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Symptomatology Patterns in Children with Allergic Rhinitis

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Background: Although allergic rhinitis (AR) is recognized as a growing global health disease with considerable importance for patients' lives, especially among children and adolescents, there is a lack of population studies concerning symptomatology patterns of the disease. The present study aimed to explore symptoms prevalence among school-aged children, to detect any correlation between allergen sensitivities with symptomatology patterns, and, finally, to evaluate the association of the sensitivity grade score with symptoms severity or seasonality.





Material/Methods: This was a cross-sectional, observational study in a childhood population. The first stage included recruitment of children and parental-completed questionnaires. The second stage included skin-prick tests for the most common allergens. Severity of symptoms was self-evaluated using a scale that ranged from "0" (no symptoms), "1" (mild), and "2" (moderate-to-severe). AR was classified as seasonal (SAR) or perennial (PAR).

Results: The most frequent symptoms were reported for nasal obstruction, sneezing, and rhinorrhea. All nasal symptoms were significantly more profound among children with *HDM* sensitivity. However, more symptoms, not only nasal, but also ocular and general ones, were detected among patients with grass pollen sensitivity. Patients with PAR reported more severe symptoms. SAR was associated with mild disease. Finally, the sensitivity grade score was significantly correlated with symptom severity.

Conclusions: Our results suggest that allergen sensitivity may be correlated with symptomatology patterns among children who have allergic rhinitis.

MeSH Keywords: **Adolescent • Rhinitis, Allergic, Seasonal • Signs and Symptoms • Skin Tests**

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Background

Allergic rhinitis (AR) is a common inflammatory disease affecting the upper and lower respiratory airways and eyes of sensitized patients [1,2]. This type of non-infectious rhinitis is caused by an IgE-mediated reaction to environmental allergens [3–6]. AR include nasal symptoms (e.g., rhinorrhea, nasal congestion, nasal itching, and sneezing), ocular symptoms (e.g., itchy and watery eyes), and general symptoms (e.g., cough and headache) [7,8]. Many studies have shown that AR symptoms are bothersome and impair patient psychosocial wellbeing and quality of life (QoL) [2,9,10], and furthermore cause a considerable socioeconomic cost [1,11,12]. Diagnosis is typically based on rhinitis symptoms in the presence of hypersensitivity to aeroallergens [13]. The most common allergens include house dust mites (HDM); grass, tree, and weed pollens; cat and dog epithelia; and molds [13,14]. The presence of sensitization is diagnosed by the skin-prick test (SPT), a primary diagnostic method to detect type I hypersensitivity reactions [15]. However, many subjects may have positive skin tests without allergic symptoms. Although AR represents a growing global health problem, now affecting up to 40% of the population [7,16–18], there are few studies, particularly for the Greek population [4–6,19,20] living in Mediterranean climate conditions, concerning AR symptom characteristics in children, even though AR is more prevalent and the health effects are more severe in children compared to adults [7,21].

Our study results could be useful not only in Greece but also in other countries with similar Mediterranean climate conditions. This is based on previous studies showing that registered airborne allergen concentrations of the most important pollen species are correlated with symptoms in AR patients who lived in the same area for a long time (more than 5 years) [22]. This means that aeroallergen prevalence may affect skin sensitivities, severity of symptoms, and time of symptoms appearance.

Consequently, the purposes of this study were: i) to explore the incidence rates of symptoms in children and adolescents with AR, ii) to detect any correlation between allergen sensitivities with symptomatology patterns and seasonality, and iii) to evaluate the association of sensitivity grade score with symptom severity or seasonal appearance.

