

Predictive factors to differentiate between allergic and nonallergic rhinitis in children

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Background: Although symptoms and signs of allergic rhinitis (AR) and nonallergic rhinitis (NAR) are similar, treatment and follow-up are different. We aimed to find predictive factors that can be used in primary health care to differentiate AR from NAR.

Methods: We made a retrospective analysis of cases aged 6–18 years old who were diagnosed as having chronic rhinitis within a 1-year period. Skin-prick tests were done and severity of rhinitis symptoms was recorded on a visual analogue scale in all patients.

Results: There were 472 cases whose medical records were complete and included in the analysis. The median age was 11 (interquartile range [IQR], 5) years. AR was diagnosed in 363 patients (76.9%) and was different from NAR with respect to: median age ($p = 0.042$), seasonality of the symptoms ($p = 0.002$), persistent symptoms ($p = 0.003$), moderate/severe according to visual analogue scale (VAS) score ($p = 0.017$), conjunctivitis ($p < 0.001$), parental history of AR ($p = 0.026$), rhinorrhea ($p < 0.001$), sneezing ($p =$

0.005), mucosal pallor ($p = 0.004$), and response to antihistamines ($p = 0.035$). All parameters with a significance of $p < 0.1$ between AR and NAR were included in logistic regression analysis. Seasonality, sneezing, moderate/severe rhinitis, and response to antihistamines were identified as significant independent parameters to differentiate AR from NAR.

Conclusion: Features of rhinitis patients with seasonality, sneezing, moderate/severe rhinitis, and response to antihistamines may help in differentiation of AR from NAR at the primary care level. © 2014 ARS-AAOA, LLC.

Key Words:

allergic; differences; nonallergic; similarities; rhinitis

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Based on parental reports, chronic rhinitis was reported to affect 23.5% of the school-age population in Turkey.¹ It has considerable effect on quality of life, sleep, school absenteeism, and socioeconomic impact as a result of healthcare utilization, treatment cost, and loss of school days. The most common form of chronic rhinitis is allergic rhinitis (AR). Although symptoms and signs of AR and nonallergic rhinitis (NAR) are similar, treatment and follow-up are different. The main distinction between AR and NAR

is aeroallergen sensitization consistent with symptoms and signs. Allergen sensitization is detected by skin-prick test (SPT) and/or measurement of specific immunoglobulin E (IgE) levels, which are mostly available in the tertiary and in some secondary care levels. In contrast, the majority of patients with chronic rhinitis first apply to primary care medical centers, where diagnosis mostly relies on history and physical findings. This approach may lead to overdiagnosis/underdiagnosis and overtreatment/undertreatment of AR at these basic medical centers. An indirect but good evidence of this problem comes from questionnaire-based studies in which underestimations as well as overestimations of AR are possible depending on how the question is put.² Therefore, differentiation of AR from other chronic rhinitis phenotypes may prevent problems in diagnosis and treatment of this entity, which may inadvertently cause an increase in physiological, psychological, and economic impact of the disease.

In this report, we aim to determine clinical symptoms and signs of rhinitis that may be used to differentiate AR from

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NAR at the primary care level by using multiple logistic regression analysis.

Patients and methods

The study was approved by the Ethics Committee of Gazi University (approval number 314/12.09.2012).

Study population

We made a retrospective analysis of cases aged 6–18 years old who were diagnosed as rhinitis between September 2011 and September 2012. We entered all the data that included demographics, age at onset of disease, duration, recurrence, seasonality, severity of symptoms, previous treatments and their response, comorbid atopic diseases, parental history of atopic diseases, signs on physical examination, classification and severity of rhinitis according to Allergic Rhinitis and its Impact on Asthma (ARIA), visual analogue scale (VAS), and SPT result for each case.

