

Prevalence and Clinical Characteristics of Local Allergic Rhinitis in Children Sensitized to House Dust Mites

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Keywords

Local allergic rhinitis · Prevalence · House dust mite · Children

Abstract

Objective: The prevalence of local allergic rhinitis (LAR) in nonatopic children remains unknown. This study aimed to determine the prevalence, clinical characteristics, and severity of LAR in children in comparison to classical allergic rhinitis (AR) and nonallergic rhinitis (NAR). **Study Design:** A total of 145 children (aged 1–18 years) were enrolled and classified into 3 groups (AR, NAR, and LAR) based on a skin prick test (SPT) and a nasal provocation test (NPT) with house dust mite, i.e., *Dermatophagoides pteronyssinus*. NPT positivity was defined as a symptom score ≥ 2 standard deviations (SDs) above the healthy control score. **Results:** Eighty-one children had AR (55.9%), and 64 (44.1%) had symptoms of rhinitis with negative SPT; 59 NAR (40.7%) and 5 LAR (3.4%) children were identified. The κ score for agreement between the SPT and the NPT results was 0.778 (95% CI 0.726–0.830, $p < 0.001$). A significant correlation was observed between wheal diameter and maximum nasal symptom score pro-

voked by *D. pteronyssinus* ($\rho = 0.589$, $p < 0.001$). Nasal severity according to the ARIA guideline did not show any differences in the 3 groups ($p = 0.693$). The AR group was older than the LAR and NAR groups ($AR > LAR > NAR$, $p = 0.003$). **Conclusions:** Despite the evidence to support the existence of LAR in pediatric populations, we found that its prevalence was relatively low, possibly due to the high rate of agreement between SPT and NPT. Further investigations are needed to identify immunological as well as clinical implications of LAR.

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Introduction

The differentiation of allergic rhinitis (AR) from non-allergic rhinitis (NAR) is essential for the selection of appropriate treatments [1] and predicting prognosis [2]. The classification is based on the development of systemic clinical manifestations following exposure to specific allergens and signs and/or symptoms provoked by exposure to specific allergens [3]. Although there is a paucity of literature on children, local allergic rhinitis (LAR) may

be diagnosed when there are symptoms of allergic rhinitis, but without evidence of systemic atopy [4–7]. Previous studies of LAR have investigated the local production of allergic mediators, and, along with positive nasal provocation tests (NPTs), have demonstrated an increase of IgE in nasal secretions [8–11].

The prevalence of LAR may vary from 47 to 62.5% [8, 12] in nonsensitized patients [9]. However, previous studies are limited in that they included only adults, did not have controls, or else used different diagnostic criteria for LAR. It may be inappropriate to apply the prevalence statistics and clinical signs and/or symptoms of LAR in adults to children because children have different sensitization rates and dynamic responses to many allergens [13].

The aims of this study are to assess the prevalence of AR, NAR, and LAR with regard to aeroallergens including house dust mites, i.e., *Dermatophagoides pteronyssinus* and *D. farinae*, in a pediatric population in Korea, and to compare clinical characteristics, such as disease severity, comorbidities, past allergic history, and family history in these 3 groups.

Methods

Study Subjects

This cross-sectional, observational study enrolled children who visited the outpatient clinics of CHA Bundang Medical Center, CHA University, Seongnam, Korean from May 2011 to June 2012 for the diagnosis or monitoring of rhinitis symptoms. Rhinitis was diagnosed by physicians who had asked patients or their caregivers about the presence of relevant symptoms during the last 12 months when they were free of a common cold. Subjects with the following symptoms were classified as the rhinitis symptom group: (i) 1 of 4 significant symptoms suggestive of rhinitis (nasal obstruction, rhinorrhea, sneezing, or an itching sensation) for at least 1 h in the past 12 months during periods without a cold or flu, and (ii) the experience of symptoms suggestive of rhinitis at least 2 times during a particular season, and/or a history of rhinitis symptoms for at least 2 consecutive years, or symptoms 3 times regardless of season. The exclusion criteria were [14]: (i) symptoms suggestive of infectious rhinitis during the previous 4 weeks [1], (ii) episodes of a respiratory tract infection during the previous 4 weeks, (iii) symptoms that mimic rhinitis [1], and (iv) symptoms suggestive of other immunological diseases [15]. We also performed NPTs on healthy controls. These were children recruited from the community who had never been diagnosed with allergic rhinitis or asthma and had no exclusion criteria. Healthy controls with positive skin prick test (SPT) results were also classified into the control group after confirmation that they had no rhinitis symptoms following in-depth interviews. Subjects aged ≥ 14 years were considered adolescents, and were analyzed separately. We explained the aim of the study to all participants and their parents or guardians and obtained their written consent. The study was approved by the institutional review board of the CHA Bundang Medical Center (IRB 2011-175).