Material and methods

Study design

In this observational study, 675 children and adolescents living in the same region of northeastern Greece participated. This study is the second part of a cross-sectional population analysis that was conducted by the University Department of

Otorhinolaryngology of the tertiary hospital of Alexandroupolis in 2 stages [23]. The method of sampling from the population was random stratified. In the first part, the parents of the children were informed in detail about the scientific purposes and the methodology of the study through a letter that was given to them through school authorities. A consent form and questionnaire had to be filled out by the parents and given back to the school authorities. The questionnaire included items to describe the medical history (symptomatology, severity, seasonality of symptoms, and concomitant diseases), as well as demographic characteristics (e.g., age and sex). There were 151 children for whom participation was refused. The second stage of the study included SPTs that were carried out by rhinologists within schools, according to the European Academy of Allergy and Clinical Immunology recommendations [24]. The allergens used were the most commonly found in the study area [4,5]: *HDM* (*Dermatophagoides pteronyssinus* and *D. farinae*), mixed grasses, *Olea europea spp.*, *Cupressaceae f. spp.*, *Pinaceae f. spp.*, *Parietaria spp.*, animal (cat and dog) danders, and molds (*Alternaria* and *Cladosporium spp.*). The SPT was performed by applying a drop of each allergen extract on the skin of the forearm aspect and measurements were made 20 min after application. SPT evaluation was made according to Demoly et al. [25] (SPT: 0 = no reaction, 1+ = 1 mm wheal above saline control; 2+ = 1–3 mm wheal; 3+ (this is registered as positive reaction) = 3–5 mm wheal and an accompanying flare; 4+ = >5 mm wheal above saline control and an accompanying flare). We used Lofarma Allergeni (Milan, Italy) commercial extracts for skin-prick testing. This manufacturer standardizes extracts in DBU (“Diagnostic Biological Units”), where 1 DBU is one-hundredth of the potency of 1 extract inducing a wheal equal to that induced by 10 mg/ml of histamine chloride. Products for skin-prick testing contain 100 DBU [26].

Study population

AR was diagnosed according to the criteria set by the 2008 ARIA guidelines [8]. SPTing was regarded as positive when a wheal of more than 3 mm and an accompanying flare were measured. Children with history of anaphylaxis or angioedema and dermographism and recent use of corticosteroids for 4 weeks prior and oral antihistamines for 1 week prior to SPT were excluded from the study (in total, 17 children). The severity of nasal symptoms (nasal obstruction or congestion, sneezing, rhinorrhea, itchy nose or throat), ocular symptoms (itchy eyes, watery eyes) and general ones (cough, headache) were self-evaluated using a scale that ranged from 0 to 2: “0” no symptoms reported, “1” mild, “2” moderate/severe symptomatology [27]. Also, participants reported the season of symptoms appearance. According to seasonality, symptoms were described as seasonal (SAR) or perennial (PAR) [8]. The study was approved by the respective school directors. Ethics approval was also obtained by the Scientific Council of the University

Hospital of Alexandroupolis and signed informed consents by the parents were provided.

Statistical analysis

For the statistical analyses, we used the IBM (SPSS) statistics software package, version 22.0. To describe the features of our study group, we used descriptive statistics measures. Spearman's rank correlation coefficient was used to reveal the relationship among allergens. The frequency distribution of age and sex for each allergen was detected through a cross-tabulation analysis (contingency table analysis), and chi-square statistical analysis was used to discover significant differences between sensitivities to allergens and age and sex of the participants.

Results

Our study participants were 675 school-aged boys and girls. Out of the 675 participants who underwent SPT, 231 (117 males and 114 females) were positive (34.2%). Out of 231 AR patients, 93 (40.3%) were monosensitized, and 138 (59.7%) were polysensitized. The most common skin sensitivities were detected for HDM (59.7%), grass pollens (48.9%) and *Alternaria alternata* (34.6%). The most frequent symptoms were nasal obstruction (55.0%), sneezing (52.8%) and rhinorrhea (48.5%). A total of 70 patients (30.3%) had no symptoms, possibly underestimated and inaccurately evaluated by parents in the questionnaire, which had to be filled in at home. Among patients with symptoms, 95 (59.0%) reported seasonal appearance, whereas 66 (41.0%) had year-round symptomatology (perennial). According to the severity of symptoms, 119 patients (51.5%) reported mild symptoms and 38 (16.5%) had moderate-to-severe symptoms. All demographic and clinical characteristics of the study group are presented in details in Table 1.