Study measurements

SPT

SPTs were performed on the forearm by use of standard skin-prick method. The test was carried out with standardized allergen extracts against the following 8 most common aeroallergens: house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass mix (*Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Anthoxanthum odoratum*, *Avana sativa*, *Festuca elatior*, *Agrostis vulgaris*, *Holcus latanus*, and *Bromus*), weed mix (*Artemisia vulgaris*, *Plantago lanceolata*, and *Chenopodium album*), cereal mix (*Hordeum vulgare*, *Triticum vulgare*, *Avena sativa*, and *Zea mays*), tree mix (*Acer pseudoplatanus*, *Aesculus hippocastanum*, *Platanus vulgaris*, *Robinia pseudoacacia*, and *Tilia platyphyllos*), mold mix (*Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium*), and animal dander (*Stallergens*, France). Histamine hydrochloride 10 mg/mL and allergen diluents were used as positive and negative controls, respectively. A mean wheal diameter of at least 3 mm greater than that of the negative control was considered positive. Any child with such a response to 1 or more allergens was defined as atopic. Patients who reacted to 1 aeroallergen were defined as monosensitized, whereas others who reacted to more than 1 aeroallergen were defined as polysensitized.

VAS

Subjects were instructed that 0 indicated “nasal symptoms not at all bothersome” and that 100 indicated “nasal symptoms extremely bothersome.” The patients assessed their total nasal symptom scores (sneezing, rhinorrhea, nasal obstruction and nasal itching) by marking the scale between 0 and 100.

Study definitions

Rhinitis

Rhinitis is defined as nasal symptoms, including anterior or posterior rhinorrhea, sneezing, nasal blockage, and/or itching of the nose. These symptoms occur during 2 or more consecutive days for more than 1 hour on most days.³

AR

The diagnosis of AR was based upon the concordance between a typical history of allergic symptoms and SPT positivity in children with rhinitis.^{3,4}

NAR

NAR was defined as rhinitis without an infection and negative SPTs.⁴

Allergic conjunctivitis

Allergic conjunctivitis was defined as presence of 1 or more of the following symptoms for >1 hour on most days: symptoms associated with rhinitis, bilateral eye symptoms, eye itching, red eyes, and no photophobia.³

Classification of rhinitis

Rhinitis was classified as intermittent (mild or moderate/severe) or persistent (mild or moderate/severe) according to ARIA guidelines.³ Although this classification was originally made for AR, we also applied it for NAR cases.

Severity of rhinitis

We also used the VAS for objective measurement of the severity of rhinitis. The severity was defined as mild, moderate, and severe based on the total severity VAS score (0–100): mild = VAS 0 to 30; moderate = VAS 31 to 70; and severe = VAS 70 to 100 (according to Bousquet et al.³).

Data analysis

SPSS 11.5.0 software for Windows (SPSS, Chicago, IL) was used for statistical analyses. Descriptive statistics were expressed as frequency and percentage for categorical variables whereas quantitative data were expressed as median (IQR) for non-normally distributed data. Comparison between groups was done by Pearson chi-square test (Fisher's exact test when needed) and by Mann-Whitney U test. A backward stepwise multiple logistic regression model was constructed by including $p < 0.1$ variables. According to this, the following variables were included in multiple logistic regression analysis: age; seasonality of symptoms; response to antihistamines; comorbid conjunctivitis; symptoms of itching, rhinorrhea, nasal obstruction, and sneezing at the time of admission; mucosal pallor, rhinorrhea, and turbinate hypertrophy in physical examination; persistent rhinitis; moderate/severe rhinitis (VAS score ≥ 31); and history of parental AR. A 2-sided $p < 0.05$ was considered statistically significant.

TABLE 1. Characteristics of allergic and nonallergic rhinitis in children 6 to 18 years old*

