is associated with airway hyperresponsiveness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread variable airflow obstruction within the lungs, which is often reversible, spontaneously or with treatment [15]. Furthermore, it was

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found that the treatment of rhinitis could improve asthma control [28]. It has recently been proposed that rhinitis and asthma are manifestations of a single chronic inflammatory syndrome, suggesting that the severity of rhinitis may correlate with the increased prevalence of asthma [14, 18, 19, 23, 24, 26]. A study by Guerra *et al.* demonstrated that the severity of rhinitis is a risk factor for developing asthma, irrespective of the presence of an allergy [16]. A significant relationship between the severity of rhinitis and the prevalence of asthma in allergic patients was found both in patients suffering from pollen-sensitive rhinitis [6], and in those suffering from perennial-allergic rhinitis (PAR) and asthma [13]. A French observational cross-sectional study of asthmatic patients in everyday general medical practice suggested that AR was associated with more severe asthma, with more difficulty in controlling asthma, and substantial impairment in quality of life [21].

Zagreb, the capital of Croatia, is on the western edge of the Pannonian Plain which is one of the 3 endemic areas for *Ambrosia elatior* in Europe, together with southern France (the Rhone valley) and northern Italy (Lombardy). In the continental climate, the pollen season of *Ambrosia elatior* is late summer. Each plant produces tens of thousands of pollens which become airborne soon after their production and wind can spread them for many kilometres. In the continental climate, especially in humid regions, mites are ubiquitous. In Zagreb, symptoms of rhinitis caused by sensitization to mites are most intense during the spring and autumn when the greatest humidity occurs.

The aim of this study was to investigate whether persistent rhinitis represents a greater risk of asthma occurrence than intermittent rhinitis in the analyzed sample of residents of Zagreb, and to determine if there were any other differences in the clinical (*in vivo*) and diagnostic (*in vitro*) presentations of the phenotype of subjects suffering from different types of rhinitis.

SUBJECTS AND METHODS

In total, 205 patients with AR symptoms referred to a specialist were included in this study and divided into 2 subgroups, comprising 102 subjects with intermittent and 103 subjects with persistent rhinitis, respectively. Sensitization to short season ragweed pollen, *Ambrosia elatior*, (*Amb e*) and sensitization to house dust mites *Dermatophagoides pteronyssinus* (*Der p*) and *Dermatophagoides farinae* (*Der f*) were chosen as a representative of intermittent and persistent rhinitis respectively. In the Croatian region, during the 2002–2005 seasons, the highest rate of airborne ragweed pollen was recorded in August and September [25]. In the northern part of Croatia, the allergen *Der p* is a more frequent cause of sensitization than *Der f*, the ratio being 97%:84%, respectively [27]. The diagnosis of AR and asthma was based on a "one-to-one doctor-patient" interview by an experienced respiratory specialist, a physical examination, spirometry, bronchoreversibility test after appliance of salbutamol and diagnostic skin prick tests. All the patients had a history documented for at least 2 previous years. The subjects were diagnosed as having intermittent or persistent rhinitis after a detailed consultation between the patient and the physician on frequency and intensity of their symptoms, and the duration of symptoms, either during the pollen season, or throughout the whole year, for 2 consecutive years. The following symptoms were taken into account: sneezing, watery or seromucous secretion, nasal blockage, nasal or other mucous itching [33]. When some or all of the mentioned symptoms lasted for less than 4 weeks subjects were classified as having only intermittent allergic rhinitis (IAR) [5]. When the symptoms lasted more than 4 weeks or occurred more frequently than 4 days in a week, subjects were classified to have persistent allergic rhinitis (PAR). The symptoms which were considered asthmatic were: a chronic cough and/or wheezing, shortness of breath, chest tightness, exercise impairment, attacks of breathlessness, a nocturnal cough, phlegm production or sleep disturbance. The severity of asthma was classified according to Global Initiative for Asthma (GINA) into intermittent, mild persistent, moderate or severe persistent asthma [15]. The age at the onset of symptoms, their frequency and duration, the specific triggers, and the effectiveness of asthma medications administered were also recorded. The presence of other allergy diseases, including aspirin hypersensitivity, was also recorded. The next step was a physical examination followed by spirometry. Spirometry was performed at least 3 times by forced expiration on a Vitalograph apparatus with a pneumatachograph. The best attempt was selected, and forced expiratory volume in the first second (FEV_1) was recorded in the body temperature pressure saturated (BTPS), according to the standard spirometric procedure (ATS) [1] and compared with the referent values, according to the European Community for Coal and Steel [29]. Obstructive ventilatory disorder was considered when FEV_1 was less than 80% of the predicted value, and the FEV_1/FVC ratio under 0.7. The bronchodilator reversibility was tested with 400 µg of the short acting β_2-agonist (salbutamol) and considered positive if the FEV_1 increased by 12% and/or 200 ml after 15–30 minutes [32]. Skin prick tests were performed on the forearm, with 12 aeroallergens manufactured by ALK-ABELLO, Denmark (tree pollen mixture, grass pollen mixture, ragweed pollen mixture, short ragweed (*Ambrosia elatior*), mugwort (*Artemisia vulgaris*), plantain (*Plantago lanceolata*), dandelion (*Taraxacum vulgare*), *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, dog dander, moulds mixture). Negative (saline solution) and positive (histamine 1 mg/ml) controls were used. After 15 minutes, the diameter was measured in millimetres (mm), the long axis (D) and its perpendicular (d). The skin prick test was considered positive when the mean wheal size was greater than 3 mm in relation to a negative control $\{(D+d)/2\} \geq 3$ [31]. The testing was performed during the autumn, after the end of the pollen season of *Amb e*. All the subjects were