Allergen sensitization patterns were correlated with symptoms characteristics

According to skin sensitivities and symptomatology, nasal symptoms (nasal obstruction, sneezing, rhinorrhea and itchy nose/throat) were significantly more profound among patients with HDM and grass pollen sensitivities ($p < 0.01$). However, patients with grass pollen allergy had significantly more symptoms, not only nasal ones ($p < 0.001$), but also ocular symptoms (itchy and watery eyes, $p < 0.001$), and general ones (headache; $p = 0.020$). Patients sensitized to fungi and especially to *Alternaria alternata* had significantly more symptoms in the nose ($p < 0.05$) and eyes (itchy eyes; $p = 0.030$), and general symptoms (cough; $p < 0.001$, headache; $p = 0.08$). Tree pollen allergy (e.g., sensitivities to pine and olive) was associated with nasal symptoms ($p < 0.05$), and patients with olive sensitivity

Table 1. Demographic and clinical characteristics of the study group.

Study group characteristics	AR patients (n=231) (%)
Sex, [(%)]	
Male	117 (50.6)
Female	114 (49.4)
Age	
6–11 years old	166 (71.9)
12–17 years old	65 (28.1)
Sensitizations	
Monosensitization	93 (40.3)
Polysensitization	138 (59.7)
Allergen sensitivities	
Dermatophagoides pteronyssinus & farinae	138 (59.7)
Grasses	113 (48.9)
Alternaria alternata	80 (34.6)
Cladosporium	18 (4.7)
Olive	34 (14.7)
Dog epithelia	30 (13.0)
Cat epithelia	27 (11.7)
Parietaria	24 (10.4)
Pine	16 (6.9)
Cypress	11 (4.8)
Symptoms	
Nasal obstruction or congestion	127 (55)
Sneezing	122 (52.8)
Rhinorrhoea (anterior or posterior)	112 (48.5)
Itchy nose or sore or scratchy throat	80 (34.6)
Itchy eyes	37 (16)
Watery eyes	24 (10.4)
Cough	52 (22.5)
Headache	18 (7.8)
No symptoms	70 (30.7)
Seasonality	
Seasonal (SAR)	95 (59.0)
Perennial (PAR)	66 (41.0)
Severity of symptoms	
Mild	119 (51.5)
Moderate/Severe	38 (16.5)
None	74 (32)
Asthma presence [(%)]	37 (16%)

complained also were more likely to have watery eyes ($p = 0.006$) and headache ($p = 0.016$). All symptoms correlations with allergen sensitivities are presented in detail in Table 2.

No correlations were found between symptoms and patient age or sex, with the exception of rhinorrhea, which was most commonly found in children 6–11 years old (Table 3). On the contrary, all symptoms were more frequent among patients who were diagnosed with PAR. However, significant differences

Table 2. Symptoms correlations to allergen sensitivities.

Symptoms		HDM	Grasses	Alternaria	Clad.	Olive	Parietaria	Cypress	Pine	Dog	Cat
Nasal obstruction	CC	.219**	.354***	.226**	.136*	.105	.087	.082	.181**	.092	.009
	Sig	.001	.000	.001	.039	.111	.189	.215	.006	.166	.888
Sneezing	CC	.179**	.358***	.210**	.112	.191**	.131*	.052	.157*	.110	.108
	Sig	.007	.000	.001	.089	.004	.047	.435	.017	.095	.102
Rhinorrhoea	CC	.179**	.358***	.201**	.170**	.155*	.076	.071	.145*	.094	.026
	Sig	.006	.000	.002	.010	.018	.250	.283	.027	.155	.696
Itchy nose or throat	CC	.286***	.353***	.189**	.127	.204**	.085	.053	.234***	.016	-.062
	Sig	.000	.000	.004	.054	.002	.196	.425	.000	.803	.347
Itchy eyes	CC	.082	.234***	.143*	.049	.120	-.034	-.044	.023	.041	.033
	Sig	.215	.000	.030	.456	.068	.610	.509	.731	.535	.619
Watery eyes	CC	.121	.233***	.000	.059	.179**	.022	-.011	.020	-.001	.059
	Sig	.066	.000	.995	.373	.006	.738	.865	.767	.989	.371
Cough	CC	.052	.049	.439***	.156*	.034	-.151	-.120	-.105	-.024	.030
	Sig	.436	.457	.000	.018	.602	.022	.068	.113	.719	.651
Headache	CC	.010	.153*	.174**	.157*	.158*	-.048	.012	-.079	-.060	-.106
	Sig	.878	.020	.008	.017	.016	.467	.854	.230	.365	.110

* Statistically significant at the p<0.05 level; ** very statistically significant at the p<0.01 level; *** extremely statistically significant at the p<0.001 level.