Study Design

At the first visit, we confirmed that the subjects fulfilled the washout criteria for medications such as intranasal corticosteroids or antihistamines: (i) mono- or nonsensitized to house dust mites, (ii) no systemic corticosteroid for 1 month, (iii) no antihistamine or antileukotriene for 1 week, (iv) no intranasal steroid for 2 weeks [16], and (v) no systemic or nasal vasoconstrictors for 1 week [10]. If the subject was on any medication, we recommended stopping for a certain period, i.e., until the second visit. At the second visit, baseline symptom scores were recorded, and nasal severity was classified by the ARIA guidelines. An NPT for *D. pteronyssinus* and an SPT for 10 allergens were performed. We delayed participation if the subject complained of severe symptoms or had signs and/or symptoms suggestive of an acute infection.

Classification of Rhinitis

Children were classified into 3 subgroups based on the SPT results to *D. pteronyssinus* and *D. farinae* and the NPT results to *D. pteronyssinus*. The AR group, had positive SPT results; the NAR group had negative SPT and NPT results; and the LAR group had negative SPT results but positive NPT results.

Rhinitis Severity: ARIA Guideline and Month Symptom Score

The severity of AR was classified according to the methods described in the ARIA guidelines [17]. We recorded the nasal severity score by using information reported by the parents/caregivers during the past month and defined this as the month symptom score (MSS). The severity of MSS was graded by using the sum of the 6 following symptom scores: a 7-point score for 5 specific nasal symptoms (sneezing, rhinorrhea, nasal obstruction, nasal itching, and postnasal drip) and a 7-point score for general nasal symptoms [1] (total range: 0–42). The study was performed while the patients were asymptomatic or mildly symptomatic.

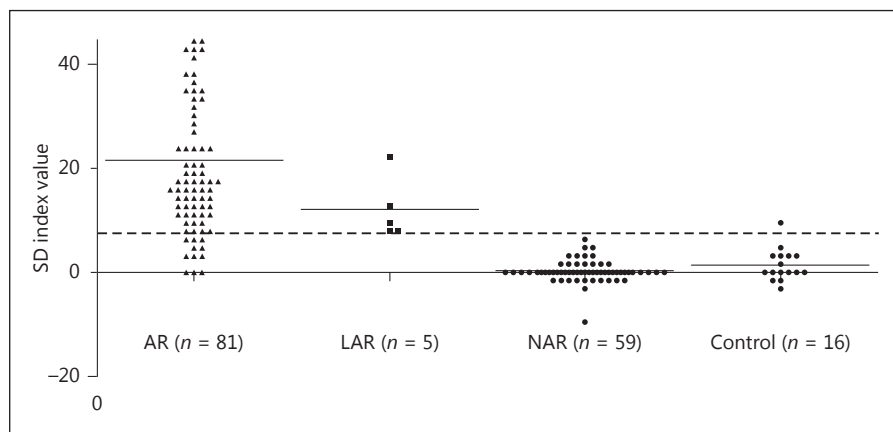
Skin Prick Test

SPTs were performed on children using a wide panel of the most prevalent inhalant allergens in Korea, including *D. farinae*, *D. pteronyssinus*, tree pollen mixture I and II, grass pollen mixture, weed pollen mixtures, mold mixtures, dog, cat, and cockroach (Allergopharma, Reinbek, Germany). The test was considered positive if the wheal was >3 mm.

NPT for *D. pteronyssinus*

A modified version of the NPT test described by Rondon et al. [10] was performed. Basal nasal function was evaluated after adaptation to room temperature for 30 min. To exclude nasal hyperactivity, we performed a saline challenge with 2 puffs (0.05 mL each) using a metered dose-delivery device, and recorded the symptom score after this test as the baseline score. Two steps of NPT (0.4 and 4 $\mu\text{g/mL}$ of freshly reconstituted freeze-dried *D. pteronyssinus*) were administered to patients who had negative results on the saline challenge test. Clinical symptom scores (rhinorrhea, sneezing, nasal obstruction, nasal itching, and optical symptoms) were each scored on a scale of 0–10 (total range: 0–50) at baseline (after the saline challenge) and after each step. Parents or caregivers were instructed to count the frequency of scratching of the nose or eyes and nose-blowing due to nasal obstruction. The test was stopped if the child could not tolerate the test and/or did not want to continue. The symptoms recorded after the last dose were used to calculate the maximum total symptom score (TSS).