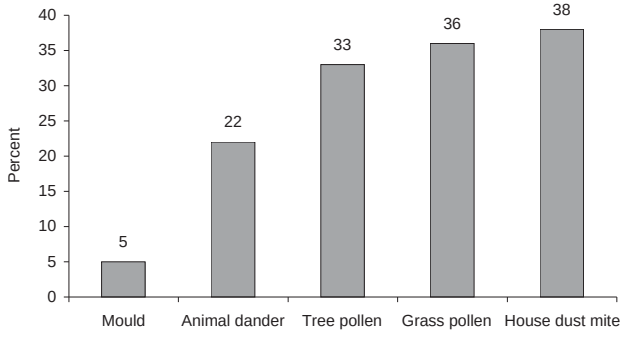

Figure 1. Covarriate sensitisation distribution among perrenial and seasonal allergens in persons sensitised to *Ambrosia elatior*.

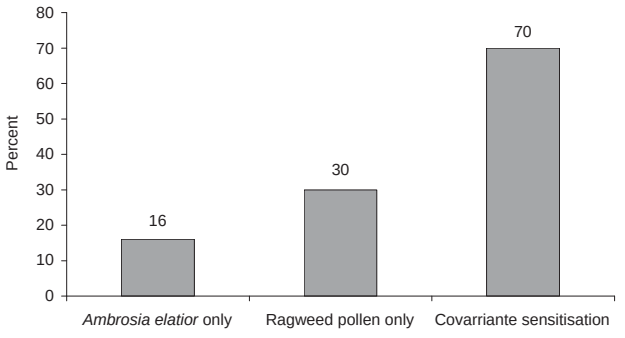

Figure 2. Sensitisation pattern in persons sensitised to *Ambrosia elatior*, according to skin prick tests.

clinically stable and had no evidence of respiratory infection in the previous 5 weeks. Total immunoglobulin E (IgE) was measured from the serum sample by Enzyme-Linked ImmunoSorbent Assay (ELISA) (Pharmacia, Sweden). Descriptive statistics, correlation, *t*-test and chi square test were used for data analysis by means of the statistical package Statistica, Version 5.0.