Table 3. Symptoms correlations to study group demographic characteristics and seasonality (SAR, PAR).

Symptoms	Seasonal (n=) (%)	p-value	Perennial (n=) (%)	p-value	Total (n=)	Age (6-11) (12-17)	p-value	Gender 0=Male 1=Female	p-value	
Nasal obstruction or congestion	68 (71.6)	<0.001	59 (89.4)	<0.001	127	ns	n=97 n=30	0.092	0=66 1=61	0.658
Sneezing	64 (67.4)	<0.001	58 (87.9)	<0.001	122	ns	n=92 n=30	0.205	0=62 1=60	0.956
Rhinorrhoea	54 (56.8)	0.045	58 (87.9)	<0.001	112	<0.001	n=89 n=23	0.006	0=57 1=55	0.835
Itchy nose or throat	30 (31.6)	0.415	50 (75.8)	<0.001	80	<0.001	n=58 n=22	0.875	0=41 1=39	0.894
Itchy eyes	21 (22.1)	0.035	16 (24.2)	0.031	37	ns	n=26 n=11	0.814	0=18 1=19	0.721
Watery eyes	11 (11.6)	0.621	13 (19.7)	0.003	24	0.003	n=17 n=7	0.906	0=15 1=9	0.22
Cough	27 (28.4)	0.072	25 (37.9)	<0.001	52	<0.001	n=35 n=17	0.407	0=22 1=30	0.172
Headache	10 (10.5)	0.195	8 (12.1)	0.121	18	ns	n=11 n=7	0.291	0=8 1=10	0.583

between SAR/PAR groups were found only for rhinorrhea and itchy nose/throat (p<0.001), watery eyes (p=0.003), and cough (p<0.001) in patients with PAR. Moreover, subjects with PAR reported more severe symptoms (p<0.001). On the contrary, mild disease was associated with SAR (p<0.001) (Table 4).

Concerning skin sensitivities, mite allergy as well as grass and fungi allergy were associated with moderate-to-severe disease (p<0.001) (Table 4). No correlations were found among the severity of symptoms as reported by patients and the age group (primary vs. secondary school-aged children), as well as sex.

Table 4. Severity of symptoms correlated to allergen sensitivities and seasonality.

Severity	SAR (n=) p-value	PAR (n=) p-value	HDM p-value	Grasses p-value	Alternaria p-value	Cladosporium p-value	Olive p-value	Parietaria p-value
Moderate to severe	4 <0.001	34 <0.001	34 <0.001	31 <0.001	21 <0.001	9 <0.001	8 0.217	9 0.002
Mild	87 <0.001	32 ns	63 0.275	60 0.263	45 0.261	8 0.543	23 0.051	8 0.068
None	4 <0.001	0 <0.001	41 -0.002	22 <0.001	14 <0.001	1 -0.011	3 -0.002	7 0.652

Table 5. Correlations of the skin prick sensitivity grade score to common aeroallergens with severity of symptoms and seasonality (ARIA based AR).