Variable	Allergic rhinitis (n = 363)	Nonallergic rhinitis (n = 109)	p ^a
Age, years (IQR)	11 (5)	10 (6)	0.042
Male	210 (57.9)	56 (51.4)	0.232
Age of onset, years (IQR)	7 (5)	6 (5.5)	0.110
Seasonal nasal symptoms	267 (73.6)	63 (57.8)	0.002
Response to antihistamines	198/212 (93.4) [†]	38/46 (82.6) [†]	0.035
Comorbid atopic disease			
Asthma	154 (42.4)	45 (46)	0.833
Eczema	21 (5.8)	6 (5.5)	1.000
Conjunctivitis	150 (41.3)	25 (22.9)	<0.001
Doctor-diagnosed adenoid vegetation/adenectomy	66 (18.2)	25 (22.9)	0.270
Nasal symptoms at the admission			
Itching	353 (97.2)	102 (93.6)	0.082
Rhinorrhea	284 (78.2)	67 (61.5)	<0.001
Nasal obstruction	308 (84.8)	84 (77.1)	0.057
Sneezing	346 (95.3)	95 (87.2)	0.005
Postnasal drip	105 (28.9)	25 (22.9)	0.220
Family history of atopic disease			
Asthma	66 (18.2)	21 (19.3)	0.908
Allergic rhinitis	117 (32.2)	23 (21.1)	0.026
Eczema	5 (1.4)	2 (1.8)	0.664
Severity of rhinitis			
Persistent	227 (62.5)	51 (46.8)	0.003
Moderate/severe rhinitis (VAS score $\geq$ 31)	281 (77.4)	72 (66.1)	0.017

*Values are n (%) except where indicated.

[†]The number of patients prescribed antihistamine.^aSignificant p values are in bold.

IQR = interquartile range; VAS = visual analogue scale.

Results

Demographics

The study population included 505 patients; 33 of these patients (6.5%) were excluded because of lack of contact or incomplete record in the file. Finally, 472 patients completed the study; 266 patients were male (56.4%) and the median age was 11 (IQR, 5) years. Rhinitis was intermittent in 194 patients (41.1%), and persistent in 278 patients (58.9%). AR was diagnosed in 363 patients (76.9%). Monosensitization and polysensitization were found in 54 (14.9%) and in 309 (85.1%) patients, respectively. Within the AR patients, 314 were sensitized to pollens (86.5%), 239 were sensitized to *Dermatophagoides* (65.8%), 115 were sensitized to animal dander (31.7%), and 37 were sensitized to *Alternaria* (10.2%). A total of 199 patients had asthma (42.2%) and 27 patients had atopic dermati-

tis (5.7%) as comorbid allergic diseases. Demographic and clinical characteristics of the patients are shown in Table 1.

Differences and similarities between AR and NAR

AR was different from NAR in the following variables: median age ($p = 0.042$); seasonality of the symptoms ($p = 0.002$); persistent symptoms ($p = 0.003$); moderate/severe according to VAS score ($p = 0.017$); conjunctivitis ($p < 0.001$); parental history of AR ($p = 0.026$); rhinorrhea ($p < 0.001$); sneezing ($p = 0.005$); mucosal pallor ($p = 0.004$) (Fig. 1); and response to antihistamines ($p = 0.035$). Both AR and NAR were similar with respect to sex, age at the onset of the disease, nasal pruritis, nasal congestion, postnasal drip, hypertrophy of the nasal turbinate, horizontal nasal crease, shiner, and comorbid asthma ($p > 0.05$ for each) (Table 1). Logistic regression analysis revealed 4

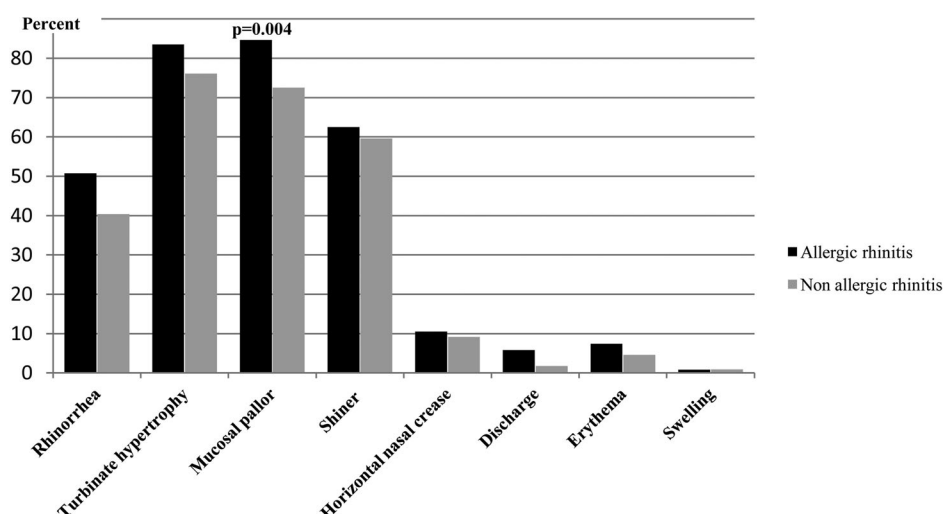


FIGURE 1. Physical signs associated with allergic and nonallergic rhinitis in children.