RESULTS

In the analysed sample of 205 subjects, 102 had symptoms of intermittent rhinitis, while 103 had symptoms of persistent rhinitis. The groups were comparable in age and sex, as well as in smoking habits with almost one third of all the subjects being smokers despite their respiratory problems. The average duration of the period during which the subjects experienced the symptoms of rhinitis – was 3.6 weeks for the subjects suffering from intermittent rhinitis, and 29.9 weeks for the subjects suffering from persistent rhinitis (Tab. 1). The clinical presentations of the rhinitis symptoms were different in the investigated types of rhinitis (Tab. 2). The most frequent symptom in the subjects with IAR (79%) was sneezing, while in those with PAR nasal blockage was their main symptom (67%). Furthermore, there were also significant differences between the occurrences of other histamine-induced symptoms such as nasal secretion or itching, which were more frequent in subjects suffering from IAR. Ocular and pharyngeal irritations were also more frequent in subjects with IAR compared to those with PAR (eyes 49%:25%, throat 21%:10%, respectively). The prevalence of asthma in the subjects with IAR and those with PAR was 35% and 57%, respectively (Tab. 3). The clinical features of rhinitis symptoms were different, as well as the features of the asthmatic symptoms in both allergy phenotypes (Tab. 4). There were no statistical differences between the values of pulmonary function parameter FEV_1 in subjects with IAR (2. 91 ± 0.29 L/s) compared to those with PAR (2.79 ± 0.32 L/s) (p=0.36, t=1.18). The concomitant presence of other allergy diseases, apart from asthma, was also investigated in both groups of subjects and was found in 17% and 18% of subjects with IAR and PAR, respectively. The most common allergy manifestations are shown in Table 5. Covariation of sensitization was found in 70% of subjects with IAR and 74% of those with PAR. The most frequent sensitization found in subjects with IAR was to house dust mites and grass pollen, 38% and 36%, respectively (Fig. 1). Among the 30% of subjects sensitised only to the group of ragweed pollen, 17% had sensitization exclusively to *Amb e*. The most frequent sensitization found in subjects with PAR was to animal dander and grass

Table 1. Descriptive statistics parameters of the investigated groups with intermittent allergic rhinitis (IAR) (n=102), and persistent allergic rhinitis (PAR) (n=103).

	x	SD	Min	Max	SE	t	p
Age in IAR (in years)	37.89	12.98	12	69	1.62	ŀ0.42	0.68
Age in PAR (in years)	34.54	15.66	7	68	1.38		
Men in IAR/PAR (percentage)	// 49/60						
Women in IAR/PAR (percentage)	51/40						
Onset of IAR (in years)	27.26	13.99	2	54	1.62	ŀ0.60	0.57
Onset of PAR (in years)	20.99	14.39	1	60	1.62		
Duration of symptoms in IAR in last 12 months (weeks)	3.63	0.91	2	6	0.22	ŀ4.67	0.001
Duration of symptoms in PAR in last 12 months (weeks)	29.91	10.34	10	50	1.52		
Smokers in IAR/PAR (percentage)	29/32						
FEV_1 in IAR and asthma (% of reference value)	86.71	9.53	55	109	3.49	ŀ1.18	0.36
FEV_1 in PAR and asthma (% of reference value)	73.65	8.14	29	94	5.18		

Table 2. Distribution of rhinitic symptoms in patients with IAR and PAR.

	IAR n=102	PAR n=103
Sneezing	80 (79%)	53 (51%)
Runny nose	76 (74%)	45 (44%)
Blocked nose	64 (63%)	69 (67%)
Itchy nose	42 (41%)	19 (18%)
Itchy eyes (conjuctivitis)	50 (49%)	26 (25%)
Itchy ears (otitis)	3 (3%)	6 (6%)
Itchy throat (pharyngitis)	22 (21%)	10 (10%)

Table 3. Distribution of newly diagnosed patients with asthma according to GINA classification (revision 2006) in patients with IAR and PAR.

	IAR (n=102) Asthmatic subjects n=36 (35%)	PAR (n=103) Asthmatic subjects n=59 (57%)
GINA I	5 (14%)	1 (2%)
GINA II	13 (36%)	17 (29%)
GINA III	16 (44%)	35 (59%)
GINA IV	2 (6%)	6 (10%)

Table 4. Presentation of asthmatic symptoms in patients with IAR and PAR.