Allergen	Sensitivity Grade score	Seasonal (n, %)	p-value	Perennial (n, %)	p-value	Mild (n, %)	p-value	Moderate to Severe (n, %)	p-value
HDM	2	4		1		4		1	
	3	6	ns	5	<0.001	9	ns	1	<0.001
	4	32		52		50		32	
Grasses	2	4		0		0		0	
	3	6	ns	3	<0.001	6	ns	0	<0.001
	4	32		42		54		31	
Alternaria	2	2		1		3		0	
	3	5	ns	2	0.027	6	ns	0	0.001
	4	31		26		36		21	
Cladosporium	2	1		2		1		2	
	3	1	ns	0	<0.001	1	ns	0	<0.001
	4	3		10		6		7	
Olive	2	2		0		2		0	
	3	4	0.025	4	ns	6	ns	2	ns
	4	14		7		15		6	
Parietaria	2	0		0		0		0	
	3	2	ns	4	ns	3	ns	3	0.002
	4	5		6		5		6	
Cypress	2	0		0		0		0	
	3	1	ns	1	ns	1	ns	1	ns
	4	3		3		3		3	
Pine	2	0		0		0		0	
	3	1	ns	6	<0.001	4	ns	3	ns
	4	2		5		4		2	
Dog	1	0		1		0		1	
	2	2		4		5		1	
	3	3	ns	4	ns	4	ns	3	ns
	4	4		4		5		3	
Cat	1	1		0		1		0	
	2	3		1		4		0	
	3	3	ns	4	ns	5	ns	2	ns
	4	4		4		5		3	

Finally, the size of the wheal and redness were found to be significantly correlated to PAR in patients with HDM ($p < 0.001$), grass ($p < 0.001$), and fungi allergies ($p < 0.05$). Moreover, higher

sensitivity grade scores were associated with more severe symptoms (Table 5).

Discussion

Allergic rhinitis is the most common non-infectious inflammation of the nasal mucosa, and is caused by an IgE-mediated reaction to environmental allergens [3–6,13]. AR symptoms are nasal (nasal obstruction or congestion, sneezing, rhinorrhea, itchy nose or throat), ocular (itchy and watery eyes), or general (cough, headache) [8,13]. Because the same symptoms can also be reported by people with non-allergic rhinitis, the diagnosis of AR should be confirmed by positive SPT results. Skin-prick tests are considered the criterion standard diagnostic method for AR, with the highest sensitivity and accuracy [15].

It is widely accepted that skin sensitivities and symptoms are greatly influenced by the aerobiology of the area. Indeed, there are studies showing that registered airborne allergen concentrations of the most important pollen species are correlated to symptoms in AR patients who live in the same area for a long time (more than 5 years) [22]. Moreover, aerobiology studies have shown similarities in pollen concentrations among countries and areas with similar climate conditions (e.g., weather, flora, vegetation), such as in countries with Mediterranean climate conditions. According to the literature, Mediterranean countries such as Italy, Turkey, Greece, Cyprus, and Spain have similar aerobiology. In a previous work [4,5] of ours, we have presented the pollen calendar of our area, with the highest total percentages of pollens recorded for olive (24.02% of total), oak (13.74%), grasses (9.08%), and cypress (7.63%). Among fungi, *Alternaria* and *Cladosporium* were detected throughout the calendar year in ranges of 0 to 217 spores/m³ and 6.5 to 1600 spores/m³ per day, respectively. We found similarities with pollen calendars from Spain [28], Cyprus [29], Italy [30], Turkey [31], and in the Mediterranean area generally [32,33], although there were small differences in the duration of pollination periods and counting among studies. In our previous work [4,5], we found similarities with the most prevalent sensitizations as described in previous studies from countries with similar climatic conditions [34]. All these findings make our results useful not only in Greece, but also in other countries with similar Mediterranean climate conditions.

In the present study, we first found that the most prevalent symptoms among AR patients were nasal, especially nasal obstruction, sneezing, and rhinorrhea, with half of the subjects reporting these symptoms. Ocular symptoms were less frequent, whereas cough was the most common general symptom (22.5%), especially in patients with rhinitis and concomitant asthma. The prevalence rates of nasal symptoms in our study agree with findings from previous studies [2,35]. However, an interesting finding of the present study was the high percentage (30.7%) of patients with no self-reported symptoms but with positive SPT results. Recent studies [2,7,36] have also shown high rates of patients reporting being symptom-free.

This can be because the symptoms and signs of AR are frequently attributed to a common cold or are considered unimportant [16]. Consequently, this problem is underestimated both by pediatric patients and parents [16], and only those with severe symptomatology visit doctors, resulting to a significant proportion of allergic rhinitis patients being untreated [16]. Underestimation of symptoms is also supported by our findings, according to which, half of the patients evaluated their symptoms severity as mild, with 32% reporting some concern and only 16.5% reporting moderate-to-severe disease. Self-reported symptom-free cases make early screening and diagnosis, as well as early treatment, clinically meaningful to prevent future disease comorbidities (e.g., asthma and chronic rhinosinusitis) [37].