Fig. 1. SD index change in the allergic rhinitis (AR), nonallergic rhinitis (NAR), and local allergic rhinitis (LAR) groups compared to controls. A subject with a change >7.6 (dashed line), corresponding to an SD index value for a change >2 standard deviations, was defined as NPT-positive. Solid horizontal lines indicate group means.



The *D. pteronyssinus* extract was kindly provided by the Yonsei University.

Within-subject standard deviation (SDw) was calculated by dividing the difference of the symptom scores between the initial value and the value after saline challenge by the square-root of 2. The SD index was calculated as the difference between the symptom score following the challenge with the Der p 1 (*D. pteronyssinus* allergen) dilution (TSS) and that following saline infusion (S_0), divided by SDw [18]: SD index = change in symptom score from post-allergen challenge measurement/SDw.

For the NPT tests, an SD index value >2 SDs was classified as positive.

Statistics

Data are expressed as mean and SD unless otherwise indicated, and were analyzed using SPSS statistical software (v22.0; IBM; Chicago, IL, USA). The Pearson correlation was used to assess the correlation of wheal diameter (sensitization to house dust mite) with MSS and TSS acquired after the NPT. The proportions of the month score, such as sneezing, rhinorrhea, nasal obstruction, nasal itching, postnasal drip, and MSS were analyzed using the linear-by-linear association trend test. MSS in the rhinitis groups was analyzed using ANOVA, and a post hoc analysis was performed using least significant difference. Agreement between prevalence rates based on different SD index criteria and SPT was analyzed using the Cohen κ statistical test. A p value ≤ 0.05 was considered statistically significant.

Results

We initially investigated 178 children with rhinitis, 114 of whom had positive SPT results; 81 subjects were monosensitized to house dust mite. Rhinitis children with negative SPT results ($n = 64$) and those monosensitized to house dust mite ($n = 81$) were enrolled for the final analysis. Table 1 shows the characteristics of the subjects. Six were adolescents (aged 14–18 years), and all of them were classified as AR. Healthy control (HC) subjects

Table 1. Clinical characteristics of the study population ($n = 145$)

Characteristic	Rhinitis group
Age, years (mean $\pm$ SD)	5.9 $\pm$ 3.3
Male sex	91 (62.8)
Family history	
Parental asthma	3 (2.1)
Parental allergic rhinitis	81 (55.9)
Parental atopic dermatitis	14 (9.7)
Admission history for LRTI	59 (40.7)
Comorbidities	
Asthma	37 (25.5)
Eczema	48 (33.6)
Environmental factors	
Secondary smoking	26 (17.9)
Pet in the house	10 (6.9)

Values are expressed as n (%), unless otherwise indicated. LRTI, lower respiratory tract infection.

Table 2. SD index score from the nasal provocation test

SD index score	Allergic rhinitis	Subjects nonsensitized to <i>D. pteronyssinus</i>
Negative	11 (7.6%)	59 (40.7%)
Positive	70 (48.3%)	5 (3.4%)

A score of >7.6 (2 standard deviations above the mean of the control) was defined as positive.

with an SD index of 7.6 (95th percentile) were defined as having positive NPT results.

Examination of the rhinitis subjects indicated that the relationship between wheal diameter and MSS was not significant ($\rho = 0.110$, $p = 0.144$), but the relationship

Table 3. Clinical characteristics of 145 patients with different types of rhinitis

	NAR (<i>n</i> = 59)	LAR (<i>n</i> = 5)	AR (<i>n</i> = 81)	<i>p</i> value ¹
Median age, years (IQR)	5.0 (3.5–6.1)	5.8 (3.8–9.8)	6.5 (4.5–9.2)	0.003
Male sex	39 (66.1)	4 (80.0)	48 (59.3)	0.497
Family history				
Parental asthma	1 (1.7)	0 (0.0)	2 (2.5)	0.900
Parental allergic rhinitis	32 (54.2)	4 (80.0)	45 (55.6)	0.536
Parental atopic dermatitis	6 (10.2)	0 (0.0)	8 (9.9)	0.757
Admission history of LRTI	29 (49.2)	3 (60.0)	27 (33.3)	0.164
Comorbidities				
Asthma	14 (23.7)	1 (20.0)	22 (27.2)	0.863
Eczema	15 (25.4)	0 (0.0)	33 (40.7)	0.046
Environmental factors				
Secondary smoking	13 (22.0)	0 (0.0)	13 (16.0)	0.375
Pet in the house	3 (5.1)	0 (0.0)	7 (8.6)	0.590

Values are expressed as *n* (%), unless otherwise indicated. The Kruskal-Wallis test was used for continuous variables and the χ^2 test for dichotomous variables. Statistically significant results are in bold. NAR, nonallergic rhinitis; LAR, localized allergic rhinitis; AR, allergic rhinitis; LRTI, lower respiratory tract infection. ¹ Difference between AR, NAR, and LAR.