TABLE 2. Logistic regression analysis to differentiate allergic rhinitis from nonallergic rhinitis (n = 472)

Variables	n	Univariate analysis		Multivariate analysis		Sensitivity (%)	Specificity (%)
		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p		
Age, years	472		0.042				
Seasonality	330	1.5 (1.208–2.19)	0.002	2.78 (1.513–5.110)	0.001	80.9	32.4
Response to antihistamines	236	2.6 (1.174–5.908)	0.035	2.61 (1.111–6.130)	0.028	82	36.7
Conjunctivitis	175	1.3 (1.149–1.502)	<0.001				
Itching symptom	455	0.9 (0.913–1.014)	0.082				
Rhinorrhea symptom	351	0.8 (0.671–0.920)	<0.001				
Nasal obstruction symptom	392	0.9 (0.813–1.015)	0.057				
Sneezing symptom	441	2.7 (1.398–5.382)	0.005	3.90 (1.331–11.481)	0.013	78.5	45.2
Parental allergic rhinitis history	140	1.1 (1.032–1.313)	0.026				
Rhinorrhea in physical exam	228	0.8 (0.620–1.022)	0.059				
Turbinate hypertrophy	386	0.9 (0.813–1.023)	0.082				
Mucosal pallor	386	1.7 (1.210–2.631)	0.004				
Persistent	278	1.4 (1.139–1.771)	0.003				
Moderate/severe rhinitis (VAS score ≥ 31)	353	1.5 (1.087–2.077)	0.017	2.05 (1.053–4.001)	0.035	79.6	31.1

VAS = visual analogue scale.

statistically significant independent factors to differentiate between AR and NAR in the study population (Table 2).

Differences and similarities between AR and NAR according to age groups

The patients were divided in 2 groups. The first group included 280 patients (59.3%) who were 6–11 years old, and the second group included 192 patients (41.7%) who were 12–18 years old. The first group included 73 patients (26.1%) diagnosed as NAR, and there was no statically

significant difference between the groups diagnosed with NAR ($p = 0.06$). The signs and symptoms that distinguish AR from NAR were different between the 2 groups. In the 6- to 11-year old group, presence of seasonality, response to antihistamines, or moderate/severe rhinitis (VAS score ≥ 31) increased the risk of being diagnosed with AR as follows: 2.2-fold, 3.4-fold, and 2.6 fold, respectively. In the 12- to 18-year-old group, seasonality, rhinorrhea in physical examination, and sneezing increased the risk of being diagnosed with AR as follows: 3.5-fold, 4.1-fold, and 10.9-fold, respectively (Table 3).

TABLE 3. Multivariate logistic regression analysis to differentiate allergic rhinitis from nonallergic rhinitis according to age groups

Variables	Children 6–11 years old (n = 280)		Children 12–18 years old (n = 192)	
	Odds ratio (95% CI)	p ^a	Odds ratio (95% CI)	p ^a
Seasonality	2.25 (1.072–4.746)	0.032	3.59 (1.176–10.982)	0.025
Response to antihistamines	3.40 (1.173–9.885)	0.024		0.958
Sneezing symptom		0.435	10.98 (1.775–67.993)	0.010
Rhinorrhea in physical exam		0.538	4.11 (1.196–14.138)	0.025
Moderate/severe rhinitis (VAS score ≥31)	2.64 (1.197–5.822)	0.016		0.756

^aSignificant p values are in bold.
VAS = visual analogue scale.