Accordingly, an important and useful finding of our study in everyday clinical practice is the correlation between the sensitivity pattern and symptoms characteristics. We found that among sensitivities, patients with HDM and tree (olive, parietaria, and pine) allergies mainly reported nasal symptoms. On the other hand, patients who has grass pollen and mold allergy in addition to nasal symptoms also reported ocular and general symptoms. Subjects with mold allergy also reported lower respiratory tract symptoms such as cough. This can be attributed to the well-described association between *Alternaria alternata* and asthma diseases [38]. Moreover, according to symptom severity, mite, grass, and mold allergies were significantly more often self-reported by patients as being moderate-to-severe. On the contrary, no correlation between tree pollen allergy and severity of symptoms was discovered. No correlation between symptom severity and age or sex was observed. A prominent feature of all comparisons is that the allergens with the greatest prevalence of positive SPTs are the same that show significance in the various outcomes examined. This may be because, according to Grant-Smith [39], grasses and olive trees are among aeroallergens with the highest allergenic potential. This finding was confirmed by a previous study of ours [4]. Therefore, this could be attributed to a special characteristic of the allergens.

Although AR has recently been divided according to the ARIA classification into intermittent versus persistent based on the duration of symptoms [34], allergen-specific treatment also needs to be incorporated with the seasonal and perennial classification to ascertain the correct allergen to be used in desensitization [37]. Therefore, according to seasonality, subjects with PAR described their symptoms as moderate-to-severe, but patients with SAR had milder symptoms. Evaluation of the symptom profile of patients with SAR/PAR indicated little difference in the spectrum of symptoms reported by each patient group. All symptoms, with the exception of nasal congestion, sneezing, and itchy eyes, were significantly more prevalent among patients with PAR. Moreover, types of

symptoms were not correlated with sex or age, with the exception of rhinorrhea, which was most common among primary school-aged children.

A clinically interesting item that we furthermore tried to discover was the association of the sensitivity grade score according to SPT results with symptoms severity or the seasonality of appearance. We observed that for the mite, grass, and mold allergies, the sensitivity grade score was significantly correlated with moderate-to-severe symptomatology. Similar results were found for the perennial appearance of symptoms. On the contrary, no correlation was discovered for tree or animal dander sensitivities. These findings mean that, for mite, grass, and mould allergies, higher sensitivity grade scores were associated with more severe disease. These findings agree with those of previous studies [7,40], showing that another factor predicting symptom presence is the wheal size of the SPT. They observed that when the wheal size of HDM and grass allergens increased, there were significantly more severe symptoms. However, we have to take into account the contribution of psychological factors to the patient's perception of allergy symptoms. On the contrary, Tatar et al. [27] found no significant correlation. This is an interesting debate that should be answered in future studies. However, our results agree with the common wisdom that strongly positive skin test results are associated with more severe symptoms.

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Conclusions

We found that among AR symptoms, the nasal ones (nasal obstruction, sneezing, rhinorrhea, and itchy nose) are the most frequent. It is important to point out, however, that 1 out of 3 children were symptom-free. This shows the need for SPT screening for early diagnosis to prevent more serious diseases in childhood and adolescence. According to sensitization pattern, more symptoms (nasal, ocular, and general) appeared among patients with grass pollen and mold allergies, but in those with mite and tree sensitivities, nasal symptoms were more frequent. Moreover, mite, grass, and mold allergies were associated with moderate-to-severe disease. Subjects with PAR described their symptoms as moderate-to-severe, but those with SAR tended to describe mild symptoms.

Higher sensitivity grade scores according to SPT results were associated with more severe symptoms reported for mite, grass, and mold allergies. Our findings provide clinically meaningful information in for use in everyday clinical practice for the appropriate management of school-aged children and adolescents suffering from AR and living in Mediterranean climate conditions.

Conflicts of interest

None.

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