	IAR n=102	PAR n=103
Cough	41 (40%)	54 (52%)
Wheezing	31 (30%)	26 (25%)
Shortness of breath	38 (37%)	51 (49%)
Exercise impairment	19 (19%)	36 (35%)
Sleeping disturbance	24 (23%)	35 (34%)

Table 5. Prevalence of concomitant allergy diseases in patients with IAR and PAR.

	IAR n=102	PAR n=103
Rhinitis + Asthma	36 (35%)	59 (57%)
Rhinitis + Urticaria	9 (9%)	4 (4%)
Rhinitis + Atopic dermatitis	1 (1%)	7 (7%)
Rhinitis + Angioedema	2 (2%)	2 (2%)
Rhinitis + Oral allergy symdrome	5 (5%)	0 (0%)
Rhinitis + Sun hypersensitivity	3 (3%)	1 (1%)
Rhinitis + Aspirin hypersensitivity	1 (1%)	6 (6%)

pollen, 40% and 38%, respectively (Fig. 2). The wheal size in the positive skin reaction to *Amb e* in subjects with IAR or to *Der p* in subjects with PAR was not significantly different (p=0.21, t=-1.42). Furthermore, no differences were found either in the histamine reactions (p=0.61, t=0.93) or in the levels of total IgE (t=1.09, p=0.57) between the 2 investigated groups (Tab. 6). Low significant correlation was found between the clinical and diagnostic parameters

Table 6. Allergy diagnostic skin prick values in the investigated groups with IAR and PAR: positive skin reactions (in mm) to histamine (1 mg/ml), *Ambrosia elatior*, *Der p*, and total serum IgE (IU/ml).

	$\bar{x}$	SD	Min.	Max.	SE
Histamine in IAR	5.71	1.26	4	12	0.18
Histamine in PAR	5.35	1.62	3	15	0.23
Ambrosia in IAR	5.95	1.87	3	13	0.20
Der p in PAR	4.20	1.54	3	10	0.19
Total IgE in IAR	381.29	391.05	21	1,835	67.06
Total IgE in PAR	352.31	274.18	30	1,000	50.91

in subjects with PAR. The correlation between the age of the onset of rhinitis symptoms and the wheal size in positive skin prick tests to house dust mite and total IgE was r=-0.39 and -0.23 respectively. Such correlation in the IAR group was not significant.

DISCUSSION

In this study we were interested in determining the different phenotypes of allergic rhinitis in a sample of residents from the city of Zagreb, Croatia. Differences were found between the investigated groups with regard to the clinical features, such as symptom manifestation, the age of onset and distribution of the disease, and the concomitance of another allergy. Furthermore, differences were compared between the diagnostic laboratory findings, such as skin reactivity to different aeroallergens, as well as their interrelationship, covariation of sensitization and the level of total IgE antibodies. Our results show that, in spite of the documented harmful effects of cigarette smoke on respiratory allergy [34], one third of the subjects with rhinitis and a smaller number of those with asthma continue to smoke. The average duration of rhinitis symptoms in the group of subjects with IAR was 3.6 weeks, while symptoms in the group with PAR lasted for 29.9 weeks. Histamine-induced symptoms such as sneezing, runny nose and itching were much more pronounced in the IAR group compared to the PAR group. Surprisingly, a blocked nose, one of the most frequent symptoms of persistent rhinitis, was also found in 63% of the subjects with intermittent rhinitis. Typical symptoms of "hay fever" appeared in approximately only one third of the subjects with PAR, which is valuable information when considering differential diagnosis. We found that the prevalence of coexisting asthma was significantly more often in the subjects with PAR (35% and 57%, respectively.) The asthma clinical phenotype, as a part of the "united airway concept" was less severe in subjects with IAR. According to GINA classification, more patients with PAR had moderate and severe persistent forms of asthma. Two extensive studies, which recently investigated the relationship between allergic rhinitis and the prevalence of asthma, produced conflicting results. A large cross-sectional study carried out in the general population of six