Discussion

This study found that medical history in a child with chronic rhinitis may help to distinguish AR from NAR. The odds of chronic rhinitis being related to AR is at least twice more than being NAR if the child has sneezing or describes that it is seasonal, moderate to severe, or responsive to antihistamines. There were no parameters requiring laboratory tests such as atopic sensitization, inflammatory and hyperreactivity parameters that are usually available in tertiary centers in this study. In contrast, all of the study parameters can be recorded in any steps of health service, enabling ease for diagnosis, especially at the primary and secondary care levels.

There are few studies investigating the similarities and differences between AR and NAR both in children^{5,6} and in adults.^{4,7–9} All previous studies made a univariate comparison of clinical characteristics between AR and NAR.^{4–6,8,9} Our results are similar to some of these studies, such as persistence, seasonality, and severity of symptoms, which were also reported to be more common in patients with AR compared to patients with NAR.^{4,7,8} Also, family history of atopy and AR were detected more often in AR than NAR in our study, similar to adult studies.^{4,7} On the other hand, nasal itching^{4–6} and nasal obstruction^{4,5,8,9} were not identified as discriminative between AR and NAR in our study.

There is only 1 study⁹ in adults that used logistic regression analysis similar to our study. In this study, the authors identified 10 parameters that significantly differentiate between AR and NAR. Among these parameters, 5 of them—effective response to antihistamines, conjunctivitis, sneezing, nasal pruritus, and severity of the disease—were found to increase the odds of AR by 22.5, 4.49, 4.09, 3.84, and 3.66, respectively. Sneezing, moderate/severe rhinitis, and response to antihistamines were also determined as significant parameters predicting AR in our study, in addition to seasonality. Older age, conjunctivitis, and presence of nasal pruritus were not found to be significant parameters to distinguish AR from NAR in our study. The median (IQR) age of children with AR and NAR was only border-

line significant (Table 1; $p = 0.042$) in our study population, which probably lost its significance in the logistic regression model. Although conjunctivitis was significantly different between children with AR and NAR, it also probably lost its significance because the number of parameters found significant in the univariate analysis was too many, which might have caused loss of its significance in the multivariate analysis. Finally, children may ignore pruritus or do not overrate it as much as adults. The sensitivity of the 4 parameters, which were sneezing, seasonality, moderate to severe rhinitis, and responsiveness to antihistamines in history, were actually quite high, rendering some false-negative results. The low specificity, on the other hand, renders a lot of false-positive results.

Comparison of physical examination findings between AR and NAR were not reported previously.^{4–9} We found mucosal pallor more predominantly in AR than NAR, as expected. On the other hand, hypertrophy of the turbinates, shiner, and horizontal nasal crease were not found more frequently in AR than NAR.

The incidence of NAR increases with older age and symptoms of disease might change with age. Nasal obstruction, headache, and no smelling complaints are seen more in NAR patients.⁷ In the current study, the rate of NAR patients are more in the 6- to 11-year-old group than the 12- to 18-year-old group, although it was not statistically significant. Seasonality increased the risk of AR approximately 3-fold in both groups. Whereas response to antihistamines and moderate/severe rhinitis symptoms increased the risk of being diagnosed with AR in the 6- to 11-year-old group, to have sneezing or rhinorrhea in physical examination increased the risk of being diagnosed with AR in the 12- to 18-year-old group. The new sensitization occurring with aging and symptoms persistent with time in the AR patients could explain these differences between the 2 groups.

Our research has some limitations. We carried out this study at a tertiary health care; it would certainly have been better if it could have been done at a primary care center. We might have missed the patients that were not referred to a tertiary center as well as we might have included more severe patients with rhinitis that were referred to a tertiary

center by conducting the study in a tertiary clinic. Second, we might have inadvertently included some AR patients who show local IgE production without an evidence of systemic atopic sensitization in the NAR patient group.¹⁰

Conclusion

The current study demonstrated that the probability of AR in a child with chronic rhinitis is increased if the symptoms

appear seasonal and if the child describes sneezing, moderate/severe rhinitis, and responsiveness to antihistamines. These independent factors may be used to guide and help primary care physicians with their decision when discriminating AR from NAR in children at the primary health care level. Although these results may help to decrease overdiagnosis/underdiagnosis and undertreatment/overtreatment of AR in children at the primary care level, there still seems no perfect predictive model that can certainly differentiate AR from NAR in primary care. 

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