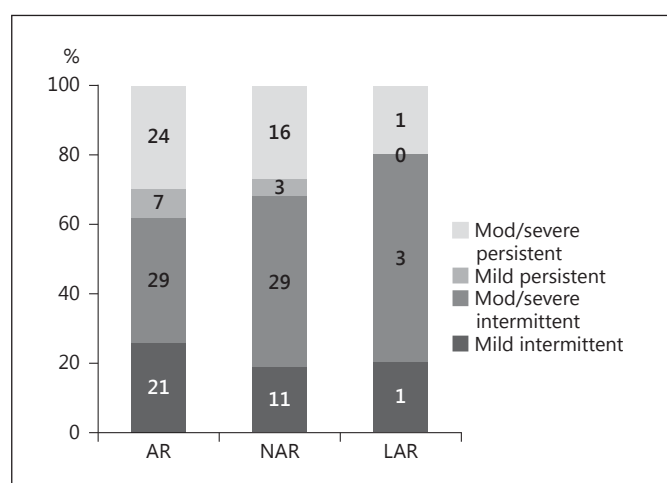


Fig. 2. Nasal severity measured with the ARIA guideline in allergic rhinitis (AR), nonallergic rhinitis (NAR), and local allergic rhinitis (LAR). “Moderate (Mod)/severe intermittent” was the most frequently rated in all 3 groups. The difference between the distribution of the number of patients with severity according to the ARIA guideline was not significant ($p = 0.693$). The number inside each shadowed box indicates the number of patients reporting each degree of symptom severity.

between wheal diameter and TSS provoked by *D. pteronyssinus* was significant ($\rho = 0.589$, $p < 0.001$). The κ coefficient (the agreement between the SPT and NPT results for house dust mites) was 0.778 (95% CI 0.726–0.830, $p < 0.001$).

Table 2 classifies rhinitis subjects according to NPT and SPT positivity based on the SD index. These results show that 81 subjects (55.9%) were classified as AR, 59 (40.7%) as NAR, and 5 (3.4%) as LAR. Figure 1 shows the SD index values of the children in the 3 rhinitis groups compared to the control.

Figure 2 displays rhinitis severity according to the ARIA guideline. There was no statistical difference between groups ($p = 0.693$). However, nasal-ocular scores in sneezing ($p = 0.024$) and itching ($p = 0.033$) differed across groups, and the MSS of the AR group (18.6 ± 7.7) was significantly different from that of the NAR (15.9 ± 6.4 , $p = 0.027$) and LAR (11.4 ± 4.5 , $p = 0.029$) groups, respectively.

Table 3 shows the clinical characteristics of the 3 groups of rhinitis children. Age showed a statistical difference ($p = 0.003$). The median age of the AR group was 6.5 years (IQR 4.5–9.2 years) which was higher than that of the NAR group at 5.0 years (IQR 3.5–6.1 years, $p = 0.002$), but similar to that of the LAR group, i.e., 5.8 years (IQR 3.8–9.8 years, $p = 1.000$). Eczema was more frequently observed in the AR group ($p = 0.046$).

Discussion

We found that the prevalence of LAR in children was lower than that previously reported in adults, and it remained relatively consistent across the different age

groups. In contrast, the prevalence of AR increased and NAR decreased with age. The different prevalence of LAR in adults and children seems to be related to the high agreement between the SPT and NPT results in children. However, it was difficult to determine whether the phenotype is an early manifestation of classical AR or a permanent phenotype that develops in some children, due to our cross-sectional study design. The results of the NPT were different in the sensitized controls and nonsensitized controls, and this influenced the distributions of the different forms of rhinitis.