European countries reported that the proportions of IAR and PAR amounted to 71% and 29% respectively, and (that) the prevalence of asthma was similar, 21% and 20%, respectively [3]. A French survey comprising patients referred by general practitioners to specialists reported an almost inverse distribution of IAR and PAR, 27% and 63%, respectively. The overall prevalence of asthma was 24% [7]. A study published by Mullarkey in 1980 showed 58% of coexisting asthma in patients with seasonal rhinitis compared to 10% in those with perennial rhinitis [22]. The high prevalence of coexisting asthma in both of our groups could partly be explained by selection bias towards the severity of patients studied in specialist practice, as well as better recognition of these conditions. Cipriandi *et al.* showed that the increased prevalence of asthma and allergic rhinitis in young Italian men between 1983–1996 was mainly due to better recognition of these conditions [10]. Although in both investigated groups the presentations of asthmatic symptoms were similar, there were differences. Based on data from the medical history, the main differences found were the incidence of sleep disturbance and exercise impairment. Nocturnal wakefulness due to respiratory problems was found in 23% of the subjects with IAR, compared to 34% of those with PAR. This could possibly be explained by the fact that nasal blockage, a symptom which is dominant in subjects with PAR, causes mucosal dryness, coughing, shortness of breath and consequent wakefulness. Exercise intolerance is probably less frequent during seasonal allergy because it is much easier to avoid short exposure to pollen and not engage in sport during the Ambrosia pollen season, than to avoid all activities during the whole year, such as in the case of perennial allergy to house dust mites.

On the whole, our data suggest that asthma, once presented in allergic rhinitis, appears to be very similar to a disease, despite the different sensitization or duration of symptoms. Our data are in agreement with a recent study by Antonicelli *et al.* in 2007, which showed that the classification of rhinitis "Allergic Rhinitis and its Impact on Asthma (ARIA)" does not correlate with the prevalence of asthma in patients with allergic rhinitis referred to by a specialist [2]. The finding of a relatively high prevalence of oral allergies in the group of subjects with IAR can be explained by the cross-reactivity existing between pollen and the wide range of food allergens [17]. Covariation of sensitization was profound in both subjects with IAR and those with PAR, 70% and 74%, respectively. The most frequent parallel sensitization in the IAR group was to house dust mites (38%), and in the PAR group to animal dander (40%). Sensitization to grass pollen was similar in both groups. To our surprise, we found a high rate (32%) of sensitization to ragweed pollen in subjects with PAR. The subjects with IAR were significantly more sensitized to tree pollen than those with PAR, 33% and 17%, respectively. Both groups had a low prevalence of sensitization to moulds of about 5%. The residents of Zagreb are less sensitized to moulds than, for example, children in Texas, who had sensitization to mould mix in 16.3% patients [9], or a Turkish population who have 14.8% sensitization to the most frequent moulds *Alternaria alternata* and *Cladosporium herbarum* [4]. Among the investigated subjects with IAR sensitized to ragweed pollen, simultaneous sensitization was significantly less intense than in patients sensitized to grass pollens (70% *vs.* 98%). [30] The rate of sensitization to only one species of ragweed pollen (*Amb e*) in Zagreb is similar to the sensitization to one of the tree pollens (e.g. olive *Olea europea*), 17% *vs.* 18% in areas with high olive pollen concentrations [20]. Concomitant sensitization of the subjects with PAR in our group was more similar to sensitization to ragweed pollen than to grass pollen. In subjects with PAR a significant correlation was found between the age of the onset of rhinitis symptoms and the allergic diagnostic tests such as positive skin prick test and total IgE antibodies. These results corroborate the clinical observation suggesting that patients who develop perennial allergy early in life suffer from a more intense allergy response.

CONCLUSIONS

• We found that the clinical appearance of intermittent allergic rhinitis differs from that of persistent rhinitis.

• The prevalence of coexisting asthma in both allergy phenotypes was also different, with more asthmatics in the group of patients with persistent rhinitis.

• Asthma phenotype was less severe in subjects with IAR than in those with PAR.

• Covariation of sensitization was present in a similar proportion – two thirds of the subjects in both groups of rhinitis were sensitive to more than one allergen.

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