Previous studies have reported the prevalence of LAR in adults [9], but few studies have reported the prevalence in pediatric populations. We found that the prevalence of LAR was 3.4% in rhinitis patients and 7.8% in nonsensitized rhinitis patients. A recent study reported that the prevalence of LAR in children was 3.7% [19]. Previous studies reported a prevalence of 25.7% in adults [20], 21.0% in elderly patients [12], and 54–62% [8, 21, 22] in nonsensitized adult rhinitis patients. The lower prevalence of LAR in children might be related to the high agreement of SPT and NPT results in children. Moreover, the lower prevalence in children might result from the use of different diagnostic criteria [23], small samples sizes [5, 8, 21], the lack of controls [12, 20, 21], the exclusion of incidentally sensitized controls [22], or innate differences between children and adults.

Our estimated prevalence of LAR, which defined controls as those with negative SPT results, was also lower than in previous studies. Our finding that wheal size correlates with a positive NPT result might be because the skin and nose are derived from the same ectodermal tissues [24]. This also implies that SPT results may correlate with nasal sensitivity, a topic that warrants further immunological investigation.

Recent studies including a cohort study that followed adults for 5 years reported that LAR and AR may be 2 separate clinical entities, and may be differentiated using diagnostic tools such as NPT and acoustic rhinometry [7, 25]. Another observational study suggested that LAR might have a life-long history, and is not limited to individuals with recently acquired allergies [4, 20]. However, a retrospective investigation of adults determined that 21% of LAR patients converted to classic AR over time [26, 27]. In pediatric populations, the prevalence of positive SPT results and rhinitis increased with age [28], and 56.3% of sensitized 4-year-old subjects progressed to AR 4 years later [2]. In our study, NAR was more frequent in younger children and AR was more frequent in older children, but the prevalence of LAR appeared not to change

with age. This might imply that LAR is either an initial stage of classical AR [19] or a transient phenotype in the progression from NAR to AR, thus resulting in a low prevalence in children. This finding differs from those in adult populations; however, it needs to be confirmed by a longitudinal study that investigates the reasons for the changing distributions in types of rhinitis with age.

The clinical characteristics, such as comorbidities and symptoms, were similar in children with different types of rhinitis, similar to results previously reported in adults [20]. Moreover, according to the ARIA classification, children with different types of rhinitis had similar disease severity.

There are several limitations to this study. We may have underestimated the prevalence of rhinitis because we excluded aeroallergens other than house dust mites, and children presumed to have seasonal allergies were not enrolled. However, this would not have influenced the overall prevalence of AR, because *D. pteronyssinus* is the most common allergen associated with AR [20]. Subjects recruited in our study had persistent, recurrent rhinitis, rather than intermittent, seasonal rhinitis. This would have resulted in a low rate of mild rhinitis cases, and thereby increased the rate of distinctive AR and NAR compared to the general population. However, the sensitization rate in our study was similar to that of a previous epidemiological study [29], and up to 90% of atopic Korean children are sensitized to house dust mites [30], so our results might represent the general rhinitis population.

Our analysis of NPT was not entirely objective, because the definition of NPT positivity depends on methodology [9]. Previous researchers have defined a positive NPT result as an increase of at least 30% in the total visual analog scale plus a decrease of at least 30% in the nasal volume in acoustic rhinometry (measured at 2–6 cm from the tip of the probe) [8, 12, 20, 21], or as an increase in unilateral nasal resistance of >50% above the baseline value [22]. These definitions are limited, in that they are not based on established criteria but on the degree of change without considering the controls. A recommended method to differentiate AR from NAR is to measure changes in nasal symptoms, and compare score changes using rhinomanometry with controls after an NPT [16, 31].

We did not include serum test results in analysis. Considering the low agreement between serum-specific IgE and the SPT [32], testing the serum might have resulted in a larger proportion of children being classified as AR, which would be contrary to the low prevalence of LAR in

our study. There is a possibility that NAR patients are classified as AR without additional aeroallergen tests. The local production of allergy inflammatory mediators such as IgE and T helper cells was also not measured. This might have changed the overall distribution of LAR and NAR. The possibility of false-positives in the NPT should also be considered, because the final dose (4 µg of *D. pteronyssinus*) was higher than typical exposures [23].

The symptoms of the subjects aged 1–4 years were not validated separately, but since we used symptom changes reported by parents/caregivers for all ages, we speculate that these reported symptom scores may be applied in younger children as well.

In conclusion, this study reported the distribution and clinical characteristics of AR, NAR, and LAR in rhinitis children monosensitized to *D. pteronyssinus*. The prevalence of the different forms of rhinitis change with age,

while LAR accounted for a small but consistent portion of rhinitis in children aged 1–18 years. Further immunological studies are needed to determine whether LAR is a distinct clinical entity or a transient phenotype.

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Disclosure Statement

All authors declare there are no conflicts of interests.

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